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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Proposed Action under the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)

AGENCY: National Institutes of Health (NIH)

ACTION: Notice of proposed changes to the NIH Guidelines

SUMMARY: The NIH seeks public comment on its proposal to amend the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines) to incorporate the recommendations of the Institute of Medicine (IOM) regarding human gene transfer clinical research protocols. The NIH proposes amendments to the following: (A) the criteria for selecting protocols for in-depth review and public discussion by the NIH Recombinant DNA Advisory Committee (RAC), (B) the process by which human gene transfer protocols are reviewed and registered with the NIH, and (C) the streamlining of the NIH protocol registration submission requirements under Appendix M-I-A of the NIH Guidelines.

DATES: To ensure consideration, comments must be submitted in writing by [INSERT DATE 45 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: Comments may be submitted by e-mail at OBA-osp@od.nih.gov, by fax at 301-496-9839, or by mail to the Office of Science Policy, National Institutes of Health, 6705 Rockledge Drive, Suite 750, Bethesda, Maryland 20892-7985. All written comments received in response to this notice will be available for public inspection at the NIH Office of Science Policy (OSP), 6705 Rockledge Drive, Suite 750, Bethesda, MD 20892-7985, weekdays between the hours of 8:30 a.m. and 5 p.m. and may be posted to the NIH OSP website.

FOR FURTHER INFORMATION CONTACT: If you have questions, or require additional background information about these proposed changes, please contact the NIH by e-mail at OBA-osp@od.nih.gov, or telephone at 301-496-9838.

SUPPLEMENTARY INFORMATION: The NIH Office of the Director requested that the IOM review whether gene transfer research raises issues of concern that warrant the current level of RAC oversight of individual clinical trials involving gene transfer techniques. The IOM noted that the RAC has served a valuable role, but concluded that the current level of oversight over individual clinical trials is no longer justifiable. In an effort to maximize the benefits of the RAC review process, the IOM recommended that the NIH maintain its protocol submission and safety reporting requirements, but restrict individual gene transfer protocol reviews to exceptional cases that meet specified criteria

(full recommendations are listed in the IOM report Oversight and Review of Clinical Gene Transfer Protocols: Assessing the Role of the Recombinant DNA Advisory Committee (http://www.iom.edu/Reports/2013/Oversight-and-Review-of-Clinical-Gene-Transfer-Protocols.aspx)).

After careful consideration of the IOM's recommendations, the NIH proposes amendments to the NIH Guidelines in the following areas:

A. Criteria and process for selecting protocols for RAC review. The following criteria (subsequently referred to as the NIH RAC review criteria) are proposed for initiating RAC review of individual human gene transfer protocols (criteria listed in both items 1 and 2 must be met):

    1. An oversight body (an Institutional Biosafety Committee (IBC) or an Institutional Review Board (IRB)) determines that a human gene transfer protocol submitted to it for approval would significantly benefit from RAC review; and
    2. One or more of the criteria below are satisfied:
        a. The protocol uses a new vector, genetic material, or delivery methodology that represents a first-in-human experience, thus presenting an unknown risk.
        b. The protocol relies on preclinical safety data that were obtained using a new preclinical model system of unknown and unconfirmed value.
        c. The proposed vector, gene construct, or method of delivery is associated with possible toxicities that are not widely known and

that may render it difficult for oversight bodies to evaluate the protocol rigorously.

The chair of an oversight body or an authorized oversight body representative may submit a request for RAC review by sending the request to the NIH as part of the submission materials provided by the PI. This request must include the rationale for why the protocol satisfies both items 1 and 2 of the NIH RAC review criteria. The NIH will review the request and notify the requestor of a decision in no more than ten working days.

1. If the NIH determines that the criteria listed in both 1 and 2 above are satisfied, the NIH Director will convene the RAC.
2. If the NIH receives a request for RAC review of a protocol that the NIH determines does not meet both of these criteria, the NIH would:
    a. inform the requestor that RAC review is not warranted, and
    b. offer to provide the requestor with information about previous protocols that have used similar products, the outcome of those studies, if available, and a summary of relevant safety data.
3. Even if the protocol does not meet the proposed criteria listed in both items 1 and 2 above, the NIH Director, in consultation (if necessary) with appropriate regulatory authorities (e.g., the Office for Human Research Protections, the Food and Drug Administration), can select protocols for review that may present significant scientific, societal, or ethical concerns.

B. Process by which human gene transfer protocols are registered with the NIH. All human gene transfer protocols subject to Section III-C of the NIH Guidelines will

continue to be registered with the NIH. However, the following changes are being proposed:

1. The Principal Investigator (PI) will continue to be responsible for submitting documentation regarding a proposed human gene transfer protocol to his or her local oversight bodies. The PI will also continue to be responsible for submitting documentation as outlined in Appendix M-I-A to the NIH. As part of the submission to the NIH, the PI shall provide documentation from oversight bodies regarding their assessment of whether RAC review is warranted.
2. Completion of the protocol registration process:
    a. If no oversight body requests RAC review, the IBC may proceed with its approval process upon receipt of documentation from the NIH indicating that the protocol registration process is complete. No research participant shall be enrolled (see definition of enrollment in Section I-E-7) in the human gene transfer protocol until the protocol registration process has been completed.
    b. If an oversight body requests review and the NIH agrees that the submission has met the criteria in A above, the protocol will undergo RAC review and public discussion. The IBC may not approve a protocol until the RAC review process has been completed. The IBC may proceed with its approval process upon receipt of documentation from the NIH indicating that the protocol registration process is complete. No research participant shall be

enrolled (see definition of enrollment in Section I-E-7) in the human gene transfer protocol until the protocol registration process has been completed.

C. Streamlining the submission requirements for protocol registration. Section III-C-1 and Appendix M of the NIH Guidelines specify the requirements for protocol submission, RAC review, and reporting requirements for human gene transfer experiments. In an effort to streamline the protocol submission process, the NIH proposes to reduce the submission requirements as outlined in Appendix M-I-A. Specifically, only a subset of the information listed under the current Appendices M-II through M-V will be required mainly for oversight bodies to determine RAC review eligibility and to support the Genetic Modification Clinical Research Information System (GeMCRIS®), which facilitates safety reporting and provides access to information about human gene transfer protocols registered with the NIH.

The proposed changes to the RAC review process, outlined above, will require amendment of multiple portions of the NIH Guidelines.

Proposed Amendments to the NIH Guidelines

Throughout the document the following global changes will be made: i) The NIH OSP will replace the NIH OBA, ii) the term "RAC review" will be replaced with the term "NIH protocol registration process" as appropriate; iii) the title for Appendix M-I-B will be changed; and iv) the requirement for a CV/biosketch of key personnel will be deleted.

Section I-E is proposed to be amended to include the following new definitions:

I-E-11. An "oversight body" is an institutional entity (an Institutional Biosafety Committee or an Institutional Review Board) that must review and approve a human gene transfer trial.

I-E-12. A "regulatory authority" is a federal entity that by statute has oversight over research involving humans.

Section III-C-1 currently states:

Section III-C-1. Experiments Involving the Deliberate Transfer of Recombinant or Synthetic Nucleic Acid Molecules, or DNA or RNA Derived from Recombinant or Synthetic Nucleic Acid Molecules, into One or More Human Research Participants

Human gene transfer is the deliberate transfer into human research participants of either:

1. Recombinant nucleic acid molecules, or DNA or RNA derived from recombinant nucleic acid molecules, or
2. Synthetic nucleic acid molecules, or DNA or RNA derived from synthetic nucleic acid molecules that meet any one of the following criteria:
   a. Contain more than 100 nucleotides; or
   b. Possess biological properties that enable integration into the genome (e.g., *cis* elements involved in integration); or
   c. Have the potential to replicate in a cell; or
   d. Can be translated or transcribed.

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, the 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, unless NIH OBA determines that there are exceptional circumstances, 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; (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.

In order to maintain public access to information regarding human gene transfer (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 III-C-1 is proposed to be amended as follows:

Section III-C-1. Experiments Involving the Deliberate Transfer of Recombinant or Synthetic Nucleic Acid Molecules, or DNA or RNA Derived from Recombinant or Synthetic Nucleic Acid Molecules, into One or More Human Research Participants

Human gene transfer is the deliberate transfer into human research participants of either:

1. Recombinant nucleic acid molecules, or DNA or RNA derived from recombinant nucleic acid molecules, or

2. Synthetic nucleic acid molecules, or DNA or RNA derived from synthetic nucleic acid molecules that meet any one of the following criteria:

a. Contain more than 100 nucleotides; or

b. Possess biological properties that enable integration into the genome (e.g., cis elements involved in integration); or

c. Have the potential to replicate in a cell; or

d. Can be translated or transcribed.

No research participant shall be enrolled (see definition of enrollment in Section I-E-7) until the NIH protocol registration process has been completed (see Appendix M-I-B, Selection of Individual Protocols for Public RAC Review and Discussion).

In its evaluation of human gene transfer protocols, the NIH will make a determination, following a request from one or more oversight bodies, whether a proposed human gene transfer experiment has one or more of the characteristics that warrant public RAC review and discussion (See Appendix M-1-B-1). 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, the 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 initiated in two exceptional circumstances: (1) the NIH will determine, following a request for RAC public review from an oversight body, whether the protocol has one or more of the following characteristics: i) the protocol uses a new vector, genetic material,

or delivery methodology that represents a first-in-human experience, thus presenting an unknown risk; ii) the protocol relies on preclinical safety data that were obtained using a new preclinical model system of unknown and unconfirmed value; or iii) the proposed vector, gene construct, or method of delivery is associated with possible toxicities that are not widely known and that may render it difficult for oversight bodies to evaluate the protocol rigorously. If an oversight body requests public RAC review, but the protocol does not have one or more of the above characteristics (listed in i, ii, or iii), then the NIH will inform the requesting oversight body that public RAC review is not warranted. (2) Public RAC review and discussion of protocols not requested for review by an oversight body may be initiated by the NIH Director if: (a) the protocol has one or more of the three characteristics listed above (i, ii, or iii) and public RAC review and discussion would provide a clear and obvious benefit to the scientific community or the public; or (b) the protocol otherwise raises significant scientific, societal, or ethical concerns.

For a clinical trial site that is added after completion of the NIH protocol registration 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 the NIH OSP: (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) the NIH grant number(s) if applicable.

In order to maintain public access to information regarding human gene transfer (including protocols that are not publicly reviewed by the RAC), the NIH OSP will maintain the documentation described in Appendices M-I through M-II. The information

provided in response to Appendix M should not contain any confidential commercial or financial 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-B-1-f currently states:

> **Section IV-B-1-f.** Ensure that when the institution participates in or sponsors recombinant or synthetic nucleic acid molecule research involving human subjects: (i) the Institutional Biosafety Committee has adequate expertise and training (using *ad hoc* consultants as deemed necessary), (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), Institutional Biosafety Committee approval has been obtained, Institutional Review Board approval has been obtained, and all applicable regulatory authorizations have been obtained. Institutional Biosafety Committee approval must be obtained from each institution at which recombinant or synthetic nucleic acids will be administered to human subjects (as opposed to each institution involved in the production of vectors for human application and each institution at which there is *ex vivo* transduction of recombinant or synthetic nucleic acid molecule material into target cells for human application).

Section IV-B-1-f is proposed to be amended as follows:

Section IV-B-1-f. Ensure that when the institution participates in or sponsors recombinant or synthetic nucleic acid molecule research involving human subjects: (i) the Institutional Biosafety Committee has adequate expertise and training (using *ad hoc* consultants as deemed necessary), (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 NIH protocol registration process has been completed (see Appendix M-I-B, Selection of Individual Protocols for Public RAC Review and Discussion), Institutional Biosafety Committee approval has been obtained, Institutional Review Board approval has been obtained, and all applicable regulatory authorizations have been obtained. Institutional Biosafety Committee approval must be obtained from the clinical trial site.

None of the other sub-sections under Section IV-B-1. General Information are proposed to be amended.

Section IV-B-2-a-(1) currently states:

> **Section IV-B-2-a-(1).** The Institutional Biosafety Committee must be comprised of no fewer than five members so selected that they collectively have experience and expertise in recombinant or synthetic nucleic acid molecule technology and the capability to assess the safety of recombinant or synthetic nucleic acid molecule research and to identify any potential risk to public health or the environment. At least two members shall not be affiliated with the institution (apart from their membership on the Institutional Biosafety Committee) and who represent the interest of the surrounding community with respect to health and protection of the environment (e.g., officials of state or local public health or environmental protection agencies, members of other local governmental bodies, or persons active in medical, occupational health, or environmental concerns in the community). The Institutional Biosafety Committee shall include at least one individual with expertise in plant, plant pathogen, or plant pest containment principles when experiments utilizing Appendix P, Physical and Biological Containment for Recombinant or Synthetic Nucleic Acid Molecule Research Involving Plants, require prior approval by the Institutional Biosafety Committee. The Institutional Biosafety Committee shall include at least one scientist with expertise in animal containment principles when experiments utilizing Appendix Q, Physical and Biological Containment for Recombinant or Synthetic Nucleic Acid Molecule Research Involving Animals, require Institutional Biosafety Committee prior approval. When the institution conducts recombinant or synthetic nucleic acid molecule research at BL3, BL4, or Large Scale (greater than 10 liters), a Biological Safety Officer is mandatory and shall be a member of the Institutional Biosafety Committee (see Section IV-B-3, Biological Safety Officer). When the institution participates in or sponsors recombinant or synthetic nucleic acid molecule research involving human research participants, the institution must ensure that: (i) the Institutional Biosafety Committee has adequate expertise and training

(using ad hoc consultants as deemed necessary); (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 or synthetic nucleic acid molecule material will be administered to human research participants (rather than the site involved in manufacturing gene transfer products).

Note: Individuals, corporations, and institutions not otherwise covered by the NIH Guidelines, are encouraged to adhere to the standards and procedures set forth in Sections I through IV (see Section IV-D, Voluntary Compliance. The policy and procedures for establishing an Institutional Biosafety Committee under Voluntary Compliance, are specified in Section IV-D-2, Institutional Biosafety Committee Approval).

Section IV-B-2-a-(1) is proposed to be amended as follows:

Section IV-B-2-a-(1). The Institutional Biosafety Committee must be comprised of no fewer than five members so selected that they collectively have experience and expertise in recombinant or synthetic nucleic acid molecule technology and the capability to assess the safety of recombinant or synthetic nucleic acid molecule research and to identify any potential risk to public health or the environment. At least two members shall not be affiliated with the institution (apart from their membership on the Institutional Biosafety Committee) and who represent the interest of the surrounding community with respect to health and protection of the environment (e.g., officials of state or local public health or environmental protection agencies, members of other local governmental bodies, or persons active in medical, occupational health, or environmental concerns in the community). The Institutional Biosafety Committee shall include at least one individual with expertise in plant, plant pathogen, or plant pest containment principles when

experiments utilizing Appendix P, Physical and Biological Containment for Recombinant or Synthetic Nucleic Acid Molecule Research Involving Plants, require prior approval by the Institutional Biosafety Committee. The Institutional Biosafety Committee shall include at least one scientist with expertise in animal containment principles when experiments utilizing Appendix Q, Physical and Biological Containment for Recombinant or Synthetic Nucleic Acid Molecule Research Involving Animals, require Institutional Biosafety Committee prior approval. When the institution conducts recombinant or synthetic nucleic acid molecule research at BL3, BL4, or Large Scale (greater than 10 liters), a Biological Safety Officer is mandatory and shall be a member of the Institutional Biosafety Committee (see Section IV-B-3, Biological Safety Officer). When the institution participates in or sponsors recombinant or synthetic nucleic acid molecule research involving human research participants, the institution must ensure that: (i) the Institutional Biosafety Committee has adequate expertise and training (using ad hoc consultants as deemed necessary); (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 NIH protocol registration process has been completed (see Appendix M-I-B, Selection of Individual Protocols for Public RAC Review and Discussion); and (iv) final IBC approval is granted only after the NIH protocol registration process has been completed (see Appendix M-I-B, Selection of Individual Protocols for Public RAC Review and Discussion). Institutional Biosafety Committee approval must be obtained from the clinical trial site.

Note: Individuals, corporations, and institutions not otherwise covered by the NIH Guidelines, are encouraged to adhere to the standards and procedures set forth in Sections I through IV (see Section IV-D, Voluntary Compliance. The policy and procedures for establishing an Institutional Biosafety Committee under Voluntary Compliance, are specified in Section IV-D-2, Institutional Biosafety Committee Approval).

None of the other sub-sections under Section IV-B2-a. Membership and Procedures of the IBC are proposed to be amended.

Section IV-B-2-b-(1) currently states:

> **Section IV-B-2-b-(1).** Reviewing recombinant or synthetic nucleic acid molecule 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: (i) independent assessment of the containment levels required by the NIH Guidelines for the proposed research; (ii) assessment of the facilities, procedures, practices, and training and expertise of personnel involved in recombinant or synthetic nucleic acid molecule research; (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), Institutional Biosafety Committee approval (from the clinical trial site) has been obtained, Institutional Review Board approval has been obtained, and all applicable regulatory authorizations have been obtained; (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 event reporting requirements set forth in the NIH Guidelines.

Section IV-B-2-b-(1) is proposed to be amended as follows:

Section IV-B-2-b-(1). Reviewing recombinant or synthetic nucleic acid molecule 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: (i) independent assessment of the containment levels required by the NIH Guidelines for the proposed research; (ii) assessment of the facilities, procedures, practices, and training and expertise of personnel involved in recombinant or synthetic nucleic acid molecule research; (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 NIH protocol registration process has been completed (see Appendix M-I-B, Selection of Individual Protocols for Public RAC Review and Discussion), Institutional Biosafety Committee approval (from the clinical trial site) has been obtained, Institutional Review Board approval has been obtained, and all applicable regulatory authorizations have been obtained; (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 NIH protocol registration process has been completed (see Appendix M-I-B, Selection of Individual Protocols for Public RAC Review and Discussion); and (vii) ensuring compliance with all surveillance, data reporting, and adverse event reporting requirements set forth in the NIH Guidelines.

None of the other sub-sections under Section IV-B-2-b. Functions of the IBC are proposed to be amended.

Section IV-B-6 currently states:

> **Section IV-B-6. Human Gene Therapy Expertise**
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> When the institution participates in or sponsors recombinant or synthetic nucleic acid molecule research involving human subjects, the institution must ensure that: (i) the Institutional Biosafety Committee has adequate expertise and training (using ad hoc consultants as deemed necessary) and (ii) all aspects of Appendix M, Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant or Synthetic Nucleic Acid Molecules into One or More Human Subjects (Points to Consider), have been appropriately addressed by the Principal Investigator prior to submission to NIH/OBA.

Section IV-B-6 is proposed to be amended as follows:

Section IV-B-6. Human Gene Therapy Expertise

When the institution participates in or sponsors recombinant or synthetic nucleic acid molecule research involving human subjects, the institution must ensure that: (i) the Institutional Biosafety Committee has adequate expertise and training (using ad hoc consultants as deemed necessary) and (ii) all aspects of Appendix M, Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant or Synthetic Nucleic Acid Molecules into One or More Human Subjects (Points to Consider), have been appropriately addressed by the Principal Investigator prior to its approval.

Section IV-B-7-b-(6) currently states:

> **Section IV-B-7-b-(6).** Ensure that all aspects of Appendix M have been appropriately addressed prior to 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; (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.

Section IV-B-7-b-(6) is proposed to be amended as follows:

Section IV-B-7-b-(6). Ensure that all aspects of Appendix M have been appropriately addressed prior to submission. No research participant shall be enrolled (see definition of enrollment in Section I-E-7) in a human gene transfer experiment until the NIH protocol registration process has been completed (see Appendix M-I-B, Selection of Individual Protocols for Public RAC Review and Discussion); 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 completion of the NIH protocol registration 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 the NIH OSP: (1) IBC approval (from the clinical trial site); (2) IRB approval; (3) IRB-approved informed consent document; and (4) NIH grant number(s) if applicable.

To implement this new process, the NIH proposes to amend **Appendix M, Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant or Synthetic Nucleic Acid Molecules into One or More Human Research Participants (Points to Consider).**

Appendix M currently states:

> Appendix M applies to research conducted at or sponsored by an institution that receives any support for recombinant or synthetic nucleic acid molecule research from NIH. Researchers not covered by the NIH Guidelines are encouraged to use Appendix M (see Section I-C, General Applicability).
>
> The acceptability of human somatic cell gene transfer has been addressed in several public documents as well as in numerous academic studies. In November 1982, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research published a report, Splicing Life, which resulted from a two-year process of public deliberation and hearings. Upon release of that report, a U.S. House of Representatives subcommittee held three days of public hearings with witnesses from a wide range of fields from the biomedical and social sciences to theology, philosophy, and law. In December 1984, the Office of Technology Assessment released a background paper, Human Gene Therapy, which concluded that civic, religious, scientific, and medical groups have all accepted, in principle, the appropriateness of gene transfer of somatic cells in humans for specific genetic diseases. Somatic cell gene transfer is seen as an extension of present methods that might be preferable to other technologies. In light of this public support, RAC is prepared to consider proposals for somatic cell gene transfer.
>
> RAC will not at present entertain proposals for germ line alterations but will consider proposals involving somatic cell gene transfer. The purpose of somatic cell gene transfer is to treat an individual patient, e.g., by inserting a properly functioning gene into the subject's somatic cells. Germ line alteration involves a specific attempt to introduce genetic changes into the germ (reproductive) cells of an individual, with the aim of changing the set of genes passed on to the individual's offspring.
>
> The RAC continues to explore the issues raised by the potential of in utero gene transfer clinical research. However, the RAC concludes that, at present, it is premature to undertake any in utero gene transfer clinical

trial. Significant additional preclinical and clinical studies addressing vector transduction efficacy, biodistribution, and toxicity are required before a human in utero gene transfer protocol can proceed. In addition, a more thorough understanding of the development of human organ systems, such as the immune and nervous systems, is needed to better define the potential efficacy and risks of human in utero gene transfer. Prerequisites for considering any specific human in utero gene transfer procedure include an understanding of the pathophysiology of the candidate disease and a demonstrable advantage to the in utero approach. Once the above criteria are met, the RAC would be willing to consider well rationalized human in utero gene transfer clinical trials.

Research proposals involving the deliberate transfer of recombinant or synthetic nucleic acid molecules, or DNA or RNA derived from such nucleic acid molecules, into human subjects (human gene transfer) will be considered through a review process involving both NIH/OBA and RAC. Investigators shall submit their relevant information on the proposed human gene transfer experiments to NIH/OBA. Submission of human gene transfer protocols to NIH will be in the format described in Appendix M-I-A, Submission Requirements for Protocol Submission. Submission to NIH shall be for registration purposes and will ensure continued public access to relevant human gene transfer information conducted in compliance with the NIH Guidelines. Investigational New Drug (IND) applications should be submitted to FDA in the format described in 21 CFR, Chapter I, Subchapter D, Part 312, Subpart B, Section 23, IND Content and Format.

Institutional Biosafety Committee approval must be obtained from each institution at which recombinant or synthetic nucleic acid molecule material will be administered to human subjects (as opposed to each institution involved in the production of vectors for human application and each institution at which there is ex vivo transduction of recombinant or synthetic nucleic acid molecule material into target cells for human application).

Factors that may contribute to public discussion of a human gene transfer experiment by RAC include: (i) new vectors/new gene delivery systems, (ii) new diseases, (iii) unique applications of gene transfer, and (iv) other issues considered to require further public discussion. Among the experiments that may be considered exempt from RAC discussion are those determined not to represent possible risk to human health or the environment. Full, 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. An individual human gene transfer experiment that is

recommended for full RAC review should represent novel characteristics deserving of public discussion. If it is determined that an experiment will undergo full RAC discussion, NIH/OBA will immediately notify the Principal Investigator. RAC members may forward individual requests for additional information relevant to a specific protocol through NIH/OBA to the Principal Investigator. In making a determination whether an experiment is novel, and thus deserving of full RAC discussion, reviewers will examine the scientific rationale, scientific context (relative to other proposals reviewed by RAC), 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. RAC recommendations on a specific human gene transfer experiment shall be forwarded to the NIH Director, the Principal Investigator, the sponsoring institution, and other DHHS components, as appropriate. Relevant documentation will be included in the material for the RAC meeting at which the experiment is scheduled to be discussed. RAC meetings will be open to the public except where trade secrets and proprietary information are reviewed (see Section IV-D-5, Protection of Proprietary Data – Voluntary Compliance*)*. RAC prefers that information provided in response to Appendix M contain no proprietary data or trade secrets, enabling all aspects of the review to be open to the public.

Note: Any application submitted to NIH/OBA shall not be designated as 'confidential' in its entirety. In the event that a sponsor determines that specific responses to one or more of the items described in Appendix M should be considered as proprietary or trade secret, each item should be clearly identified as such. The cover letter (attached to the submitted material) shall: (1) clearly indicate that select portions of the application contain information considered as proprietary or trade secret, (2) a brief explanation as to the reason that each of these items is determined proprietary or trade secret.

Public discussion of human gene transfer experiments (and access to relevant information) shall serve to inform the public about the technical aspects of the proposals, meaning and significance of the research, and significant safety, social, and ethical implications of the research. RAC discussion is intended to ensure safe and ethical conduct of gene transfer experiments and facilitate public understanding of this novel area of biomedical research.

In its evaluation of human gene transfer proposals, RAC will consider whether the design of such experiments offers adequate assurance that their consequences will not go beyond their purpose, which is the same as the traditional purpose of clinical investigation, namely, to protect the health and well being of human subjects being treated while at the same time gathering generalizable knowledge. Two possible undesirable

consequences of the transfer of recombinant or synthetic nucleic acid molecules would be unintentional: (i) vertical transmission of genetic changes from an individual to his/her offspring, or (ii) horizontal transmission of viral infection to other persons with whom the individual comes in contact. Accordingly, Appendices M-I through M-V request information that will enable RAC and NIH/OBA to assess the possibility that the proposed experiment(s) will inadvertently affect reproductive cells or lead to infection of other people (e.g., medical personnel or relatives).

Appendix M will be considered for revisions as experience in evaluating proposals accumulates and as new scientific developments occur. This review will be carried out periodically as needed.

Appendix M is proposed to be amended as follows:

Appendix M applies to research conducted at or sponsored by an institution that receives any support for recombinant or synthetic nucleic acid molecule research from NIH. Researchers not covered by the NIH Guidelines are encouraged to use Appendix M (see Section I-C, General Applicability).

The acceptability of human somatic cell gene transfer has been addressed in several public documents as well as in numerous academic studies. In November 1982, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research published a report, Splicing Life, which resulted from a two-year process of public deliberation and hearings. Upon release of that report, a U.S. House of Representatives subcommittee held three days of public hearings with witnesses from a wide range of fields from the biomedical and social sciences to theology, philosophy, and law. In December 1984, the Office of Technology Assessment released a background paper, Human Gene Therapy, which concluded that civic, religious, scientific, and medical groups have all accepted, in principle, the appropriateness of gene transfer of somatic cells in humans for specific genetic diseases.

Somatic cell gene transfer is seen as an extension of present methods that might be preferable to other technologies. In light of this public support, the NIH is prepared to consider proposals for somatic cell gene transfer.

The NIH will not at present entertain proposals for germ line alterations but will consider proposals involving somatic cell gene transfer. The purpose of somatic cell gene transfer is to treat an individual patient, e.g., by inserting a properly functioning gene into the subject's somatic cells. Germ line alteration involves a specific attempt to introduce genetic changes into the germ (reproductive) cells of an individual, with the aim of changing the set of genes passed on to the individual's offspring.

The NIH continues to explore the issues raised by the potential of in utero gene transfer clinical research. However, the NIH concludes that, at present, it is premature to undertake any in utero gene transfer clinical trial. Significant additional preclinical and clinical studies addressing vector transduction efficacy, biodistribution, and toxicity are required before a human in utero gene transfer protocol can proceed. In addition, a more thorough understanding of the development of human organ systems, such as the immune and nervous systems, is needed to better define the potential efficacy and risks of human in utero gene transfer. Prerequisites for considering any specific human in utero gene transfer procedure include an understanding of the pathophysiology of the candidate disease and a demonstrable advantage to the in utero approach. Once the above criteria are met, the NIH would be willing to consider well rationalized human in utero gene transfer clinical trials.

Research proposals involving the deliberate transfer of recombinant or synthetic nucleic acid molecules, or DNA or RNA derived from such nucleic acid molecules, into

one or more human subjects (human gene transfer) will be considered through a registration process involving the NIH, oversight bodies, and regulatory authorities, when appropriate. Investigators shall submit the relevant information on the proposed human gene transfer experiment to the oversight bodies and then to the NIH. The format of the submission is described in Appendix M-I-A, Requirements for Protocol Submission. Submission to the NIH OSP shall be for registration purposes and will ensure continued public access to relevant human gene transfer information conducted in compliance with the NIH Guidelines.

Public RAC review and discussion of a human gene transfer experiment may be initiated in two exceptional circumstances: (1) the NIH will determine, following a request for RAC review from an oversight body, whether the protocol has one or more of the following characteristics: i) the protocol uses a new vector, genetic material, or delivery methodology that represents a first-in-human experience, thus presenting an unknown risk; ii) the protocol relies on preclinical safety data that were obtained using a new preclinical model system of unknown and unconfirmed value; or iii) the proposed vector, gene construct, or method of delivery is associated with possible toxicities that are not widely known and that may render it difficult for oversight bodies to evaluate the protocol rigorously. If an oversight body requests public RAC review, but the NIH determines that the protocol does not have one or more of the above characteristics (listed in i, ii, or iii), then the NIH will inform the requesting oversight body that public RAC review is not warranted. (2) Public RAC review and discussion of protocols not requested for review by an oversight body may be initiated by the NIH Director, after consultation (if needed) with appropriate regulatory authorities, if: (a) the protocol has

one or more of the three characteristics listed above (i, ii, or iii) and public RAC review and discussion would provide a clear and obvious benefit to the scientific community or the public; or (b) the protocol otherwise raises significant scientific, societal, or ethical concerns.

If it is determined that a human gene transfer trial will undergo RAC review, the NIH will immediately notify the Principal Investigator. RAC recommendations following public review on a specific human gene transfer experiment shall be forwarded to the Principal Investigator, oversight bodies, and regulatory authorities, as appropriate. Relevant documentation will be included in the material for the RAC meeting at which the human gene transfer trial is scheduled to be discussed. RAC meetings will be open to the public except where trade secrets and proprietary information are reviewed (see Section IV-D-5, Protection of Proprietary Data – Voluntary Compliance). The NIH prefers that information provided in response to Appendix M contain no proprietary data or trade secrets, enabling all aspects of the review to be open to the public.

Some but not all sections of Appendix M-IRequirements for Protocol Submission, Review, and Reporting – Human Gene Transfer Experiments are proposed to be amended to decrease the number and amount of supporting documentation that must be submitted upon protocol registration, and to modify the timing of the registration processes. As proposed, Principal Investigators must submit the material as outlined below to oversight bodies at the proposed clinical trial sites; however, submission of responses to Appendices M-II through M-V or curriculum vitae will no longer be required.

Appendix M-I-A currently states:

Appendix M-I.A. Requirements for Protocol Submission

The following documentation must be submitted (see exemption in Appendix M-III-A, **Footnotes of Appendix M**) in printed or electronic form to the: Office of Biotechnology Activities, National Institutes of Health, 6705 Rockledge Drive, Suite 750, Bethesda, MD 20892-7985 (20817 for non-USPS mail), 301-496-9838, 301-496-9839 (fax), E-mail: rosenthg@od.nih.gov. NIH OBA will confirm receipt within three working days after receiving the submission. Investigators should contact NIH OBA if they do not receive this confirmation.

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 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.
7. Curriculum 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-A is proposed to be amended as follows:

Appendix M-I-A. Requirements for Protocol Submission

The following documentation must be submitted according to institutional policy, to the appropriate oversight bodies and subsequently in electronic form to the NIH OSP:

1. A scientific abstract.
2. The proposed clinical protocol, including tables, figures, and any relevant publications.
3. Summary of preclinical studies conducted in support of the proposed clinical trial or reference to the specific section of the protocol providing this information.
4. A description of the product:
    a. Describe the derivation of the delivery vector system including the source (e.g., viral, bacterial, or plasmid vector); and modifications (e.g., deletions to attenuate or self-inactivate, encapsulation in any synthetic complex, changes to tropisms, etc.). Please reference any previous clinical experience with this vector or similar vectors.
    b. Describe the genetic content of the transgene or nucleic acid delivered including the species source of the sequence and whether any modifications have been made (e.g. mutations, deletions, and truncations). What are the regulatory elements contained in the construct?
    c. Describe any other material to be used in preparation of the agent (vector and transgene) that will be administered to the human research subject (e.g., helper virus, packaging cell line, carrier particles).
    d. Describe the methods for replication-competent virus testing, if applicable.

e. Describe the intended ex vivo or in vivo target cells and transduction efficiency.

f. Describe the gene transfer agent delivery method.

5. The proposed informed consent document.

6. Specifically for submission to the NIH OSP, the PI shall provide additional documentation from oversight bodies regarding their assessment of whether RAC review is warranted. In the event that review is requested, the documentation shall include a justification that the protocol characteristics (see Section III-C-1) that would warrant RAC public review have been met.

Note: Any application submitted shall not contain any document that is designated as 'confidential' in its entirety. In the event that a sponsor determines that a portion of a specific document should be considered as proprietary or trade secret, each portion of the document should be clearly identified as such. In the event that a specific portion of the submission does contain information that a sponsor considers to be proprietary or trade secret, the submission to the NIH OSP must contain a letter from the sponsor that: (1) clearly indicates what select portions of the application contain information considered as proprietary or trade secret, (2) provides an adequate and convincing justification as to the reason that this information is considered to be proprietary or trade secret. The justification must be able to demonstrate with specificity how release of that information will reveal a trade secret or will result in substantial competitive harm.

Appendix M-I-B, RAC Review Requirements is proposed to be amended to change the process and timing of initial and RAC review. Currently, investigators are informed within 15 working days whether or not the protocol requires public RAC

review. Public discussion of selected protocols then occurs at the next quarterly RAC meeting, which occurs, at a minimum of, eight weeks after receipt of a complete protocol submission. Under the proposal, individual RAC members will no longer make a recommendation regarding whether a protocol should be selected for review at a public meeting.

Therefore, Appendix M-1-B-1 and Appendix M-1-B-2 are being amended as follows to form a consolidated Appendix M-1-B:

Appendix M-1-B. Selection of Individual Protocols for Public RAC Review and Discussion

As part of the NIH protocol registration process, documentation from oversight bodies regarding their assessment of whether RAC review is warranted. If no oversight body would significantly benefit from public RAC review and discussion, then the Principal Investigator shall submit all of the documentation required to register the submission (see Appendix M-I-A) to the NIH OSP at any time but shall occur not less than three working days prior to the anticipated date of enrollment of the first subject (see definition of enrollment in Section I-E-7), and shall be provided in electronic form to the Office of Science Policy, National Institutes of Health, 6705 Rockledge Drive, Suite 750, Bethesda, MD 20892-7985 (20817 for non-USPS mail), 301-496-9838, 301-496-9839 (fax), E-mail: HGTprotocols@mail.nih.gov. Enrollment may proceed upon acknowledgement that the submission is registered.

If an oversight body determines that: (1) a protocol submission would significantly benefit from public RAC review and discussion and (2) that one or more of the following NIH RAC review criteria are met: (i) the protocol uses a new vector,

genetic material, or delivery methodology that represents a first-in-human experience, thus presenting an unknown risk; or (ii) the protocol relies on preclinical safety data that were obtained using a new preclinical model system of unknown and unconfirmed value; or (iii) the proposed vector, gene construct, or method of delivery is associated with possible toxicities that are not widely known and that may render it difficult for local and federal regulatory bodies to evaluate the protocol rigorously, and is therefore requesting RAC review and public discussion, the Principal Investigator shall submit the documentation as outlined in Appendix M-I-A at least 8 weeks prior to the next scheduled meeting in order to be reviewed at that RAC meeting. The submission shall include documentation from oversight bodies regarding their assessment of whether RAC review is warranted and that one or both have justified their request according the NIH RAC review criteria listed above. The submission shall be provided to the NIH in electronic form to the Office of Science Policy, National Institutes of Health, 6705 Rockledge Drive, Suite 750, Bethesda, MD 20892-7985 (20817 for non-USPS mail), 301-496-9838, 301-496-9839 (fax), E-mail: HGTprotocols@mail.nih.gov. If NIH determines that any of the criteria listed in subsections (i), (ii), or (iii) above is met, the protocol will undergo public RAC review and discussion.

If an oversight body requests that the RAC review a protocol and the NIH determines that the protocol does not satisfy one or more of the above NIH RAC review criteria, the NIH OSP will inform the Principal Investigator, oversight bodies, and regulatory authorities, as appropriate, that RAC review is not warranted.

Even if an oversight body does not request that a particular protocol be reviewed by the RAC, the NIH Director, after consultation (if needed) with appropriate regulatory

authorities, may initiate RAC review if (a) the protocol has one or more of the characteristics listed above (i, ii, or iii) and public RAC review and discussion would provide a clear and obvious benefit to the scientific community or public; or (b) the protocol otherwise raises significant scientific, societal, or ethical concerns.

Completion of the registration process is defined as: (1) receipt by the Principal Investigator of a letter from the NIH OSP indicating that protocol registration process is complete and that enrollment may proceed; or (2) receipt by the Principal Investigator of a letter from the NIH after public RAC review that summarizes the committee's key comments and recommendations (if any).

A complete human gene transfer protocol package must be submitted at least eight weeks before a scheduled RAC meeting to be reviewed at that upcoming meeting.

After a human gene transfer experiment is publicly reviewed by the full RAC at a regularly scheduled meeting, the NIH OSP will send a letter summarizing the RAC's key comments and recommendations (if any) regarding the protocol to the Principal Investigator(s), oversight bodies, and regulatory authorities as appropriate. Completion of RAC review is defined as receipt by the Principal Investigator(s) of a letter from the NIH OSP summarizing the committee's findings. Unless the NIH determines that there are exceptional circumstances, the letter containing recommendations and comments made following public review will be sent within 10 working days after the completion of the RAC meeting at which the protocol 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-I-A should not contain trade secrets or confidential commercial or financial information. An application submitted to the NIH OSP shall not contain any document that is designated as 'confidential' in its entirety. In the event that a determination has been made that a specific portion of a document submitted as one of the items described in Appendix M should be considered as confidential commercial or financial 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 or financial information or a trade secret; and (2) explain and justify each designation to demonstrate with specificity how release of that information will reveal a trade secret or will result in substantial competitive harm.

There are no proposed amendments to Appendix M-I-C, Reporting Requirements and Appendix M-I-D, Safety Assessments in Human Gene Transfer Research.

The current appendices Appendix M-II, Description of the Proposal; Appendix M-III, Informed Consent; Appendix M-IV, Privacy; and Appendix M-V, Special Issues are proposed to be deleted in their entirety, except for Appendix M-III-B-2-b, Long Term Follow-Up which will be updated to include a reference to FDA's current guidance on this issue and will become Appendix M-II.

Appendix M-II is proposed to be amended as follows:

Appendix M-II. Long Term Follow-Up

To permit evaluation of long-term safety and efficacy of gene transfer, prospective subjects should be informed that they are expected to cooperate in long-term follow-up that extends beyond the active phase of the study. A list of persons who can be contacted in the event that questions arise during the follow-up period should be provided

to the investigator. In addition, the investigator should request that subjects continue to provide a current address and telephone number.

The subjects should be informed that any significant findings resulting from the study will be made known in a timely manner to them and/or their parent or guardian including new information about the experimental procedure, the harms and benefits experienced by other individuals involved in the study, and any long-term effects that have been observed.

Additional guidance is available in the FDA Guidance for Industry: Gene Therapy Clinical Trials - Observing Subjects for Delayed Adverse Events (available at the following URL: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/default.htm).

Appendix M-VI Footnotes of Appendix M will be renumbered to Appendix M-III. Footnotes of Appendix M. There will be no amendment to the language.

Dated: October 9,2015

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Francis S. Collins, M.D., Ph.D.

Director

National Institutes of Health

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