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Office of Biotechnology Activities; Recombinant DNA Research: Action Under the Guidelines; Notice

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Office of Biotechnology Activities; Recombinant DNA Research: Action Under the Guidelines

AGENCY: National Institutes of Health (NIH), PHS, DHHS.

ACTION: Notice of Actions Under the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines).

SUMMARY: This notice describes amendments to the NIH Guidelines regarding research participant enrollment in human gene transfer studies and the submission of study protocols for NIH Recombinant DNA Advisory Committee (RAC) review. NIH's goal in making these modifications to the NIH Guidelines is to ensure that no research participant is enrolled in a human gene transfer study until the RAC review process has been completed, IBC and IRB approvals have been obtained, and applicable regulatory authorization(s) have been obtained.

The NIH is modifying the requirements for protocol submission to the NIH Office of Biotechnology Activities (OBA) for RAC review so that clinical trial proposals: 1) may be submitted for RAC review prior to local Institutional Review Board (IRB) approval; and 2) must be submitted to the NIH OBA for RAC review and the RAC review process completed prior to local Institutional Biosafety Committee (IBC) approval.

In the case of clinical trial proposals that are reviewed publicly and lead to specific recommendations from the RAC with regard to the protocol, the NIH will send written RAC recommendations to the Principal Investigator and the IBC and the IRB within 10 working days of public RAC review and discussion. Once the local IBC is in receipt of the RAC recommendations, the IBC may proceed with its protocol approval process. Investigators may initiate research participant enrollment when they have obtained final IBC and IRB approvals and all applicable regulatory authorization(s).

No later than 20 working days after enrollment of the first research participant, the investigator must have provided to NIH OBA: (1) the final protocol, as approved by the local IRB and IBC and as authorized by the FDA along with the IND number; (2) the NIH grant number(s), if applicable; (3) a copy of the IRB and IBC approvals; (4) as applicable, a written response addressing each of the RAC recommendations resulting from public review and discussion of the protocol; and (5) the date of the initiation of the trial.

FOR FURTHER INFORMATION CONTACT: Background documentation and additional information can be obtained from the Office of Biotechnology Activities, National Institutes of Health, MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, Phone 301–496–9838, FAX 301–496–9839. The OBA web site is located at http://www.nih.gov/od/oba/.

Background Information

Since the inception of both basic and clinical recombinant DNA research, the NIH RAC has publicly reviewed and discussed the full range of scientific, medical, ethical, legal, and social issues attendant to this field of research. Prior to the action described in this notice, local IBC and IRB approval of human gene transfer protocols were prerequisites for submission of the protocol to the NIH OBA for RAC review.

The actions set forth here: (1) allow all gene transfer protocols that meet the requirements set forth in Appendix M of the NIH Guidelines (Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Research Participants) to be submitted for RAC review prior to local IRB review and approval; (2) require all gene transfer protocols that meet the requirements set forth in Appendix M of the NIH Guidelines to be submitted for RAC review prior to local IBC approval; (3) require, for protocols selected for public discussion by the RAC, that the discussion occur prior to final IBC approval of those protocols; and (4) ensure that no research participant is enrolled on a clinical study until the RAC review process is completed, and IBC and IRB approvals and applicable regulatory authorizations are obtained. For the purposes of this action, research participant enrollment is defined as the process of obtaining consent from a potential research participant, or a designated legal guardian of the participant, to undergo any test or procedure associated with the gene transfer experiment.

With this change, research participants can be assured that, prior to their participation in a gene transfer clinical trial that is either novel and/or raises significant ethical or safety concerns, their local IRB and IBC, as well as the principal investigator will be apprised of the results of public RAC review and discussion.

Public RAC discussion of selected gene transfer protocols and issues of general relevance to the field enhances human subjects protection by informing research participants, investigators, and local and Federal oversight bodies about the current state of knowledge of risks and benefits, potential safety and ethical concerns, and clinical trial design issues associated with gene transfer research. Local institutional review bodies, which generally see only that subset of gene transfer trials conducted at their institution, benefit from the expertise, broad perspective, and the experience of the RAC.

In developing the actions set forth here, the NIH consulted extensively with the public, the RAC, and the Advisory Committee to the Director, NIH (ACD). A version of this proposed action was initially published in the **Federal Register** for public notice and comment on August 11, 1999 (64 FR 43884). The draft proposal and public comments were discussed by the RAC at the September 2–3, 1999, meeting. During this discussion, some RAC members noted that optimizing the effectiveness of the RAC review process was a high priority, but expressed concern that elimination of the requirement for approval of gene transfer protocols by IRBs and IBCs before submission of protocols to NIH might result in the submission of incomplete or inadequately developed clinical protocols. To address these concerns, the NIH proposed that protocols submitted to NIH OBA for RAC review must address all the elements set forth in Appendix M of the *NIH Guidelines.* Other RAC members expressed concern that RAC review prior to local institutional review might be perceived as diminishing the critical role of IRBs and IBCs in protecting human research participants and the community. To address this concern, NIH proposed that in evaluating gene transfer protocols, the IBC should take into consideration the issues raised and recommendations made during public RAC review and discussion, as well as the Principal Investigator's response to those recommendations. The RAC voted on September 3, 1999, to recommend implementation of this revised proposal.

This proposal was not implemented immediately due to events that occurred shortly thereafter. For the first time in the history of gene transfer research, a research participant's death was attributed directly to participation in a gene transfer study. This event raised concerns about the safety of gene transfer research. In response, the NIH

Director established in December, 1999, the ACD Working Group on NIH Oversight of Clinical Gene Transfer Research (the ACD Working Group) to review the role of NIH and the RAC in oversight of clinical gene transfer research. The ACD Working Group included scientists, clinicians, bioethicists, and representatives of the general public. The ACD Working Group was asked to develop recommendations on whether the current NIH framework for oversight and public discussion of clinical gene transfer research is appropriate, especially with regard to the role of the RAC and the *NIH Guidelines*; whether current NIH mechanisms are adequate for coordination of the oversight of clinical gene transfer research with the FDA, the Office for Human Research Protections, IRBs, and IBCs; whether additional NIH measures are needed to minimize risk associated with clinical gene transfer research; and the appropriate role of the NIH with regard to reporting, analysis, and public discussion of serious adverse events.

The ACD Working Group concurred that participants must not be enrolled in a gene transfer protocol until NIH OBA and the RAC have determined whether the protocol requires public RAC review and, in the case of a protocol selected for public review and discussion, until that review has occurred. If the RAC expresses concerns about the safety or design of a protocol, there must be a systematic and established mechanism that allows RAC to communicate those concerns to the investigators prior to enrollment of participants.

The ACD Working Group specifically recommended the following:

- Research participant safety would be optimally enhanced if participants are not enrolled in gene transfer protocols selected for public RAC review and discussion until that public review has occurred and the investigator has responded to the RAC recommendations.
- The timing of review of gene transfer protocols by RAC, the IRB, the IBC, and the FDA should be altered to ensure that RAC functions as an effective advisory committee to investigators, local IRBs and IBCs, NIH, and FDA.
- The requirement that the investigator obtain IBC and IRB approval prior to submission of a protocol to OBA/RAC should be eliminated. This change would allow investigators to receive RAC input at an earlier stage of protocol development.
- Final IBC approval should be withheld until RAC review is complete. In the case of protocols not selected for public RAC review and discussion, IBC approval can be granted as soon as the IBC is notified that the protocol has not been selected for further review. In the case of protocols selected for public RAC review and discussion, 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 public RAC review.

The RAC unanimously endorsed the ACD Working Group recommendations on June 29, 2000. On July 15, 2000, the ACD unanimously voted to accept the ACD Working Group recommendations regarding review of human gene transfer protocols by the NIH RAC. Through this notice of action, the NIH is amending the *NIH Guidelines* in light of the recommendations of the RAC and the ACD.

The actions described in this notice implement fundamental changes in the NIH process for protocol submission and review of gene transfer clinical research protocols. These changes affect multiple sections of the *NIH Guidelines*, as set forth below. In addition, Appendix M of the *NIH Guidelines* is significantly modified. Specifically, the text has been substantially changed and reorganized in order to convey the revised protocol review process in a clear and logical manner. For the convenience of the reader, those portions of Appendix M that contain amended language, as well as those containing reorganized text, are reprinted below. The revised *NIH Guidelines*, in their entirety, can be accessed at http://www4.od.nih.gov/oba/guidelines.html. (**Note:** In the text below, adverse event reporting requirements remain unchanged; however, a subsequent notice will describe proposed changes for reporting to NIH on serious adverse events that occur during clinical gene transfer research.)

Actions Amending the NIH Guidelines

Section I. Scope of the NIH Guidelines

Section I-A–1-a under Purpose is amended to read:

''Section I–A–1–a. For experiments involving the deliberate transfer of recombinant DNA, or DNA or RNA derived from recombinant DNA, into human research participants (human gene transfer), no research participant shall be enrolled (see definition of enrollment in Section I–E–7) until the RAC review process has been completed (see Appendix M–I–B, RAC Review Requirements); Institutional Biosafety Committee (IBC) approval (from the clinical trial site) has been obtained; Institutional Review Board approval has been obtained; and all applicable regulatory authorization(s) have been obtained.

''For a clinical trial site that is added after the RAC review process, no research participant shall be enrolled (see definition of enrollment in Section I-E–7) at the clinical trial site until the following documentation has been submitted to NIH OBA: (1) IBC approval (from the clinical trial site); (2) Institutional Review Board approval; (3) Institutional Review Board-approved informed consent document; and (4) curriculum vitae of the principal investigator(s) (no more than two pages in biographical sketch format); and (5) NIH grant number(s) if applicable.''

A new Section I–E–7 is added to read:

''Section I–E–7. ''Enrollment'' is the process of obtaining informed consent from a potential research participant, or a designated legal guardian of the participant, to undergo a test or procedure associated with the gene transfer experiment.''

Section III. Experiments Covered by the NIH Guidelines

Section III–C is amended to read:

''Section III–C. Experiments that Require Institutional Biosafety Committee and Institutional Review Board Approvals and RAC Review Before Research Participant Enrollment

''Section III–C–1. Experiments Involving the Deliberate Transfer of Recombinant DNA, or DNA or RNA Derived from Recombinant DNA, into One or More Human Research Participants

''For an experiment involving the deliberate transfer of recombinant DNA, or DNA or RNA derived from recombinant DNA, into human research participants (human gene transfer), no research participant shall be enrolled (see definition of enrollment in Section I–E–7) until the RAC review process has been completed (see Appendix M–I–B, *RAC Review Requirements*).

''In its evaluation of human gene transfer proposals, the RAC will consider whether a proposed human gene transfer experiment presents characteristics that warrant public RAC review and discussion (See Appendix M-I-B–2). The process of public RAC review and discussion is intended to foster the safe and ethical conduct of human gene transfer experiments. Public review and discussion of a human gene transfer experiment (and access to relevant information) also serves to inform the public about the technical aspects of the proposal, meaning and significance of the research, and any significant safety, social, and ethical implications of the research.''

''Public RAC review and discussion of a human gene transfer experiment may be: (1) initiated by the NIH Director; or (2) initiated by the NIH OBA Director following a recommendation to NIH OBA by: (a) three or more RAC members; or (b) a Federal agency other than NIH. After a human gene transfer experiment is reviewed by the RAC at a regularly scheduled meeting, NIH OBA will send a letter within 10 working days to the NIH Director, the Principal Investigator, the

sponsoring institution, and other DHHS components, as appropriate, summarizing the RAC recommendations.

''For a clinical trial site that is added after the RAC review process, no research participant shall be enrolled (see definition of enrollment in Section I–E–7) at the clinical trial site until the following documentation has been submitted to NIH OBA: (1) Institutional Biosafety Committee approval (from the clinical trial site); (2) Institutional Review Board approval; (3) Institutional Review Board-approved informed consent document; and (4) curriculum vitae of the principal investigator(s) (no more than two pages in biographical sketch format).

''In order to maintain public access to information regarding human gene transfer protocols (including protocols that are not publicly reviewed by the RAC), NIH OBA will maintain the documentation described in Appendices M–I through M–V. The information provided in response to Appendix M should not contain any confidential commercial information or trade secrets, enabling all aspects of RAC review to be open to the public.

''Note: For specific directives concerning the use of retroviral vectors for gene delivery, consult Appendix B–V–1, *Murine Retroviral Vectors.''*

Section IV. Roles and Responsibilities

Section IV is amended to read in part:

Section IV–B. Responsibilities of the Institution

Section IV–B–1. General Information. . .

Section IV–B–1–f. Ensure that . . . (ii) all aspects of Appendix M have been appropriately addressed by the Principal Investigator; and (iii) no research participant shall be enrolled (see definition of enrollment in Section I–E–7) in a human gene transfer experiment until the RAC review process has been completed (see Appendix M–I–B, RAC Review Requirements). . . .''

''Section IV-B–2. Institutional Biosafety Committee (IBC). . .

''Section IV–B–2–a. Membership and Procedures

Section IV–B–2–a–(1). . . . When the institution participates in or sponsors recombinant DNA research involving human research participants, the institution must ensure that: . . . (ii) all aspects of Appendix M have been appropriately addressed by the Principal Investigator; (iii) no research participant shall be enrolled (see definition of enrollment in Section I–E–7) in a human gene transfer experiment until the RAC review process has been completed (see Appendix M–I–B, RAC Review Requirements); and (iv) final IBC approval is granted only after the RAC review process has been completed (see Appendix M–I–B, RAC Review Requirements). Institutional Biosafety Committee approval must be obtained from the institution at which recombinant DNA material will be administered to human research participants (rather than the site involved in manufacturing gene transfer products).''

Section IV–B–2–b. Functions. . .

On behalf of the Institution, the Institutional Biosafety Committee is responsible for:

''Section IV–B–2–b–(1). Reviewing recombinant DNA research conducted at or sponsored by the institution for compliance with the NIH Guidelines as specified in Section III, Experiments Covered by the NIH Guidelines, and approving those research projects that are found to conform with the NIH Guidelines. This review shall include: . . . (iii) ensuring that all aspects of Appendix M have been appropriately addressed by the Principal Investigator; (iv) ensuring that no research participant is enrolled (see definition of enrollment in Section I–E–7) in a human gene transfer experiment until the RAC review process has been completed (see Appendix M–I–B, RAC Review Requirements); (v) for human gene transfer protocols selected for public RAC review and discussion, consideration of the issues raised and recommendations made as a result of this review and consideration of the Principal Investigator's response to the RAC recommendations; (vi) ensuring that final IBC approval is granted only after the RAC review process has been completed (see Appendix M–I–B, RAC Review Requirements); and (vii) ensuring compliance with all surveillance, data reporting, and adverse reporting requirements set forth in the NIH Guidelines.''

''Section IV–B–7. Principal Investigator (PI). . .

''Section IV–B–7–b. Information to Be Submitted by the Principal Investigator to NIH OBA

''The Principal Investigator shall: . . . .

''Section IV–B–7–b–(6). Ensure that all aspects of Appendix M have been appropriately addressed prior to the submission of a human gene transfer experiment to NIH OBA, and provide a letter signed by the Principal Investigator(s) on institutional letterhead acknowledging that the documentation being submitted to NIH OBA complies with the requirements set forth in Appendix M. No research participant shall be enrolled (see definition of enrollment in Section I–E–7) in a human gene transfer experiment until the RAC review process has been completed (see Appendix M–I–B, RAC Review Requirements); IBC approval (from the clinical trial site) has been obtained; Institutional Review Board (IRB) approval has been obtained; and all applicable regulatory authorization(s) have been obtained.

''For a clinical trial site that is added after the RAC review process, no research participant shall be enrolled (see definition of enrollment in Section I–E–7) at the clinical trial site until the following documentation has been submitted to NIH OBA: (1) IBC approval (from the clinical trial site); (2) IRB approval; (3) IRB-approved informed consent document; and (4) curriculum vitae of the principal investigator(s) (no more than two pages in biographical sketch format). . . .''

Appendix M. Points To Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules Into One or More Human Research Participants (Points To Consider)

Note: For the convenience of the reader, those portions of Appendix M that contain amended language, as well as those containing reorganized text, are reprinted below.

Appendix M is amended to read in part:

''Appendix M–I. Requirements for Protocol Submission, Review, and Reporting—Human Gene Transfer Experiments

''Appendix M–I–A. Requirements for Protocol Submission

''The following documentation must be submitted (see exemption in Appendix M–VII–A, Footnotes of Appendix M) in printed or electronic form to the: NIH Office of Biotechnology Activities, National Institutes of Health/MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, Telephone: 301–496–9838, Facsimile: 301–496–9839, E-mail: rosenthg@od.nih.gov. NIH OBA will confirm receipt within three working days after receiving the submission.

''1. A cover letter on institutional letterhead, signed by the Principal Investigator(s), that: (1) acknowledges that the documentation submitted to NIH OBA complies with the requirements set forth in Appendix M–I–A, Requirements for Protocol Submission; (2) identifies the Institutional Biosafety Committee (IBC) and Institutional Review Board (IRB) at the proposed clinical trial site(s) responsible for local review and approval of the protocol; and (3) acknowledges that no research participant will be enrolled (see definition of enrollment in Section I–E–7) until the RAC review process has been completed (see Appendix M–I–B, RAC Review Requirements); IBC approval (from the clinical trial site) has been obtained; IRB approval has been obtained; and all applicable regulatory authorizations have been obtained.

''2. The scientific abstract.

''3. The non-technical abstract.

''4. The proposed clinical protocol, including tables, figures, and relevant manuscripts.

''5. Responses to Appendices M–II through M–V, Description of the Proposal, Informed Consent, Privacy and Confidentiality, and Special Issues. Responses to Appendices M–II through M–V may be provided either as an appendix to the clinical protocol or incorporated in the clinical protocol. If responses to Appendices M–II through M–V are incorporated in the clinical protocol, each response must refer to the appropriate Appendix M–II through M–V.

''6. The proposed informed consent document (see Appendix M–III, Informed Consent).

''7. Curricula vitae of the principal investigator(s) (no more than two pages in biographical sketch format).

Note: A human gene transfer experiment submitted to NIH OBA should not contain

confidential commercial information or trade secrets, enabling all aspects of the review to be open to the public.

''Appendix M–I–B. RAC Review Requirements

''Appendix M–I–B–1. Initial RAC Review

''The initial RAC review process shall include a determination as to whether the human gene transfer experiment presents characteristics that warrant public RAC review and discussion. During the RAC's initial review, individual committee members may request additional information relevant to the protocol. NIH OBA will immediately notify the Principal Investigator(s) of RAC requests for additional information. In making a determination whether an experiment presents characteristics warranting public RAC review and discussion, reviewers will 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.

''Initial RAC review shall be completed within 15 working days of receipt of a complete submission (see Appendix M–I–A, Requirements for Protocol Submission). At the end of the15-day review period, NIH OBA will notify the Principal Investigator(s) in writing about the results of the RAC's initial review. Two outcomes are possible: (1) the experiment does not present characteristics that warrant further review and discussion and is therefore exempt from public RAC review and discussion; or (2) the experiment presents characteristics that warrant public RAC review and discussion. Completion of the RAC review process is defined as: (1) receipt by the Principal Investigator(s) of a letter from NIH OBA indicating that the submission does not present characteristics that warrant public RAC review and discussion; or (2) receipt by the Principal Investigator(s) of a letter from NIH OBA after public RAC review that summarizes the committee's key comments and recommendations (if any).

''If a human gene transfer protocol is submitted less than eight weeks before a scheduled RAC meeting and is subsequently recommended for public RAC review and discussion, the review of the protocol by the RAC will be deferred until the next scheduled RAC meeting. This eight-week period is needed to ensure adequate time for public notice and comment and thorough review by the committee members.

''No research participant shall be enrolled (see definition of enrollment in Section I–E–7) in the human gene transfer experiment until: (1) the RAC review process has been completed; (2) Institutional Biosafety Committee (IBC) approval (from the clinical trial site) has been obtained; (3) Institutional Review Board (IRB) approval has been obtained; and (4) all applicable regulatory authorization(s) have been obtained.

''For a clinical trial site that is added after the RAC review process, no research participant shall be enrolled (see definition of enrollment in Section I–E–7) at the clinical trial site until the following documentation has been submitted to NIH OBA: (1) IBC approval (from the clinical trial site); (2) IRB approval; (3) IRB-approved informed consent document; and (4) curriculum vitae of the principal investigator(s) (no more than two pages in biographical sketch format).''

''Appendix M–I–B–2. Public RAC Review and Discussion

''Public RAC review and discussion of a human gene transfer experiment may be: (1) initiated by the NIH Director; or (2) initiated by the NIH OBA Director following a recommendation to NIH OBA by: (a) three or more RAC members; or (b) a Federal agency other than NIH. In making a determination whether an experiment presents characteristics warranting public RAC review and discussion, reviewers will 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.

''After a human gene transfer experiment is reviewed by the full RAC at a regularly scheduled meeting, NIH OBA will send a letter summarizing the RAC key comments and recommendations (if any) regarding the protocol to the NIH Director, the Principal Investigator, the sponsoring institution, and other DHHS components, as appropriate. Completion of RAC review is defined as receipt by the Principal Investigator(s) of a letter from NIH OBA that summarizes the committee's findings. Unless NIH OBA determines that there are exceptional circumstances, the RAC summary letter will be sent to the Principal Investigator(s) within 10 working days after the completion of the RAC meeting at which the experiment was reviewed.

''RAC meetings will be open to the public except where trade secrets or confidential commercial information are reviewed. To enable all aspects of the protocol review process to be open to the public, information provided in response to Appendix M should not contain trade secrets or confidential commercial information. No application submitted to NIH OBA shall be designated as 'confidential' in its entirety. In the event that an investigator determines that specific responses to one or more of the items described in Appendix M should be considered as confidential commercial information or a trade secret, each item must be clearly identified as such. The cover letter (attached to the submitted material) shall: (1) clearly designate the information that is considered as confidential commercial information or a trade secret; and (2) explain and justify each designation.''

''Appendix M–I–C. Reporting Requirements

''Appendix M–I–C–1. Initiation of the Clinical Investigation

''No later than 20 working days after enrollment (see definition of enrollment in Section I–E–7) of the first research participant on a human gene transfer experiment, the Principal Investigator(s) shall submit the following documentation to NIH OBA: (1) a copy of the informed consent document approved by the Institutional Review Board (IRB); (2) a copy of the protocol approved by the Institutional Biosafety Committee (IBC) and IRB; (3) a copy of the final IBC approval from the clinical trial site; (4) a copy of the final IRB approval; (5) a brief written report that includes the following information: (a) how the investigator(s) responded to each of the RAC's recommendations on the protocol (if applicable); and (b) any modifications to the protocol as required by FDA; (6) applicable NIH grant number(s); (7) the FDA Investigational New Drug Application (IND) number; and (8) the date of the initiation of the trial. The purpose of requesting the FDA IND number is for facilitating interagency collaboration in the Federal oversight of human gene transfer research.''

''Appendix M–I–C–2. Additional Clinical Trial Sites

''No research participant shall be enrolled (see definition of enrollment in Section I–E–7) at a clinical trial site until the following documentation has been submitted to NIH OBA: (1) Institutional Biosafety Committee approval (from the clinical trial site); (2) Institutional Review Board approval; (3) Institutional Review Board-approved informed consent document; (4) curriculum vitae of the principal investigator(s) (no more than two pages in biographical sketch format); and (5) NIH grant number(s) if applicable.''

''Appendix M–I–C–3. Annual Reporting

''Investigators shall comply with annual data reporting requirements. Annual data report forms will be forwarded by NIH OBA to investigators. Information submitted in these annual reports will be evaluated by NIH OBA and the RAC, and possibly considered at a future RAC meeting. Information obtained through the annual data reporting process will be included in the NIH Human Gene Transfer Information System to: (1) provide clinical trial information; (2) provide administrative details of protocol registration; (3) provide annual status reports of protocols; (4) facilitate risk assessment of individual applications of human gene transfer; and (5) enhance public awareness of relevant scientific, safety, social, and ethical issues.''

''Appendix M–I–C–4. Serious Adverse Event Reporting

''Investigators who have received authorization from FDA to initiate a human gene transfer protocol must report any

serious adverse event immediately to the local Institutional Review Board, Institutional Biosafety Committee, Office for Human Research Protections (if applicable), and NIH OBA, followed by the submission of a written report filed with each group. Reports submitted to NIH OBA shall be sent to the Office of Biotechnology Activities, National Institutes of Health/MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, (301) 496–9838.''

''Appendix M–II. Description of Proposal . . .''

''Appendix M–III. Informed Consent . . .

''M–III–B. Informed Consent Document

''Submission of a human gene transfer experiment to NIH OBA must include a copy of the proposed informed consent document. A separate informed consent document should be used for the gene transfer portion of a research project when gene transfer is used as an adjunct in the study of another technique, e.g., when a gene is used as a ''marker'' or to enhance the power of immunotherapy for cancer. . . .''

''Appendix M–IV. Privacy and Confidentiality . . .''

''Appendix M–V. Special Issues . . .''

Appendix M–VI, RAC Review—Human Gene Transfer Experiments has been incorporated into new Appendix M–I–B, RAC Review Requirements.

Appendix M–VII, Reporting Requirements, has been incorporated into new Appendix M–I–C, Reporting Requirements.

Appendix VIII, Footnotes of Appendix M, will be renumbered to Appendix VI.

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OMB's ''Mandatory Information Requirements for Federal Assistance Program Announcements'' (45 FR 39592) requires a statement concerning the official government programs contained in the Catalog of Federal Domestic Assistance. Normally, NIH lists in its announcements the number and title of affected individual programs for the guidance of the public. Because the guidance in this notice covers virtually every NIH and Federal research program in which recombinant DNA techniques could be used, it has been determined not to be cost effective or in the public interest to attempt to list these programs. In addition, NIH could not be certain that every Federal program would be included as many Federal agencies, as well as private organizations, both national and international, have elected to follow the NIH Guidelines. In lieu of the individual program listing, NIH invites readers to direct questions to the information address above about whether individual programs listed in the Catalog of Federal Domestic Assistance are affected.

Dated: September 30, 2000.

Ruth L. Kirschstein,

Principal Deputy Director, National Institutes of Health.

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