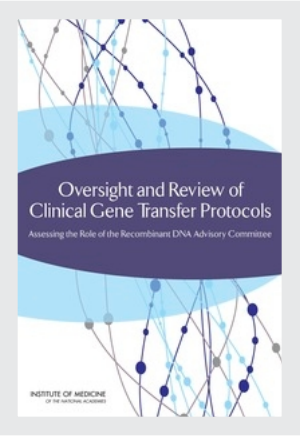

Oversight and Review of Clinical Gene Transfer Protocols: Assessing the Role of the Recombinant DNA Advisory Committee

DETAILS

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Oversight and Review of Clinical Gene Transfer Protocols

Assessing the Role of the Recombinant DNA Advisory Committee

Committee on the Independent Review and Assessment of the Activities of the NIH Recombinant DNA Advisory Committee

Board on Health Sciences Policy

Rebecca N. Lenzi, Bruce M. Altevogt, Lawrence O. Gostin,
Editors

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

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"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

RITA COLWELL, University of Maryland at College Park
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BRIGID HOGAN, Duke University
MICHAEL KATZ, March of Dimes Foundation
SUSAN M. WOLF, University of Minnesota

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by **Wylie Burke,** University of Washington, and **Floyd E. Bloom,** Scripps Research Institute. Appointed by the Institute of Medicine, they were responsible for making certain that an independent examination of this

report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Preface

In the following report, the Institute of Medicine (IOM) Committee on the Independent Review and Assessment of the Activities of the National Institutes of Health (NIH) Recombinant DNA Advisory Committee (RAC) sought to provide an assessment of the state of existing gene transfer science and the current regulatory and policy context under which research is investigated. The charge to this committee, reproduced in the report, had two main aspects, the first of which was to assess whether the current oversight of individual gene transfer protocols by the RAC continues to be necessary. This task required understanding the circumstances that led to the creation of the RAC and assessing the current validity of these, and other, concerns. It was thus important to root our report in both scientific and historical contexts. The second major aspect of the committee's charge was to offer recommendations concerning the criteria the NIH should employ to determine whether individual protocols should receive public review. The issue was not simply should individual protocol review continue, but, if so, what standards the RAC and the NIH should use in exercising its oversight function. An examination of criteria could assist not only the RAC, but also research institutions and the general public with respect to utilizing and improving existing oversight processes.

The committee strove, above all, to maintain the public's confidence in the integrity of gene transfer research, consistent with the value of scientific advancement. Thus, the committee considered it vital to ensure that the recommended processes adequately safeguard the ethical integrity of the conduct of human subject research, including human subjects' and patients' rights and safety. At the same time, the committee aimed to achieve a regulatory and oversight environment that would advance the

important mission of science—including removing as much regulatory duplication and delay as possible.

Even when a new discovery or novel technology offers the potential for valuable treatment, it can also bring with it troublesome scientific and technical challenges, as well as social and ethical concerns. The committee found that while gene transfer research continues to raise important scientific, social, and ethical questions, and while gene transfer research is constantly evolving, not all of gene transfer research is still considered an entirely new scientific enterprise or novel technology and therefore not all protocols warrant special/public oversight by the RAC. It is also important to stress that a number of applications of emerging technologies with the potential to make significant contributions to clinical medicine may also raise questions of significant and/or uncertain risk. These technologies could benefit from the model of oversight established by the RAC. This led the committee to the conclusion that the time had arrived for the NIH director to consider developing a rigorous review process that—instead of being limited to a single body of gene transfer research—was fair and consistent across scientific realms.

After careful study of the social and historical context of recombinant DNA research, the committee concluded that the RAC had served all parties admirably, ranging from human subjects and their families, to the research community and broader society. The RAC's commitment to providing a public forum in which the scientific, technical, and ethical considerations of gene transfer research were discussed instilled public confidence in a controversial new research field that at the time was not well understood. After 40 years of experience, the time for modernization has arrived. The committee concluded that the NIH should consider developing a process—using the RAC as a model—to rigorously review human subject research that is so novel, and carries significant unknown risks, that the normal regulatory apparatus lacks the capacity to conduct an adequate review. Until such a process is developed and agreed upon, the RAC should continue to review individual gene transfer protocols but should use new, more focused criteria in order to direct its resources to exceptional cases that warrant special oversight.

We are most grateful to the NIH for entrusting us with the opportunity to conduct this timely review. Gene transfer research remains highly important to the public and scientific community, and the RAC's oversight standards and processes can serve as a model for other areas of evolving science.

I am deeply appreciative of the expert work of our dedicated committee members and their extraordinary commitment and contributions to the task at hand. Our committee comprised some of the most eminent scientists and ethicists in the United States. Our study director Rebecca Lenzi—together with Monica Gonzalez and Shelli Goldzband—offered superb leadership and guidance. Andy Pope and Bruce Altevogt also offered exceptional guidance. Over a course of about 5 months, we convened 3 in-person committee meetings, 2 public meetings, including scientific presentations, and an abundance of teleconferences and e-mail exchanges. We trust that this report will assist not only the NIH in its vital efforts, but also the broader research and patient community. It is the committee's sincere hope that policy makers, scientists, research participants and their families, and others concerned about or hopeful of the promise of gene therapy, will find the report valuable.

The committee gave generously of its time, demonstrating tireless devotion to this task. I also wish to express the committee and staff's appreciation to the NIH Office of Biotechnology Activities for its openness and responsiveness to the committee's many requests for information during the course of this study.

Lawrence O. Gostin, *Chair*
Committee on the Independent Review and Assessment of the
Activities of the NIH Recombinant DNA Advisory Committee

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Acronyms and Abbreviations

AAV	adeno-associated virus
BLA	Biologic License Application
CBER	Center for Biologics Evaluation and Research
CMC	chemistry, manufacturing, and controls
DNA	deoxyribonucleic acid
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
GeMCRIS	Genetic Modification Clinical Research Information System
HHS	U.S. Department of Health and Human Services
IBC	institutional biosafety committee
IND	investigational new drug
IOM	Institute of Medicine
IRB	institutional review board
NAS	National Academy of Sciences
NIH	National Institutes of Health
OBA	Office of Biotechnology Activities
OCTGT	Office of Cellular, Tissue, and Gene Therapies
OHRP	Office of Human Research Protections

OTD	ornithine transcarbamylase deficiency
RAC	Recombinant DNA Advisory Committee
rDNA	recombinant DNA
RNA	ribonucleic acid
SCID	severe combined immune deficiency

Summary

Gene transfer research is a rapidly advancing field that involves the introduction of a genetic sequence into a human subject for research or diagnostic purposes. Clinical gene transfer trials are subject to regulation by the U.S. Food and Drug Administration (FDA) at the federal level and to oversight by institutional review boards (IRBs) and institutional biosafety committees (IBCs) at the local level before human subjects can be enrolled. In addition, at present all researchers and institutions funded by the National Institutes of Health (NIH) are required by NIH guidelines to submit human gene transfer protocols for advisory review by the NIH Recombinant DNA Advisory Committee (RAC). Some protocols are then selected for individual review and public discussion.

Since the RAC's creation in the early 1970s, its roles and responsibilities have changed from those of a formal regulatory body to an advisory body that functions within a complex regulatory oversight system that includes FDA and oversight bodies at research institutions—IRBs and IBCs. The RAC's individual protocol review of proposed clinical gene transfer research was instituted at a time when there was a somewhat unique combination of new technology, limited scientific and public understanding, heightened social concern about genetics, and uncertainty regarding the risks to individuals and the environment (Berg, 2004).

The decades since have seen the creation of overlapping and arguably redundant oversight roles for the RAC, FDA, and institutional oversight. With the accumulation of safety data and experience with gene transfer research, its associated risks are becoming better understood, as are the strengths and weaknesses of federal and institutional oversight mechanisms. Hundreds of clinical gene transfer trials—predominantly

phase I trials designed to evaluate safety—have been performed (Ginn et al., 2013). Although public fears and anxieties surrounding gene transfer research have not completely abated, positive public perceptions have also developed, particularly with respect to the promise of more effective treatments or even cures or preventive interventions for devastating and debilitating diseases (see, for example, Seymour and Thrasher [2012]). While all gene transfer protocols must still be submitted to the RAC, over the years, fewer have been selected for additional public review. Indeed, over the past year, the RAC selected only 20 percent of all submitted protocols for additional review (Corrigan-Curay, 2013). Even with the decline over the years in the number of protocols reviewed, however, gene transfer research continues to engage the public imagination. Therefore, it is reasonable to consider whether the concerns articulated in the early days of gene transfer research are still relevant and continue to warrant special oversight today. It is in this context that NIH approached the Institute of Medicine (IOM) for an examination of the role of the RAC. Given the involvement of multiple regulatory and oversight bodies in reviewing and approving gene transfer protocols at the present time, and given arguments that gene transfer is no longer itself so novel, NIH commissioned the IOM to review the current state of the science and regulatory process and to assess whether gene transfer research raises issues of concern that warrant continuing extra oversight, specifically with respect to individual clinical trial protocols by the RAC.

The committee found that many of the main concerns that led to the creation of the RAC have been alleviated. After more than four decades of clinical experience and extensive research efforts, many of the original fears associated with gene transfer, such as the perceived danger of creating transmissible pathogens, causing accidental germ-line modification or contamination, or harming third parties and society at large, have not been borne out. Furthermore, public perception has largely transitioned from negative to positive because of the promise of more effective treatments, cures, or preventive interventions for devastating and debilitating diseases that gene therapy holds today (Yarborough, 2009).

CRITERIA FOR GENE TRANSFER RESEARCH REVIEW

The committee found that although gene transfer research continues to raise important scientific, social, and ethical questions and is constantly evolving, not all of gene transfer research is novel enough or contro-

versial enough to justify all the current forms of additional oversight. Therefore, the committee concluded that individual protocols should not be reviewed by the RAC except in exceptional circumstances, such as when novel gene therapy technologies and treatment strategies move forward into the realm of clinical trials. The committee outlines three criteria that characterize these exceptional circumstances. In-depth public individual protocol review would be warranted only if one or more criteria are satisfied:

Criterion 1 The protocol uses a new vector, genetic material, or delivery methodology that represents a first-in-human experience, thus presenting an unknown risk.

Criterion 2 The protocol relies on preclinical safety data that were obtained using a new preclinical model system of unknown and unconfirmed value.

Criterion 3 The proposed vector, gene construct, or method of delivery is associated with possible toxicities that are not widely known and that may render it difficult for local and federal regulatory bodies to evaluate the protocol rigorously.

When individual gene transfer protocols are reviewed publicly, the purpose will be to advise prospective research participants, the investigator, and NIH's Office of the Director, as well as to inform the public and other regulatory bodies, such as FDA and IRBs. Emerging technologies in gene transfer science, as presented in new clinical trials protocols (for example, first-in-human trials), may present scientific or ethical concerns that would require additional oversight and represent significant departure from familiar techniques, such that protocol review could not be adequately performed by other regulatory and oversight processes. Furthermore, the committee concluded that in order to minimize the administrative burden of the RAC's assessment, its protocol review can be accomplished using FDA's investigational new drug (IND) file, thereby decreasing the administrative burden that investigators shoulder as they deal with the diverse requirements of multiple oversight bodies.

Recommendation 4-1: <u>Restrict individual gene transfer protocol reviews to exceptional cases that meet specified criteria.</u>

The National Institutes of Health's (NIH's) Office of the Director should continue to register all gene transfer protocols and, in consultation with appropriate regulatory and/or oversight authorities, should identify protocols for additional public review only if both items 1 and 2 below are satisfied

1. **Protocol review could not be adequately performed by other regulatory and oversight processes (for example, institutional review boards, institutional biosafety committees, the U.S. Food and Drug Administration);**
2. **One or more of the criteria below are satisfied:**

    - **The protocol uses a new vector, genetic material, or delivery methodology that 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 and that may render it difficult for local and federal regulatory bodies to evaluate the protocol rigorously.**

Even if the protocol does not meet the foregoing criteria listed in items 1 and 2, the NIH director in consultation with appropriate regulatory and/or oversight authorities should have the flexibility to select protocols for review that may present significant societal or ethical concerns.

EVOLUTION OF OVERSIGHT OF EMERGING CLINICAL RESEARCH

The RAC was designed to respond to the human applications of an emerging area of science: recombinant DNA technology. The area was of great public interest, with risks and benefits only barely understood. The RAC has successfully provided oversight over a complex technolo-

gy for nearly 40 years, providing a valuable service to NIH, the scientific community, and to the public. Its value has been demonstrated by its help in assembling experts from diverse fields with the shared goal of ensuring safe clinical protocols. By engaging the public in a focused discussion on the technology and its potential societal impacts, the RAC engendered trust and credibility. Gene transfer research, although still not entirely without areas of uncertainty or public concern, is now better understood, and many of its risks have been minimized. Therefore, the committee recommends that the RAC's review of gene transfer oversight be narrowed to those areas still in need of special review or expertise.

The committee also notes that the experience with gene transfer research may offer valuable lessons for how to proceed with human trials of other medical advances that depend on emerging technologies. For this reason, it recommends that NIH assess whether other areas of clinical research might benefit from a venue for targeted, transparent oversight beyond that provided by existing regulatory mechanisms. If so, then consideration of an appropriate mechanism would be in order.

The RAC's origins lie in a particular confluence of events. Gene transfer research used a disruptive technology, one that dramatically altered human capacity to alter the natural environment, including humans themselves. This not only meant that its risks and benefits would be particularly difficult to predict, but also that it pushed on the edges of what some thought should be the limits of human control (Berg, 2004). The most recent example of another disruptive technology has been nuclear fission, which brought both electrical power and the atomic bomb. Recombinant DNA technology and its power to create new properties in old organisms came into public consciousness at the same time that public appreciation for the fragility of the ecosystem was rising, as evidenced by the spate of federal initiatives to protect land, water, and air.[1] It also arrived hard on the heels of a world war that, among its many horrors, had demonstrated the evils of eugenics, a field linked to (though obviously distinct from) genetics, gene transfer, and gene therapy.

Today, various areas of laboratory and clinical research share some of these characteristics. Nanotechnology presents basic science questions about the chemical, optical, and other properties of familiar materials in unfamiliar sizes. In the context of human applications, these questions

[1]See, for example, Marine Protection, Research and Sanctuaries Act. 1972. Public Law 92-532. October 23; Safe Drinking Water Act. 1974. Public Law 93-523. December 16; Surface Mining Control and Reclamation Act. 1977. Public Law 95-87. August 3.

may affect how well we are able to assess risks to subjects, as well as risks to the manufacturing workforce that handles the materials and to the environment as the materials are excreted. Synthetic biology has the potential to raise public concerns once again about the appropriate scope of human endeavors to shape the natural world. Neurobiology may blur the line between what is commonly thought of today as body and soul. Gene transfer research no longer stands alone as the only human application of an emerging technology that might benefit from additional avenues of oversight. Nor is it even necessarily the one most deserving of such attention. This is why the committee recommends that NIH explore whether a need exists for additional or different oversight for other clinical applications of emerging technologies, and if so, whether some of the procedures used by the RAC to provide both expertise and a venue for public deliberation might serve as a good model. Taking these questions seriously is a logical next step and constitutes a commitment to forward thinking.

Therefore, the committee makes the following recommendation.

Recommendation 4-2: Consider integrating oversight for gene transfer and other applications of emerging technologies.

The National Institutes of Health (NIH) director should convene an ad hoc working group that will be responsible for considering whether additional oversight and a venue for public deliberation are indicated for other applications of emerging technologies, and if so, to explore procedural options, including the possibility of an integrated oversight body. In this task, the focus 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 Recombinant DNA Advisory Committee (RAC) should be used as one possible model, particularly with regard to these functions:

- **Provide a public forum for the review and discussion of emerging areas of science.**
  - **Include the capacity for a partnership to consult, inform, and educate institutional review boards (IRBs) and institutional biosafety committees (IBCs).**

- **Provide a venue to foster scientific and public awareness regarding emerging science in order to address concerns about clinical investigation and future societal implications.**
- **Integrate the capacity to surveil, aggregate, and analyze adverse events across related trials of emerging technologies.**
- **Perform an additional level of review of individual protocols that are identified by the NIH director, in consultation with one or more IRBs and IBCs, on the basis of exceptional issues raised as articulated in the committee's gene-transfer protocol criteria.**

For the present, however, the RAC should continue to review individual gene transfer protocols but use the criteria set forth in Recommendation 4-1 to help limit review and focus resources on exceptional cases.

The committee recommends that any expanded process established to evaluate and advise on new technologies be focused on those that are anticipated to be part of clinical research interventions and that pose uncertain risk and consequences to individual and/or public health. To be clear, the criteria presented in Recommendation 4-1 are meant to be used to select gene transfer protocols that require an exceptional level of review and are not meant to apply in whole or in part to other technologies. Similar concepts may be considered, however, if in the future there is a need to select protocols for review in other areas of emerging science.

The committee's recommendations reflects its view that the RAC has been an example of a valuable forum in which members of the research community can discuss and disseminate new information and share best practices, and where members of the public can express and discuss their concerns. Equally important, whatever processes are used, they should complement the efforts of existing regulatory bodies, not hamper or duplicate them. Thus, oversight and review should focus only on the cases where the existing regulatory structure lacks that capacity to do so or when there is significant expression of public concern. To the extent that the new forums can provide guidance generally and increase institutional capacity and expertise, the need for review of selected individual protocol should be a relatively uncommon occurrence.

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1

Introduction

Gene transfer research is a rapidly advancing field that draws from genetics, molecular biology, and clinical medicine. It has fascinated scientists and the public but, particularly in its early years, has also raised anxieties about its potential for harm to individuals and communities. These anxieties prompted the creation of special oversight procedures for gene transfer research.

CHARGE TO THE COMMITTEE

The Institute of Medicine (IOM), in collaboration with the National Research Council, convened an ad hoc committee to provide an independent review and assessment of the role of the Recombinant DNA Advisory Committee (RAC) in advising on clinical gene transfer protocols at the request of the Office of the Director of the National Institutes of Health (NIH). Specifically, NIH asked the committee to specify the scientific, safety, ethical, and other concerns that justify a special level of oversight for this and potentially other areas of clinical research. The committee was to consider the current regulatory context, which includes the U.S. Food and Drug Administration (FDA) and institutional bodies, and determine whether gene transfer research raises issues of concern today that warrant additional individual protocol review by the RAC. If the committee concludes that this particular function of the RAC should remain intact, it was asked to describe the criteria that the RAC should use to select protocols for review (see Box 1-1).

BOX 1-1
Charge to the Committee

In response to a request from the Office of the Director of the National Institutes of Health (NIH), an ad hoc committee of the Institute of Medicine (IOM) will provide an independent review and assessment of selected activities of the NIH's Recombinant DNA Advisory Committee (RAC). Specifically, the committee will determine if gene transfer research raises issues of concern that warrant extra oversight by the RAC of individual clinical trial protocols involving gene transfer techniques and will describe the criteria used in making this determination. If the committee determines that RAC oversight is still warranted, it will recommend criteria to guide when the RAC should review this research. In conducting the review and assessment, the committee will give due consideration to the current state of the science. It will also consider the current regulatory and policy context, including the roles of the U.S. Food and Drug Administration, institutional review boards, institutional biosafety committees, and other entities in overseeing gene transfer research and also the scientific, safety, ethical, and other concerns and objectives that would justify a special level of oversight for this area of research (and potentially others).

WHAT IS GENE TRANSFER RESEARCH?

The technique of gene transfer can be broadly understood as the introduction of genetic material, through a vector, into cells with the intent of altering gene expression (Kay, 2011). The NIH Office of Biotechnology Activities (OBA) currently defines clinical gene transfer research as

> the deliberate transfer into human research participants of either 1) recombinant nucleic acid molecules, or deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) derived from recombinant nucleic acid molecules, or 2) synthetic nucleic acid molecules,[1] or DNA or RNA derived from synthetic nucleic acid molecules that either contain more than 100 nucleotides; or possess biological properties that enable integration into the genome; or have the potential to replicate in a cell; or can be translated or transcribed. (NIH, 2013, p. 17)

[1]Synthetic DNA, a more recent genetic engineering technology, differs from rDNA in that it does not require a preexisting DNA sequence template. Instead, it is possible to chemically synthesize nucleic acids to form a double-stranded DNA molecule de novo (Clark, 2005).

The committee worked with a more general and functional definition of gene transfer: the transfer of nucleic acids (or a nucleic acid–like molecule) into a cell using ex vivo or in vivo techniques, intending to produce a biological effect, which could include therapeutic or symptomatic effects in humans. This expanded definition of gene transfer accommodates newly emerging technologies that would test the limits of the standard used by OBA, such as mitochondrial DNA transfer or the techniques of gene transfer using pluripotent stem cells.

OVERSIGHT OF CLINICAL GENE TRANSFER TRIALS

Some observers argue that human gene transfer research[2] is the most heavily regulated type of biomedical research (Kahn, 2009). Because clinical gene transfer trials involve both rDNA and human subjects, investigators must submit clinical gene transfer protocols to the RAC and FDA at the federal level and to institutional review boards (IRBs) and institutional biosafety committees (IBCs) at the local level before human subjects can be enrolled. The history and changes over time in gene transfer research oversight demonstrate the difficulties and advantages of oversight by more than one agency. For example, the partially overlapping functions of NIH and FDA have prompted much discussion about tension between transparency and protection of proprietary information, between preventing harm and encouraging scientific progress, and between creating standards and remaining responsive to an evolving area of science (Wolf et al., 2009).

The additional layer of review has been the source of discussion and frustration within the research and patient-advocacy communities. Gene transfer is not the only clinical research that receives additional oversight, however. Several forms of clinical research receive additional levels of scrutiny, including but not limited to certain forms of pediatric research, research with pregnant women and fetuses, and research involving prisoners (Wolf and Jones, 2011).

[2]*Gene transfer* is the introduction of a genetic sequence with any function into a cell for research or diagnostic purposes. The process of gene transfer may or may not have a therapeutic purpose or demonstrated therapeutic effect. *Gene therapy* is gene transfer, but with the intent to produce beneficial health consequences.

Establishment of the RAC

As scientists began to experiment with rDNA technologies in the early 1970s, ethicists, policy makers, and many scientists raised concerns about the potential hazards that genetic engineering posed to individuals, communities, and future generations. In the early days of gene transfer investigations, a critical argument was that the technology was so novel and its risks so little understood that it warranted special review (see, for example, Rainsbury [2000], Wolf and colleagues [2009], and Chapter 3 of this report).

From virtually the outset, the development of rDNA technology has raised concerns about its risks (see, for example, Berg and Mertz [2010], Fredrickson [2001], OTA [1984], President's Commission [1982], and Rainsbury [2000]). These concerns can be roughly divided into three categories. One category—the subject of most early discussion—focuses on biohazards that might harm investigators and laboratory staff or affect the wider community. The potential hazards cited at the time included the creation of new cancer risks from altered organisms and the emergence of novel, deadly pathogens.

A second category of concerns, which intensified as scientific investigations approached the phase of studies in humans, focuses on short- and long-term health risks to individual research participants. Related concerns include the extent to which preclinical studies would provide sufficient evidence that it was ethical to proceed with human investigation and the extent to which potential research participants (or their parents or guardians) could be adequately informed about risks and could provide informed consent. These issues were considered and debated in the broader context of evolving views on ethical principles for research involving humans and continuing efforts to apply more explicit and stringent protections through education, regulation, and other means (DHEW, 1971). A key product of this evolution was the creation, under federal guidelines, of IRBs to review and approve federally funded biomedical and social-behavioral research involving human subjects, including gene transfer research.

A third category of concerns involves risks to future generations. A primary focus here is rDNA investigations involving germ-line cells that could produce heritable changes in organisms; concern has also been expressed about somatic-cell studies that unintentionally do so (RAC, 1990).

EARLY RESPONSES

The uncertainty that characterized the nascent gene transfer technology increased worries among scientists and eventually the broader public about the nature and magnitude of both short- and long-term risks (see, for example, Berg et al. [1975]). This uncertainty led very early to organized efforts to better identify risks and develop safeguards.

Conferences and Deliberations

One of the first safeguards was the postponement of further research by individual investigators until risks were better understood. For example, in the early 1970s, pioneer researchers in the field voluntarily delayed further research on rDNA techniques after considering and discussing with their peers the uncertain dangers of these investigations (Fredrickson, 2001). These individual actions were followed by collective recommendations from investigators and expert groups for moratoria on certain kinds of research (see below).

Another early response to worries about the safety of rDNA research was the organizing of scientific conferences to discuss the technology and research approaches and to assess risks and uncertainties (see, for example, Berg [2004] and Fredrickson [2001]). A conference in 1973 on laboratory safety or containment issues and strategies (sometimes referred to as Asilomar I, for the conference site) considered evidence on the risk of cancer from genetically modified viruses and safety precautions that might be taken. Another conference later that year (the Gordon Conference) produced further discussions of safety issues. These discussions prompted the drafting of a letter from participants asking that the National Academy of Sciences (NAS) establish a committee to examine safety concerns and create guidelines for rDNA research.

The NAS responded positively by creating the Committee on Recombinant DNA Molecules, which met once, in April 1974. The conclusions of the seven-member committee were disseminated through a press conference and a letter published in the *Proceedings of the National Academy of Sciences of the United States of America* in July 1974 (Berg et al., 1974). The committee proposed that

> until the potential hazards of [rDNA] molecules have been better evaluated or until adequate methods are de-

> veloped for preventing their spread, scientists throughout the world should voluntarily defer the following types of experiments:
>
> **TYPE I:** Construction of new, autonomously replicating bacterial plasmids that might result in the introduction of genetic determinants for antibiotic resistance or bacterial toxin formation into bacterial strains that do not at present carry such determinants, or construction of new bacterial plasmids containing combinations of resistance to clinically useful antibiotics unless plasmids containing such combinations of antibiotic resistance determinants already exist in nature.
>
> **TYPE II:** Linkage of segments of the DNAs from oncogenic or other animal viruses to autonomously replicating DNA elements such as bacterial plasmids or other viral DNAs. Such [rDNA] molecules might be more easily disseminated to bacterial populations in humans and other species, and thus possibly increase the incidence of cancer or other diseases. (Berg et al., 1974, p. 2593)

In addition, the committee recommended caution in the undertaking of certain other research, and it proposed another international conference to consider scientific developments and discuss strategies for dealing with safety concerns. It further recommended that the director of NIH consider promptly establishing a committee to

> (i) [oversee] an experimental program to evaluate the potential biological and ecological hazards of the above types of [rDNA] molecules,
> (ii) [develop] procedures which will minimize the spread of such molecules within human and other populations, and
> (iii) [devise] guidelines to be followed by investigators working with potentially hazardous [rDNA] molecules. (Berg et al., 1974, p. 2593)

Formation of the Recombinant DNA Molecule Program Advisory Committee

Despite some apprehension in the scientific community about government interference, the establishment of federal oversight of some aspects of rDNA research, as recommended by the NAS committee, was another response to concerns about the risks of the technology. NIH acted in October 1974 to create the Recombinant DNA Molecule Program Advisory Committee (a name later shortened to its present form and abbreviated as RAC). Although the initial membership of the committee was restricted to experts with knowledge of rDNA technology, NIH soon expanded the panel to include not only people with a broader range of scientific expertise but also lay members. The first lay member was a professor of government; the second was a professor of ethics, who later served as chair of the committee (Fredrickson, 2001; RAC, 1993).

Donald Fredrickson, the director of NIH and the official who chartered the RAC, noted that establishing extra oversight for rDNA out of an overabundance of caution was necessary and appropriate: "Uncertainty of risk . . . is a compelling reason for caution. It will occur again in some areas of scientific research, and the initial response must be the same" (Fredrickson, 2001).

Debating the Continued Need for the RAC

Some observers have suggested that the early creation of special review procedures may have insulated gene transfer researchers from "shifting winds of public opinion and politics" (Wolf et al., 2009) as public concerns about the technology have periodically intensified and ebbed. Today, rDNA and human gene transfer research has progressed as a function of both scientific advancement and the changing regulatory context, with the RAC providing an avenue for broad public participation and mechanisms for accountability as a key feature of oversight. However, at present in the United States, all gene transfer products remain investigational; none has received a New Drug Application (NDA)/ Biologic License Application (BLA) for an approved product or biological licensing by FDA thus far.

The 1990s saw increasing debate about the continued need for the additional RAC review. Support for gene transfer protocol review was reinforced, in particular, by the controversy created by the tragic death of

a participant in a gene transfer trial in 1999. The death of 18-year-old Jesse Gelsinger, who suffered from the rare metabolic disorder ornithine transcarbamylase deficiency (OTD), attracted widespread attention and public scrutiny of the trial protocol and its implementation, the investigators, and the infrastructure and process of human research protections in the United States (Deakin et al., 2009). Investigations launched by FDA, the University of Pennsylvania, and the Office of Human Research Protections at the U.S. Department of Health and Human Services (HHS) exposed a number of shortcomings in the OTD gene transfer trial and significant gaps in oversight. However, at the time that the RAC approved the OTD protocol, the RAC was unaware of study aspects that were not in compliance with the rules and regulations imposed on clinical gene transfer trials; therefore, these violations occurred despite RAC review. A general assessment of the state of gene transfer research in the aftermath of the death of this research subject was that this was a technology in which investigators were overestimating potential benefits, the media was hyping its curative potential, and oversight mechanisms were struggling to stay ahead of the technology (Kahn, 2009).

STUDY ORIGIN AND STRATEGY

The decades have also seen the creation of overlapping and arguably redundant oversight roles for the RAC, FDA, and institutional bodies. With the accumulation of safety data and experience with gene transfer research, its associated risks are becoming better understood, as are the strengths and weaknesses of federal and institutional oversight mechanisms. Hundreds of clinical gene transfer trials—predominantly phase I trials designed to screen for safety—have been initiated and completed (Ginn et al., 2013). In addition to fears and anxieties surrounding gene transfer research, positive public perceptions can also be cited, notably the promise of more effective treatments or even cures or preventive interventions for devastating and debilitating diseases (see, for example, Seymour and Thrasher [2012]). Although all gene transfer protocols must still be submitted to the RAC, over the years, fewer have been selected for additional public review. In the past year, only 20 percent of all submitted protocols were selected by the RAC for additional review. Nevertheless, even with the decline over the years in the number of protocols reviewed, gene transfer research continues to engage the public imagination. Therefore, it is reasonable to consider whether the concerns

articulated in the early days of gene transfer research are still relevant and continue to warrant special oversight today. It is in this context that NIH approached the IOM for an examination of the role of the RAC.

Committee Approach to the Charge

To complete its task, the IOM formed a committee of experts from a range of disciplines to conduct an 8-month study. The committee was composed of members with expertise in clinical medicine; molecular biology; virology; molecular genetics; high-risk clinical trials; gene transfer technologies; biomedical ethics; law; public policy; and advocacy for research participants, patients, and families. The committee invited input from experts in the field of gene therapy and received many statements from stakeholders and members of the public. To conduct this expert assessment and evaluate the necessity for the extra oversight of individual gene therapy protocols by the RAC, the committee deliberated from June 2013 through October 2013. During this period, the committee held three 2-day meetings and two public information-gathering sessions on June 5, 2013, and August 6, 2013 (see Appendix A). Committee members also participated in multiple conference calls.

Given its charge, the committee first interpreted its goal as advising NIH on the individual protocol review role of the RAC rather than its other functions (for example, organizing scientific conferences). The committee understood that an essential element of the RAC review is the balancing of two critical values—the protection of human participants in research and the advancement of medical science to the benefit of society—and it recognized that inherent tensions exist between advancing science and ensuring the adequate protection of research participants. These tensions revolve around the burdens associated with assessing the ethics of research protocols, including whether the anticipated benefits (taking into account the quality of the research strategy) are in reasonable balance with potential harms. If the regulatory burden can be eased, however, without endangering research participants (and intended patient beneficiaries), then the committee's stance was that regulatory burdens should be reduced. Another element of the committee's approach was the consideration of the state of gene transfer science from its inception to modern developments. A third element of the approach was the determination of whether there remains a justification for continued individual protocol review by the RAC given the current regulatory and policy con-

text. If a justification for extra oversight remains, the final element of the task is to develop criteria for selecting protocols for the RAC public review.

Organization of This Report

The report is organized into three chapters following this introduction. Chapter 2, "Gene Transfer Research: The Evolution of the Clinical Science," offers an assessment of the scientific progress made in gene transfer over the years and outlines risks and concerns that still exist today. Chapter 3, "Oversight of Gene Transfer Research," provides policy and historical context regarding regulation and oversight of gene transfer research and describes the complex oversight mechanisms that exist today for human gene transfer trials. Chapter 4, "Evolution of Oversight of Emerging Clinical Research," offers the committee's findings, conclusions, and recommendations.

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2

Gene Transfer Research: The Evolution of the Clinical Science

Gene transfer research builds on technical advances in many fields, notably genetics, molecular biology, and clinical medicine. Hundreds of clinical trials have generated better understanding of the technology's promise and risks and the increasing evidence of clinical benefits in various areas. This chapter explores the scientific foundations of gene transfer as well as how the field has advanced over time, outlining recent notable clinical developments in the basic techniques of gene transfer and illustrating the potential of gene transfer as a therapeutic approach. The current chapter also outlines the scientific community's initial understandings of risks involved in clinical gene transfer research and describes how those theoretical risks and uncertainties look today, summarizing how and why many risks and uncertainties have been minimized and noting those that persist today.

GENE TRANSFER RESEARCH

Gene transfer can be broadly understood as the introduction of genetic material, through a vector, into cells with the intent of altering gene expression (Kay, 2011). Approaches to gene transfer fall into three categories, sometimes used in combination: adding a functional gene, correcting a dysfunctional gene, or altering the expression of a naturally occurring gene. Most clinical studies rely on the introduction of a functional gene in individuals possessing a nonfunctional or mutated gene (Kresina and Branch, 2001). The hypothesis is that the new functional gene (or corrected gene) will be translated into a protein that will allow for the restoration of a biochemical pathway interrupted in the disease

and therefore will eliminate or lessen the clinical manifestation (Kay, 2011).

A variety of gene transfer vectors have been developed over the years and studied extensively, and researchers are currently developing alternative non-viral strategies for gene delivery to overcome some of the limitations associated with viral vectors (Al-Dosari and Gao, 2009; Pathak et al., 2009). Much of the effort, however, to develop clinical gene therapy has focused on viral vector systems (Nienhuis, 2013). Naturally occurring viruses have evolved sophisticated strategies to infect specific target cells and co-opt cellular machinery to express viral genes stably and heritably (Vannucci et al., 2013). The use of viral vectors for gene transfer seeks to exploit these abilities with the intent to genetically modify the target natural cell (Vannucci et al., 2013). The basic strategy is to eliminate viral genes that are essential for replication and pathogenicity while making space for the therapeutic genes (Vannucci et al., 2013).

Gene transfer and *gene therapy* are not synonyms. *Gene transfer* is a broad category encompassing technique of introducing a genetic sequence with any function, for example, the transfer of a fluorescent protein marker into a cell for diagnostic purposes. The process of gene transfer may or may not have a therapeutic purpose or demonstrated therapeutic effect. *Gene therapy* is the clinical application of gene transfer, with the intent to produce beneficial health consequences. In research ethics, the term *therapy* is generally reserved for a product or intervention with demonstrated safety and efficacy—it is not applied to interventions that are still being investigated, a distinction that is important, given that all gene transfer products are investigational; none has received a Biologic Licensing Application[1] (BLA) approval by the U.S. Food and Drug Administration (FDA) thus far. Conceptually, gene transfer is disarmingly simple. Introduce a gene into a cell, tissue, or organ, and a functional protein product will express a protein useful for clinical diagnostics or nonfunctional pathway to ameliorate treatment of a disease. The translation of the concept into effective therapies has not, however, been simple (see, generally, Bersenev and Levine [2012] and Kay [2011]).

[1]A Biologic License Application is a request for permission from FDA to introduce, or deliver for introduction, a biologic product into interstate commerce. The BLA is regulated under the Code of Federal Regulations 21 § 601.

RECOMBINANT DNA

Although the idea of gene transfer has been explored by the scientific community for decades, it was launched into the national spotlight with the advent of recombinant DNA (rDNA) technology in the early 1970s. An rDNA molecule is made up of DNA sequences that have been artificially modified or joined together so that the new genetic sequence differs from naturally occurring genetic material. The recombination of genetic material can happen as a result of normal biochemical processes in nature, but the term rDNA is typically reserved for genetic sequences that have been engineered in a scientific laboratory. Recombinant DNA technology is the product of advances in enzymology, biochemistry, and molecular genetics, and it has provided the foundation for other important technologies and applications, including genetic sequencing, sophisticated medical diagnostics, the elucidation of the molecular basis of many diseases, new avenues of disease prevention, and, in some cases, new and precisely targeted treatments of serious medical conditions (Berg and Mertz, 2010).

EARLY EXPERIENCE IN HUMAN GENE TRANSFER RESEARCH

In the 1960s, about one decade after the discovery that viruses could transfer genetic material between bacteria, it became apparent that viruses might be used to deliver genes into cells of interest (Wirth and Ylä-Herttuala, 2013). Before this technology could be utilized, scientists first had to learn how to remove the virus's natural ability to cause illness. Unfortunately, a technology to engineer such a virus did not exist until the 1970s, and early experiments utilized wild-type viruses.

The first series of direct human gene transfer experiments were performed between 1970 and 1973 when a wild-type Shope papilloma virus was introduced into two young research participants with genetic deficiency in arginase, an enzyme that degrades arginine and prevents it from accumulating in the bloodstream (Rogers et al., 1973; Terheggen et al., 1975). The procedure was carried out with the goal of transferring a functional arginase gene to the research participants. Unfortunately, the subjects showed neither improvement in arginase levels nor any other clinical benefits. Years later, sequencing of the Shope papilloma virus genome revealed that it does not actually code for arginase (Wirth and

Ylä-Herttuala, 2013). This first attempt at human gene transfer with therapeutic intent involved only a wild-type virus and no rDNA techniques, but as will be discussed further in Chapter 3 and Appendix B, these experiments prompted public concerns about the risks and uncertainties of gene transfer (Friedmann and Roblin, 1972).

In 1980, sentiment within the U.S. scientific community leaned toward favoring tighter research regulations in the name of patient protection when a U.S. researcher conducted gene transfer experiments in Italy and Israel without the Recombinant DNA Advisory Committee (RAC) or institutional review board (IRB) approval. Martin Cline attempted gene therapy in two research subjects who had beta thalassemia, a hereditary blood disorder (Jacobs, 1980). Cline allegedly failed to disclose to the Israeli IRB that the proposed gene transfers involved rDNA, and Italy did not have an IRB system at the time (see discussion in Rainsbury [2000]). The *Los Angeles Times* published an article reporting on the details of his activities (Jacobs, 1980; Rainsbury, 2000). Although the expression of therapeutic genes was not achieved, there was no evidence of further harm to the already gravely ill research participants. Ultimately, in 1981 Cline resigned as department chair at the University of California, Los Angeles (Fredrickson, 2001, p. 272). Cline's behavior led to a decline in confidence in the scientific community, which increased the willingness of many scientists to tolerate tighter regulations in the name of research participant protection (Rainsbury, 2000).

The first clinical gene transfer protocol approved by the RAC in December 1988 was proposed by Rosenberg and colleagues, who were developing specialized white blood cells known as tumor-infiltrating lymphocytes (Merrill and Javitt, 2000; Rosenberg et al., 1990). The protocol was not designed to induce a therapeutic outcome. Instead, Rosenberg mapped the in vivo distribution and survival of the marked tumor-infiltrating cells in cancer patients. Rosenberg concluded that the procedure was safe and feasible (Rosenberg et al., 1990).

In 1995, Michael Blaese and colleagues proposed a gene transfer protocol designed to test an experimental intervention for adenosine deaminase severe combined immunodeficiency disorder, a single-gene disorder that severely compromises immune system function (Blaese et al., 1995). In research approved by the RAC, two children with the condition were infused with their own white blood cells, which had been modified ex vivo to express the normal adenosine deaminase gene. One of the research participants, who has since been identified as Ashanti DaSilva, exhibited a temporary increase in functional enzyme production, but the

effects of the gene transfer experiment were difficult to differentiate from the effects of enzyme replacement therapy she was receiving simultaneously (Wirth and Ylä-Herttuala, 2013).

In 1995, as gene transfer research progressed, the National Institutes of Health director convened a multidisciplinary panel, co-chaired by Stuart Orkin and Arno Motulsky, to review the field of gene therapy. By then, 5 years had passed since the first research participants received genetically modified cells, and the RAC had reviewed and approved more than 100 clinical protocols (NIH, 2013). The panel concluded that most clinical gene transfer protocols were not sufficiently well designed to answer fundamental biological questions about gene transfer and that, despite anecdotal claims of success, the protocols lacked statistical power to demonstrate clinical efficacy (Orkin and Motulsky, 1995). The panel also concluded that actual progress in gene transfer research had been oversold, and it recommended that the field focus on understanding the basic biology of vector systems, target cells, and tissues; accumulating preclinical evidence of effective protocol design; and developing strategies to improve targeted and sustained gene expression (Orkin and Motulsky, 1995).

In sum, the first few years of clinical research experience showed that developing effective gene transfer strategies was more technically demanding than originally anticipated (Mountain, 2000). Inadequate vector performance demonstrated significant gaps in knowledge, and the duration of clinical experience at the time was as yet too short to rule out long-term adverse effects from gene transfer protocols. The combined absence of foundational knowledge and experience presented a serious ethical challenge in that researchers were unable to identify genuine hazards or make judgments about acceptable levels of risk.

UNDERSTANDING RISKS IN GENE TRANSFER

Risk is ubiquitous in clinical research, and discussing risk requires an understanding of what it is and how it is perceived. Risk can be defined as the probability of an adverse outcome within a defined period of time (Deakin et al., 2009). In gene transfer and other biomedical research, basic biological and preclinical studies provide objective knowledge about probable outcomes and their severity. Ultimately, determining an *acceptable level* of risk is a value judgment that takes into account other factors beyond absolute risk, most notably the nature of potential benefits.

Furthermore, research involving human subjects with life-threatening terminal or severe diseases who have few if any other treatment options are likely to deem a much higher degree of risk as acceptable compared to diseases that are less severe or have existing successful therapies or that address lifestyle conditions or even genetic enhancement (Kimmelman, 2007). The acceptability of the risks posed by gene transfer research should be understood as a function of acceptable risk rather than any absolute measure. Early gene transfer studies were being undertaken at a time when the absence of scientific knowledge regarding the various agents and processes involved in gene transfer exposed the human subjects, third parties, and society at large to an unacceptable amount of theoretical and uncertain risk. Some early risks of human gene transfer were real and continue to drive research, and others were found to have no scientific basis.

Understandings of Risk and Uncertainty in Initial Gene Transfer Research

In the early years of gene transfer research, the members of the scientific community generally agreed that gene transfer research had new risks and contained many uncertainties. Many concerns were also brought to attention by the public involving the potential social and ethical implications of the idea of gene transfer, while scientists articulated scientific uncertainties and technical and safety concerns.

Social and Ethical Concerns

Many of the public's ethical concerns were captured in the 1982 report by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical Research and Behavioral Research. The report, titled *Splicing Life*, noted that the interchangeability of genetic material raised questions in the scientific community about the unpredictable consequences of genetic engineering (President's Commission, 1982). The report also described public unease about the "Frankenstein factor"—"the notion that gene splicing might change the nature of human beings, [which was] compounded by the heightened anxiety people often feel about interventions involving high technology that rests in the hands of only a few" (President's Commission, 1982, p. 16). Furthermore, germline research (modification of gametes [sex cells] that would then persist

across generations) was a particular concern and sometimes led to a "slippery slope" argument. An extreme version of the argument contended that if society began to permit germ-line genetic engineering, this would lead before long to coercive social policies mandating genetic enhancement of all embryos (Kresina and Branch, 2001). Another version of this argument expressed the concern that, over time, the collective social attitudes—peer pressure—would subtly induce individuals to choose germ-line therapy and enhancement. Scientists were uncertain about the possibility that new genes could be integrated into the germ line inadvertently, potentially affecting future generations (Marshall, 2001). Finally, there was concern about risks to people involved in the research enterprise and to the environment, including the potential for research participants to shed viral vectors that might go on to infect research staff or escape from the laboratory and into the environment with unknown but conceivably serious consequences (Spink and Geddes, 2004).

Over the years, commentators disagreed about whether the existing knowledge about gene transfer was sufficiently robust to justify moving into clinical trials. Theodore Friedmann and Richard Roblin wrote an opinion piece in 1972 in which they opposed attempts at gene therapy in human patients until technical advances were made and regulatory structures were put into place. Referencing Rogers's failed Shope papilloma experiment, Friedmann and Roblin argued that "our understanding of such basic processes as gene regulation and genetic recombination in human cells is inadequate" (Friedmann and Roblin, 1972). They proposed ethical and scientific criteria that gene transfer should satisfy before moving forward to human trials, acknowledging that physicians would consider the risks and potential benefits for each individual patient. There was also reasonable belief among some that starting clinical trials was appropriate (see, generally, President's Commission [1982]). The fact that this was the subject of disagreement highlights how difficult it is to set clear boundaries between what is wise and unwise, ready and unready.

Scientific and Technical Concerns

In addition to these ethical and social issues, early gene transfer research was characterized by a high degree of technical uncertainty and its associated risks. The use of this new investigational agent, rDNA enclosed in a vector, was supported by relatively little pre-clinical experience or testing of similar agents. Therefore, gene transfer carried

more uncertainties than chemical drugs, for example, which were able to draw predictability from more than a century of pharmacology (Kimmelman, 2008).

Scientists' ability to quantify risks to subjects was further complicated by the permanent nature of changes to the human genome intended by gene transfer, and these changes had yet to be explored. The prospect of an individual undergoing continuous, life-long exposure to transgenes and vectors meant that long-term side effects might not be detected for years, even decades, after the end of a trial—and few to no investigations had taken place to evaluate this. Gene transfer research was perceived to be fundamentally different from research with chemical drugs, which have a finite kinetic lifetime in a research subject (although these chemicals can also produce adverse consequences that are not evident for years). At the time, few biologics (e.g., bone marrow transplant) had been studied for life-long effects.

Another area where scientific understanding was not well developed was the interaction of new genes and vectors with host immune systems. Very little was known about what might trigger a host's immune response to vectors or to the transgene products or how researchers might mitigate any potential adverse events.

CURRENT UNDERSTANDING OF THE SAFETY OF GENE TRANSFER

Since the first RAC-approved gene transfer trial in 1988, hundreds of clinical gene transfer trials have been initiated and completed. Most trials have been early-stage phase I or phase I/II trials (Ginn et al., 2013). Phase I trials are primarily designed to generate safety data that will allow investigators and research review bodies to assess whether it is safe to pursue further clinical investigations. Phase I/II trials begin to develop evidence that the agent has the hypothesized physiological effects. These early-stage trials are critical to assessing safety for the research subject. These assessments have been the major focus of gene transfer experiments and constitute a fundamental requirement for the government approval of any medication. Central to progress in the field have been advances in vector design and the accumulation of long-term follow-up data. As gene transfer science has matured, so too has the understanding of potential harms.

Some Potential Hazards Found to Not Be a Problem

Many original uncertainties have been replaced by scientific clarity, and fears have been alleviated by decades of experience. Some of the early concerns about gene therapy, such as the perceived danger of creating transmissible pathogens, accidental germ-line modification, and unspecified xenogeneic dangers, have not been verified by clinical experience (Deakin et al., 2010). In general, risks that gene transfer might originally have been thought to pose to third parties and society at large have been determined to be minimal (Deakin et al., 2010). This is due in large part to the effectiveness of techniques developed to render viral vectors incapable of replicating. Since the early 1980s, researchers have devoted a great deal of effort into determining how to rearrange the viral genome in order to impede the replication or generation of infectious viral particles while still maintaining the virus's ability to deliver nucleic acids (Vannucci et al., 2013). These technological advances, along with the ever-growing knowledge of molecular virology and virus-host cell interactions, have constantly improved the safety profile of viral vectors that are now used in gene therapy.

Technical Advances

The safety profile of most viral vectors has been considerably enhanced by advances in vector design strategies as well as better understanding of molecular virology and virus–host cell relationships (Vannucci et al., 2013). For example, the risk of adenoviral vectors regaining the ability to replicate was reduced considerably with the deletion of select genome components found to play an important role in adenovirus-specific immunity (Campos and Barry, 2007). Another improvement was a strategy known as pseudotypization, in which the spectrum of infectable (or transducible) cells by retroviral and lentiviral vectors is controlled by separating select viral genes into separate constructs (Vannucci et al., 2013).

In addition to advances in safety, long-term follow-up data demonstrating effectiveness have also been generated from many gene transfer clinical trials for a variety of diseases. For example, researchers have shown that intravenous injection of recombinant adeno-associated virus particles resulted in long-term production of human factor IX in patients with hemophilia with only minimal, effectively managed complications from treatment up to 3.3 years after treatment (Nathwani et al., 2011).

Clinical Research Successes

A number of clinical research successes have emerged in gene transfer since 2008. For example, patients with Leber's congenital amaurosis, a genetic blindness for which there is no alternative therapy, have shown modest but sustained improvements in subjective and objective measurements of vision following a gene transfer experiment, with the greatest improvements noted in children enrolled in the study, all of whom gained ambulatory vision (Maguire et al., 2008).

Gene transfer trials involving hematopoietic stem cells show particular promise in the treatment of blood disorders, especially Wiskott-Aldrich syndrome and beta thalassemia, as well as metabolic disorders, such as X-linked adrenoleukodystrophy and metachromatic leukodystrophy (Booth et al., 2011). In 2010, clinical trials were initiated using lentiviral vectors to transfer functional genes to young patients with metachromatic leukodystrophy, and 3 of these patients experienced no further disease progression for up to 24 months. These children were predicted to otherwise experience disease onset in 7 to 21 months without treatment (Biffi et al., 2013). Long-term follow-up data on 90 research participants who received the gene transfer treatment to treat inherited primary immunodeficiencies in the past decade show a survival rate of more than 90 percent and indicate that most experience significant clinical benefit (Seymour and Thrasher, 2012). Promising results are also being recorded in the treatment of several degenerative conditions. For example, patients with Parkinson's disease who received dopamine-biosynthetic enzymes using lentiviral vectors have shown signs of improvement, as measured on the Unified Parkinson's Disease Rating Scale. Long-term benefits have been observed, with some patients experiencing sustained improvements up to 3 years after treatment (Eberling et al., 2008; Marks et al., 2010).

CHARACTERISTICS OF GENE TRANSFER TRIALS

The *Journal of Gene Medicine* has compiled summary data on gene transfer research, beginning with trials approved or initiated from January 1989 through January 2013. The summary provides information on approved, ongoing, or completed gene transfer clinical trials worldwide and outlines indications addressed, vectors used, gene types transferred, and clinical indications (Ginn et al., 2013). Most trials (63 percent) were

undertaken in the United States.[2] Sixty percent of gene transfer clinical trials included in the database are phase I trials, designed to gather safety data (n = 1,171). Another 20 percent of trials are phase I/II studies (n = 376), with the smallest proportion at phases II and III (Ginn et al., 2013).

To date, most gene transfer trials have targeted cancer (64 percent). The next most common target conditions are a diverse array of monogenetic diseases (9 percent), cardiovascular disease (8 percent), and infectious diseases (8 percent) (Ginn et al., 2013). Gene delivery can be accomplished with viral or non-viral vectors. Vectors used most commonly in clinical gene transfer trials from 1989 to 2013 are adenoviral (23 percent), retroviral (19 percent), and plasmid DNA (18 percent). The most clinically relevant viral vectors for gene transfer today include retroviral, lentiviral, adenoviral, and adeno-associated viral vectors. Viral vectors offer the best efficiency in terms of gene delivery, but they carry risk of extreme immune response and insertional mutagenesis, which may lead to the development of cancer (Molina, 2013). Non-viral vectors may be safer, but are limited by very low transfection efficiency (Molina, 2013). Viral vectors currently dominate clinical gene transfer trials (Ginn et al., 2013).

REGULATORY STATUS OF GENE TRANSFER PRODUCTS

Gene transfer is currently coming to fruition as a therapeutic strategy with the potential for broad application. As of November 2013, FDA has not yet approved a gene transfer product for marketing, but several products have advanced to late-stage trials that could serve as the basis for such approval in the near future. Therefore, gene transfer products may be available as a therapeutic strategy with the potential for broad application beyond clinical trials in the near term. Three gene therapy products have been approved outside the United States. Two were approved by China's State Food and Drug Administration: Gendicine, which involves a non-replicative virus for squamous cell carcinoma treatment, was approved in 2003; and Oncorine, which delivers genetic material through a conditionally replicative adenovirus to treat nasopharyngeal carcinoma in combination with chemotherapy, was approved in 2005 (Wirth and Ylä-Herttuala, 2013). To date, U.S. approval has not been granted.

[2]The *Journal of Gene Medicine* database does not present information on trials' sponsors (e.g., governments, industry).

The third gene therapy product approved is Glybera, which received marketing authorization from the European Commission in November 2010 on the basis of the evaluation and recommendation of the European Medicines Agency (Bryant et al., 2013). Glybera is designed to treat severe lipoprotein lipase deficiency, a rare inherited condition associated with increased levels of fat in the blood; the product uses an adeno-associated viral vector (Hildegard, 2013; Watts, 2012). The company launching this product commercially is expected to pursue FDA approval (UniQure, 2012).

REMAINING CONCERNS IN GENE TRANSFER RESEARCH

Although dramatic advances have taken place regarding the techniques of human gene transfer and mechanisms of action, some gaps in scientific knowledge remain. First, although active viral vectors are designed to be replication incompetent and no longer pathogenic, predicting severe immune response remains difficult. Second, each component of a transfer carries its own risk, thus complicating risk assessments. For example, the cases of leukemia that arose in a trial for X-linked severe combined immunodeficiency (discussed above) may have been attributable to the combined toxicity of the vector and the transgene (Baum et al., 2003). Third, permanent genetic modification may involve life-long exposure risks. There are few long-term studies of any low-level toxic effects of a transgene product or assessments of cumulative effects on the health of a research participant over time. Many features of human gene transfer, although not unique, raise concerns and present complex risks for research participants.

Risk Assessment

Even with these pivotal advances and dramatic examples of clinical success, risk assessment remains difficult in gene transfer research (Deakin et al., 2010). Some of the theoretical risks have been invalidated, and some genuine risks have exceeded expectations or were never uncovered by preclinical studies. For example, as discussed above, the risk of extreme immune reaction and death was not fully appreciated by preclinical studies in the case of Jesse Gelsinger.

The risks of gene transfer products (and cellular therapy products) can be different from those typically associated with other types of pharmaceuticals, as seen in current draft guidance from FDA (2013). Nevertheless, the risks and uncertainties associated with gene therapy are not altogether unique, although some risks may be amplified or arise more often (Kimmelman, 2005). For example, genotoxicity is a high-profile concern in gene therapy, but it also occurs with chemotherapy and radiation (Deakin et al., 2009). Still, unlike research on many small molecule pharmaceuticals, the complicated logistics and feasibility of manufacturing a cell and gene therapy product sometimes influence the design of the clinical trials and further complicate assessment of risk. In addition, the preclinical data generated for cell or gene therapy products may not always be as informative as for small molecule pharmaceuticals, particularly because it usually is not feasible to conduct traditional preclinical pharmacokinetic studies with cell and gene therapy products. Gene therapy products, along with cell therapy products, often involve consideration of clinical safety issues; preclinical issues; and chemistry, manufacturing, and controls issues that are encountered less commonly or not at all in the development of other pharmaceuticals.

Several characteristics of gene therapy products (as well as cell therapy products) present increased risk for patients, including researchers' relatively limited clinical experience with these therapies, the persistence of the transgene in humans for an extended period after a single administration, the potential to elicit an immune response (immunogenicity), the potential for the integration into host DNA and its interference with normal function of existing genes (genotoxicity), and the possibility that viral or bacterial matter could be transmitted to other individuals (FDA, 2013). To add to these considerations, the committee recognizes that in vivo gene therapy can inadvertently target transgene expression to an unintended and clinically unaffected cell or tissue type, with a potential for toxicity. Further, some gene transfer vectors, such as adeno-associated virus (AAV), introduced into non-dividing cells, such as neurons or striated muscle, present the potential for life-long persistence of vector and transgene expression (Lee et al., 2013). This may also produce a potential for toxicity, particularly if the sustained function of gene-modified cells alters relationships with unmodified cells.

Additional considerations regarding gene therapy include the following:

a) In vivo gene therapy can inadvertently target transgene expression to an unintended and clinically unaffected cell or tissue type, with a potential for toxicity.
b) Some gene transfer vectors, such as adeno-associated virus, introduced into non-dividing cells, such as neurons or striated muscle, present the potential for lifelong persistence of vector and transgene expression (Lee et al., 2013). This may also produce a potential for toxicity, particularly if the sustained function of gene-modified cells alters relationships with unmodified cells.

The potential for off-target toxic effects of modified cells must be considered. For example, one study involving the infusion of T cells that were genetically engineered to target tumors resulted in unexpected off-target cardiac toxicity. The engineered T cells bound to cardiac muscle tissue, and the resulting toxic effects on the heart were lethal to the research participant. Available preclinical models did not demonstrate this risk (Ertl et al., 2011; Morgan et al., 2010).

Insertional mutagenesis (genotoxicity) was a predicted risk, and although it is not unique to gene transfer, in some cases it presented more problems than expected in clinical studies. In a 2008 trial involving 12 patients with X-linked severe combined immunodeficiency disorder, 4 patients developed vector-induced T-cell leukemia (Aiuti and Roncarolo, 2009). Immediate treatment with chemotherapy to all four patients with leukemia sent three into remission, but one died. Although 11 participants in the trial survived and regained normal immune function, the trial results were a major setback for the field (Aiuti and Roncarolo, 2009; Hacein-Bey-Abina et al., 2008).

Scientific Hurdles

Some scientific hurdles—such as the absence of efficient delivery systems, difficulty with sustained expression, insertional mutagenesis and host immune reactions—remain formidable challenges to the field (Kay, 2011). Some practical limitations associated with even the most successful gene transfer techniques remain to be resolved before any gene transfer procedure can be demonstrated to be a safe and effective

therapy (Grigsby and Leong, 2010). Many of the major hurdles have to do with providing efficient gene delivery.

First, the vector uptake and distribution must be tightly controlled so that expression of the vector-encoded gene remains within the therapeutic range—if expression is too low, the functional protein product may not be produced at a high enough concentration to effectively restore the intended biochemical pathway, and if expression is too high, the research subject may experience toxic effects. Transcription of the new genetic material must also remain stable so that the transgene is expressed as long as necessary to treat the disease. For a given patient, this could range from a limited period to life-long expression (Kay, 2011). The degree to which the vector containing the corrective gene is taken up in a sufficient number of target cells is influenced by vector size and stability, the extent of target tissue vasculature, and the efficiency of interactions between vector and host cell receptors. The ideal vector would be cell-type specific, but the design of either non-viral or viral vectors that successfully target a specific cellular receptor has been elusive despite a great deal of effort. To date, re-engineered viral vectors are often too large, too unstable, or otherwise unable to reach the nucleus of some cell types (Kay, 2011). Non-viral vectors are attractive because of their suitability for pharmaceutical considerations such as scale-up, storage stability, and quality control; however, non-viral gene delivery remains prohibitively inefficient for most therapeutic applications (Grigsby and Leong, 2010).

Second, a substantial proportion of the population has been exposed to viruses from which vectors have been derived (or engineered), especially adenoviral and adeno-associated viral vectors. Exposed individuals thus have circulating antibodies that can interfere with transduction of closely related recombinant vectors. If researchers or clinicians must control an unanticipated immune response that arises in a research participant, this could then be complicated by the challenge of "turning off" expression of transgenes driven by constitutive, non-conditional promoter sequences specifically designed to always be "on" (Bessis et al., 2004; Jooss and Chirmule, 2003).

Third, gene transfer involves the interaction of many agents. The combined risk factors associated with the individual components, risks that may be amplified by their interaction, complicate risk assessments (Kimmelman, 2005). For example, the cases of leukemia that arose in the X-linked severe combined immunodeficiency disorder trial may have

been the result of the combined toxic effects of the vector and the transgene (Baum et al., 2003).

Finally, permanent genetic modification may expose patients to life-long risks. Few long-term studies have been conducted to detect potential low-level toxic side effects of gene transfer products or assess cumulative effects on patient health over time (Hedman et al., 2011).

CONCLUSION

The committee concluded that, although not without challenges, the field of gene transfer research has experienced dramatic advances in scientific knowledge and that somatic gene transfer clinical investigations may today be considered part of an established scientific research enterprise. Whereas the field of gene transfer research was characterized in its early years by considerable uncertainty and concern about theoretical risks—on the part of the public as well as the scientific community—this field has matured to a state in which some of the early concerns about risk, and uncertainty overall, have been minimized. With the experience of more than 40 years of gene transfer trials and nearly 1,700 currently approved clinical trials; much has been learned about potential adverse events and how to ensure the safety of research participants. The committee concluded that many gene transfer clinical trials pose acceptable risks and are fast becoming an established modality of modern medicine.

Although the state of gene transfer research is constantly evolving, not all of gene transfer research can still be considered a completely new scientific enterprise or novel technology. This conclusion has significant repercussions for the oversight required for research projects to proceed; the committee's assessment of the current regulatory structure is the subject of the next chapter.

Considerations of an appropriate regulatory structure, one that protects human research subjects while not adding to researchers' administrative burden unnecessarily or impeding scientific advancements, focus to a large extent on how to assess risk. Given that such questions about risk assessment are not unique to gene transfer research—they are shared by other cutting-edge scientific and clinical research—the committee considered the question of oversight with a broader lens. In the following two chapters, the committee explores how the regulatory considerations for the evolving field of gene transfer research may shine light on potential needs in all emerging areas of clinical sciences.

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3

Oversight of Gene Transfer Research

In any area of biomedical research, many scientific and regulatory challenges stand between promising ideas generated from basic research and the approval of a therapeutic product. Among these emerging technologies, gene transfer research, in particular, stands out as a highly regulated area of scientific investigation. Because clinical gene transfer trials involve both recombinant DNA (rDNA) and human subjects, investigators must submit clinical gene transfer protocols to the Recombinant DNA Advisory Committee (RAC) and the U.S. Food and Drug Administration (FDA) at the federal level and institutional review boards (IRBs) and institutional biosafety committees (IBCs) at the local level before human subjects can be enrolled. This chapter summarizes the current regulatory, oversight, and policy context of this area of research in the United States with a focus on the National Institutes of Health (NIH) and the RAC, followed by a briefer consideration of the roles of FDA, IRBs, and IBCs, noting relationships among the oversight bodies.

NIH AND THE RECOMBINANT DNA ADVISORY COMMITTEE

The late 1960s and early 1970s saw the rapid progression of the concepts and technology that led to the first intentional creation of rDNA molecules (Berg and Mertz, 2010). The RAC was established by then–NIH Director Donald Frederickson in 1974 in response to scientific, public, and political concerns about the potential use and misuse of rDNA technologies, as well as the associated and unknown risks (described later in this chapter). In the original formulation of the RAC

membership, Frederickson proposed that one-third of members be nonscientists or so-called public members. These nonscientists, among whom were ethicists, theologians, and university presidents, were to offer a broader public perspective on the emerging technology. Over time, RAC membership and responsibilities have evolved in response to scientific developments and public concerns.

Early Activities of the RAC

Early actions by the RAC included defining certain conditions for the awarding of grants for rDNA research pending adoption of more comprehensive guidelines. One of these conditions was that every research institution create a "biohazard review committee" (later renamed an "institutional biosafety committee") to review risks and certify the presence of adequate safety measures. The major initial task of the RAC was the drafting of guidelines for rDNA research as advised by the National Academy of Sciences committee. The RAC was guided in considerable measure by the conclusions from a second conference at Asilomar in February 1975 (Berg et al., 1975). Those conclusions provided a framework for

- identifying and categorizing types and risks of different types of experiments,
- defining protective strategies tailored to the expected risks presented by an experiment, and
- deciding what research should continue to be postponed pending more knowledge and better safeguards.

The guidelines, first published in 1976 (Recombinant DNA Research Guidelines, 1976) and amended through the years, have provided a comprehensive description of facilities and practices to prevent unintended release of or human exposure to genetically modified organisms and material. They define the procedures for the RAC and outline requirements for research institutions' oversight of rDNA research, including the creation of IBCs. Although some officials within what was then the Department of Health, Education, and Welfare argued that the guidelines should be issued as formal regulations, in the end they were not. NIH also established what is now the Office of Biotechnology Activities (OBA) to facilitate the operation of the RAC, the

implementation of the guidelines, and the coordination of rDNA-related activities at NIH (Rainsbury, 2000). Today, OBA describes its role as promoting "science, safety, and ethics in biotechnology through advancement of knowledge, enhancement of public understanding, and development of sound public policies" (OBA, 2013).

The guidelines are now formally known as the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (but are commonly referred to within the field as simply the "NIH Guidelines") (NIH, 2013c) and remain a key vehicle for NIH oversight of rDNA research. The guidelines are applicable to *all* rDNA research that is conducted by or sponsored by a public or private institution that receives NIH funding for any such research (NIH, 2013a). In addition, many other U.S. government agencies and private institutions require that their funded research be conducted in accordance with the NIH Guidelines (Corrigan-Curay, 2013).

Changes in the Role of the RAC

Initially, the RAC reviewed and approved all gene transfer research protocols included in proposed research at institutions receiving NIH funds for rDNA research, advising the NIH director in issuing official approvals (technically, official approvals came from the director of NIH, based on the RAC's decision (Freidmann, 2001). As discussed below, there have been several attempts to reshape the RAC's scope and oversight, including legislative proposals by members of Congress, a report by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical Research and Behavioral Research, *Splicing Life* (President's Commission, 1982), evaluation by the congressional Office of Technology Assessment (OTA, 1984), and an ad hoc committee appointed by the NIH director (Verma, 1995).

As rDNA technology developed and understanding of its risks accumulated, the role of the RAC has evolved in a number of ways, as have the rDNA guidelines. In the 1990s, after a brush with termination, the RAC shifted into an advisory capacity and initiated the first of many revisions to the NIH Guidelines to ease constraints on rDNA research, including the implementation of an accelerated review process in 1993 (Rainsbury, 2000).

During the 1970s, however, as scientists were convening to establish the RAC, public interest and concern, even alarm, about rDNA research

grew (see, for example, Rainsbury [2000]). Both the Senate and the House of Representative held hearings in the 1970s and early 1980s. Members of Congress proposed various pieces of legislation that would have replaced the guidelines with regulations, extended the NIH Guidelines to include privately funded research, and created a national commission that would have diminished the role of NIH and scientific experts in overseeing rDNA investigations. Ultimately, no legislation along these lines emerged.

The controversy surrounding rDNA research was not eased in 1980 by the discovery that an U.S. investigator had conducted the first gene transfer experiment (which was not successful) in Italy and Israel in order to avoid RAC oversight (discussed in Chapter 2). The investigator was later censured (for misleading foreign regulators) and barred from NIH funding (Rainsbury, 2000).

Parties outside Congress also called for modifications in the public oversight of rDNA research. For example, in 1982, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical Research and Behavioral Research submitted to President Reagan and Congress a report titled *Splicing Life* (President's Commission, 1982). The report reviewed public concerns and moral issues in genetic engineering and made recommendations for greater oversight related to ethical issues in gene therapy. Overall, however, the panel found that although some "have suggested that developing the capability to splice human genes opens a Pandora's box, releasing mischief and harm far greater than the benefits for biomedical science, [t]he Commission has not found this to be the case" (President's Commission, 1982). Two years later, the congressional Office of Technology Assessment concluded that existing oversight procedures were adequate for cell therapy that does not create changes that can be inherited (OTA, 1984).

One response at NIH to the *Splicing Life* report was the creation in 1984 of what became the Human Gene Therapy Subcommittee (RAC, 1990). The next year, the subcommittee, which was chaired by an ethicist, Leroy Walters, drafted guidance ("Points to Consider") for the preparation and review of protocols for human gene transfer studies (somatic cell research only) (Points to consider, 1985). The guidance, which was revised after public comment and later integrated into the NIH Guidelines, identified more than 100 questions that covered both scientific and ethical aspects of protocols. This oversight framework was in place well before the first protocols for human trials were submitted.

The first protocol approved by the RAC (in 1988) involved a gene marker study. The approval was delayed by investigators' reluctance to produce requested data on the safety of the procedure for fear of compromising their publication prospects (Rainsbury, 2000). The second approved protocol (1989) involved a test of gene transfer for severe combined immunodeficiency (SCID) (Wolf et al., 2009).

Initially, the RAC (through a subcommittee) reviewed all gene transfer research protocols. As the amount of research accelerated in the early 1990s, however, and a large number of similar protocols came under review, the review process became strained, which, in turn, increased criticism of the process. This strain occurred in the context of multiple other phases of protocol review, including reviews by IRBs, IBCs, and FDA. (For research involving investigators at different institutions, several IRBs and IBCs could be involved.) Among other responses (including attempts to expedite the review process), NIH and FDA agreed in 1995 that NIH would limit its public reviews to novel protocols, while FDA would assume primary responsibility for reviewing gene therapy protocols (Rainsbury, 2000; Wolf et al., 2009).

FDA first asserted a role in the oversight of gene therapy products—and therefore the research undertaken to develop such products—in 1984 (Wolf et al., 2009). The agency began to assert a greater role in regulation of gene therapy products in 1986 (Statement of policy for regulating biotechnology products, 1986), and in 1995, NIH and FDA agreed that primary regulatory responsibility for review of gene therapy protocols would rest with FDA (Rainsbury, 2000; Wolf et al., 2009). As a result, the RAC became an advisory body. FDA issued its own document, "Points to Consider in Human Somatic Cell Therapy and Gene Therapy," in 1991 and issued guidance for industry on gene therapy in 1998 (FDA, 1991, 1998). FDA categorized these therapies as involving a type of biological drug[1] and assigned oversight responsibility to what is now the Center for Biologics Evaluation and Research (CBER). By 1993, FDA had reviewed hundreds of clinical research proposals involving somatic cell and gene transfer technologies (Kessler et al., 1993).

At the behest of a RAC member in the early 1990s, the RAC began to review adverse event reports as part of semiannual reviews of NIH

[1]A synthetic oligonucleotide is regulated as a drug, not a biologic. See Intercenter Agreement Between the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research, available at http://www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm121179.htm (accessed November 1, 2013).

data management reports on gene transfer trials. Since 1997, tables of adverse event reports from gene transfer trials have been posted with the RAC meeting minutes. The summary descriptions vary significantly in the extent to which they include specific statements about the likelihood that a reported event can be linked to the gene transfer procedure.

In 1995, an ad hoc committee appointed by the director of NIH to advise on the future role of the RAC concluded that gene transfer research was different enough from other research to deserve continued public scrutiny. The committee concluded that the RAC should, however, no longer review every protocol; rather, its reviews should focus on protocols raising special concerns (e.g., those using novel vectors) (Verma, 1995).

In 1996, NIH published a notice in the Federal Register proposing to eliminate the RAC entirely (Notice of intent, 1996). The notice observed that NIH "has continuously relinquished oversight of various elements in the field of recombinant DNA research, as such elements reached maturity" (Notice of intent, 1996, p. 35775), and it proposed to transfer all responsibilities for approving gene transfer research to FDA. In the face of public resistance to this proposal, NIH did not eliminate the RAC, but it did end the RAC's role in approving individual research protocols (Rainsbury, 2000; Wolf et al., 2009). Although the RAC thus became an advisory body, NIH still required and continues to require that NIH-supported investigators submit gene transfer protocols for advisory review. The RAC's public reviews are selective, limited to protocols that present certain safety or ethical issues.

Concern about the conduct of gene transfer trials reached a new level of intensity after the death of Jesse Gelsinger in 1999. Subsequent investigations identified shortcomings in trial oversight and transparency related to reporting of serious adverse events in the trial, FDA's sharing of information with NIH and the RAC, and investigator conflicts of interest. NIH's response to the findings of the investigation included the creation of a working group to review NIH's oversight of gene transfer trials (Advisory Committee to the Director, 2000). FDA and NIH also agreed on steps to coordinate adverse event reporting and expand public access to reports of serious events, for example, through the creation at NIH of the Genetic Modification Clinical Research Information System (GeMCRIS) (NIH, 2004), discussed further below. Congress again held hearings on rDNA oversight but did not act further (Rainsbury, 2000).

In 2000, NIH shifted the timing of the public reviews undertaken by the RAC so that they would occur before, rather than after, protocol re-

views by IRBs and IBCs. This would allow these entities to benefit more fully "from the expertise, broad perspective, and the experience of the RAC" (Recombinant DNA research, 2000, p. 60329). For example, the RAC could help IRBs and IBCs identify deficiencies in the informed-consent approach proposed by investigators.

Today, the RAC has responsibilities in addition to its advisory role in reviewing gene transfer protocols. As described in its updated charter, "as necessary, and with the approval of the Designated Federal Officer, the Committee and its subcommittees may call upon special consultants, assemble ad hoc working groups, and convene conferences, workshops and other activities" (NIH, 2011, p. 1). In recent years, OBA has sponsored or cosponsored meetings on gene transfer and rare diseases, vector and trial design challenges in studying retroviral and lentiviral vectors for long-term gene correction, challenges in trial design in research with gene-modified T cells, and future directions for gene therapy (NIH, 2011).

Current Role of the RAC

The RAC is currently administered and supported by OBA, located within the Office of the Director of NIH, as part of OBA's responsibility to oversee federally funded rDNA research. The current charter of the RAC describes its role as providing "advice to the Director, NIH, on matters related to: (1) the conduct and oversight of rDNA, including the content and implementation of the NIH Guidelines for Research Involving Recombinant DNA Molecules, as amended, and (2) other NIH activities pertinent to rDNA technology" (NIH, 2011, p. 1). The current guidelines also specify that research proposals involving the deliberate transfer of recombinant or synthetic nucleic acid molecules, or DNA or RNA derived from such nucleic acid molecules, into human subjects (human gene transfer) are to be subject to a review process involving both NIH/OBA and the RAC (NIH, 2013c).

Within the entire gene transfer research oversight system, the RAC is the only oversight or regulatory body that provides a public venue for the review of a protocol. FDA, IRBs, and IBCs all convene in private; however, IRBs and IBCs often include nonscientists as members of their committees. Therefore, gene transfer protocols are one of very few areas of emerging human subjects research that receive additional oversight, and the only area for which that review occurs through an additional oversight body—even though, as previously discussed, its risk portfolio

is similar to other areas of emerging science. The public nature of the RAC is due to its status as a public advisory committee under the Federal Advisory Committee Act (FACA) of 1972. In order to comply with FACA regulations, the RAC must have open meetings with advance notice of the time and place, provide detailed transcripts, and allow public participation at meetings (Steinbrook, 2004). Thus, the RAC is an advisory body with oversight defined in NIH guidelines that require NIH-supported researchers and institutions to submit gene transfer protocols for advisory review. Human gene transfer trials conducted at or sponsored by institutions receiving NIH funding for rDNA research must be registered with OBA and reviewed by the RAC (NIH, 2013c). Completion of the RAC review process is compulsory based on adherence to NIH guidelines.

Currently, the RAC is "a panel of up to 21 national experts representing various fields of science, medicine, genetics, ethics, and patient perspectives that considers the current state of knowledge and technology regarding research with recombinant or synthetic nucleic acid molecules" (NIH, 2013a, p. 2). A majority of the 21 voting members must have expertise in relevant scientific fields, such as molecular genetics, molecular biology, and rDNA research, including clinical gene transfer research. Further, at least four voting members must have expert knowledge in fields dealing with public health and safety, such as human subjects protection, environmental safety, ethics, and law. An FDA CBER representative is also an ex-officio member of the RAC. Terms for the chair and committee members, who are appointed by the director of NIH, are 4 years. The RAC meets in person quarterly in an open forum, with a webcast of the full meeting and the meeting transcript later posted online.

The RAC also may form ad hoc working groups, and currently it has several. For example, the Gene Transfer Safety Assessment Board consists of clinical members of the RAC who meet quarterly to review all serious adverse events that may possibly be trial-related as well as summaries of more than 400 amendments and annual reports filed on active protocols (Corrigan-Curay, 2013). The safety board reviews safety information from gene transfer trials for the purpose of assessing toxicity and safety data across trials and identifying significant trends or single events, and it reports such findings and aggregated trend data to the full RAC (Corrigan-Curay, 2013; NIH, 2013c). OBA considers this role as being akin to a "national Data Safety Monitoring Board," responding in real time to emerging information (Corrigan-Curay, 2013).

The RAC also continues to sponsor public symposia on important scientific and policy questions related to rDNA research (Friedmann et al., 2001), providing a public forum for scientific experts to discuss emerging issues in the field of gene transfer. Along with the RAC's protocol review and mechanisms to inform institutional oversight bodies, this transparent system is intended to optimize the conduct of individual research protocols and to advance gene transfer research generally (O'Reilly et al., 2012). In this way, the RAC serves as an important mechanism for scientific debate, informing institution-level oversight, increasing transparency, and promoting public trust and confidence in the field of gene transfer.

RAC Review of Individual Clinical Trial Protocols

Although the RAC no longer has formal approval authority, all human gene transfer protocols that are directly funded by NIH or conducted at institutions that receive NIH funding for rDNA research must submit responses to Appendix M of the NIH Guidelines for RAC review (see the following section for more information on Appendix M) (NIH, 2013a). One criticism of RAC oversight is that it does not apply to privately funded research. Private institutions, however, often voluntarily submit protocols and comply with NIH guidelines (Corrigan-Curay, 2013), in part because any NIH-funded institution involved in gene therapy clinical trials needs RAC approval. Consequently, there are very few gene transfer protocols that are not initially reviewed by the RAC (personal communication, Amy Patterson, OBA, August 21, 2013).

Public review of protocols is intended to achieve two purposes: (1) to disseminate information so that other scientists may incorporate new scientific findings and ethical considerations in their research, and (2) to enhance public awareness and build public trust in gene transfer research, allowing for a public voice in the review of the research (Scharschmidt and Lo, 2006). According to OBA, protocol review by the RAC serves many functions (Corrigan-Curay, 2013), including

- optimizing clinical trial design, increasing safety for research subjects, and, in some instances, strengthening biosafety protections necessary for researchers, health care workers, and close contacts of research subjects;

- improving the efficiency of gene therapy research by allowing scientists to build on a common foundation of new knowledge emanating from a timely, transparent analytic process; and
- informing the deliberations of FDA, the NIH Office of Human Research Protections (OHRP), IRBs, IBCs, and other oversight bodies, whose approval is necessary for gene therapy research projects to be undertaken.

Appendix M of the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules

Appendix M of the NIH Guidelines is a "Points to Consider" document that details the process and guidelines for information submission to the RAC for gene transfer protocols and describes the oversight employed by the RAC for clinical trials (NIH, 2013c). The guidelines stipulate that the RAC will not accept either clinical research protocols involving germ-line modification or procedures involving in utero gene transfer. This means, in practice, that NIH does not fund these lines of clinical research.

After an investigator submits a protocol, including responses to the points listed in Appendix M, OBA sends a summary to the RAC members for an initial review. During this preliminary review, the individual RAC members may request additional information or clarification or make specific comments or suggestions about the protocol design, the informed-consent document, or other matters. Any individual RAC comments of this nature are then conveyed to the investigator (NIH, 2013a). Based on the materials submitted by the investigator, including responses to Appendix M, only a subset of submitted protocols is selected for additional review by the RAC in its public forum (see Figure 3-1). Appendix M of the NIH Guidelines provides guidance to the RAC members about general characteristics that warrant public RAC review and discussion. Currently, the guidelines state that the RAC reviewers should

> examine the scientific rationale, scientific content, whether the preliminary in vitro and in vivo safety data were obtained in appropriate models and are sufficient, and whether questions related to relevant social and ethical issues have been resolved. Other factors that may warrant public review and discussion of a human gene

> transfer experiment by the RAC include: (1) a new vector/new gene delivery system; (2) a new clinical application; (3) a unique application of gene transfer; and/or (4) other issues considered to require further public discussion. (NIH, 2013c)

As an outcome of this initial review, each RAC member makes a recommendation as to whether the protocol raises important scientific, safety, medical, ethical, or social issues that warrant in-depth public discussion at the RAC's quarterly public meetings (NIH, 2013a).

All comments by the RAC members are conveyed to the investigator (NIH, 2013a), and within 15 days of submission of the protocol, the investigator is notified as to whether the protocol has been selected for public review and discussion by the RAC. The in-depth, public review of a protocol may occur when either (1) the OBA director initiates a review following recommendations from at least three RAC members (current practice is at least five votes) (personal communication, J. Corrigan-Curay, OBA, September 1, 2013), or a federal agency other than NIH; or (2)

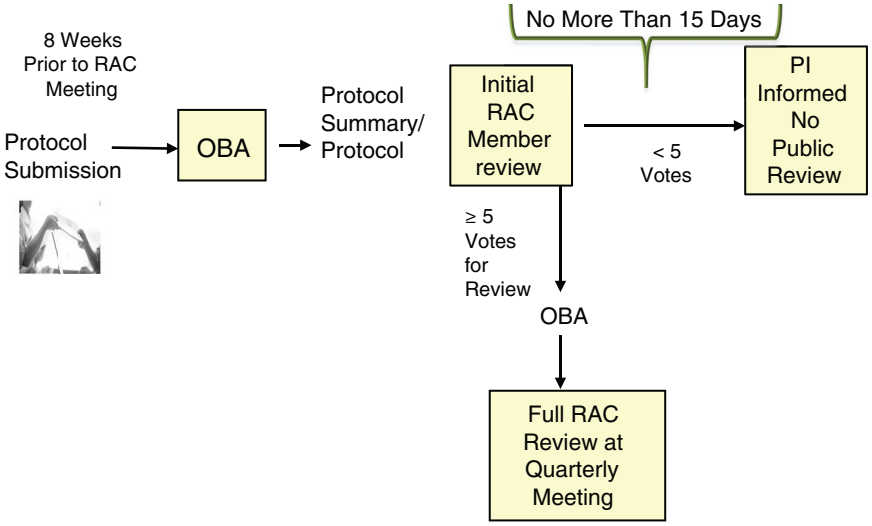

FIGURE 3-1 Summary of the human gene transfer protocol review process.
NOTE: PI = principal investigator.
SOURCE: Corrigan-Curay, 2013.

the NIH director initiates a review. All correspondence with the investigator is part of the public record for the protocol in question and is available to the investigator, sponsor(s), IRB(s), IBC(s), FDA, and OHRP (NIH, 2013a).

Prior to a scheduled public review, RAC members (and sometimes ad hoc members chosen for their expertise in the field) pose a series of questions in writing to the investigator about the gene transfer protocol. The investigator's written responses are required to be submitted to the RAC prior to public meeting. At the meeting, the investigator responsible for the design and conduct of the trial makes a 15- to 20-minute presentation about the gene transfer protocol. The investigator will often bring colleagues to the meeting to help answer questions from the RAC members.

The current process is highly transparent. The OBA website posts protocols that are to undergo public review, and the protocols themselves are made available to members of the public upon request (OBA, 2013). Also, as mentioned previously, all correspondence between the RAC and investigators is also part of the public record for the protocol and is available to the investigators, sponsor(s), IRB(s), IBC(s), FDA, and OHRP (NIH, 2013a). However, according to OBA, in the past decade, there has been a decreasing emphasis on individual protocol review by the RAC; the percentage of protocols selected for public review dropped from 100 percent in 1992 to 37 percent in 2002 to 20 percent in 2012 (Corrigan-Curay, 2013).

Protocols Exempt from RAC Review

There are policy exemptions in place for certain types of human gene transfer protocols that are exempt from the RAC review. Appendix M Section VI-A of the NIH Guidelines details exemption for protocols for certain gene transfer vaccines against infectious diseases, specifically, those using plasmids and other vectors that usually do not persist (e.g., adenoviral vectors) and usually are administered intradermally or intramuscularly. The RAC does, however, review vaccine protocols that include a recombinant or synthetic construct that is not a microbial antigen, such as a gene to express a cytokine. It also reviews cancer vaccines for which the goal is not an immune response to a microbial antigen (NIH, 2013a).

Results of RAC Public Review

The RAC process of public review is defined as complete when, after the public review, the investigator receives a letter summarizing the RAC findings. A similar letter is then sent to the relevant IRB(s) and IBC(s) (NIH, 2013a). Minutes of the RAC meetings and webcasts of the meetings are made available on the public website. Neither investigators nor IRBs or IBCs are required to follow any of the RAC's recommendations. Rather, a protocol's approval comes from a collection of other regulatory bodies. A protocol must be approved by the relevant IBC(s) and IRB(s) before research participants can be enrolled in a clinical trial. These bodies often rely on the RAC recommendations in order to make their decisions, but the RAC's approval per se is not required for the research to move forward (Wolf et al., 2009). FDA, the agency responsible for regulatory approval, considers the RAC recommendations as a basis for review decisions in its investigational new drug (IND) application process (described later in this chapter) (Takefman, 2013).

OTHER ENTITIES WITH REGULATORY OVERSIGHT OF GENE TRANSFER RESEARCH

In addition to the RAC oversight, gene transfer research faces several layers of federal and local oversight and regulations, which are required to initiate clinical gene transfer research protocols. This section briefly describes other entities with authority over gene transfer research and summarizes their interactions with the RAC, including each body's legal establishment, roles and responsibilities, membership, and transparency, and notes any independent evaluation or assessment of impact of each body. This section also describes the relationship of each oversight body to the RAC and the timing of the work of each (in cases where this is dictated)—relationships that are important for assessing continuing need for the level and type of oversight currently provided by the RAC.

Food and Drug Administration IND Review

Although NIH provides funding for gene transfer research and has broad authority to oversee research involving rDNA and therefore gene

transfer research, the agency ultimately responsible for the regulation and approval of gene transfer technologies is FDA (which refers to these technologies as "gene therapy products"). An unapproved drug or, in this case, an unapproved gene therapy product, must undergo FDA review as an IND prior to human use.[2] Gene therapy INDs[3] are regulated by the Office of Cellular, Tissue, and Gene Therapies (OCTGT) in FDA's CBER. A key purpose of IND review is to ensure the safety and rights of subjects. The purpose of reviews of phase II and III clinical trials specifically is to help ensure that the quality of the scientific evaluation is adequate to permit determination of drug efficacy and safety. FDA receives approximately 40 to 60 gene transfer INDs each year. FDA's review follows a regulatory framework in which FDA and the sponsor interact throughout the product's life-cycle, from pre-IND to post-marketing surveillance. Since 1996, FDA has reviewed 840 gene transfer IND submissions, of which 370 are still active (Takefman, 2013). To date, none of the INDs has progressed to approval for marketing.

CBER regulates cellular transfer products, human gene therapy products, and certain devices related to cell and gene transfer. Within CBER, oversight of gene therapy research and products is the responsibility of the OCTGT. FDA defines gene therapy products as products that "mediat[e] their effects by transcription and/or translation of transferred genetic material and/or by integrating into the host genome … and [that] are administered as nucleic acids, viruses, or genetically engineered microorganisms" (FDA, 2006, p. 4). The general types of gene therapy products that FDA has reviewed to date are non-viral vectors (plasmids), replication-deficient viral vectors (e.g., adenovirus, adeno-associated virus), replication-competent oncolytic vectors (e.g., measles, reovirus), replication-deficient retro and lentiviral vectors, cytolytic herpes viral vectors, genetically modified microorganisms (e.g., *Listeria*, *Salmonella*, *E. coli*), and ex vivo genetically modified cells (FDA, 2013a). According to a statement by Jay Siegel to the U.S. Senate (U.S. Congress, 2000), CBER uses both the Federal Food, Drug and Cosmetic Act of 1938[4] and the Public Health Service Act of 1944[5] as enabling statutes for oversight. FDA regulates "all products that mediate […] ge-

[2]Investigational New Drug Application. 2013. 21 Code of Federal Regulations 312 § 1.

[3]A biological product is "any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of [humans]" (21 CFR 600.3[h]).

[4]Federal Food, Drug and Cosmetic Act. 1938. Public Law 75-717. June 25.

[5]Public Health Service Act. 1944. Public Law 78-410. July 1.

netic material by integration into the host genome, and that are administered as nucleic acids, viruses, or genetically engineered microorganisms" (FDA, 2006, p. 4). FDA also maintains a federal advisory committee, the Cellular, Tissue and Gene Therapies Advisory Committee, which reviews and evaluates available data related to the safety, effectiveness, and appropriate use of human cells, human tissues, gene transfer therapies, and xenotransplantation products that are intended for transplantation, implantation, infusion, and transfer in the prevention and treatment of a broad spectrum of human diseases and in the reconstruction, repair, or replacement of tissues for various conditions (Statement of policy for regulating biotechnology products, 1986).

The FDA approval process for new biologic drugs involves an investigator's obtaining permission from the agency to commence human subjects research by filing an IND application. Unlike NIH's regulations, which require the RAC review for all gene therapy protocols funded by NIH or intended to be carried out at institutions receiving NIH funding for rDNA research, the FDA process applies to all gene therapy research, regardless of source of funding. During FDA's review of INDs and its subsequent review of major steps in the research process (e.g., movement from phase I to phase II studies), the RAC's preliminary scientific and ethical review of human gene transfer, as well as its public discussion of novel applications, is taken into account (Takefman, 2013). Unlike RAC review, FDA's review process and approval of INDs are closed to the public until a gene therapy product is licensed for marketing. Although several gene transfer products have progressed to late-stage trials, FDA has not yet approved any gene transfer product for marketing. When it does, the agency will post on its website key documents summarizing the findings of its assessments of the evidence submitted by sponsors.

FDA has a "Points to Consider" document that presents the current thinking of FDA/CBER staff about important issues in gene transfer (FDA, 1991). This document is intended to guide investigators in understanding FDA perspectives and requirements (development and testing) as they prepare their INDs. In 2013, FDA released an updated draft version available for public comment, "Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products" (FDA, 2013a).

Early Consultation: Pre-IND Meetings

To ensure that all regulatory requirements are met, FDA encourages an early "pre-IND" meeting between investigators and FDA officials

early in the protocol development process to discuss specific questions related to the planned clinical trial design. The meeting also provides an opportunity for the discussion of various scientific and regulatory aspects of the drug as they relate to safety and/or potential clinical hold[6] issues, such as plans for studying the gene transfer product in pediatric populations (FDA, 2001). "Pre-IND" meetings are scheduled at least 4 weeks before a formal IND meeting with FDA officials and require investigators to submit information packages that describe the gene transfer product structure; proposed clinical indication; dosage and administration; preclinical and clinical study descriptions and data summary; chemistry, manufacturing, and controls (CMC) information; and objectives expected from the meeting (FDA, 2000).

For certain types of protocols—including those involving gene transfer products—it is sometimes necessary to discuss special issues regarding rDNA proteins from cell-line sources, for example, adequacy of characterization of cell banks, potential contamination of cell lines, removal or inactivation of adventitious agents, or potential antigenicity of the product (FDA, 2013a). An investigator is expected to consider and address FDA guidance from the "pre-IND" meeting, or an earlier informal "pre-pre-IND" meeting, for the gene therapy product before initiating the IND meeting with FDA review officials.

IND Process

As a general rule, when reviewing IND submissions, FDA balances potential benefits and risks to participants of gene therapy clinical trials (Au et al., 2012; Takefman and Bryan, 2012). Upon the investigator's submission of the IND, FDA has 30 days to approve the IND or put it on clinical hold in order to obtain more data from the sponsor.

Content of an IND There are three main content areas covered by an IND: CMC, preclinical studies, and the clinical protocol.[7] The CMC section of the IND includes details of product manufacturing, product safety and quality testing, product stability, and shelf life for all the components and procedures used in generating a gene therapy product. The CMC section also covers purity, identity, potency, and cell viability (for cell-

[6]A clinical hold is an order issued by FDA to the sponsor that delays a proposed clinical investigation or suspends an ongoing investigation.

[7]Investigational New Drug Application. 2013. 21 *Code of Federal Regulations* 312 § 1.

based products). FDA publishes detailed guidance about CMC requirements specifically for gene therapy products (FDA, 2008).

The preclinical studies section covers pharmacological and toxicological testing—both in vitro and in animals—necessary to judge whether the clinical protocol is of sound scientific rationale and reasonably safe and can thus proceed to human trials. Information is also required on absorption, distribution, metabolism, and excretion. Safety testing required specifically of gene therapy products includes (1) potential adverse immune responses to the ex vivo transduced cells, the vector, or the transgene; (2) vector and transgene toxicities, including distribution of the vector to germ cells in testicular and ovarian tissues; and (3) potential risks of the delivery procedure (FDA, 2012).

The clinical protocol section includes information about phase I, II, and/or III studies, including start dose, dose escalation, route of administration, dosing schedules, definition of patient population (detailed entry and exclusion criteria), and safety monitoring plans. It also includes information regarding study design, including description of clinical procedures, laboratory tests, or other measures to monitor the effects of the gene therapy product. Because vectors and transgenes of gene therapy products may persist for the lifetime of the research subject, FDA has issued guidance for observing subjects for delayed adverse events (FDA, 2006).

FDA Transparency

Federal regulations require that information about many clinical trials be posted at ClinicalTrials.gov, the government's database for information about a large proportion of clinical trials, or a similar site, but, by virtue of statutory mandates, there is little to no transparency in FDA reviews during the IND stage, including whether the agency is considering an IND for a specific product. After FDA has approved a product, it may post the clinical, pharmacology, and other technical reviews on its website (see, for example, information for Ducord, an umbilical cord–derived stem cell product for use in certain transplantation procedures, as reported by Zhu and Rees [2012]). Although proprietary information is redacted from these posted reviews, the clinical reviews provide considerable information about the trials. They may summarize early-stage discussions about trial design and assessments of whether sponsors conformed to certain ethical and good trial practices standards. Also, as described in the following section, the GeMCRIS, a joint effort

of FDA and NIH, provides additional public information about gene therapy trials (Corrigan-Curay, 2013).

When necessary, FDA can engage its advisory committee (the Cellular, Tissue and Gene Therapies Advisory Committee) to receive public input about a pressing issue of broad applicability. FDA advisory committees can also review issues related to specific products; in fact, FDA clinical reviews of products have a specific section to summarize any advisory committee discussion.

Genetic Modification Clinical Research Information System

One area in which there is strong interplay between FDA and NIH is the GeMCRIS[8] system. This database, which became operational in 2004, includes summary information on human gene transfer trials registered with NIH (NIH, 2004). GeMCRIS, a joint effort of NIH and FDA, is a comprehensive information resource and analytical tool for scientists, research participants, institutional oversight committees, research sponsors, federal officials, and others with an interest in human gene transfer research. Included in the GeMCRIS summaries is information about the medical conditions under study, institutions where trials are being conducted, investigators carrying out these trials, gene products being used, routes of gene product delivery, and summaries of study protocols. As of summer 2013, GeMCRIS provided information about more than 1,000 human gene transfer protocols, including type of vector and adverse events, and provided abstracts and links to materials from RAC reviews. In addition, the GeMCRIS system allows investigators and sponsors of human gene transfer trials to report adverse events using a secure electronic interface. As described earlier in this report, this feature was developed in response to the discovery that many investigators were submitting required adverse event reports to FDA but not to NIH.

Role of IRB Review

In addition to oversight by federal agencies, gene transfer protocols are reviewed at the institutional level by IRBs. The purpose of the IRB review is to protect the rights and welfare of research subjects in clinical

[8]GeMCRIS is accessible at http://www.gemcris.od.nih.gov/Contents/GC_HOME.asp (accessed September 1, 2013).

investigations. IRB review and approval is required for any research with human subjects supported by the U.S. Department of Health and Human Services (HHS)[9] or regulated by FDA.[10] IRB review is required for research conducted or supported by any of the federal agencies subscribing to the Common Rule, for research on products regulated by FDA, and for research conducted by investigators at any institution giving Federalwide Assurance (e.g., universities assuring the federal government that all of their research will conform to federal rules on human subjects research). The origins of IRB review date back almost 40 years to the *Belmont Report* (National Commission, 1978), which was issued by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in response to a mandate from Congress "to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research."[11] The nationwide infrastructure for local review of research involving human subjects focuses on the protection of human participants in research and the consideration of ethical issues involved in such research. In recent years, the number of IRBs has dramatically increased, from 491 in 1995 to about 4,000 in 2008 (Catania et al., 2008).

For federally funded research, registration requirements and administrative oversight of IRBs is handled by OHRP within HHS. For research supporting applications for FDA approval of products, including privately funded research, FDA also has requirements for IRB review (FDA, 2013b). For gene transfer protocols, IRB approval can occur before or after RAC review (NIH, 2013a).

IRB Roles and Responsibilities

An IRB has the authority to approve, require modifications to (as a condition of approval), or deny approval to research and informed-consent documents. An IRB must also approve amendments to a study and review a progress report at least yearly. Further, an IRB has the authority to suspend or terminate any study for noncompliance. Federal regulations do not specify whether or not an IRB must hold open meet-

[9]Public Welfare: Protection of Human Subjects. 2009. 45 Code of Federal Regulations 46 § 101.

[10]Institutional Review Boards. 2013. 21 Code of Federal Regulations 56 § 101.

[11]National Research Service Award Act. (July 12, 1974). Public Law 93-348. July 12.

ings or make minutes and other IRB documents available to the public. These are matters for individual institutional policies or state law.

For any given research project, an IRB must have at least five members with varying backgrounds to perform an adequate review of the research protocol.[12] An IRB must have sufficient expertise to be able to determine the acceptability of the proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. It must include at least one member whose primary expertise is in the relevant scientific area and at least one member whose primary concern is in a nonscientific area. It must have at least one lay member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution. In addition, an IRB has the discretion to invite individuals with competence in special areas to assist in the review of complex issues, but those individuals may not vote. No IRB may consist entirely of members of one profession, and no IRB may have a member with a "conflicting interest"; however, regulations fail to define what a conflicting interest is.

Federal regulations[12] require an IRB to determine that all of the following requirements are satisfied:

- Risks to research subjects are minimized.
- Risks to subjects are reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge that may be expected to result.
- Selection of subjects is equitable.
- Informed consent will be sought from each prospective subject or the subject's legally authorized representative.
- Informed consent will be appropriately documented.
- The research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects, where appropriate.
- There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data, where appropriate.
- Additional safeguards have been included in the study to protect the rights and welfare of vulnerable subjects, such as children, prisoners, pregnant women, and handicapped or disabled persons.

[12]Institutional Review Boards. 2013. 21 Code of Federal Regulations 56 § 101.

In order to evaluate a study's informed consent documents and process, an IRB needs guidance as to the basic elements of informed consent. Those elements, listed in HHS regulations (known as the Common Rule),[13] are as follows:

- a description of any reasonably foreseeable risks or discomforts to the subject;
- a description of any benefits to the subject or to others that may reasonably be expected from the research;
- the disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
- a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
- for research involving more than minimal risk, an explanation as to whether any compensation and/or medical treatments are available if injury occurs, and, if so, of what they consist and where further information may be obtained;
- an explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights and whom to contact in the event of a research-related injury to the subject; and
- a statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

The Common Rule states that 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."[13]

A centralized IRB is one that conducts reviews on behalf of all study sites that agree to participate in a centralized review process. For sites at institutions that have an IRB that would ordinarily review research conducted there, the central IRB should reach agreement with the institutions and their IRBs about how to apportion the review responsibilities

[13]Public Welfare: Protection of Human Subjects. 2009. 45 Code of Federal Regulations 46 § 101.

between local IRBs and the central IRB.[14] Arrangements have been proposed in which a central IRB conducts an in-depth review of multisite clinical trials and makes detailed reviews, minutes, and correspondence with investigators available to local IRBs, which can then choose to accept the centralized review rather than perform a full local review (Lo and Grady 2009). For example, the centralized IRB for the National Cancer Institute is designed to help reduce the administrative burden on local IRBs and investigators while maintaining a high level of protection for human research participants.

Independent Evaluation of IRB Impact

The IOM committee did not identify many evaluations of IRB performance in reviewing gene transfer protocols specifically. More generally, editorials and commentaries have criticized IRBs as slow, unnecessarily burdensome, inconsistent, and lacking expertise needed for reviewing clinical research (Emanuel et al., 2004; Silberman and Kahn, 2011; Straight, 2009). Otherwise, there is relatively little empirical study of IRBs.

The Gelsinger case provides the most in-depth assessment of one IRB's performance with gene transfer research (the University of Pennsylvania's IRB) (Riley and Merrill, 2005). To better understand the circumstances surrounding Gelsinger's death and what might be learned and improved, the RAC created a working group and had further discussions of the protocol and related issues in December 1999 and March 2000. Other groups—including FDA, the University of Pennsylvania, and OHRP—also investigated. Collectively, they identified a number of shortcomings in the trial and its administration. These shortcomings included investigator conflicts of interest, unapproved changes in the trial protocol, omissions in informed-consent documents and procedures, insufficient resources for the IRB, problems in trial record keeping and monitoring by the investigators, and deficient reporting of adverse events. Among subsequent regulatory responses to reporting deficiencies were a strengthening of requirements for prompt reporting of adverse events, review of reports by independent analysts, sharing with NIH of FDA adverse event data from gene transfer trials, creation of an improved reporting system for adverse events in gene transfer trials, and

[14]Institutional Review Boards. 2013. 21 Code of Federal Regulations 56 § 101.

more public access to safety data from trials (Finn, 2000; Raper et al., 2003; Steinbrook, 2008).

In a 2002 assessment of the RAC as an oversight model (and the oversight of clinical gene transfer research general), Nancy King noted a need for increased education for investigators and local oversight bodies. King points out that "IRBs that review a lot of gene transfer research have a relatively limited experience of gene transfer review in comparison with other fields, simply because the overall volume is small. Thus, what IRBs need to know about gene transfer presumably needs to be relearned periodically" (King, 2002, p. 384). A 2011 review attempting to define the actual burden of IRB review found that IRBs presented with identical protocols did not always make recommendations consistent with each other or even necessarily consistent with federal policy guidance (Silberman and Kahn, 2011).

Role of IBC Review

IBCs are mandated by the NIH Guidelines, Section IV-B-2, to undertake review of safety risks at the level of the investigators' own institutions (e.g., universities and research centers) for all forms of research utilizing recombinant (or synthetic) DNA. Because an IBC is a type of local review developed specifically for rDNA research, it has been suggested that because they are "developed specifically to provide additional review of rDNA research—[IBCs] should be considered part of 'extra,' not basic, review'" (Wolf and Jones, 2011, p. 6). Furthermore, OBA—the entity that administers the RAC—has official authority over IBCs as directed by the NIH Guidelines.

An IBC is required to have no fewer than five members with experience and expertise in rDNA technology. Two of the five members cannot be affiliated with the institution and must represent the interests of the surrounding community regarding health and environmental protection. Depending on the types of research conducted at an institution, these two members may need specific types of expertise (e.g., plant experts if research on plant rDNA is being conducted). The institution must ensure that the IBC has adequate expertise and training, using ad hoc consultants as necessary (NIH, 2013b). The NIH Guidelines encourage institutions to open IBC meetings to the public when possible and when consistent with the protection of privacy and proprietary interests (NIH,

2013c). The guidelines also require institutions to make meeting minutes available to the public upon request.

At each research institution covered by the NIH Guidelines, an IBC is charged with assessing risks to the environment of rDNA research and ensuring that the research is conducted safely and in compliance with the NIH Guidelines. The specific roles and responsibilities of the IBC are to

- provide independent assessment of containment levels required by the NIH Guidelines;
- provide assessment of facilities, procedures, practices, and the training and expertise of personnel involved in the research;
- ensure that all aspects of Appendix M of the NIH Guidelines have been addressed by the principal investigator;
- ensure that no research subject is enrolled in a human gene transfer experiment until the RAC review process has been completed and IBC approval has been obtained;
- for human gene transfer protocols selected for public RAC review and discussion, consider the issues raised and recommendations made as a result of review and consider the principal investigator's response to the RAC recommendations; and
- implement contingency plans for handling accidental spills and personnel contamination.

Under the NIH Guidelines, IBC approval of a gene transfer protocol is necessary regardless of whether the RAC elects to publicly review the protocol. Moreover, although IBCs were created "to provide local review and oversight of nearly all forms of research utilizing recombinant or synthetic nucleic acid molecules" (NIH, 2013a, p. 3). OBA notes that many institutions—at their own discretion—have expanded the scope of IBC review to cover "a variety of experimentation that involves biological materials (e.g., infectious agents) and other potentially hazardous agents (e.g., carcinogens)" (NIH, 2013a, p. 3).

RAC RELATIONSHIP TO OTHER GENE TRANSFER REGULATION AND OVERSIGHT BODIES

An analysis of whether a line of research warrants special review depends on what is special about it in relation to what regulatory and oversight functions already exist. In the RAC's capacity to review individual

clinical gene transfer protocols, it has functions that complement and partially overlap those of FDA and institutions' IRBs and IBCs (Ertl, 2009). All four entities review the safety of gene transfer protocols (Ertl, 2009). However, they differ with regard to the extent to which they discuss broader social and ethical implications of these new technologies in their deliberations, have broad stakeholder representation, and allow public access and participation in their meetings and deliberations (Ertl, 2009).

RAC and FDA

At the time of the original chartering of the RAC in 1974, there was little overlap in the responsibilities of the RAC and FDA for gene therapy studies (Friedmann et al., 2001). Since FDA was given jurisdiction over human gene therapy products in 1986, however, there has been increasing interaction through dual agency review of human gene therapy trials. More recently, it has been suggested that the RAC has strong redundancy with CBER in terms of expertise; CBER has specialized experience and a regulatory mandate (Ertl, 2009). When the RAC was formed 40 years ago, experience in FDA was limited and it was reasonable to assume that FDA reviewers might not have the requisite knowledge base in rDNA technology. Currently, however, FDA has increased expertise, particularly with establishment of the CBER Office of Cellular, Tissue and Gene Therapies. FDA is staffed by professional reviewers whose expertise in the areas of cell and gene therapy, and whose knowledge of drug development, is broad and deep. FDA staff have authored a number of well-reasoned and well-annotated guidance documents that address critical aspects of drug development within the field of gene therapy (see, for example, FDA [1998, 2006, 2013a]).

There are a number of similarities in types of data required by FDA and the RAC, particularly surrounding gene transfer product characteristics, preparation, and safety (preclinical studies and adverse events), and proposed clinical procedures. As a general rule of thumb, FDA requires far more detail about preclinical studies (e.g., specification of acute, subacute, and chronic toxicity testing) than does the RAC, and it requires details of manufacturing and chemistry that are largely omitted in the NIH Guidelines.

Differences remain between the RAC's and FDA's approach to oversight of gene transfer research. FDA, as the sole federal regulatory agency for biomedical products in the United States, focuses on safety and efficacy when evaluating gene transfer products, from the first time they

are used in humans through their commercial distribution (Kessler et al., 1993) and over the lifetime of their use. FDA regulation includes many steps that, by statutory provision, are confidential due to the presence of proprietary information (Wolf et al., 2009). In contrast, the RAC reviews address broader scientific, social, and ethical issues raised by gene transfer research, and the RAC is permitted to address these broader questions in its review of individual protocols as well (NIH Guidelines, see Section IV-C-2-e). In addition to scrutinizing a clinical trial's safety, the RAC assesses its scientific value (Ertl, 2009). Lastly, RAC review is conducted publicly by a number of experts who are not necessarily employed by the government (Wolf et al., 2009).

In an attempt to encourage communication between the agencies, the RAC charter calls for a member of FDA's OCTGT to be one of the nonvoting federal representatives to the RAC (NIH, 2011). This FDA representative keeps the RAC apprised of relevant new regulatory developments, including FDA's receipt of gene therapy protocol INDs for review. In 2001, NIH and FDA harmonized reporting of adverse events, an issue cited in the aftermath of Gelsinger's tragic death. The same forms now must be submitted to both agencies, and the reporting must adhere to the same definitions of the various types of adverse events—such as life-threatening, serious, expected, and unexpected adverse events.[15] Adverse events must also be communicated to the appropriate IRB[s] and IBC[s].) (Adverse events can be reported through GeMCRIS. FDA collaborated with the RAC and NIH on the development of GeMCRIS (discussed earlier in this chapter). Finally, upon FDA approval of an IND, the principal investigator must submit a written report to NIH that includes any modifications to the protocol as required by FDA (Beach, 1999).

RAC and IRBs

Unlike the RAC, the IRB review protocols are part of a formal approval process for conduct at the sponsoring institution. One benefit of the RAC process noted by OBA is that it informs discussions these other bodies will undertake in making certain determinations about the protocol (Corrigan-Curay, 2013). In addition, not only does the RAC have a larger membership than most IRBs (and IBCs as well) and offer more diverse expertise, it also is governed by even more stringent conflict-of-

[15]Investigational New Drug Application. 2013. 21 Code of Federal Regulations 312 § 1.

interest rules (Ertl, 2009). The RAC members who are associated with the institutions involved in the clinical trial in any fashion are not permitted to participate in the discussion of the protocol, nor are they allowed to cast a vote (Ertl, 2009). Lastly, although IRB members may have concerns about potential long-term social implications in protocol review, federal regulations strongly discourage IRBs from considering them in their review decisions (Fleischman et al., 2011).

To guide local IRBs, NIH issued additional guidance on informed consent in gene transfer trials specifically intended to help investigators, IRBs, and others understand and follow the NIH Guidelines and regulations on rDNA research (NIH, 2002). IRB review is independent of and can occur after or before approval by the RAC. If a protocol is selected for public review by the RAC, however, the resulting RAC recommendations are communicated to the IRB, as well as to the IBC, FDA, and investigators (NIH, 2013a).

RAC and IBCs

The study sponsor must complete the research protocol and responses to Appendix M of the NIH Guidelines, which are then reviewed by the local IBC and OBA—the entity that administers the RAC and has official authority over IBCs. Before final IBC approval of a gene transfer protocol, the protocol must be submitted to OBA. Although no stipulations are made regarding what to do with the RAC recommendations, final IBC approval can only be granted *after* the RAC review process is complete (NIH, 2013c), and the local IBC is ultimately accountable to OBA (Kresina, 2001, p. 314).

INTERNATIONAL RESEARCH OVERSIGHT AND REGULATIONS

Given the international and multisite nature of clinical trials and the increasing drive for transparency across clinical trials, it is important to note that the NIH Guidelines apply only to research for which at least one of the sponsoring institutions has received NIH funding. According to one recent review of gene transfer trial information from regulatory and other sources, as of June 2012, more than 1,800 trials have been approved, initiated, or completed in 31 countries (Ginn et al., 2013). The review reported that 65.1 percent of the trials were based in the Americas

(compared to 64.2 percent in 2007), 28.3 percent in Europe (compared to 26.6 percent in 2007), and 3.4 percent in Asia (compared to 2.7 percent in 2007). (Recent data for a number of countries are less complete than earlier data because some countries have stopped specific tracking of gene transfer trials.) More than half of all trials (63.7 percent, or 1,174) are associated with U.S. investigators or institutions (Ginn et al., 2013). For products for which FDA approval is sought, FDA review applies regardless of trial site and funding source.

Internationally, the regulation of gene transfer research is based on national policies, most of which apply to clinical research more generally. Many countries have voluntarily adopted international guidelines for the conduct of clinical research, and some have adopted special policies for the review of gene transfer trials. In the European Union, the European Medicines Agency (EMA) has the responsibility to evaluate and supervise human and veterinary medicines and thereby protect and promote public and animal health (EMA, 2013).

In 2007, EMA established the Committee for Advanced Therapies as the unit responsible for assessing the quality, safety, and efficacy of medicines made from genes and cells, medicines that are termed "advanced-therapy medicinal products." This committee provides a centralized procedure for the assessment and approval of medicines for marketing in the European Union. This process is mandatory for biologics (including gene and cell therapy products) and a number of other product categories, including medicines for the treatment of HIV/AIDS and cancer (Cichutek, 2008).

EMA, however, does not have authority to review and approve protocols for clinical research, including gene transfer research (Pignatti, 2013). Rather, that authority resides with national regulatory agencies. Every European Union (EU) state has, however, adopted the EU Directive on Clinical Trials (Kong, 2004), which requires states to adopt a system for the review of clinical research consistent with internationally recognized standards for good clinical practice for the ethical and scientifically valid design, conduct, and reporting of trials (Kong, 2004). FDA, which participated in the international process for developing these standards, also recognizes these standards and publishes them as guidance documents (FDA, 2012).

ASSESSING GENE TRANSFER RESEARCH OVERSIGHT

Assessments of the RAC Review Process

Some claim that the current mandate of the RAC adds another layer of non-regulatory review to protocols, thereby increasing time and expense (Breakefield, 2012). However, others note that in most public reviews of individual protocols, the RAC has recommended ways to improve safety. Examples of recommended protocol changes include tightening exclusion criteria for study participants with increased risk of complications, making safety end points more specific, and increasing efforts to detect serious adverse events (Lo and Grady, 2009). One analysis of the RAC review examined 53 full public reviews of gene transfer clinical trial protocols performed by the RAC between December 2000 and June 2004 to determine what trial design concerns or suggestions the RAC members raised during written review or public discussion or in a formal letter to investigators post-review (Scharschmidt and Lo, 2006). The analysis found that the selection of subjects was the most-frequently-raised issue related to study design (particularly the need to exclude patients at greater risk for adverse events), followed by dose escalation scheme, the selection of safety end points/adverse events, the overall design analysis, and biologic activity measures. Because this assessment was looking only at protocols that had been publicly reviewed, not all protocols submitted to OBA in that time frame, it is likely that fewer issues of trial design would have been found among protocols exempted from full public review (Scharschmidt and Lo, 2006). Further, the seriousness of the concerns was not noted, nor was how many RAC members shared the concerns. There was no examination of clinical trials employing other technologies matched for stage of development to assess whether concerns regarding trial design were specific to gene transfer or would also be found with other innovative clinical interventions (Scharschmidt and Lo, 2006).

In another study, Kimmelman analyzed an example of a public RAC review, a gene transfer protocol for Parkinson's disease, to describe the ethical issues in complex translational clinical trials (Kimmelman, 2012). Kimmelman noted that often absent from the conversation about the risks of gene therapy are the risks of delivering and administering the gene transfer product, which includes the surgical procedure itself and the needle tracks. Kimmelman noted, however, that the RAC review did, in

this case, focus on surgical procedures—recommending a procedure while the patient is awake, rather than general anesthesia (Kimmelman, 2012).

CONCLUSION

The RAC and the complex array of regulatory infrastructure surrounding it was developed in response to a new technology that, like many emergent technologies, presented a special challenge to the protection of human subjects and raised an array of complex social and ethical issues. At the outset, the RAC review of individual protocols and the opportunity for public discussion were deemed necessary to shepherd in the new medical intervention in a responsible manner. Furthermore, at the time of the formation of the RAC, other regulatory entities were not yet in place to properly oversee the safety and ethical consideration of gene transfer research.

The IOM committee concludes that the RAC has successfully provided oversight for a complex technology for almost 40 years, and its value has been immense in ensuring safe clinical protocols that benefited from input from diverse experts. During this time, it has served as the primary avenue for public awareness of the scientific and ethical dialogue about the pace and boundaries of gene transfer research. After 40 years of experience, it is time for modernization. Concerns surrounding gene transfer, discussed in Chapter 2, are applicable to all new and emerging technologies. The committee found that although gene transfer research continues to raise important scientific, social, and ethical questions, not all gene transfer research is unique, and the time has arrived to develop an oversight process that has matured along with the science.

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4

Evolution of Oversight of Emerging Clinical Research

The roles and responsibilities of the Recombinant DNA Advisory Committee (RAC) have evolved since its creation, providing a significant contribution to the general public and the scientific community. Today, the RAC no longer has a formal regulatory role in gene transfer clinical trials, but retains an advisory role to the National Institutes of Health (NIH), U.S. Food and Drug Administration (FDA), and research institutions' institutional review boards (IRBs) and institutional biosafety committees (IBCs) and provides a forum for public discussion to ensure that gene transfer research has the necessary public transparency. With increased knowledge about gene transfer technologies and their associated risks, as few as 20 percent of protocols submitted have been selected for public review and discussion by the RAC, leading to the question of whether the service the RAC provides is still necessary, given the involvement of other regulatory bodies whose approval is required for gene therapy protocols to be implemented. The charge for this independent review is to determine whether the RAC remains critical to the oversight of clinical gene transfer protocols and, if so, to provide criteria to guide when those protocols should be reviewed.

LIMIT PUBLIC REVIEW OF SELECTED GENE TRANSFER PROTOCOLS

Today, gene transfer research has matured to a state that has reduced some of the early concerns and uncertainty regarding risks; much has been learned about these technologies' safety and possible adverse events. The committee found that although gene transfer research contin-

ues to raise important scientific, social, and ethical questions and the state of gene transfer research is constantly evolving, not all gene transfer research can still be considered a completely new scientific enterprise or novel technology. Individual protocol review by the RAC no longer offers unique benefits except in special circumstances. Although patient safety is always paramount, regulatory oversight should not be required unless it provides a benefit; regulation without benefit is unnecessary and burdensome and should be eased.

Therefore, the committee concluded that individual gene transfer protocols should not be subject to additional public review by the RAC except in exceptional circumstances, such as when human subjects research involves novel technologies and treatment strategies or when the protocols cannot be adequately performed by other oversight and regulatory bodies. The purpose of such public review should be to continue to inform the scientific community, IRBs and IBCs and other regulatory and oversight bodies, as well as the public. Going forward, the committee recommends new specific criteria that should guide selection of protocols that represent exceptional circumstances and thus public review.

Minimizing the Administrative Burden

To minimize the administrative burden to the applicant that the current RAC protocol review process entails, the committee concludes that the protocol review can be accomplished by the investigator's submission of FDA's investigational new drug (IND) protocol and does not require the additional information required in the current mechanisms. As is current practice and accounted for in the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (the NIH Guidelines), proprietary information can be redacted from INDs when reviewed by the RAC (NIH, 2013, p. 36). The committee notes that the European Union has developed streamlined oversight processes that decrease the regulatory burden. For example, the Gene Therapy Advisory Committee in the United Kingdom has been substantially streamlined, with duties largely transferred to and embedded in other review groups, thereby reducing the regulatory burden (NHS, 2013). Comments from those engaged in drug development attest to improved efficiencies and absence of impact on patient safety (NHS, 2013).

All clinical trials involving gene transfer should continue to be registered with the Office of the NIH Director. However, this registration pro-

cess can be accomplished through the use of the FDA-approved IND application and IRB-approved protocol, which is sufficient to provide the context critical for subsequent adverse event review. Upon registration of a protocol, the Office of the NIH Director, in consultation with IRBs and IBCs, may request additional public review of individual protocols if one or more of the criteria described below are satisfied. The committee expects that allowing the NIH director, in consultation with IRBs and IBCs, to select protocols for review will eliminate the role of the RAC as a self-perpetuating body both selecting protocols to review and performing the review. The expertise and authority of the RAC is best utilized to provide additional oversight for exceptional circumstances, such as when human subjects research involves novel technologies and treatment strategies. RAC review should continue to be performed in an open and transparent manner.

Supporting Institutional Review

The committee recognizes that not all IRBs and IBCs will have the necessary expertise to properly review a particular gene transfer clinical trial. Therefore, inquiries to the Office of the NIH Director are intended to establish a dynamic process whereby the Office of the Director has the capacity to help provide IRBs with examples of precedent-setting protocol reviews, which may obviate the requirement for review beyond the IRB. In addition, there is significant potential for centralized IRBs to broadly disseminate more protocol-specific information in this dynamic process than would be possible with individual IRBs.

An important feature of this new process is a collaborative relationship between the NIH director and oversight bodies. For example, in many cases, an IRB or IBC may believe that a protocol meets one of the below described criteria. However, it may be the case that the RAC, or another oversight body, has already reviewed a similar protocol. The NIH director can now serve as a resource, providing guidance based on precedence to the requesting oversight body to cite and reference the original protocol review—thereby ensuring that only protocols not previously addressed or outside the capacity of the oversight bodies get reviewed. The NIH director may also choose to organize workshops to promote greater expertise for reviews of emerging science issues versus reviews of individual protocols, which also help strengthen the capacity of local institutions.

Because this is a change from the status quo, the committee recognizes that not all IRBs and IBCs may currently have the capacity and capability to undertake all protocol reviews. However, with time and additional guidance from NIH, it is expected that this capacity will significantly increase in a short period of time. An example of how capacity can be increased is provided by the Embryonic Stem Cell Research Oversight Committees (ESCROs) (CIRM, 2013). Furthermore, the Genetic Modification Clinical Research Information System (GeMCRIS) provides the ability for accessing information on specific historical and ongoing protocols registered with the Office of Biotechnology Activities (OBA), which can and should be used to augment institutional capacity and convey previous RAC discussions and recommendations. For example, reviewers can search for a specific medical condition like arthritis and receive links to information on the investigators, vectors, cells and genes involved in the study, as well as to minutes of the public discussion.

Modified RAC Review Process

The protocol review process should also be modified to enable expeditious review to minimize delays in bringing sound and ethical protocols into human subjects trials. Investigators and their IRBs should be notified in a timely manner of either (1) the need for public review by the RAC, or (2) an exemption from RAC review because none of the criteria is met. When the RAC performs public reviews of gene transfer protocols, the goal will be to advise prospective research participants, the investigator, the Office of the NIH Director, FDA, IRBs, and the public.

If a protocol is judged exempt from public RAC review because none of the specific criteria for review is satisfied, the investigator and relevant IRBs and IBCs will be notified. Prior to subject enrollment, however, the final IND application approved by FDA (including the IRB-approved treatment protocol and consents) must be submitted to the Office of the NIH Director both to ensure that no amendments have occurred that would alter the prior determination of review exemption and to ensure future evaluations of adverse events. All protocol amendments must be submitted to the Office of the NIH Director. The protocol and protocol amendments will be abstracted and registered in GeMCRIS and made accessible to the public.

CRITERIA TO GUIDE PROTOCOL REVIEW

The committee established three specific criteria to guide which protocols should continue to receive additional RAC review. These criteria are intended to limit additional review to only exceptional circumstances. It is otherwise expected that the remainder of the oversight and regulatory system can address the protocol. The criteria sufficient for initiating public review and their rationales are as follows:

Criterion 1 The protocol uses a new vector, genetic material, or delivery methodology that represents a first-in-human experience, thus presenting an unknown risk.

Areas of science that are novel, quickly evolving, and yielding scientifically complex materials and components should garner additional attention from oversight bodies. Novelty indicates an untested area of science, one that brings an additional layer of uncertainty as compared to research in areas of greater experience and one for which institutional review bodies typically do not have the requisite expertise. In gene therapy research, novelty encompasses such things as a new vector, gene, or route of administration. It does not include, however, a new clinical indication, testing in a vulnerable population, or use for the first time to produce a nontherapeutic benefit (e.g., enhancement). Therefore, these attributes of a protocol would not trigger the need for public review by the RAC. Although these may be important questions generally, with regard to the individual protocol, other agencies are well-equipped to evaluate these issues. Furthermore, it is possible that the Office of the NIH Director will provide a platform for general discussion, beyond a single protocol, of more wide-ranging issues, such as societal impact.

Criterion 2 The protocol relies on preclinical safety data that were obtained using a new preclinical model system of unknown and unconfirmed value.

Although the use of new models is encouraged by the committee and may offer potential advantages, their use requires justification. In addition to assessing the value of these new models, a required public RAC review would provide benefits to the scientific community by disseminating data on new models and offering a forum for public discussion.

Criterion 3 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.

Because adverse events of a specific vector, gene product, or mode of delivery may be realized only across protocols, adverse events may not be known by individual investigators or the public at a given time. Review of adverse events across protocols should be used to evaluate trends in adverse events that may lead to a greater awareness of safety concerns, necessitating public review and discussion in the context of the proposed protocol. This aggregation of protocol information and adverse events is a key function of the current GeMCRIS and should be maintained. This information should assist the investigator, IRB, IBC, and FDA in the development of a treatment plan that optimizes safety and assists the research participant in making an informed decision about whether to participate.

In addition, when considering which protocols are chosen for additional public review, the NIH director, in consultation with the other oversight and regulatory bodies, should consider broader societal issues that may warrant a public forum. Emerging technologies in gene transfer science, as presented in new clinical trials protocols (e.g., first-in-human trials), may present scientific or ethical concerns and represent a significant departure from familiar techniques, requiring additional oversight. Therefore, in considering which protocols are chosen for review, the NIH director, in consultation with an IRB, should consider broader societal issues that may warrant public concern.

Recommendation 4-1: <u>Restrict individual gene transfer protocol reviews to exceptional cases that meet specified criteria.</u>

The National Institutes of Health's (NIH's) Office of the Director should continue to register all gene transfer protocols and, in consultation with appropriate regulatory and/or oversight authorities, should identify protocols for additional public review only if both items 1 and 2 below are satisfied

1) **Protocol review could not be adequately performed by other regulatory and oversight processes (for example, institutional**

review boards, institutional biosafety committees, the U.S. Food and Drug Administration);

2) One or more of the criteria below are satisfied:

- **The protocol uses a new vector, genetic material, or delivery methodology that 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 and that may render it difficult for local and federal regulatory bodies to evaluate the protocol rigorously.**

Even if the protocol does not meet the foregoing criteria listed in items 1 and 2, the NIH director in consultation with appropriate regulatory and/or oversight authorities should have the flexibility to select protocols for review that may present significant societal or ethical concerns.

Illustrative Case Studies

In order to illustrate how the new criteria should be used to limit the number of protocol reviews that are selected by the Office of the NIH Director, three historical cases are provided below that compare the outcomes that could be reached by using the proposed framework versus the present-day RAC review (see Boxes 4-1, 4-2, and 4-3). The examples were selected from the 10 most recent protocols that have been chosen for public review by the current RAC as of August 2013. It is important to note that the committee did not single out any specific gene transfer research protocol or any particular area of investigation, but rather selected a few current examples for the purpose of illustration. In each case, the RAC briefly reviews the protocol and makes a determination of whether or not the protocol requires additional oversight—in the form of a public review—with the proposed new criteria. The proposed criteria are intended to streamline review and limit the additional review of individual gene transfer protocols to a smaller number. Individual gene transfer protocol review is intended for only exceptional cases like those

described. The committee notes that the criteria should be interpreted as strictly as possible, as has been highlighted in its case studies. Furthermore, it is the committee's intent that these reviews serve to provide models to the public and oversight/regulatory bodies to enable reviews to be increasingly performed at institutional level.

BOX 4-1
CASE STUDY 1

Protocol #1304-1230
Phase I Ascending Dose Trial of the Safety and Tolerability of Toca 511, a Retroviral Replicating Vector, Administered Intravenously to Subjects Undergoing Subsequent Resection for Recurrent High Grade Glioma and Followed by Treatment with Toca FC, Extended-Release 5-FC.

Trial Design
This Phase I study proposes to evaluate dose escalation of a gene transfer product made up of a replication-competent retroviral vector expressing cytosine deaminase (Toca 511). The cytosine deaminase will convert the oral prodrug flucytocine (Toca FC) into a drug that is toxic in transduced tumor cells. The study will evaluate whether the product is safe and well tolerated when injected and whether it can enter into the brain tumor.

Eligibility
Study subjects will be patients with recurrent high-grade glioma who have previously received surgery, radiation therapy, and chemotherapy.

Treatment Plan
Up to five escalating doses of Toca 511, administered intravenously 10 days prior to cranial surgery, will be evaluated in this study. The first subject will receive an initial intravenous dose level at half of the highest dose of Toca 511 determined to be safe in a previous study. Subsequent subjects will receive ascending doses of Toca 511, depending on how well previous subjects tolerate lower doses. Subjects will then undergo planned surgery to remove the brain tumor. During surgery, Toca 511 will be injected intracranially at the tumor site. About 4 weeks after surgery, Toca FC prodrug will be administered orally until the subject's tumor progresses or intolerance to the prodrug develops. All subjects will be followed for 32 weeks.

Decision and Rationale for RAC Review Under Current Guidelines
This study was chosen for in-depth review and public discussion by the RAC because a trial involving the intratumoral administration of Toca 511 was associated with detection of viral RNA sequences in the blood. Another study involving intracranial administration of Toca 511 resulted in one subject experiencing a dose-limiting toxicity, with 193,000 copies of virus/uL in the blood at the time of cough and fever and partial lung collapse

Because of the risk of significant viremia associated with intracranial administration, the risks and benefits of intravenous administration deserve in-depth discussion.

Decision and Rational for RAC Review Under Recommended Guidelines
Under the recommended guidelines, this study may be chosen for individual protocol review on the basis of Criterion 3 if the proposed method of delivery is associated with possible toxicities that are not widely known and beyond the capacity of FDA or local oversight bodies to evaluate. There is a marked absence of discussion of the risks of intravenous administration relative to those of intratumoral or intracranial administration in both the protocol and consent form.

BOX 4-2
CASE STUDY 2

Protocol #1304-1231
Phase I Study of Intrathecal Administration of scAAV9/JcT-GAN for the Treatment of Giant Axonal Neuropathy.

Trial Design
This Phase I study proposes to evaluate an adeno-associated virus (AAV) vector to deliver the gigaxonin gene to subjects, including children, with a genetic diagnosis of giant axonal neuropathy (GAN). The AAV vector will be administered by injection to the brain and spinal cord. Providing a functional gigaxonin gene into affected cells may restore normal organization of structural proteins which are a hallmark of the disease and restore axonal function. In turn, this may increase communication between the central and peripheral nervous systems and slow, halt, or reverse the deterioration of motor function. This study will primarily evaluate whether the gene transfer product is safe, and secondarily include clinical assessment of motor and sensory function and effect on disease pathology in subjects' peripheral nerves.

Eligibility
Study subjects will be children over 4 years of age with a genetic diagnosis of GAN, a neurodegenerative disease generally associated with progressive loss of motor and sensory function over time and with death by age 30.

Treatment Plan
Each subject will receive one dose of AAV vector expressing gigaxonin injected to the brain and spinal cord, at a dose tested in animal models in pre-clinical studies. Follow up assessments will continue up to 15 years after administration of the product.

Decision and Rationale for RAC Review Under Current Guidelines
This study was chosen for in-depth review and public discussion by the RAC because it involves the testing of a novel transgene and delivery route for a new disease indication in children.

Decision and Rational for RAC Review Under Recommended Guidelines
Under the recommended guidelines, this study would be chosen for public review. Criterion 1 is satisfied because the transgene and route of administration have not been previously evaluated.

BOX 4-3
CASE STUDY 3

Protocol #1304-1224
E10-A (Endostatin Adenovirus) for the Treatment of Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck.

Trial Design
This Phase III study proposes to evaluate the benefit of the gene transfer product E10-A, a replication deficient adenovirus containing the human endostatin gene. Endostatin has been shown to inhibit vascular endothelial cell proliferation and tumor angiogenesis, and block tumor blood supply, thereby specifically inhibiting tumor growth and inducing apoptosis of tumor cells. The study will evaluate whether combining E10-A with currently available chemotherapeutic agents (1) is more effective at shrinking or stopping the growth of tumors or (2) results in participants living any longer than chemotherapy alone.

Eligibility
Study subjects will be adult patients with recurrent or unresectable squamous cell carcinoma of the head and neck.

Treatment Plan
Intravenous injection of replication deficient adenoviral vector containing the human endostatin transgene. Participants with receive up to 6 cycles of treatment (1 treatment cycle for this trial is 21 days).

Decision and Rationale for RAC Review Under Current Guidelines This study was chosen for in-depth review and public discussion by the RAC because it is the first time this agent had been used in a U.S. clinical trial. RAC members determined that additional aspects of study design, including the rational for additional chemotherapy agents not included in Phase II trial testing of E10-A, the exclusion of a chemo-radiation arm, and the question of whether tumor location would be factored into analysis of results deserved in-depth discussion.

Decision and Rational for RAC Review Under Recommended Guidelines
Under the recommended guidelines, this study would not be chosen for public review. Criterion 1 is not satisfied because the transgene, vector and route of administration have been previously evaluated. Criterion 2 is not satisfied because the protocol relies on preclinical safety data obtained using a reliable preclinical model system of confirmed value. Criterion 3 is not satisfied as the proposed vector, gene construct, and method of delivery are not associated with uncertain risks or toxicities.

SPECIAL REVIEW OF OTHER EMERGING SCIENCES AND TECHNOLOGIES

Evolution of Oversight of Emerging Clinical Research

The RAC was established to respond to an emerging technology of great public interest and with risks and benefits only barely understood. The RAC has successfully provided oversight for a complex technology for almost 40 years, providing exceptional service to NIH, the scientific community, and the public. Its value has been immense in ensuring safe clinical protocols that benefited from input from diverse experts. By engaging the public in a focused discussion on the technology and its potential societal impacts, the RAC engendered trust and credibility. Over time, gene transfer research, although not entirely without areas of uncertainty or public concern, has become better understood, and many risks have been minimized. The committee recommends not only that the RAC's review of gene transfer oversight be narrowed to areas still in need of special review or expertise, but also that the necessity of a RAC model for other emerging technologies that might benefit from lessons learned and structures built for the responsible development of gene transfer science be explored.

Emerging areas of science within human clinical intervention (including but not limited to gene transfer) can be defined as areas of research that pose an uncertain risk, may pose harms to individuals' or the public's health, and which could not otherwise be adequately assessed by existing regulatory processes. Many emerging technologies represent groundbreaking advances and innovation in science and may provide tools to solve challenging problems. In the field of medicine, emerging technologies have the potential to lead to better health outcomes, lower health care costs, and earlier patient access to more effective treatments (Anatol et al., 2013). Currently, in addition to gene transfer research,

there are many emerging technologies with clinical applications that present their own risks and uncertainties, including combination products (drugs and biologics), nanotechnology, and regenerative medicine (including cell- and tissue-based products). Also, gene transfer products, as noted in the FDA guidance discussed in Chapter 2, have many characteristics in common with cellular therapies, but also present additional concerns in the context of combination cell and gene transfer products. Nanomedicine, for example, presents additional concerns and uncertain risks related to the special properties of nanoparticles, such as their greater ability to penetrate and translocate across cell membranes or different parts of the body (Wolf et al., 2009). Furthermore, many nanotechnology techniques involve putting materials into humans that have not previously been used in any clinical intervention and present uncertain risks. However, different areas of emerging sciences are often at different stages of development, and therefore differ in their materials characterization and understanding, process development, understanding of uncertainties and establishment of safety to research participant, close contacts, community, and environment, in addition to raising different societal concerns. For example, technology creating chimeras raises different societal concerns than nanomedicine, and embryonic stem cell research raises still others. Because different areas of science are at different stages along this developmental trajectory, the committee stresses that this mechanism should only apply when a technology is at the level of science being used in clinical research.

The committee also notes that experience with gene transfer research may offer valuable lessons for how to proceed with human trials of other medical advances that depend on emerging technologies. For this reason, it recommends that NIH assess whether there are other areas of clinical research that might benefit from a venue for targeted, transparent oversight beyond that provided by existing regulatory mechanisms. If so, then consideration of an appropriate mechanism would be in order.

Future technologies, whether gene transfer–related or emerging from other areas of science, will be novel, may present significant risks and uncertainties, and could benefit from review such as that currently provided by the RAC. The RAC has served an important function and its contributions to gene transfer research not otherwise available from other bodies should continue, although these could be reframed and offered through an expanded process. The oversight of an emerging science should be triggered when it reaches the stage of human subjects research. Any review process should be sensitive to the fundamental understand-

ing that different areas of science may be at different stages of development, as discussed previously. The committee recommends exploring an approach that considers, among other criteria, the uncertainty of risk posed by a research protocol.

The Use of the RAC Model in a New Process

The necessity of any new process that could both focus resources on a limited number of gene transfer protocols that meet the criteria described above and address other emerging technologies. Like the current RAC, a forum for emerging technologies in which investigators could discuss and disseminate new information and share best practices and where members of the public could express and discuss their concerns would serve as a public good and could be beneficial to the scientific and broader communities alike. The committee recommends exploration of the potential for a new process that would have ad hoc capacity to review the full breadth of emerging areas of research supporting human clinical intervention that may have special risks and that could not be adequately assessed under the existing regulatory processes for clinical research. To be clear, the criteria presented in Recommendation 4-1 are meant to be used to select gene transfer protocols that require an exceptional level of review and are not meant to apply in whole or in part to other technologies. Similar concepts may be considered, however, when developing any criteria to select protocols for review in other areas of emerging science.

The new review process may need to include a continuation and expansion of the current NIH processes of symposia and workshops that inform the larger gene transfer research community, broadening them to include emerging science and technologies. Symposia and public workshops provide opportunities for discussion about a broad array of issues at the forefront of emerging technologies, including gene transfer research, both as a response to and in anticipation of scientific, ethical, and societal concerns. As described in OBA's mission statement, one of its primary roles is to foster and enable public discussions of the science of gene transfer research and the public concerns it raises:

> The NIH Office of Biotechnology Activities (OBA) promotes science, safety, and ethics in biotechnology through advancement of knowledge, enhancement of public understanding, and development of sound public

> policies. OBA accomplishes its mission through analysis, deliberation, and communication of scientific, medical, ethical, legal, and social issues.[1]

The committee believes that this role remains critical and could serve an important benefit if it were expanded to other areas of emerging, novel, or risky science. This function could be fulfilled through symposia and workshops focusing on two areas, which may take place in unison: (1) the state of the science, and (2) societal concerns and implications of the science. The identification of symposia and workshops topics should remain NIH's responsibility, with the process for identifying topics and timing responsive to and in consultation with the scientific community and other interested stakeholders, including the public.

Symposia and workshops that foster awareness in these two areas will be an important part of NIH's ongoing education and support of institutional review processes via IRBs and IBCs, which may lack expertise in specific areas, and will also assist state and federal regulatory bodies as increasingly complex sciences move forward. These forums will also aid regulatory oversight (via FDA). Finally, and importantly, the expanded process will contribute to maintaining public trust that new areas of potentially risky science will be responsibly managed.

The capacity to enable a public discussion of issues, concerns, and challenges in emerging gene transfer science and other technologies is of great value to the scientific and stakeholder communities and also serves the public's interest. This capacity must be maintained going forward. There are many options to be considered for implementation of an expanded process to evaluate and advise on new technologies that are anticipated for use in clinical interventions and which pose uncertain risk and consequences to individual and/or public health. The committee acknowledges that this process should leverage scientific knowledge sharing and commitment to advancing novel technologies.

The committee reviewed many of the proposals and assessments for the design of oversight for emerging technologies, which can be considered going forward. For example, Kuzma and colleagues (2008) developed a broad set of criteria to describe and assess relationships among features, outcomes, and tradeoffs of oversight systems. Others note that nanotechnology is challenging the capacity of current oversight systems and that using a nano-vector to deliver genetic material in gene transfer

[1]From the OBA website, http://oba.od.nih.gov (accessed August 1, 2013).

research in humans will involve multi-stakeholder concerns, including FDA, NIH, the Occupational Safety and Health Administration (OSHA), the National Institute for Occupational Safety and Health (NIOSH), and the Environmental Protection Agency (EPA) (Fatehi et al., 2012). As of yet, there is no coordinated framework to deal with issues related to nanotechnology, suggesting that the RAC should undertake ethical analysis of this challenging topic to provide adequate guidance and protections going forward (Fatehi et al., 2012).

Others suggest that RAC oversight of gene transfer therapies could serve as a model for other areas of emerging science, noting that the RAC's historical contribution has been its expertise and promise of producing generalizable guidance and drawing attention to questions that have broad applicability across clinical trials (King, 2002). Marchant and colleagues (2010) also notes that although many emerging technologies raise important ethical and social issues, there are implications unavoidable in any regulatory scheme. Marchant describes several proposals, including ethical impact statements and ethics review boards, both of which could be considered in Recommendation 4-2. Further efforts to analyze oversight indicate that for emerging technology governance to be effective, collaboration is required among scientists, the government, and the public (Wiek et al., 2007).

Therefore, the committee makes the following recommendation.

Recommendation 4-2: Consider integrating oversight for gene transfer and other applications of emerging technologies.

The National Institutes of Health (NIH) director should convene an ad hoc working group that will be responsible for considering whether additional oversight and a venue for public deliberation are indicated for other applications of emerging technologies, and if so, to explore procedural options, including the possibility of an integrated oversight body. In this task, the focus 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 Recombinant DNA Advisory Committee (RAC) should be used as one possible model, particularly with regard to these functions:

- **Provide a public forum for the review and discussion of emerging areas of science.**
  - **Include the capacity for a partnership to consult, inform, and educate institutional review boards (IRBs) and institutional biosafety committees (IBCs).**
- **Provide a venue to foster scientific and public awareness regarding emerging science in order to address concerns about clinical investigation and future societal implications.**
- **Integrate the capacity to surveil, aggregate, and analyze adverse events across related trials of emerging technologies.**
- **Perform an additional level of review of individual protocols that are identified by the NIH director, in consultation with one or more IRBs and IBCs, on the basis of exceptional issues raised as articulated in the committee's gene-transfer protocol criteria.**

For the present, however, the RAC should continue to review individual gene transfer protocols but use the criteria set forth in Recommendation 4-1 to help limit review and focus resources on exceptional cases.

This expanded process could take a number of forms. One option would be an Emerging Technologies Advisory Committee that would function much like the RAC, but with the expanded purview of any emerging science supporting human clinical intervention. However, effective processes that would not require the creation of another formal ongoing convening activity, but instead could be dynamic and performed on an ad hoc basis, could be established. For example, another option would be to retain a pool of subject-matter experts to consult on an ad hoc basis as warranted. There are certainly other options as well. Although there are many potential models, in considering the new process for oversight, NIH should pay special attention to the value that the public nature of the RAC process has played.

The decision to include new emerging technologies that warrant additional oversight in the expanded process would arise from IRBs, IBCs, and the Office of the NIH Director. The committee recommends that the newly established process retain the following key functions historically provided by the RAC. These include the capacity to

- **provide a public forum for the review and discussion of gene transfer science;**
- **provide a venue to foster scientific and public awareness regarding emerging science in order to address concerns about clinical investigation and future societal implications;**
- **integrate the capacity to monitor, aggregate information about, and analyze adverse events across related trials of emerging technologies; and**
- **perform an additional level of review of individual protocols.**

The committee recognizes that the current NIH Guidelines limit the function of some parts of the regulatory and oversight system, for example, the need for additional clarity about what standards IBCs should use for review of emerging sciences. Therefore, in the development of this process, it is expected that NIH will also have to review and assess the current NIH Guidelines to ensure that they are updated to provide consistent guidance to all parts of the regulatory and oversight system it oversees.

Understanding that the NIH director will need time to establish a new process for monitoring emerging technologies, the committee recommends that the Office of the NIH Director continue the RAC in its currently constituted form for a limited period of time until the new process is established. In the interim, all gene therapy protocols should continue to be registered with the NIH director, but should only be selected for public review according to the three criteria detailed above, in order to help make the process less burdensome and more efficient. The suggested continued registration and newly recommended criteria for review will maximize efficiency by removing duplication in the regulatory process and will optimize scientific advancement while providing rigorous human subjects protection. In addition, centralized IRBs may serve as an important mechanism to provide subject matter expertise for specific areas of emerging science that IRBs may not have the capacity and/or expertise to address.

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A

Data Sources and Methods

The Institute of Medicine (IOM) Committee on the Independent Review and Assessment of the Activities of the NIH Recombinant DNA Advisory Committee (RAC) was tasked with evaluating the necessity for the additional oversight of individual gene therapy protocols by the RAC. The specific goals of this review were to specify the scientific, safety, and ethical concerns that may justify a special level of oversight for this and potentially other areas and determine whether gene transfer research raises issues of concern that warrant extra oversight by the RAC, considering the current regulatory context. The IOM committee was instructed that if it concluded that this particular function of the RAC should remain intact, it should then describe the criteria that the RAC should use to select protocols for public review. The IOM committee reviewed information collected from a variety of sources, including scientific literature, previous evaluations and progress reports, open-session meetings and conference calls, public testimony and input, and other publicly available resources.

COMMITTEE EXPERTISE

To complete its task, the IOM formed a committee of 11 experts to conduct an 8-month study to respond to the statement of task. The committee was composed of members with expertise in clinical medicine, molecular biology, virology, molecular genetics, high-risk clinical trials, gene transfer technologies, biomedical ethics, law, public policy, and patient advocacy. Appendix C provides biographical information for each committee member.

MEETINGS AND INFORMATION GATHERING ACTIVITIES

The committee deliberated from June 2013 through October 2013 to conduct this expert assessment. During this period, the committee held three 2-day meetings, and committee members also participated in multiple conference calls. Two of the committee meetings were open-session, which allowed committee members to hear input from a wide range of stakeholders and members of the public. Experts in the field of clinical gene transfer research shared their perspectives on the role of the RAC, how and why some protocols are chosen for individual protocol review, the degree of harmonization among oversight bodies, the oversight of gene transfer compared with other cutting-edge areas of science, and the importance of public education and trust in the oversight process. Experts in the field of financial and scientific investment in gene transfer research presented their perspectives on whether individual protocol review by the RAC brings expertise and transparency to the oversight process and whether additional oversight has a significant impact on financial investment in potential gene transfer products. Investors also compared gene transfer oversight in the United States to that in Europe. Patient advocacy groups shared their perspectives on acceptable risk and oversight of clinical gene transfer research.

Each open-session meeting included a public comment period in which the committee invited input from any interested parties. All open-session meetings were held in Washington, DC. A conference call number and online public input tool were provided to allow opportunity for input from individuals unable to travel to the meetings. A link to the public input tool was made available on the National Academies' website from April 2013 through October 2013, and all online input was catalogued in the study's public access file. All information provided to the committee from outside sources or through the online input tool is available by request through the National Academies' Public Access Records Office. The agendas for the two open-session committee meetings are reproduced below.

MEETING ONE

Committee on the Independent Review and Assessment of the Activities of the NIH Recombinant DNA Advisory Committee

June 4, 2013
Keck Center, Room 109
500 Fifth Street, NW
Washington, DC

1:00 p.m. **Welcome and Introductory Remarks**
Larry Gostin, J.D., *Committee Chair*

SESSION 1: THE STATE OF GENE TRANSFER RESEARCH OVERSIGHT

1:10 p.m. **The Charge to the Committee: A Discussion with the Sponsor**
Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
Office of the Director, National Institutes of Health

2:10 p.m. **The RAC Process**
Jacqueline Corrigan-Curay, J.D., M.D.
Acting Director, Office of Biotechnology Activities, National Institutes of Health

2:40 p.m. **Committee Discussion**

3:00 p.m. **Presentation—The Role of the FDA in Gene Therapy Products**
Daniel Takefman, Ph.D.
Chief, Gene Therapy Branch, Division of Cellular and Gene Therapies, Office of Cellular, Tissue, and Gene Therapies, Center for Biologics Evaluation and Research, Food and Drug Administration

3:30 p.m. **Committee Discussion**

3:45 p.m. **Break**

4:00 p.m. **Presentation—Perspectives on RAC and Gene Therapy**
Xandra Breakefield, Ph.D.
Former President, American Society for Gene and Cellular Therapy
Professor of Neurology, Harvard Medical School
Geneticist, Department of Neurology and Radiology, Massachusetts General Hospital

4:20 p.m. **Committee Discussion**

4:45 p.m. **Presentation—Patient Perspective**
Edward R. B. McCabe, M.D., Ph.D.
Senior Vice President and Chief Medical Officer, Office of Medicine and Health Promotion, March of Dimes

5:00 p.m. **Follow-Up Discussion with Sponsor**

5:15 p.m. **Public Comment Period**

5:30 p.m. **Closing Remarks**
Larry Gostin, J.D., *Committee Chair*

MEETING TWO

Committee on the Independent Review and Assessment of the Activities of the NIH Recombinant DNA Advisory Committee

August 6, 2013
Keck Center, Room 100
500 Fifth Street, NW
Washington, DC

9:00 a.m. **Welcome and Introductory Remarks**
Larry Gostin, J.D., *Committee Chair*

SESSION 2:
FINANCIAL AND SCIENTIFIC INVESTMENT

9:10 a.m. **Panel Discussion**

Session Objectives: Understand the current state of regulation of gene transfer research and compare its regulatory landscape to other areas of science. Discuss any models that exist for gene transfer oversight, including those that add value or may no longer be necessary. Explore the investigator experience of individual gene transfer protocol review by the RAC.

Moderator: Howard Federoff, M.D., Ph.D.
Committee Member

Panelists: Barry Byrne, M.D., Ph.D.
Director of the University of Florida Powell Gene Therapy Center
Professor of Pediatrics, Molecular Genetics, and Microbiology
Associate Chair of Pediatrics
University of Florida

Helen Heslop, M.D.
Professor in the Department of Medicine
Director of Adult Stem Cell Transplant Program
Baylor College of Medicine

Elizabeth Hohmann, M.D.
Chair and Director of Partners Human Research Committee
Partners Healthcare

Carl June, M.D.
Richard W. Vague Professor in Immunotherapy
Director of the Translational Research Program
University of Pennsylvania

Margaret Riley, J.D.
Professor of Law
Professor of Medicine
University of Virginia

10:30 a.m. **Panel Discussion**

Session Objectives: Explore the state of clinical gene transfer oversight from the perspective of those who analyze the regulatory context when making decisions about whether to invest finances or scientific resources in the field.

Moderator: Alta Charo, J.D.
Committee Member

Panelists: Jeffrey Chulay, M.D.
Chief Medical Officer and Vice President of Regulatory Affairs
Applied Genetic Technologies Corporation

Todd Foley, M.B.A.
Managing Director
MPM Capital

Manuel Litchman, M.D.
Vice President and Global Program Head, CTL019
Oncology Global Development
Novartis Pharmaceuticals Corp.

SESSION 3: PATIENT ADVOCACY EFFORTS AND PERSPECTIVES

11:15 a.m. **Panel Discussion**

Session Objectives: Discuss the patient, consumer, and public perspective on oversight of clinical gene transfer protocols and how patients who may benefit from future gene therapies view the relevant regulatory landscape.

Moderator: Sharon Terry
Committee Member

Panelists: Nicholas Dainiak, M.D., FACP
Clinical Professor of Medicine
Chairman of Medicine
Yale University School of Medicine

Jennifer Farmer, M.S., CGC
Executive Director
Friedreich's Ataxia Research Alliance

Margie Frazier, Ph.D., LISW-S
Executive Director
Batten Disease Support and Research Association

12:30 p.m. **Lunch**

SESSION 4: OVERSIGHT OF CONTROVERSIAL SCIENCE

1:45 p.m. **Panel Discussion**

Session Objectives: Explore the policy implications of emerging sciences and the underlying reasons for establishing layers of oversight. Understand overlapping ethical, legal, and social issues that warrant elevated scrutiny of gene transfer research and other areas of scientific research. Discuss assessments of oversight in gene transfer research and other areas.

Moderator: Jeffrey Kahn, Ph.D., M.P.H.
Committee Member

Panelists: Alexander Capron, L.L.B.
Professor of Law and Medicine
University of Southern California

Ellen Wright Clayton, M.D., J.D.
Professor of Pediatrics
Professor of Law
Vanderbilt University

Hank Greely, J.D.
Professor of Law
Stanford University

Peter Palese, Ph.D.
Professor and Chair of the Department of Microbiology
Mount Sinai Icahn School of Medicine

Steven Rosenberg, M.D., Ph.D.
Chief of Surgery
National Cancer Institute
National Institutes of Health

3:00 p.m. **Public Comment Period**
Harry Malech, M.D.
President-Elect, American Society of Gene and Cell Therapy

3:15 p.m. **Concluding Remarks**
Larry Gostin, J.D., *Committee Chair*

B

Historical and Policy Timelines for Recombinant DNA Technology

TABLE B-1 Timeline of Key Developments in rDNA Technology During the Late 1960s and Early 1970s

1969–1970	Paul Berg and Peter Lobban independently conceive an approach to create rDNAs in vitro and use them to manipulate genes across species.
1971	Douglas Berg and colleagues isolate the first plasmid bacterial cloning vector, *λdvgal* 120.
1971	Robert Pollack raises first concerns about potential biohazards of cloning.
1971–1972	David Jackson and colleagues, Peter Lobban, and A. D. Kaiser develop the method for joining DNAs in vitro.
1972	Jackson and colleagues create the first chimeric DNA in vitro.
1972	Janet Mertz and Ronald Davis discover a new approach to create SV40-*λdvgal* 120 chimeric DNAs in vitro.
1972–1973	Stanley Cohen and colleagues isolate a new cloning vector, pSC101, and create bacterial intra- and interspecies rDNAs.
1973	John Morrow and colleagues clone and propagate ribosomal DNA genes from a eukaryote in *E. coli*.

TABLE B-2 Timeline of Notable Events in the Oversight of rDNA Research

1972	Scientists publish details of first intentional creation of rDNA molecules (Berg and Mertz, 2010). Some leading researchers delay further investigation pending better understanding of potential biohazards, including cancer-causing potential of laboratory-altered viruses (Swazey et al., 1978).
1972–1973	Several conferences feature discussions of rDNA technology and possible safety risks and containment options related to rDNA procedures (Fredrickson, 2001).
1973	Participants at the first Asilomar conference consider laboratory safety and containment issues and discuss evidence on the risk of cancer from genetically modified viruses.
1973	Concerned researchers draft a letter requesting that the NAS establish a committee to examine the risks and benefits of rDNA research and propose guidelines for such research.
1974	July: The chair of the seven-member NAS committee presents the committee's recommendations, including for the deferral of certain risky types of rDNA research; the establishment by NIH of an advisory committee to assess the risks of the research, develop procedures to limit such risks, and develop guidelines for research; and the convening of a conference to further discuss ways to deal with hazards of rDNA research (Berg et al., 1974).
1974	October: The NIH creates the Recombinant DNA Molecule Program Advisory Committee (later called the Recombinant DNA Advisory Committee, or the RAC).
1975	Participants at a second Asilomar conference discuss whether research moratorium should continue. The summary statement proposes that research proceed with safeguards tailored to the risks of specific investigations and that education and training in containment methods be developed (Berg et al., 1975).
1976	Following a public meeting in February, in June NIH issues guidelines for rDNA research and defines responsibilities of investigators, research institutions, and government (Recombinant DNA research guidelines, 1976).
1980	The first gene transfer experiments with humans are conducted by a U.S. investigator in Italy and Israel. The investigator is later censured for misleading regulators and barred from NIH funding (Rainsbury, 2000).

1982	The President's Commission for the Study of Ethical Problems in Medicine and Biomedical Research and Behavioral Research releases a report, *Splicing Life*, which proposed changes in the oversight of rDNA research (President's Commission, 1982).
1984	The RAC establishes a working group on human gene therapy to review and respond to the report of the President's Commission and establish procedures for reviewing and approving gene transfer research.
1984	FDA determines that it will regulate gene therapy products (Rainsbury, 2000).
1985	A working group on human gene therapy presents its first version of Points to Consider in its report, "Design and Submission of Human Somatic-Cell Gene Therapy Protocols" (Points to consider, 1985).
1988	The RAC approves its first clinical research protocol, one for a gene marker study, amidst controversy over the investigators' reluctance to provide requested information on safety (Rainsbury, 2000).
1990	Researchers undertake the first approved gene transfer study on a child with SCID disorder (Coutts, 2011).
1991	FDA issues a guidance document, Points to Consider in Human Somatic Cell Therapy and Gene Therapy, updated again in 1998 (FDA, 1991, 1998).
1992	NIH director approves a "compassionate use" exemption to allow gene transfer procedures to be used in individual patients without regular protocol review.
1993	Responding to industry concerns and questions, FDA publishes a description of its regulatory authority and approach to regulating gene therapy products.
1995	NIH and FDA outline an agreement for FDA to assume review of gene therapy research protocols, with the RAC and FDA jointly determining which protocols warrant public review by the RAC (Advisory Committee to the Director, 2000).
1996	NIH Director proposes ending the RAC (Notice of intent, 1996).

1997	NIH guidelines confirm the shift of the RAC to an advisory role; FDA assumes sole authority to approve gene transfer protocols as well as gene therapy products (Advisory Committee to the Director, 2000; U.S. Congress, 2000).
1997	The RAC minutes start to include summary tables of adverse event reports received.
1999	Jesse Gelsinger dies while participating in a gene transfer trial; subsequent investigations identify several shortcomings in research oversight.
2000	FDA announces a new gene therapy clinical trials monitoring plan to strengthen protections for trial participants.
2000	NIH amends guidelines to place the RAC advisory review of protocols before IBC and IRB review (Recombinant DNA research: Action under the guidelines, 2000).
2002	FDA elevates the administrative unit that evaluates cellular, tissue, and gene therapy products from division to office.
2003	FDA imposes a temporary moratorium on gene transfer trials using retroviral vectors in blood stem cells, and eases the restrictions later the same year.
2004	NIH launches GeMCRIS, an interactive Web-based database allowing public access to information about gene transfer trials (NIH, 2004).
2013	NIH proposes to revise the rDNA guidelines to remove the requirement for IBC review of certain low-risk gene transfer clinical trials that follow a dose safety trial previously approved by an IBC (Recombinant DNA research: Proposed actions under the NIH Guidelines for research involving recombinant or synthetic nucleic acid [NIH Guidelines], 2013).

SOURCE: Adapted from Berg and Mertz, 2010.

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C

Committee Biographies

Lawrence O. Gostin, J.D. (*Chair*), is University Professor, Georgetown University's highest academic rank, conferred by the university's president. Dr. Gostin directs the O'Neill Institute for National and Global Health Law and was the founding O'Neill Chair in Global Health Law. He served as associate dean for research at Georgetown Law from 2004 to 2008. He is a professor of medicine at Georgetown University, a professor of public health at the Johns Hopkins University, and director of the Center for Law and the Public's Health at Johns Hopkins and Georgetown universities. Dr. Gostin holds a number of international academic professorial appointments. He is a visiting professor (faculty of medical sciences) and research fellow (Centre for Socio-Legal Studies) at the University of Oxford, United Kingdom. Dr. Gostin is the Claude Leon Foundation Distinguished Scholar and visiting professor at the University of Witwatersrand, Johannesburg, South Africa. He serves as secretary and a member of the governing board of directors of the Consortium of Universities for Global Health. Dr. Gostin is the director of the World Health Organization (WHO) Collaborating Center on Public Health Law and Human Rights. He also serves on the WHO director-general's Advisory Committee on Reforming the World Health Organization. In 2007, the WHO director-general appointed Dr. Gostin to the International Health Regulations Roster of Experts and the Expert Advisory Panel on Mental Health. Dr. Gostin holds numerous editorial appointments in prestigious academic journals throughout the world. His principal position is as health law and ethics editor, contributing writer, and columnist for the *Journal of the American Medical Association*. He is also founding editor-in-chief of *Laws*, an international open-access law journal. He was formerly the editor-in-chief of the *Journal of Law,*

Medicine & Ethics. He is an elected member of the Institute of Medicine (IOM) and serves on the IOM's Board on Health Sciences Policy, the Human Subjects Review Board, and the Committee on Science, Technology, and Law. He recently chaired the IOM Committee on Global Solutions to the Challenge of Counterfeit Medicines. He has also chaired National Academies committees on national preparedness for mass disasters, health informational privacy, public health genomics, and human subject research on prisoners. In 2006, the IOM awarded Dr. Gostin the Adam Yarmolinsky Medal for distinguished service to further its mission of science and health. He received the Public Health Law Association's Distinguished Lifetime Achievement Award "in recognition of a career devoted to using law to improve the public's health," presented at the Centers for Disease Control and Prevention.

Kenneth I. Berns, M.D., Ph.D., is director of the University of Florida (UF) Genetics Institute and distinguished professor, department of molecular genetics and microbiology, College of Medicine, University of Florida. He has served as a member of the composite committee of the U.S. Medical Licensing Examination, chairman of the Association of American Medical Colleges, president of the Association of Medical School Microbiology and Immunology Chairs, president of the American Society for Virology, president of the American Society for Microbiology, and vice president of the International Union of Microbiological Societies. He is a member of the National Academy of Sciences and the Institute of Medicine. Dr. Berns' research examines the molecular basis of replication of the human parvovirus and adeno-associated viruses and the ability of an adeno-associated virus to establish latent infections and be reactivated. His work has helped provide the basis for use of this virus as a vector for gene therapy. Dr. Berns' M.D. and Ph.D. in biochemistry are from the Johns Hopkins University.

R. Alta Charo, J.D., is the Warren P. Knowles Professor of Law and Bioethics at the University of Wisconsin–Madison (UW), where she is on the faculty of the law school and the department of medical history and bioethics of the medical school. Dr. Charo is an elected member of the World Technology Network (2004) and the Wisconsin Academy of Sciences, Arts and Letters (2005). In 2006, she was elected to membership in the Institute of Medicine (IOM). Dr. Charo served on President Obama's transition team, focusing her attention particularly on transition issues related to the National Institutes of Health (NIH), the U.S. Food

and Drug Administration (FDA), bioethics, stem cell policy, and women's reproductive health. She was on leave from 2009 to 2011 to serve as a senior policy advisor on emerging technology issues in the Office of the Commissioner at FDA. Dr. Charo offers courses on public health law, bioethics, biotechnology law, food and drug law, reproductive rights, torts, and legislative drafting. In addition, she has served on the UW Hospital clinical ethics committee, the UW institutional review board, and the UW bioethics advisory committee. Her federal advisory committee service includes the 1994 NIH Human Embryo Research Panel and President Clinton's National Bioethics Advisory Commission (1996 to 2001). From 2001 to 2008, she was a member of the National Academies' Board on Life Sciences, and from 2006 to 2012, she was a member of the IOM Board on Population Health and Public Health Practice.

Howard J. Federoff, M.D., Ph.D., is executive vice president for health sciences at Georgetown University and executive dean of the School of Medicine. Dr. Federoff is responsible for Georgetown University Medical Center. He is a professor of neurology and neuroscience. Prior to his time at Georgetown, he held appointments as senior associate dean for basic research; professor of neurology, medicine, microbiology, and immunology; and professor of oncology and genetics at the University of Rochester School of Medicine and as founding director of the Center for Aging and Development Biology at the Aab Institute of Biomedical Sciences and founding division chief of molecular medicine and gene therapy. After joining the Rochester faculty in 1995, he also served as director of the university's Interdepartmental Neuroscience Program. Dr. Federoff's research interests include gene therapy and neurodegenerative diseases such as Parkinson's and Alzheimer's. His research has received support from the National Science Foundation, the National Institutes of Health, and the Department of Defense. He has published widely in peer-reviewed journals and served as a reviewer for many journals, and currently serves on the editorial boards of the *Journal of Parkinson's Disease*, *Open Genomics Journal*, and the *Journal of Experimental Neurology*. He is a fellow of the American Association for the Advancement of Science and National Academy of Inventors. Before joining the Rochester community, he was associate professor of medicine and neuroscience at Albert Einstein College of Medicine, from which he received M.S., Ph.D., and M.D. degrees. He completed his internship, residency, and clinical and research fellowships at Massachusetts Gen-

eral Hospital/Harvard Medical School and practiced medicine at the Albert Einstein College of Medicine and University of Rochester.

Jeffrey P. Kahn, Ph.D., M.P.H., is the inaugural Robert Henry Levi and Ryda Hecht Levi Professor of Bioethics and Public Policy at the Johns Hopkins University Berman Institute of Bioethics. Prior to joining the faculty at Johns Hopkins in 2011, Dr. Kahn was director of the Center for Bioethics and the Maas Family Endowed Chair in Bioethics at the University of Minnesota, positions he held from 1996 to 2011. Earlier in his career, Dr. Kahn was director of the graduate program in bioethics and assistant professor of bioethics at the Medical College of Wisconsin and associate director of the White House Advisory Committee on Human Radiation Experiments. Dr. Kahn works in a variety of areas of bioethics, exploring the intersection of ethics and public health policy, including research ethics, ethics and genetics, and ethical issues in public health. He has served on many advisory panels, including for the National Institutes of Health, the Centers for Disease Control and Prevention, the Institute of Medicine, and others, and speaks nationally and internationally on a range of bioethics topics. He has published 3 books and more than 125 articles in the bioethics and medical literature. From 1998 to 2002, he wrote the biweekly column *Ethics Matters* for CNN.com. Dr. Kahn earned his B.A. in microbiology from the University of California, Los Angeles, his M.P.H. from Johns Hopkins University, and his Ph.D. in philosophy/bioethics from Georgetown University.

Terry Magnuson, Ph.D., is vice dean for research of the School of Medicine, S.G. Kenan Professor and chair of the department of genetics, and director of the Cancer Genetics Program of the Lineberger Comprehensive Cancer Center at the University of North Carolina (UNC) at Chapel Hill. Dr. Magnuson was recruited to UNC in 2000 as founding chair of the department of genetics and director of the newly established Carolina Center for Genome Sciences. He also created the Cancer Genetics Program in the UNC Lineberger Comprehensive Cancer Center. He was appointed vice dean for research in the School of Medicine in July 2010. The work in Dr. Magnuson's laboratory focuses on the role of mammalian genes in unique epigenetic phenomena such as genomic imprinting, X-chromosome inactivation, and stem cell pluripotency. The laboratory also studies the tumor suppressor role of the BAF/PBAF chromatin remodeling complexes and has developed a novel genome-wide mutagene-

sis strategy. Dr. Magnuson received his Ph.D. from Cornell University and was a postdoctoral fellow at the University of California, San Francisco.

Joseph G. Perpich, M.D., J.D., is principal and senior medical adviser at JBS International, Inc., a behavioral health consulting firm in North Bethesda, Maryland. He joined JBS in 2012 and is responsible for overseeing the ongoing development and management of behavioral health research networks developed at JGPerpich, LLC. As president of JGPerpich, LLC (2001–2012), he led the development of digital interactive collaborative research and training programs by facilitating network building, establishing work groups, providing training and mentoring programs, producing 508-compatible webinar series, promoting capacity-building activities in developing countries, and organizing scientific conferences and workshops. The virtual collaborations that Dr. Perpich supports for the National Institutes of Health (NIH) focus on international drug abuse, suicide prevention, and behavioral health services; they reach more than 2,000 scientists. During the past 35 years, Dr. Perpich has held key leadership positions in biomedical research and education, including as associate director for program planning and evaluation at NIH, where he directed government-wide activities related to rDNA research and regulatory policies (1976 to 1981). Before founding JGPerpich, LLC, in 2002, Dr. Perpich was vice president for grants and special programs at the Howard Hughes Medical Institute, where he created and managed the grants program for science education and international biomedical research.

Sharon F. Terry, M.A., is president and CEO of Genetic Alliance, a network of more than 10,000 organizations, of which 1,200 are disease advocacy organizations. Genetic Alliance enables individuals, families, and communities to reclaim their health and become full participants in translational research and services. She is the founding CEO of PXE International, a research advocacy organization for the genetic condition pseudoxanthoma elasticum (PXE). As co-discoverer of the gene associated with PXE, she holds the patent for ABCC6 to act as its steward and has assigned her rights to the foundation. She developed a diagnostic test and conducts clinical trials. Ms. Terry is also a co-founder of the Genetic Alliance Registry and Biobank. She is the author of more than 100 peer-reviewed articles. In her focus at the forefront of consumer participation in genetics research, services, and policy, she serves in a leadership role on many of the major international and national organizations, including the Institute of Medicine (IOM) Health Sciences Policy Board, the IOM

Roundtable on Translating Genomic-Based Research for Health, the National Coalition for Health Professional Education in Genetics Board, the International Rare Disease Research Consortium Executive Committee, Map My Genome (India), and the EspeRare Foundation (as president). She is on the editorial boards of several journals. She was instrumental in the passage of the Genetic Information Nondiscrimination Act. She received an honorary doctorate from Iona College for her work in community engagement in 2005; the first Patient Service Award from the University of North Carolina Institute for Pharmacogenomics and Individualized Therapy in 2007; the Research!America Distinguished Organization Advocacy Award in 2009; and the Clinical Research Forum and Foundation's Annual Award for Leadership in Public Advocacy in 2011. In 2012, she became an honorary professor of Hebei United University in Tangshan, China, and also received the Facing Our Risk of Cancer Empowered (FORCE) Spirit of Empowerment Advocacy Award. She was named one of the Food and Drug Administration's "30 Heroes for the Thirtieth Anniversary of the Orphan Drug Act" in 2013. She is an Ashoka Fellow.

Inder M. Verma, Ph.D., is a professor in the Laboratory of Genetics and American Cancer Society Professor of Molecular Biology at the Salk Institute and is one of the world's leading authorities on the development of viruses for gene therapy vectors. Dr. Verma uses genetically engineered viruses to insert new genes into cells that can then be returned to the body, where they produce the essential protein whose absence causes disease. Dr. Verma and Salk colleagues developed a gene therapy vector based on a stripped-down version of HIV that can deliver genes to nondividing cells, which constitute the majority of the cells in our bodies. They have used this vector successfully to deliver the clotting factor gene to laboratory animals and to transfer a therapeutic gene to retinal cells to mice with an inborn deficiency. Dr. Verma's group is also studying two genes implicated in familial breast cancer, BRCA1 and BRCA2, and recently demonstrated that their action is linked to the cell's division cycle and that BRCA1 regulates gene activity.

John E. Wagner, M.D., is a professor of pediatrics at the University of Minnesota Medical School. He is the first recipient of the Children's Cancer Research Fund/Hageboeck Family Chair in Pediatric Oncology and holds the University of Minnesota McKnight Presidential Chair in Cancer Research. He is the director of the division of pediatric blood and

marrow transplantation, scientific director of clinical research of the UMN Stem Cell Institute and co-director of the Center for Translational Medicine. Dr. Wagner is a member of numerous societies, including the American Society of Hematology, the International Society of Experimental Hematology, and the American Society of Blood and Marrow Transplantation. He is a member of several honorary societies, including Alpha Omega Alpha (1980), the American Society of Clinical Investigation (2000), and the Association of American Physicians (2006). Dr. Wagner holds a patent on the isolation of the pluripotential quiescent stem cell population. Dr. Wagner holds a B.A. in biological sciences and a B.A. in psychology from the University of Delaware and an M.D. from Jefferson Medical College. Dr. Wagner's research has focused on the development of novel cellular therapies for tissue repair and suppression of the immune response using subpopulations of neonatal umbilical cord blood and adult bone marrow and peripheral blood. His projects are funded by the National Institutes of Health and industry, and he is the principal investigator of a National Cancer Institute program project grant entitled "Stem Cell Biology and Transplantation." Dr. Wagner was the recipient of the 2009 Simon Gratz Research Prize from the Jefferson Medical College, which is awarded to an alumnus who has furthered the advancement of medical/surgical treatments. Dr. Wagner has written more than 275 articles and book chapters in the field of hematopoietic stem cell transplantation. He previously served as a member of the scientific board of directors of the National Marrow Donor Program, the Institute of Medicine's Committee on Establishing a National Cord Blood Stem Cell Banking Program, and the National Academies' Human Embryonic Stem Cell Research Advisory Committee. He is currently a member of the Scientific and Medical Accountability Standards Working Group of the California Institute of Regenerative Medicine.

Lt. Col. Daniel J. Wattendorf, M.D., joined the Defense Advanced Research Projects Agency as a program manager in the defense sciences office in 2010. His interests focus on applying methodological advances in genomics and biotechnology to optimize health and prevent disease—specifically to achieve simple solutions that improve health care at the point of care. He holds a B.S. in microbiology from Cornell University and an M.D. with distinction from George Washington University. He completed a residency in family medicine at the National Capital Consortium; a residency in clinical genetics at the National Institutes of Health's (NIH's) National Human Genome Research Institute (NHGRI);

a fellowship in clinical cytogenetics at Georgetown University; and a fellowship in health policy from the NHGRI Office of the Director. Dr. Wattendorf previously served as director, Air Force Medical Genetics Center, and program manager for an advanced-concept technology demonstration integrating advanced diagnostics and informatics with surveillance systems to rapidly detect natural and hostile pathogens in the Office of the Air Force Surgeon General. In addition to Defense Advanced Research Projects Agency programs, he is a geneticist at the National Naval Medical Center and the Cancer Genetics Branch, National Cancer Institute, NIH.