Enhancing the Protection of Human Subjects in Gene Transfer Research at the National Institutes of Health

Advisory Committee to the Director Working Group on NIH Oversight of Clinical Gene Transfer Research

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EXECUTIVE SUMMARY

Gene therapy is a set of approaches to the treatment of human disease based on the transfer of genetic material (DNA) into a human subject. As a sophisticated extension of conventional medical therapy, the goal of gene therapy is to treat disease in an individual patient by the administration of DNA rather than a drug. In September 1999, Jesse Gelsinger, an 18-year-old patient enrolled in an adenoviral vector gene transfer clinical protocol, died. His death was seemingly a direct result of administration of a gene transfer product, not the result of his underlying medical condition. The death of this young man prompted concern about the processes by which gene transfer trials are reviewed, conducted, and monitored by the National Institutes of Health (NIH) and the Food and Drug Administration (FDA).

In response to these events, then NIH Director Dr. Harold Varmus, established the Advisory Committee to the Director Working Group on NIH Oversight of Clinical Gene Transfer Research (the Working Group) to review the role of NIH in oversight of clinical gene transfer research. The Working Group, which includes scientists, clinicians, bioethicists, and representatives of the general public, met over a period of four months, from February to May 2000, and was asked to advise the NIH Director and to develop recommendations to address the following questions:

1) Is the current NIH framework for oversight and public discussion of clinical gene transfer research appropriate, especially with regard to the respective roles of the Recombinant DNA Advisory Committee (RAC) and the *NIH Guidelines for Research Involving Recombinant DNA Molecules*;

2) Are current NIH mechanisms adequate for coordination of the oversight of clinical gene transfer research with the FDA, the Office for Human Research Protections (OHRP, formerly the Office for Protection from Research Risks), Institutional Review Boards (IRBs), and Institutional Biosafety Committees (IBCs);

3) Are additional NIH measures needed to minimize risk associated with clinical gene transfer research; and

4) What should the NIH role be with regard to reporting, analysis and public discussion of serious adverse events?

The Working Group agreed that four primary goals should guide its discussion of options for NIH in oversight of gene transfer research.

- Research in the field of human gene transfer should meet the highest ethical and scientific standards.
- Human subjects who participate in clinical gene transfer should receive maximum possible protection by investigators, institutions, and oversight agencies.
- Human subjects in gene transfer trials should provide full informed consent, and should be provided synoptic, up-to-date information regarding the potential benefits and risks of any gene transfer procedures or possible therapies.
- All risks, adverse events, and outcomes in clinical gene transfer trials should be monitored, interpreted, and communicated in a timely fashion to current and prospective subjects, the public, investigators, IRBs, and research sponsors.

These goals can best be met by infusing the review and oversight system with more requirements for accountability; simplifying, streamlining, and harmonizing

reports of adverse events to ensure they are timely and accurate; and assuring that an expert and responsible body receives all relevant information regarding adverse events, interprets the data, and makes public what it learns. For these goals to be met greater coordination must occur at the federal level and the scientific community must be held to higher levels of accountability.

The Working Group developed a unanimous recommendation to change the process of protocol review. Although there was no unanimous recommendation regarding the handling of serious adverse event reports, there was a consensus view. Finally, the Working Group made recommendations regarding professional and public education and clinical research practices in general.

PROTOCOL REVIEW

- Safety will be best protected if subjects are not enrolled in novel gene transfer trials until RAC discussion has occurred and the investigator has responded to the RAC recommendations.
- The timing of review of gene transfer protocols by RAC, the local IRB and IBC, and FDA should be altered to ensure that RAC can function as an effective advisory committee to investigators, institutional IRBs and IBCs, and FDA. Specifically,
    - The requirement that the investigator obtain IRB approval prior to submission to OBA/RAC should be eliminated. This change would allow investigators to receive RAC input at an earlier stage of protocol development.
    - IBC approval should be withheld until RAC review is complete. In the case of non-novel protocols, IBC approval can be granted as soon as the IBC is notified that the protocol has been deemed non-novel.
    - In the case of novel protocols, IBC approval must be withheld until after RAC discussion and the investigator has responded to the review, thereby, preventing the initiation of a trial prior to RAC review.
    - RAC should complete its review and revision of the definition of "novel" gene transfer protocols and the process/mechanism for determining whether or not a protocol is "novel." Public comment and input should be solicited.
    - To clarify the types of research that are subject to the NIH Guidelines, RAC should complete its review and revision of the definition of gene transfer research to ensure that all applicable and appropriate areas of research are subject to oversight and review.

SERIOUS ADVERSE EVENT REPORTING

- Public discussion of serious adverse events is an important component of the oversight process.
- NIH/OBA should continue to receive from investigators reports of serious adverse events. The Working Group acknowledged that FDA is working on a proposed rule to make public some information regarding serious adverse events in gene transfer, and encourages the agency to move expeditiously in meeting this goal.
- Serious adverse events should not be considered trade secrets or proprietary, and must be reported to RAC.
- Data in aggregate made available to the public should be analyzed and interpreted.
- All reasonable measures must be taken to protect the privacy of the individual(s) who suffered the adverse event, without compromising the health of others in similar trials.
- A majority of the Working Group recommended that NIH and FDA must work together to simplify, streamline, and harmonize reporting of serious adverse events. This includes clarification of the timing requirements for reporting specific types of serious adverse events.
- NIH should work with FDA to expand and enhance education and outreach programs to investigators and sponsors conducting gene transfer research to inform them of their reporting obligations.
- NIH should explore ways for promoting the communication of serious adverse events to the relevant IBCs and IRBs.
- A standing body should be established to conduct ongoing analyses of adverse event data. This body should include basic scientists, clinicians, patient advocates, and ethicists. Additional ad hoc members can be appointed for their expertise on an as needed basis. This group would:
    - review all reports of adverse events
    - analyze the data for trends
    - develop a cumulative report that would be presented annually at a public RAC meeting and made available to the public, and
    - identify trends or even single events that may warrant further public discussion or federal action.

PROFESSIONAL AND PUBLIC EDUCATION

- NIH/OBA should target education efforts at specialty clinical centers where gene transfer studies are likely to be conducted or subjects recruited, such as CF centers or hemophilia clinics. In addition, OBA/RAC should produce a pamphlet or brochure on gene transfer research targeted to families and consumers and post such information on its website.
- In collaboration with OHRP and other relevant groups, OBA should continue its initiatives for a series of workshops for IRBs and IBCs on gene transfer research.
- OBA should work with OHRP to encourage IRB cooperation in ensuring that human subjects are not enrolled in gene transfer trials until RAC deems a protocol non-novel, or if novel, the protocol has completed the RAC review process.
- NIH should work with OHRP to encourage the inclusion of additional resource sites for information regarding participation in clinical trials in the informed consent form. For gene transfer clinical trials, this information should include a reference to the RAC review process and directions regarding how to obtain relevant information from OBA/RAC.

IMPROVEMENTS IN CLINICAL RESEARCH PRACTICES

- NIH should evaluate a variety of mechanisms to increase financial resources for IRBs.
- NIH should increase support or develop innovative programs to improve the general institutional infrastructure (e.g., data collection and analysis, monitoring) for clinical research.
- Although NIH has developed guidance on conflict of interest, the issue deserves a more sustained analysis than can be conducted by this review group at this time. However, the Working Group believes that: 1) any guidance about conflict of interest must take into consideration the potential for conflict on the part of the investigator and the institution; 2) that disclosure of conflict of interest in the informed consent process is necessary but not sufficient; and 3) increased attention must be paid to how research institutions investigate and resolve conflicts.

The success of clinical research in any field of medicine relies on openness, trust, and accountability by investigators, sponsors, and institutions. Moreover, the integrity of clinical research is enhanced by a transparent oversight system. The public's confidence in gene transfer therapy, particularly in light of recent events, can only be restored by a fair and open system in which all parties are held accountable for their activities. The Working Group recognizes, however, that no set of rules and guidelines can ensure complete compliance or absolute safety. Innovative clinical research by nature includes a degree of risk, some of it unknown. Because risks are not fully known, and unanticipated harm might occur, monitoring and oversight must be diligent, timely, and accountable. Investigators in this arena must proceed with the highest level of integrity and accountability. In addition, those agencies and institutions entrusted with this responsibility must work together in a collaborative manner with open communication.

INTRODUCTION

Gene therapy is a set of approaches to the treatment of human disease that encompasses a variety of techniques. For instance, gene therapy may be used to: 1) alter or supplement the function of a mutated gene by providing a copy of a normal gene; 2) directly alter or repair the mutated gene; or 3) provide a gene that adds missing functions or regulates the expression of other genes. As an extension of conventional medical therapy, the goal of gene therapy is to treat disease in an individual patient by the administration of genetic material (DNA) rather than a drug. The success of this technology is dependent on not only the delivery of genetic material into the target cells, but also the expression of the gene once it reaches its target site. Both of these requirements pose considerable technical challenges. With regard to gene delivery to target cells, a variety of "vectors" have been developed to serve this purpose. Most of these vectors are disabled viruses that work by delivering genes into certain human cell types, in much the same way that ordinary viruses infect cells. Because only somatic cells, and not germ cells (eggs and sperm), are the target of these efforts, gene transfer is intended to affect only the individuals under treatment and not their offspring.

In altering the genetic material of somatic cells, gene therapy may correct the underlying specific disease pathophysiology and, in some instances, may offer the potential of a cure for devastating, inherited disorders. In principle, gene therapy should be applicable to many diseases for which current therapeutic approaches are ineffective. Recently, promising findings from gene transfer research have been described for the treatment of primary immunodeficiencies and hemophilia. Patients with one form of X-linked severe combined immune deficiency (SCID) appeared to have had their disorder corrected by the transplantation of their own bone marrow cells into which a normal copy of the disease-causing gene had been introduced by retroviral gene transfer. The patients have developed sustained immunological function similar to that seen in SCID patients transplanted with normal allogeneic bone marrow cells. Gene transfer also has shown promise in patients with hemophilia B, which is caused by the absence of functional coagulation factor IX. Recent studies have shown that intramuscular injection of a gene using an adeno-associated viral (AAV) vector into hemophilia B patients resulted in long-term expression of biologically active factor IX at near therapeutic levels.

Because genetic material is the putative therapeutic agent in gene transfer, some observers have viewed and continue to view gene transfer as qualitatively different from other forms of treatment, stating concerns about changing the genetic makeup of human beings. These concerns, in addition to the fact that the field of gene transfer is relatively new, have led to special scrutiny of gene transfer trials.

RECENT EVENTS

In September 1999, Jesse Gelsinger, an 18-year-old patient enrolled in an adenoviral vector gene transfer clinical protocol, died-not as a result of his underlying condition, but seemingly as a direct result of administration of a gene transfer product. In the 10-year history of clinical gene transfer, this is presumed to be the first death directly related to the gene transfer itself. The death of this young man prompted concern about the processes by which gene transfer trials are reviewed, conducted, and monitored by the Food and Drug Administration (FDA) and the National Institutes of Health (NIH), through its Office of Biotechnology Activities (OBA) and its advisory body, the Recombinant DNA Advisory Committee (RAC).

In response to these concerns, then NIH Director Dr. Harold Varmus established the Advisory Committee to the Director Working Group on NIH Oversight of Clinical Gene Transfer Research (the Working Group) to review the role of NIH in oversight of this area of research. The Working Group was encouraged to consult with other experts and solicit public comment in the course of its work. The Working Group, which included scientists, clinicians, bioethicists, and representatives of the general public, met four times in person and via teleconference over a period of four months, from February to May 2000. In its meetings it heard testimony from representatives of OBA, FDA, the NIH Office of Extramural Research, the NIH Office for Protection from Research Risks (OPRR, now the Office for Human Research Protection, or OHRP), and former members of RAC, and reviewed congressional testimony. In addition, it met with RAC in an open forum on March 9, 2000 to discuss RAC's role in the review of gene transfer research. (See Appendix A for meeting dates and a list of invited speakers.)

CHARGE TO THE WORKING GROUP

The Working Group was asked to advise the NIH Director on how NIH should proceed in oversight of gene transfer research and to develop recommendations to address the following specific questions:

1) Is the current NIH framework for oversight and public discussion of clinical gene transfer research appropriate, especially with regard to the respective roles of RAC and the *NIH Guidelines for Research Involving Recombinant DNA Molecules*?

2) Are current NIH mechanisms adequate for coordination of the oversight of clinical gene transfer research with the FDA, OHRP, Institutional Review Boards (IRBs), and Institutional Biosafety Committees (IBCs)?

3) Are additional NIH measures needed to minimize risk associated with clinical gene transfer research? and

4) What should the NIH role be with regard to reporting, analysis, and public discussion of serious adverse events?

The Working Group specifically was asked to consider whether RAC should return to review and approval of novel gene transfer protocols.

FINDINGS AND RECOMMENDATIONS

The Working Group studied the current status of NIH oversight of gene transfer research and reviewed its evolution over the past decade. Discussions focused on two general topics; protocol review and reporting of serious adverse events. The Working Group was able to reach a unanimous recommendation on protocol review and a consensus view regarding the handling of serious adverse event reports.

The Working Group agreed on four primary goals to guide its discussion of options for NIH oversight of gene transfer research.

1. Research in the field of human gene transfer should meet the highest ethical and scientific standards.

2. Human subjects who participate in clinical gene transfer should receive maximum possible protection by investigators, institutions, and oversight agencies.

3. Human subjects in gene transfer trials should provide full informed consent, and should be provided synoptic, up-to-date information regarding the potential benefits and risks of any gene transfer procedures or possible therapies.

4. All risks, adverse events, and outcomes in clinical gene transfer trials should be monitored, interpreted, and communicated in a timely fashion to current and prospective subjects, the public, investigators, IRBs, and research sponsors.

The Working Group concluded that these goals can best be met by infusing the review and oversight system with more requirements for accountability; simplifying, streamlining, and harmonizing the requirements to report serious adverse events to NIH and FDA to ensure that reports are timely and accurate; and assuring that by using an expert body, NIH receives all relevant information regarding adverse events, interprets the data, and makes public what it learns. For these goals to be met, greater coordination must occur at the federal level and the scientific community must be held to higher levels of accountability. These guiding principles are the underpinnings of the conclusions and recommendations presented in this report.

Protocol Review

Immediately prior to October 1997, RAC had approval authority over novel gene transfer protocols. In its deliberations, the Working Group considered the pros and cons of returning to approval of novel protocols. The Working Group, in general, thought it likely that the loss of approval authority had several adverse impacts on the oversight of gene transfer clinical trials. These negative effects included: 1) the loss of the ability of RAC, through the approval process, to make informative and effective policy statements about the types of trials that were considered acceptable on scientific and ethical grounds; and 2) the sense expressed by many that the loss of authority made service on RAC less desirable and sent a message to the gene transfer community that the committee's recommendations were not important.

On the other hand, the Working Group recognized that the approval of protocols by RAC could be perceived as being at odds or confused with the scientific peer review process required of all research protocols (whether gene transfer or not) eligible for NIH funding. In this regard, peer review of protocols for scientific merit, combined with FDA authorization of INDs (Investigational New Drug applications), and IRB and IBC review for safety was believed by many to be sufficient. RAC review of novel protocols was considered duplicative.

Moreover, in discussion with the Working Group, when RAC members were pressed on the issue of whether they desired reinstitution of the authority to approve novel protocols, it became clear that the key issue was assurance that subjects not be enrolled in novel protocols until RAC review had occurred.

The Working Group agreed with RAC's view and recommended that the process of protocol review be changed so that no subject can be entered into a gene transfer clinical trial until RAC review is complete. The current process of protocol review (described briefly below and in more detail in Appendix B) allows investigators to enroll subjects into protocols prior to RAC discussion. Under such circumstances, RAC discussions may be viewed as after-the-fact or unimportant. In these cases, if RAC expresses concerns about the safety or design of the protocol, there is no systematic and established mechanism that ensures RAC can communicate those concerns to the investigator or sponsor prior to enrollment of subjects.

In order to understand how to achieve the goal of RAC review prior to subject enrollment, it is first necessary to understand some of the basics of the current oversight system. (For a more detailed description, see Appendix B.) Gene transfer clinical trials are unique in that they undergo review by both NIH/OBA and FDA. NIH's oversight process is conducted by RAC and through the *NIH Guidelines for Research Involving Recombinant DNA Molecules (the NIH Guidelines)*. FDA regulations apply to all clinical gene transfer research; whereas, NIH/OBA governs gene transfer research that is supported with NIH funds or conducted at or sponsored by institutions that receive NIH funding for recombinant DNA research. Currently, the majority of gene transfer research is subject to the *NIH Guidelines*.

An investigator is permitted to enroll subjects in a clinical gene transfer protocol as soon as three elements are completed: 1) FDA authorizes an IND application; and approval to proceed has been granted by 2) an IRB and 3) an IBC. IRBs are governed by the Federal Policy for the Protection of Human Subjects (45 CFR 46), and parallel FDA regulations for the protection of human subjects in research (21 CFR, Parts 50 and 56). The IBC is governed by the *NIH Guidelines* and is responsible for, and authorized by, the research institution to review and approve potentially biohazardous lines of research. It is charged with conducting an independent assessment of the containment levels required by the *NIH Guidelines* for the proposed research; assessing the facilities, procedures, practices, and training and expertise of personnel involved in recombinant DNA research; and ensuring compliance with all surveillance, data reporting, and adverse event reporting requirements required by the *NIH Guidelines*.

Currently, investigators governed by the *NIH Guidelines*
must first obtain IRB and IBC approvals and then submit their proposal to OBA/RAC. Protocols that present novel scientific, ethical or safety issues are selected for public review — at present, approximately 10 percent are selected. But, because an investigator is allowed to enroll subjects as soon as an IND authorization and IRB and IBC approvals have been obtained, neither protocol submission to OBA/RAC nor RAC discussion are necessary prior to subject enrollment.

The Working Group concluded that, in order to implement the recommendation that no patient be enrolled in a clinical trial until RAC review is complete, the NIH Guidelines should be changed to mandate that the IBC cannot approve a protocol until RAC review is completed.

- Safety will be best protected if subjects are not enrolled in novel gene transfer trials until RAC discussion has occurred and the investigator has responded to the RAC recommendations.

- The timing of review of gene transfer protocols by RAC, the local IRB and IBC, and FDA should be altered to ensure that RAC functions as an effective advisory committee to investigators, institutional IRBs and IBCs, and FDA. Specifically,

    - The requirement that the investigator obtain IRB approval prior to submission to the Office of Biotechnology Activities (OBA)/RAC should be eliminated. This change would allow investigators to receive RAC input at an earlier stage of protocol development.

- IBC approval should be withheld until RAC review is complete. In the case of non-novel protocols, IBC approval can be granted as soon as the IBC is notified that the protocol has been deemed non-novel.

- In the case of novel protocols, IBC approval must be withheld until after RAC discussion has occurred and the investigator has responded to the review, thereby preventing the initiation of a trial prior to RAC review.

In addition, the Working Group recommended a detailed process for the review of protocols. This process is described in Appendix C and is visually summarized in an accompanying diagram.

The Working Group believes that this modified process of protocol review serves many purposes. First, it ensures that no human subject will be enrolled in a gene transfer trial until protocol submission to OBA/RAC and, in the case of a novel protocol, until after public discussion. Second, by allowing submission to NIH prior to IRB and IBC review, novel trials need not be unduly delayed by public RAC review. Third, it allows local IRBs and IBCs to benefit from RAC recommendations. Fourth, it retains the important function of RAC to publicly discuss the scientific, clinical, and ethical aspects of novel protocols. Fifth, it provides potential or current research subjects with information on which to base an informed consent decision in an environment where there might be little information available other than that provided by the investigator or sponsor. Finally, it bolsters the impact of RAC review and public discussion by holding investigators and review agencies accountable for their actions, particularly if they are not in accord with the consensus view and recommendations of RAC.

Reporting and Responding to Serious Adverse Events

The *NIH Guidelines*
clearly direct principal investigators to: "report any serious adverse event immediately to the local IRB, IBC, OPRR (if applicable), NIH/ORDA (now OBA), and FDA." The events that unfolded after the death of Jesse Gelsinger highlight the importance of these notification requirements.

Sharing of such serious adverse event data among government and institutional officials is critical to ensuring public safety and advancing gene transfer research. Because this field is still in its early stages, it is important to have a reporting system that provides responsible parties with the information necessary to respond quickly to safety concerns and to develop a body of knowledge about the risks and benefits inherent to this unique form of experimental therapy.

Currently, most gene transfer clinical studies include only small numbers of subjects and target severe diseases or conditions in which there is a high incidence of naturally occurring serious adverse events, including deaths. Thus, it is often difficult to establish a direct correlation between the event and the administration of gene transfer. In the event of a death or a serious and life-threatening event, it is important to exercise caution and, when appropriate, stop similar trials until a correlation can be ruled out. In addition, a systematic and publicly accountable review of the safety and toxicity data from these trials over time is essential for identifying trends and recognizing patterns that may have important implications for the future development of gene transfer research.

In addition to a review of the response to the Gelsinger death and discussion with the RAC members themselves, the Working Group also reviewed the RAC proposal to amend the *NIH Guidelines* regarding serious adverse event reporting, which was published for public comment in the November 22, 1999 *Federal Register*. The proposed amendments would add three provisions to the NIH Guidelines. The first would define serious adverse events and stipulate the time frame in which they are to be reported in writing. The second provision would mandate that serious adverse event reports not contain any trade secret or confidential commercial information-this is because all information submitted in accordance with the *Guidelines* should be considered public. In order to ensure patient confidentiality, the third provision would help ensure that serious adverse event reports do not contain individually identifiable patient information.

The Working Group listened to the RAC Serious Adverse Event Reporting Working Group report at the March 9-10, 2000 RAC meeting. There were significant differences of opinion among RAC members about the timing of reporting and the types and scope of events that should be reported to NIH/OBA.

There is no question that better coordination among responsible agencies and review bodies is required if gene transfer trials are to continue in as safe a manner as possible. The Working Group commends recent efforts by NIH and FDA to coordinate oversight and improve communication. In November 1999, FDA informed the gene transfer research community of a new interagency notification process. According to the new process, FDA will notify NIH when it receives serious adverse event reports from sponsors. One of the main goals of this information exchange is to enhance compliance with the NIH Guidelines. However, the new policy is limited because, according to statute and regulation, any information FDA discloses to NIH/OBA about the nature of the adverse event must be considered confidential. Thus, if NIH/OBA wants to be able to publicly disseminate specific information regarding a serious adverse event, NIH/OBA must contact the investigator directly.

There are two specific needs that must be considered in developing an NIH system for adverse event reporting-review and response. A critical reason is the need to respond on a real-time basis to serious, life-threatening, unexpected events that are related to the investigational product-this response is currently the responsibility of FDA. (See Appendix B for details about the current reporting requirements.)

The second reason is to disseminate adverse event information to investigators and the public, a function that has been the responsibility of NIH/OBA, in part because by statute FDA cannot publicly disclose information that is submitted under statutory protections as proprietary. Of note, FDA is developing a rule that would allow public disclosure of selected information that it receives about gene transfer and xenotransplantation trials, but until that rule is finalized, FDA can only make information public if the permission of the sponsor is obtained, or if the FDA Commissioner determines that public health needs mandate disclosure. The Working Group assessed the current status of reporting and review in both FDA and NIH/OBA and noted that any recommendations should be reconsidered when, and if, FDA is able to make such public disclosures.

The issue of reporting of serious adverse events is complex. This complexity reflects the aforementioned differences in the mission, regulatory, and statutory authorities of FDA and NIH in the field of gene transfer research, and the scientific and medical uncertainties surrounding the significance and even the definition of such events.

The Working Group was unable to unanimously agree on key recommendations in this area. There were members of the group who believed strongly that NIH/OBA should not continue to receive serious adverse events reports, stating that this requirement duplicates FDA's responsibilities, creates confusion in the field, and does little to improve patient safety. It was suggested by some that FDA alone should receive these reports and notify NIH/OBA as needed. But, a majority of the Working Group did not agree to this because when NIH receives confidential information from FDA, FDA's rules for disclosure must be followed. Therefore, NIH/OBA would not be able to make such reports public without the express consent of the sponsor. At the other end of the spectrum, there were a few members who felt that NIH should continue to receive all adverse event reports immediately and make such data public in its redacted, "raw" form on a real-time basis (see Appendix D for Supplemental Comments and Recommendations).

The majority of the Working Group did agree, however, that because FDA is unable to disclose information about adverse events, NIH/OBA should continue to directly receive reports of serious adverse events. Also, a majority of the Working Group believed that the data discussed or presented publicly should not be "raw" or unprocessed; rather, the information should be analyzed and interpreted by a diverse panel of expert individuals who have the time to carefully examine and translate its implications. Although the goal may be to only disseminate "analyzed" data, it is important to understand that any information received by NIH/OBA is governed by the Freedom of Information Act (FOIA).This means that raw data received by NIH could be made public under FOIA requirements.

Obviously, this has implications for the protection of patient privacy.

- Public discussion of serious adverse events is an important component of the oversight process.
- NIH/OBA should continue to receive from investigators reports of serious adverse events. The Working Group acknowledged that FDA is working on a proposed rule to make public some information regarding serious adverse events in gene transfer, and encourages the agency to move expeditiously in meeting this goal.
- Serious adverse events should not be considered trade secrets or proprietary, and must be reported to RAC.
- Data in aggregate made available to the public should be analyzed and interpreted.
- All reasonable measures must be taken to protect the privacy of the individual(s) who suffered the adverse event, without compromising the health of others in similar trials.

Compliance with reporting requirements is essential and is likely to improve with harmonization between FDA and NIH. A majority of the Working Group believed that the development of a single set of requirements for reporting is the best course of action and that special attention should be paid to making NIH's and FDA's requirements consistent with regard to both the criteria for what must be reported and when it should be reported. This was not a unanimous opinion. Some members of the Working Group proposed that NIH continue to receive all serious adverse events reports immediately and not adhere to the FDA timing requirements. Other members of the Working Group suggested that NIH/OBA should create its own criteria for adverse events that should be reported immediately. There was some concern that while harmonization is an important goal, the FDA criteria for what must be immediately reported (only events that are serious, related and unexpected) is problematic when the field is still so new.

- A majority of the Working Group recommended that NIH and FDA must work together to simplify, streamline, and harmonize reporting of serious adverse events. This includes clarification of the timing requirements for reporting specific types of serious adverse events.
- NIH should work with FDA to expand and enhance education and outreach programs to investigators and sponsors conducting gene transfer research to inform them their reporting obligations.

In addition to improving coordination between FDA and NIH regarding serious adverse events, communication and coordination between the federal agencies and the local review boards must also be improved.

- NIH should explore ways for promoting the communication of serious adverse events to the relevant IBCs and IRBs.

In its role as the nation's prime biomedical enterprise, NIH through OBA/RAC can serve an important function by conducting ongoing analyses of the nature and frequency of adverse events reported over time. Beyond the requirement for immediate response to serious or life-threatening events, there is need to gather cumulative data on gene transfer trials to improve the conduct and overall safety of such research. Systematic analyses of adverse event data could reveal trends related to, for example, specific diseases, routes of administration, or vectors. These analyses would then be available to RAC, FDA, the scientific community, and the public.

The Working Group considered several options for conducting analyses of adverse event data with the goal of fulfilling a function currently missing from the oversight process. The purpose of conducting trend analysis in public is to provide up-to-date and useful information to investigators and the public. Several options for locating and conducting such analyses were considered. A variety of options were considered, including FDA, NIH/OBA/RAC, and the Department of Health and Human Services.

One proposed mechanism was to place the function within FDA and to detail NIH/OBA employees to FDA to participate in the review process. Because these employees would be bound by the same confidentiality agreements as are FDA employees, the NIH mandate for public disclosure would not be served by this option.

Another option discussed was creation of a national Data Safety and Monitoring Board (DSMB). In the current clinical trials system, DSMBs are traditionally charged with the oversight of single large Phase III clinical trials. The DSMB does not provide real-time oversight and review, rather, the DSMB generally meets several times a year while the study is being conducted. Consideration of DSMBs for the continuous analysis of adverse events in all phases of gene transfer clinical trial development raises several questions. NIH has established a working group to address these questions and assess the feasibility and utility of creating one or more national Data and Safety Monitoring Boards (DSMB) for gene transfer clinical research. This group will make recommendations to NIH in the near future.

Although unanimous agreement could not be achieved on this point, a majority of the Working Group believed that a working group of FDA and NIH (perhaps established through a Memorandum of Understanding and consisting of diverse membership with liaison members from FDA and RAC) is the most reasonable and efficient approach to analyzing trends and recognizing patterns on adverse event reports that might have important scientific or safety implications. It was recognized that the option to create a standing review group of RAC members would require a huge time commitment from RAC members. This would necessitate not only that RAC membership would have to be expanded well beyond its current size, but that the workload of RAC members would dramatically increase. Thus, in lieu of making this a subcommittee of RAC, there was strong support for making RAC responsible for oversight of this group, and having one or two RAC members serve on it, but selecting the majority of members from outside RAC. Thus, this body could be a working group of RAC.

- A standing body should be established to conduct ongoing analyses of adverse event data. This body should include basic scientists, clinicians, patient advocates, and ethicists. Additional ad hoc members can be appointed for their expertise on an as needed basis. This group would:
    - review all reports of adverse events
    - analyze the data for trends
    - develop a cumulative report that would be presented annually at a public RAC meeting and made available to the public, and
    - identify trends or even single events that may warrant further public discussion or federal action.

Once FDA and NIH have agreed on the requirements for reporting, investigators and/or sponsors would be required to file adverse event reports with both agencies. FDA would continue to take the lead in responding on a real-time basis to events that are serious and life threatening, as it did following the death of Jesse Gelsinger. FDA is the only agency with the statutory authority to determine if a gene transfer trial will be allowed to proceed or, if for safety reasons, should be put on clinical hold. The FDA system relies on real-time, medical and scientific analysis of the events being reported.

Simultaneously, NIH/OBA would take the necessary actions to inform principal investigators of the report(s). NIH's responsibility is to provide information about serious adverse events to investigators and the public in a timely manner. When an event requires immediate action, e.g., in the interest of safety, OBA has

the responsibility to immediately inform its community of investigators as well as the public. The Working Group believes that the functions of FDA and NIH are complementary. In the event that FDA's proposed rule to permit public disclosure becomes effective, the relative role of OBA in this process should be reconsidered.

As efforts toward harmonization progress, NIH and FDA should continue to evaluate the best mechanism to maintain and protect public confidence in gene transfer research and the promise it holds.

Additional Recommendations Regarding RAC Review

The Working Group notes that a RAC ad hoc committee as well as RAC has been reviewing the definition of what constitutes "novel," as well as the process by which a protocol is determined to be "novel." Clarification of this issue is critically important so that investigators/sponsors can anticipate whether a protocol is likely to undergo the proposed review process.

- RAC should complete its review and revision of the definition of "novel" gene transfer protocols and the process/mechanism for determining whether or not a protocol is "novel." Public comment and input should be solicited.

The Working Group notes that the field of gene transfer research is evolving rapidly and that it might be necessary to redefine the criteria on which protocols are categorized for registration with OBA or review by RAC.

- To clarify the types of research that are subject to the NIH Guidelines, RAC should complete its review and revision of the definition of gene transfer research to ensure that all applicable and appropriate areas of research are subject to oversight and review.

OBA should take advantage of the rich information it receives when gene transfer protocols are registered. These data can serve many purposes, including informing the science and notifying the public of trials proposed or underway. Moreover, there is a critical need for a centralized repository of information regarding gene transfer clinical trials. Public dissemination by OBA of pertinent information contained in the database must protect the confidentiality of participants where possible, as well as relevant proprietary information.

NIH, as the Nation's principal funder of biomedical research, has assumed primary responsibility for developing, maintaining, and making publicly available information about gene transfer trials. One mechanism is the interactive NIH/OBA database, which will be completed by the end of 2000.

Additional Measures to Minimize Risks Associated with Clinical Gene Transfer Research

In addition to evaluating the process by which gene transfer protocols are reviewed, the Working Group considered five areas in which NIH could make improvements to enhance the safety of clinical gene transfer research: 1) professional education and public outreach; 2) training for IRBs and IBCs; 3) resolution of conflict of interest issues; 4) ongoing monitoring of active protocols; and 5) support of the institutional infrastructure for clinical research.

In the areas of education and outreach, the Working Group commends efforts by OBA to increase communication and outreach to the NIH community, academia (through education sessions with professional scientific and medical organizations), industry, and patient communities. In addition, the planned development of a Web-accessible database to provide current information to the public and scientific communities is an important measure. However, additional measures can be taken to improve communication among the many groups participating in the review and conduct of clinical gene transfer research and to ensure that individuals who volunteer to participate in such studies have access to up-to-date and accurate information.

- NIH/OBA should target education efforts at specialty clinical centers where gene transfer studies are likely to be conducted or subjects recruited, such as CF centers or hemophilia clinics. In addition, OBA/RAC should produce a pamphlet or brochure on gene transfer research targeted to families and consumers and post such information on its website.

- In collaboration with OHRP and other relevant groups, OBA should continue its initiatives for a series of workshops for IRBs and IBCs on gene transfer research.

- OBA should work with OHRP to encourage IRB cooperation in ensuring that human subjects are not enrolled in gene transfer trials until RAC deems a protocol non-novel, or if novel, the protocol has completed the RAC review process.

- NIH should work with OHRP to encourage the inclusion of additional resource sites for information regarding participation in clinical trials in the informed consent form. For gene transfer clinical trials, this information should include a reference to the RAC review process and directions regarding how to obtain relevant information from OBA/RAC.

- NIH should evaluate a variety of mechanisms to increase financial resources for IRBs.

- NIH should increase support or develop innovative programs to improve the general institutional infrastructure (e.g., data collection and analysis, monitoring) for clinical research.

The Working Group recognizes that concerns about conflicts of interest transcend gene transfer research and are relevant to may other areas of clinical endeavor. However there is a perception that conflicts of interest especially influence investigator/sponsor behavior in the conduct of gene transfer clinical trials. To the extent that this perception is held or correct, the integrity of clinical gene therapy is compromised in the public's eye. Testimony from the NIH Office of Extramural Research educated the Working Group that although NIH is informed that a conflict of interest has been identified at a grantee institution, NIH does not receive automatically specific information about the conflict, only an assurance that it has been resolved. However, the specifics of a given case must be reported if requested by NIH.

- Although NIH has developed guidance on conflict of interest, the issue deserves a more sustained analysis than can be conducted by this review group at this time. However, the Working Group believes that: 1) any guidance about conflict of interest must take into consideration the potential for conflict on the part of the investigator and the institution; 2) that disclosure of conflict of interest in the informed consent process is necessary but not sufficient; and 3) increased attention must be paid to how research institutions investigate and resolve conflicts.

It was noted that a Conference on Human Subject Protection and Financial Conflict of Interest will be convened at NIH in August 2000. The issue of financial conflict of interest is one of the five main issues identified by the Secretary of Health and Human Services in her announcement of steps being taken to strengthen human subject protection during clinical trials. In that announcement, the Secretary stated that there would be a public process to review this issue. The Working Group believes this is an important first step toward resolving some of these issues and that NIH should continue to explore the best mechanisms for understanding and resolving the influence of conflicts of interest on the protection of research subjects..

Risks can be reduced by increased knowledge of the science of gene transfer. In terms of research, NIH has the scientific expertise and resources to determine

areas of gene transfer research in need of greater exploration. For example, the small size of many trials precludes the collection of sufficient data points, and thus, some analyses might be required across studies. Basic scientific studies must be conducted to determine endpoints, characterize risk, and develop safer vectors. NIH could support multi-center studies that do have adequate size and power to lead to valid conclusions.

In order to confront the major outstanding obstacles to successful somatic cell gene therapy, greater focus on basic aspects of gene transfer, and gene expression within the context of gene transfer approaches is required. Such efforts need to be applied to improving vectors for gene delivery, enhancing and maintaining high level expression of genes transferred to somatic cells, achieving tissue-specific and regulated expression of transferred genes, and directing gene transfer to specific cell types. As far as possible, preclinical studies should be performed in relevant animal models, if they exist, to assess the potential impact and complications of the prospective somatic gene transfer protocol.

CONCLUSIONS

The success of clinical research of any kind in any field of medicine is contingent on openness, trust, and institutional accountability by investigators, sponsors, and institutions. Moreover, the integrity of clinical research is enhanced by a transparent oversight system. The public's confidence in gene transfer therapy, particularly in light of recent events, can only be restored by an open system in which all parties are held accountable for their activities. The Working Group recognizes, however, that no set of rules and guidelines can ensure complete compliance or absolute safety. Clinical research by nature includes a degree of risk, some of it unknown. Because risks are not fully known, and unanticipated harms might occur, trial monitoring and oversight must be exemplary and investigators and institutions must be held accountable for this oversight. In addition, those agencies and institutions entrusted with this responsibility must work together to ensure proper oversight.

As in any other area of clinical research, it will take many years before new therapies using gene transfer are shown to be effective. As the scientific foundations of the field are built and clinical studies are conducted, it is the obligation of the scientific community to ensure that the individuals who volunteer to participate in such research fully understand the risks and potential benefits of participation and that all efforts are made to protect their safety. NIH, as the nation's premier publicly supported biomedical research organization, plays a preeminent role in seeing that gene transfer research goes forward under appropriate guidance and oversight and with safety of the human subjects in mind.

APPENDIX A

Meeting Dates and Presentations

Meetings

February 28, 2000	Bethesda, Maryland
March 9, 2000	Bethesda, Maryland Joint session with the Recombinant DNA Advisory Committee (public meeting) ACD Working Group meeting
April 17, 2000	Conference call
May 30, 2000	Conference call

Presentations

Wendy Baldwin, Ph.D., Director, Office of Extramural Research, NIH
Gary Ellis, Ph.D., Director, OPRR
Joseph Glorioso, Ph.D., former RAC member; Professor and Chairman, Department of Molecular Genetics and Biochemistry, University of Pittsburgh School of Medicine
Robert Lanman, J.D., NIH Legal Advisor
Stuart Orkin, M.D., co-chair, ACD Working Group
Robertson Parkman, M.D., member, ACD Working Group
Amy Patterson, M.D., Director, OBA, NIH
Stephen Strauss, M.D., Former RAC member; Director, NCCAM, NIH
Karen Weiss, M.D., Director of the Division of Clinical Trial Design and Analysis, CBER, FDA
Kathryn Zoon, Ph.D., Director, CBER, FDA; member, ACD Working Group

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APPENDIX B:

BACKGROUND INFORMATION

Oversight of Gene Transfer Research

Recommendations to improve the system of oversight of gene transfer research must take into consideration the evolution and current status of the existing federal and local review and multi-tiered regulatory structure. Gene transfer clinical trials have a unique oversight process that is conducted by NIH through RAC and the *NIH Guidelines for Research Involving Recombinant DNA Molecules (the NIH Guidelines)*, and by FDA through regulation (via scientific review, regulatory research, testing, and compliance activities, including inspection and education). Of note, FDA regulations apply to all clinical gene transfer research; whereas, NIH/OBA governs gene transfer research that is supported with NIH funds or conducted at or sponsored by institutions that receive funding for recombinant DNA research. Currently, the majority of gene transfer research is subject to the *NIH Guidelines*.

Although NIH and FDA each make unique and complementary contributions to the scientific evaluation of the safety and potential efficacy of human gene transfer trials, their respective roles differ. FDA oversees all clinical gene transfer research, regardless of funding source, and has the statutory authority to authorize the start of testing of an IND (Investigational New Drug) to which clinical protocols are applied and conducted. FDA also relies on its Biological Response Modifiers Advisory Committee (BRMAC), which is responsible for providing advice and recommendations on development, testing, and approval of biological response modifiers, including gene therapy. The committee advises FDA on policy and provides advice/recommendations on gene therapy products submitted to FDA, including product, preclinical, and clinical issues. It is important to emphasize that FDA primarily deals with the sponsor. However, FDA does interact with the investigator when conducting inspections. When FDA receives an IND application, it must make a decision regarding authorization within 30 days. The decision can be either to grant authorization to proceed as proposed or with modifications, or to place the IND on clinical hold. FDA action proceeds independently of the RAC process; in fact, INDs can be authorized before RAC even sees the protocol.

From 1989 to May 2000, more than 280 new gene transfer INDs were submitted to FDA, with 55 submitted in FY 1999. As of May 1, 2000, 206 INDs were still active, with more than 900 supplements (changes to protocol) to these INDs submitted each year. A single IND may involve more than one clinical trial protocol

conducted at more than one site. The protocols or plans for the clinical studies are evaluated for safety, study design, and conformance with good clinical practices. Examples of modifications that may be required or recommended by FDA, include:

- Exclusion of individuals who may be at high risk for serious adverse events
- Additional laboratory testing of human subjects to detect possible toxicities
- Lower starting doses in humans and slower escalation of doses
- Modifications to the written informed consent to warn of specific risks, and
- Modifications to "stopping rules," which assure that the trial will be stopped if certain adverse events should occur.

Even after a trial is underway FDA has the authority to place it on clinical hold in order to ensure the safety of human subjects.

In contrast, through RAC, NIH's relationship is with the Principal Investigator, not the sponsor. Investigators must submit to OBA a copy of the proposed research protocol and must comply with the policies and procedures for the conduct of human gene transfer clinical research set forth in the NIH Guidelines. As mentioned previously, a single sponsor may be collaborating with several Principal Investigators under a single IND. Thus, for the same scope of research activity, FDA may have on record one sponsor and one IND, whereas NIH may have on record multiple Principal Investigators. Unlike FDA, NIH does not have statutory authority to either put a protocol on hold or allow it to proceed, rather NIH is responsible for the *NIH Guidelines* and for convening RAC, which on a selective basis conducts public review and discussion of the scientific, safety, and ethical issues raised by specific human gene transfer research protocols.

In addition to registering with OBA, filing an IND with FDA, and following the *NIH Guidelines*, investigators and/or sponsors also must obtain all applicable local institutional and federal regulatory approvals-this includes approval by their institution's IRB (as required by 45 CFR 46 or the parallel FDA regulations for the protection of human subjects in research (21 CFR, Part 50 and 56), and IBC (as required by the *NIH Guidelines*). The IRB reviews human subjects research supported with federal funds or conducted at institutions that receive federal funds. The IBC is governed by the *NIH Guidelines* and is responsible for and authorized by the research institution to review and approve potentially biohazardous lines of research. It is charged with conducting an independent assessment of the containment levels required by the *NIH Guidelines*
for the proposed research; assessing the facilities, procedures, practices, and training and expertise of personnel involved in recombinant DNA research; and ensuring compliance with all surveillance, data reporting, and adverse event reporting requirements required by the *NIH Guidelines*.

It is important to note that in order to initiate a gene transfer trial, an investigator must obtain authorization from FDA, and IRB and IBC approvals. Investigators governed by the *NIH Guidelines*
are required to submit their proposals to OBA/RAC, but neither this submission nor the RAC discussion are necessary prior to the initiation of a trial.

Evolution of RAC

NIH established RAC in 1975. In that year it held its first meeting to create appropriate biological and physical containment practices and procedures for recombinant DNA research. These were later developed into a set of guidelines for the safe conduct of recombinant DNA research, the *NIH Guidelines*. NIH has continually refined its oversight of recombinant DNA research as the field has developed. From 1979 to 1983, several major revisions were made to the *NIH Guidelines*
as the understanding of the actual levels of risks became clear, that is, they were lower than had been expected. In 1991, NIH ceded oversight of environmental release of genetically modified organisms to the U.S. Department of Agriculture and the Environmental Protection Agency when putative risks to the public of such releases did not materialize.

In 1990 the *NIH Guidelines*
were amended to include guidance on clinical gene transfer research. In the earliest stage of this research each protocol invariably set a new precedent, thus it was critical for RAC to conduct a case-by-case review. At the same time FDA was developing its guidance in this area of research. In 1991 FDA issued a document "Points to Consider in Human Somatic Cell Therapy and Gene Therapy," which discussed FDA regulatory requirements.

By 1995, RAC had reviewed and recommended to NIH the approval of 113 gene transfer protocols. RAC, the scientific community, and the public had a substantial base of information regarding the use and safety of many of the vectors employed in, and target diseases addressed by, human gene therapy. Subsequent analyses revealed that the human health and environmental safety concerns expressed at the inception of gene transfer clinical trials had not materialized.

As the number of protocol submissions burgeoned, in 1995 NIH Director, Harold Varmus, appointed an *ad hoc* review committee (the "Verma Committee") to assess the activities of RAC and to make recommendations about its role in oversight and facilitation of gene transfer research. The Verma committee recommended that in view of the reasonably safe experience with clinical gene transfer research, RAC should no longer conduct case-by-case review of all protocols in that this presented duplication of effort with FDA. However, the committee recommended that RAC continue to review novel protocols in an open forum (i.e., protocols that involved new disease indications, vulnerable populations, and new classes of viral vectors). Also in 1995, NIH convened a committee (referred to as the "Orkin/Motulsky Committee") to assess the status of gene therapy's efficacy and to make recommendations about NIH's investment in the field. (These reports are available at www.nih.gov/oba/documents)

Simultaneously, absent evidence of substantial safety concerns for gene transfer protocols that had been previously tested, on March 6, 1995, RAC voted to recommend approval of amendments to the *NIH Guidelines*
that would eliminate RAC review and approval of human gene transfer experiments not considered to be novel. Under this mechanism, all protocols determined not to represent a novel gene transfer delivery strategy, or that did not pose unusual safety concerns were considered exempt from RAC review and approval (although IRB and IBC review were still required). This streamlined process, which became known as the NIH and FDA "Consolidated Review," was believed to eliminate unnecessary and time-consuming duplication of effort by NIH and FDA. On April 17, 1995, NIH Director Varmus approved these amendments to the *NIH Guidelines*.

In December 1996, the RAC review process was modified to require a rapid initial analysis of every protocol to determine which protocols presented significant novel scientific, safety, ethical, legal or social issues. Only those protocols deemed to present novel issues would receive full RAC review and public discussion.

In 1997, after public notices and the receipt of public comment, NIH no longer required RAC approval of gene transfer protocols, novel or otherwise. These changes did not alter the ongoing requirement for all investigators conducting gene transfer trials supported by NIH funding or at institutions receiving NIH funds to register their protocols with OBA, adhere to the *NIH Guidelines*, receive IRB and IBC approvals, and participate in public discussion as determined by RAC.

Reporting Adverse Events

All gene transfer clinical trials are subject to FDA regulations, found in Title 21 of the Code of Federal Regulations (CFR), including specific requirements at 21 CFR 312.32 related to adverse events. FDA regulations require that unexpected fatal or life-threatening adverse events associated with the use of the product are

to be reported as soon as possible, but in no event later than seven calendar days after the sponsor's initial receipt of the information. Serious and unexpected events associated with the use of the investigational product are to be reported as soon as possible, but in no event any later than 15 calendar days after the sponsor's initial receipt of the information. Sponsors also must submit a comprehensive report of all adverse events to FDA in annual reports and other regulatory documents.

The *NIH Guidelines* currently require the immediate reporting to OBA of *all serious adverse events* associated with human gene transfer clinical research. The *Guidelines*
do not define serious adverse event; however, on a practical basis NIH uses the FDA definition of adverse event. If a reported adverse event is judged by NIH/OBA to be serious and related to a gene transfer protocol, OBA confers with FDA and the RAC Chair regarding follow-up evaluation of the event and any need for action. As appropriate, the following groups are notified: RAC, OHRP, IBCs, and all Principal Investigators engaged in related clinical research.

Although NIH and FDA both require expeditious reports of serious adverse events in human gene transfer, the agencies initiate different, but complementary, processes in response to this information. FDA reviews the information provided in the adverse event reports in the context of other information from that study and from other studies of the same or related products. Actions that FDA might take to assure the safety of study participants include:

- changing the eligibility criteria to exclude individuals at high risk
- changing the dose, route, and schedule of administration of the product
- changing the informed consent to disclose new toxicities
- obtaining additional consent from the study participants to reflect new information, or
- updating the clinical investigator's brochure.

FDA also conducts an analysis of the event and relevant data and, if necessary, places the study, and others like it, on clinical hold until the safety issues have been adequately addressed. FDA is required by law to maintain the confidentiality of all information connected with an IND[a]. However, FDA does contact other sponsors if adverse events might affect the health and safety of individuals in other clinical trials. The FDA Commissioner may disclose a summary of selected portions of safety and effectiveness as are appropriate for public consideration of a specific pending issue (601.51(d)), including important safety issues.

In contrast to FDA, NIH does not have statutory authority either to authorize the initiation of a clinical trial or place a clinical trial on hold. But, the reporting to NIH/OBA of serious adverse events initiates, if warranted, a notification process and public discussion of the event. Serious adverse event reporting by investigators allows OBA to notify RAC rapidly and, as appropriate, other IBCs, IRBs, and Principal Investigators in the field. Expeditious reporting also provides a mechanism for early recognition of trends regarding the occurrence of serious adverse events that may raise significant implications for the safety of individuals enrolled in similar human gene transfer studies. When deemed appropriate, OBA initiates additional data collection for a comprehensive and public review by the RAC and ad hoc experts. This process fosters broad public awareness of issues and developments in human gene transfer research.

Exactly what must be reported when a serious adverse event occurs is the topic of much discussion, in part because there are different reporting requirements not only for FDA and NIH, but also for OHRP. For example, FDA requires that the sponsor notify FDA of any adverse experience associated with the use of the drug that is related and both serious and unexpected. *The NIH Guidelines* require that the *principal investigators* must report immediately any serious adverse event to the local IRB, IBC, OHRP (if applicable), NIH/OBA, and FDA. The Common Rule (with oversight by OHRP) requires that institutions (through the Multiple Project Assurance mechanism) have in place written procedures for ensuring prompt reporting to the IRB, appropriate institution officials, and the department or agency head of *any unanticipated problems involving risks to subjects or others*.

Activities following the death of Jessie Gelsinger are illustrative of the process. When notified of Gelsinger's death, FDA immediately placed the trial on clinical hold and informed the sponsor that presentation at the next meeting of the RAC would likely be required. FDA reviewers then identified other gene transfer protocols in which adenoviral vectors were being administered intravascularly, contacted these sponsors to alert them of the death, requested that they add appropriate language to the informed consent, and inquired as to whether other adverse events were observed in their INDs, particularly thrombocytopenia, DIC, and/or abnormal liver function tests. In October 1999, FDA placed two other protocols that used a high dose adenoviral vector via intrahepatic inoculation for cancer on clinical hold.

On September 21, 1999, the day after OBA received notification of the Gelsinger death, OBA sent a notification letter to RAC members, IBC chairs, FDA, and OPRR informing them of the death and describing plans for RAC review and discussion of issues associated with adenoviral vectors. Also in October, NIH sent a letter to all Principal Investigators (approximately 70) who were using the same or similar method of gene delivery, requesting safety and toxicity data, including adverse events.

Subsequently, a working group of RAC was formed to conduct an in-depth analysis of the data and, if necessary, develop guidance regarding the use of adenoviral vectors in gene transfer studies. In addition, a scientific symposium was held at the December 1999 RAC meeting to provide comprehensive scientific review and public discussion of the data.

As a result of these enhanced oversight activities, it has become clear that many investigators and sponsors either did not submit serious adverse event reports to NIH as they occurred or labeled them as confidential. In September 1999, NIH requested that RAC consider the need to clarify and strengthen the *NIH Guidelines*
for adverse event reporting, specifically, what NIH should do to ensure that adverse events reports required by NIH not be classified as confidential, trade secrets, or proprietary information. During its September 2-3, 1999 meeting, RAC developed the following consensus statement regarding serious adverse event reporting:

> "Adverse event reports shall not be designated as confidential, either in whole or in part. Adverse event reports are essential to decision making by IBCs, IRBs, and potential subjects of gene transfer research in humans. The public disclosure of adverse events [in human gene transfer research] is also essential to public understanding and evaluation of gene transfer in humans. Adverse event reports must be made available for public discussion [by the RAC] without the inclusion of proprietary or trade secret information."

RAC subsequently directed NIH to prepare a proposed amendment to the NIH Guidelines that states, "adverse event reports should be devoid of individually identifiable information and should not be marked as confidential."

Proposed Changes to the NIH Guidelines

Several proposals have been made in the past six months for modification of the NIH Guidelines.

A November 22, 1999 proposed action published in the *Federal Register* intended to strengthen compliance with the *NIH Guidelines* (November 22, 1999, Federal Register notice) would add three provisions to the *Guidelines*: 1) a definition of serious adverse events and a stipulation of the time frame in which serious adverse events are to be reported in writing; 2) a mandate that serious adverse event reports must not contain any trade secret or commercial or financial information that is privileged or confidential and that all information submitted in accordance with the *Guidelines* will be considered public unless NIH

determines there to be exceptional circumstances; and 3) a directive that serious adverse event reports submitted to NIH be stripped of individually identifiable information in order to ensure confidentiality. These changes are intended to clarify the NIH requirements for reporting adverse events, as well as ensure that all pertinent information regarding the safe and ethical conduct of human gene transfer trials is provided in a timely fashion to RAC for review and analysis.

Also in 1999, in another effort to optimize and streamline this process, NIH considered modifying the requirements for protocol submission by allowing proposals to be submitted for RAC review before they have been approved by the local IBC and IRB. Pursuant to this revised process, clinical trial investigations would not be initiated (that is, no human subjects enrolled) until the RAC review process had been completed, and IBC and IRB approvals and applicable regulatory authorization(s) have been obtained. The proposed changes would allow investigators to receive RAC input at an earlier stage of protocol development, allow multiple levels of protocol review to occur simultaneously, and reduce the delays in initiating clinical protocols. A human gene transfer protocol that meets the requirements set forth in Appendix M-I of the *NIH Guidelines* would be submitted for RAC review prior to receiving final IBC and IRB approval. For the purposes of this proposed action, "enrollment" is defined as the process of obtaining consent from a potential research subject, or a designated legal guardian, to undergo any test or procedure associated with the gene transfer experiment.

NIH accepted RAC's recommendations but has delayed implementation pending related reviews of RAC activities by one of RAC's internal working groups and by this Advisory Committee to the Director Ad Hoc Working Group.

Also of relevance, RAC formed a working group in July 1999 to redefine the scope of the *NIH Guidelines*. The working group developed a proposal that was discussed and met with broad acceptance by the RAC at the September 2-3,1999 meeting. The proposal broadened the scope of the *Guidelines* by acknowledging the development of many new technologies, and expanded, accordingly, the definition of encompassed research to include research that is based on the aim/intent of modifying the human genome, as opposed to research that utilizes a particular, currently recognized, genome-modifying technology. RAC has delayed final action on the recommendations of that working group pending the outcome of this and other reviews.

APPENDIX C:

RECOMMENDED PROCESS FOR RAC REVIEW OF PROTOCOLS

1. Concurrent registration by the investigator of the original protocol with OBA and submission of the protocol for review to the relevant IRB and IBC. The IBC cannot grant final approval of a protocol until the RAC process has been completed.

2. In addition to the protocol, the submission to OBA should include documentation of the status of IRB and IBC submission and review, and the status of the IND authorization if an application to FDA has been made. RAC should work with OPRR to encourage IRBs to consider their reviews provisional pending RAC review.

3. Upon receipt of a protocol, OBA staff determines whether the application is complete and, if so, initiates the process to determine whether the protocol is novel. NIH should ask investigators to encourage sponsors to withhold application for an IND until either: 1) the proposal is deemed non-novel, or 2) the protocol has undergone the RAC review process.

4. Protocols deemed non-novel are subject to the standard scrutiny and review now required by FDA for IND authorization. If RAC deems a protocol non-novel, notification is sent to the IRB, IBC, FDA, and the investigator, informing them of this determination. The IBC can now grant approval. Once an IND is authorized, the investigator should register the final protocol with OBA.

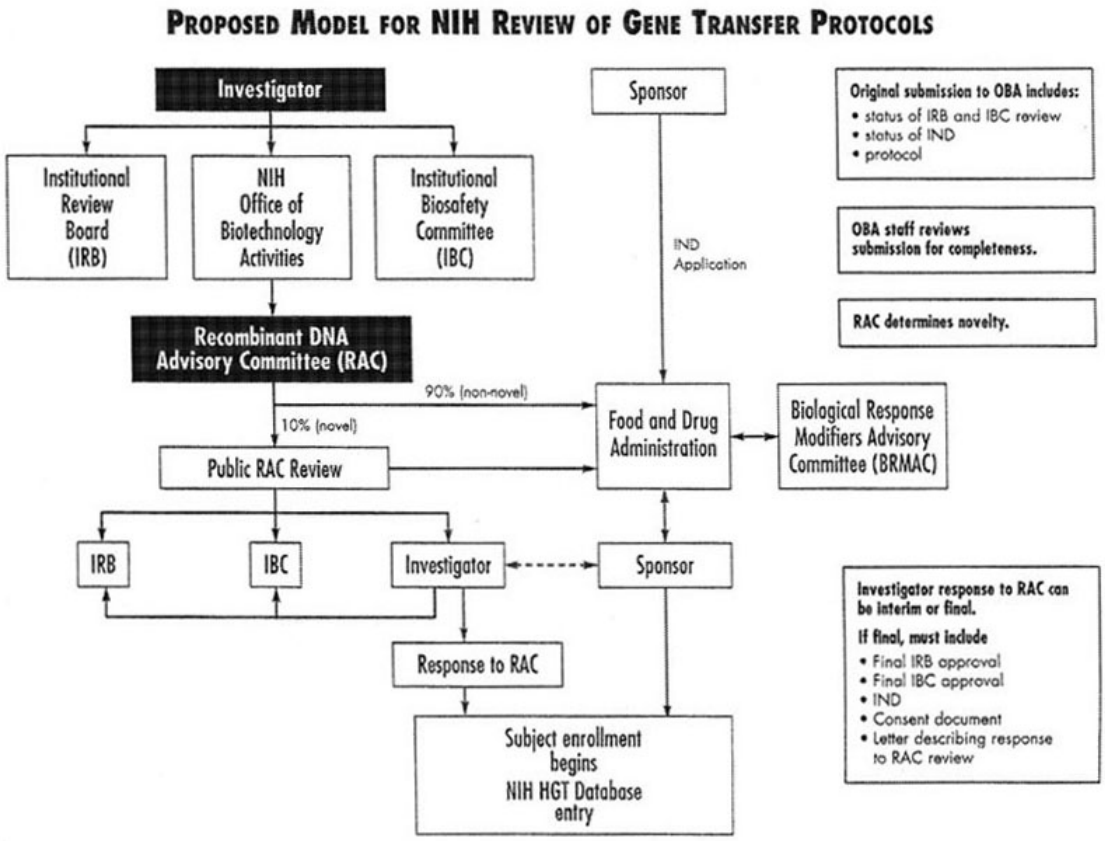
5. Protocols deemed novel are scheduled for public RAC review and discussion, the results of which are reported to the investigator, relevant IRB and IBC, and FDA. Following receipt of these comments, and investigator response to the RAC, the IBC can now make a decision regarding approval. IRBs should work with investigators to ensure that the results of RAC review are incorporated into the informed consent process.

6. The investigator is responsible for communicating with the IRB, IBC, and the sponsor and FDA, as appropriate, to prepare a publicly available response to RAC. It is assumed that the investigator will notify the sponsor, and that any FDA requirements will be followed. The investigator may submit an interim response outlining a plan that may include, for example, more pre-clinical work that may alter the protocol design enough to require a new submission at a later date. If the response is final, it must include the final IRB and IBC approval, the final consent document, the final IND (once received), and a letter describing any actions taken in response to the RAC review.

7. If no actions are to be taken, the response must contain a detailed explanation in support of the investigator's rationale for electing not to comply with RAC's recommendations. The investigator should copy the IRB, IBC, and FDA on the final response.

8. As with all gene therapy protocols, as stated in Appendix M-VII-A of the NIH Guidelines: Upon receipt of notification of permission [from FDA] to proceed with an Investigational New Drug Application for a human gene transfer protocol, the Principal Investigator(s) shall submit a written report [to NIH OBA] that includes the following information: (1) how the investigator(s) responded to RAC's recommendations on the protocol (if applicable), and (2) any modifications to the protocols as required by the FDA. Once the IND is authorized, the protocol should be registered with OBA.

9. Subject enrollment begins and the protocol is entered into the NIH Human Gene Transfer database.



APPENDIX D

SUPPLEMENTAL COMMENTS AND RECOMMENDATIONS

Bob Roehr, Debra Lappin, Ruth Macklin

The Working Group was appointed because something is seriously wrong with the conduct of gene transfer research in human subjects. While the catalyst was the death of Jesse Gelsinger, subsequent investigations revealed additional violations of regulations at other research sites. Perhaps the most disturbing aspect is that the failures are not just of one man or one institution but extend far beyond that.

Gene transfer stands on a cusp: It is still basic research and not quite yet medicine. It has the potential to be the next big wave of innovation in biomedical research. The public has been encouraged, perhaps at times unreasonably so, to see it as relief from some of life's most devastating and elusive illnesses.

If it is to fulfill these promises, gene transfer research must lead not only with the high tech of cutting edge science, but also with the high touch of human interactions that value and empower patients as full partners in the research process.

Presently, the vast majority of American men, women, and children who participate in gene transfer enter the earliest phases of clinical trials where the goal is to identify toxicities and a reasonable dosing regimen in light of those toxicities. Therapeutic improvement is a long-term hope rather than a likely immediate benefit for those who enter the trials.

Protection of participants in clinical trials derives from two critical and independent sources that complement each other. One is through creation of an institutional system that instills within each member of the research community the highest ethical value for human life, and demands that behavior reflects those values. Accountability and enforcement is crucial.

The recommendations made in the majority report will enhance institutional protection of human subjects and we support all of them.

The other, less apparent, route of protection of patients is through decisions made by patients themselves. It is the basis for informed consent. Empowerment of patients for self-protection is achieved through information and through creation of an attitude of equality within both researchers and patients. Thus participants become more than passive "subjects," they become truly equal partners in the research endeavor.

But consent is only "informed" if it is predicated upon both full knowledge of the proposed trial and an understanding of medical options other than those available through trial participation. This points to the need for greater public transparency of information on all clinical trials for the prospective patient to be able to make truly informed consent.

Recommendation: *One of the principal goals of gene transfer oversight should be:*

To enhance the base of public information so that patients and their independent advisers can make better informed decisions on whether or not to enter or continue in a clinical trial protocol.

Adverse Events and Reporting

The Working Group faced its most difficult challenges in examining what constitutes adverse events, which ones need to be reported, when do they need to be reported, and the extent to which those reports shall be open to the public.

The HHS Office of Inspector General recommended increased use of data safety monitoring boards (DSMBs) in "high risk" clinical trials in the 1998 report Protecting Human Research Subjects. In an April 2000 Status of Recommendations it lamented that little progress had been made in this area.

Gene transfer epitomizes "high risk" clinical trials. Factors leading to that conclusion include: The transforming nature of the science; the basic questions surrounding it that remain unanswered; the small patient populations and data sets involved with virtually every trial; and the fact that no gene transfer mechanism has moved from basic research completely through the approval process to become a prescribed therapy. Of the hundreds of clinical trials initiated, only three have advanced as far as Phase III trials.

It is precisely because of its nascent state and its potential as the next revolution in medicine that gene transfer should become the model paradigm of how expanded patient protection, public participation, and information-based research is conducted. It is a once in a generation opportunity to improve the standards for biomedical discovery.

The NIH, FDA, and OPRR, now reshaped as the Office of Human Research Protections (OHRP), regulate gene transfer. Each has overlapping but differing audiences, responsibilities, and information requirements. This fragmentation of oversight has resulted in some confusion and duplication of activity. There are calls for consolidation and harmonization of reporting from all corners. These efforts are worthy of support.

However, in areas involving high risk research, such as gene transfer and likely others, it has become too tempting to allow the goal of harmonization to blur our focus on the public's need for and entitlement to more comprehensive, timely reporting of serious adverse events.

Gene transfer is not the Nth version of a "me too" drug but an area of biomedicine where much remains unknown. There are valid issues of science and public perception that justify treating gene transfer differently.

Harmonization should be in the direction of greater transparency and greater availability of information, not less. If we are to err with oversight of this new science, let it be in the direction of protecting patients "too much."

Recommendation:
All serious adverse events (SAEs) both anticipated and unanticipated, whether believed related or unrelated to the trial, should be reported electronically, in real time, to a centralized agent, using a standardized reporting mechanism and nomenclature.

The agent would immediately retransmit relevant sections of the report to FDA, NIH, OHRP and others as appropriate. The agent may be housed within one of those organizations or elsewhere.

Patient privacy should be respected to the greatest extent possible. Data on SAEs, stripped of patient identifiers, should be made publicly available as soon as is reasonably possible. NIH should make public its analysis of data sets prior to or simultaneous with public release of that data.

Historically, the NIH has led the way in expanding patient protection and in opening up the research process to the American public. But the scope of its jurisdiction is limited. The May 23 initiatives of President Clinton and Secretary Shalala promise to further explore enhancements to patient protections in clinical trials within a context that is broader than NIH. We heartily support those efforts.

APPENDIX E.

ROSTER

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[a] See Title 21, U.S.C., Section 331(j); 18 U.S.C., Section 1905; 21 CFR, Parts 20 and 21; 42 CFR Parts 5 and 5B, 42 U.S.C, Section 301(d).