NIH Guidelines April 2019

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Abstract

Following the required review period initiated in August 2018, the Department of Health and Human Services, National Institutes of Health (NIH), published the final changes to the Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines) in April 2019. This amendment focused on the review, registration, and reporting requirements for human gene transfer studies. In addition, the Recombinant DNA Advisory Committee (RAC) was renamed the Novel and Exceptional Technology and Research Advisory Committee (NeXTRAC) to serve as an advisory body on emerging technologies.

Keywords

NIH guidelines, human gene transfer, IBC, recombinant or synthetic nucleic acids, NIH

Following the required review period initiated in August 2018, the Department of Health and Human Services, National Institutes of Health (NIH), published the final changes to the Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines) in April 2019.^{1,2}

Salient changes to the NIH Guidelines include the following:

1. The requirement to register and report human gene transfer (HGT) protocols to the NIH Office of Science Policy (OSP) was eliminated.
2. The Recombinant DNA Advisory Committee (RAC) was renamed the Novel and Exceptional Technology and Research Advisory Committee (NeXTRAC) to align with the role initially assigned to the RAC as the advisory body on emerging biotechnologies.
3. Roles and responsibilities of investigators, institutional biosafety committees (IBCs), and the NIH were modified.

The changes to the NIH Guidelines are summarized in Table 1.

Relevant topics associated with the NIH Guidelines 2019 amendment are as follows:

1. Revised template for reporting incidents under the NIH Guidelines: https://osp.od.nih.gov/wp-content/uploads/Incident-Reporting-Template_42319.docx
2. FAQs—April 2019 amendment of the NIH Guidelines: <https://osp.od.nih.gov/biotechnology/faqs-on-the-nih-guidelines-research-synthetic-nucleic-acid-molecules/>

3. FAQs on IBC administration—May 2019: <https://osp.od.nih.gov/biotechnology/faqs-on-ibc-administration/>
4. FAQs on the vaccine exemption: Appendix M-III-A of the NIH Guidelines exempted certain vaccine trials from the NIH OSP registration requirements; these studies must comply with all other requirements of the NIH Guidelines: <https://osp.od.nih.gov/wp-content/uploads/2016/04/Vaccine%20Exemption%20FAQ%20sheet.pdf>

Additional resources available to IBCs reviewing HGT studies are the following:

- IBCs may seek expertise outside the committee members and outside the institution.
- The points to consider included in the former Appendix M are now available on the NIH OSP web page “NIH Guidelines Frequently Asked Questions”
- RAC archives are available in the NIH OSP website.
- The ClinicalTrials.gov website contains information on publicly and privately supported clinical studies.

The Genetic Modification Clinical Research Information System (GeMCRIS[®]) will not be available after September 30, 2019. This database has not been updated since August 2018.

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Table 1. Comparison between the 2016 and 2019 Amendments to the NIH Guidelines.

Section	Context	NIH Guidelines 2016	NIH Guidelines 2019
I-A-I	HGT protocol registration requirement	Exception statement in section I A-I-a regarding requirement for HGT protocol registration	Exception statement was removed
I-A-I-a	Participant enrollment	... no research participant shall be enrolled until the NIH protocol registration process has been completed clinical trial site that is added after completion of NIH protocol registration	... no HGT experiment shall be initiated NIH protocol registration was removed ... clinical trial site that is added after ... was removed
I-E	General definitions	I-E-4 Recombinant DNA Advisory Committee I-E-7 Enrollment I-E-8 Serious adverse Event I-E-9 Adverse event associated with the use of gene transfer product I-E-10 Unexpected serious adverse events I-E-11 Oversight body I-E-12 Regulatory authority	I-E-4 definition for RAC was replaced with the definition for “initiation” I-E-7 through I-E-12 were removed
III	Experiments covered by the NIH Guidelines—scope	... RAC review ...	RAC review was removed
III-A	Scope of III-A	... RAC review III-A-I-a ... will be reviewed by the RAC	RAC review was removed III-A-I-a ... will require NIH Director approval
III-C	Scope of III-C Experiments involving HGT into 1 or more human research participants	... require Institutional Biosafety Committee and Institutional Review Board Approvals and RAC review before research participant enrollment. III-C-I participant enrollment, NIH protocol registration, public RAC review, clinical trial site added after NIH protocol registration, public access to information regarding HGT	... require Institutional Biosafety Committee Approval Prior to Initiation III-C-I removed NIH protocol registration, public RAC review, clinical trial sites added, public access to information provided as part of the registration with NIH Added: Research cannot be initiated until IBC and all other applicable institutional and regulatory authorizations and approvals have been obtained Added: deliberate transfer of recombinant or synthetic nucleic acids to 1 human research participant
III-D-7	Highly pathogenic avian influenza H5N1 strains	III-D-7-b and III-D-7-d OSP available to IBCs to provide consultation with RAC	RAC consultation or RAC review were removed
III-F-6	Exempt experiments: exchange of DNA by physiological processes	... with the advice of the RAC ...	Reference to RAC was removed
III-F-8	Exempt experiments: no significant risk to health or environment	... with the advice of the RAC ...	Reference to RAC was removed
IV-B-I-f	Institutional responsibilities	... Appendix M-I-B	Reference to Appendix M-I-B removed Revised (ii) to require IBC approval prior to initiation
IV-B-2-a-(I)	IBC membership and procedures	(ii) Appendix M (iii) NIH protocol registration (iv) IBC approval after NIH protocol registration	(ii), (iii), (iv) were removed
IV-B-2-b-(I)	IBC functions	(iii) Appendix M requirements (iv) Participant enrollment (v) RAC review, if needed (vi) IBC approval after NIH protocol registration (vii) Compliance with surveillance, data reporting, and adverse event requirements	(iii) through (vii) have been removed and replaced with (iii) assessment focused on biosafety issues and oversight

(continued)

Table 1. (continued)

Section	Context	NIH Guidelines 2016	NIH Guidelines 2019
IV-B-2-b(8)	Experiments explicitly covered by NIH guidelines	... with the advice of the RAC when required ...	Reference to RAC was removed
IV-B-6	Human gene therapy expertise	(ii) all aspects of Appendix M...	(ii) Reference to Appendix M was removed
IV-B-7	PI	IV-B-7-b(6) Appendix M	IV-B-7-b(6) was removed
IV-C-1	PI reporting requirements	IV-B-7-e(5) HGT reporting requirements	IV-B-7-e(5) was removed
IV-C-1	NIH director: general responsibilities	IV-C-1-a(2) maintaining RAC IV-C-1-a(3) and IV-C-1-a(4) IV-C-1-a(5) gene therapy policy conferences	IV-C-1-a(2) maintaining RAC was removed Made as one statement IV-C-1-a(3) IV-C-1-a(5) was removed
IV-C-2	Recombinant DNA Advisory Committee	Section IV-C-2. RAC	Section IV-C-2. RAC removed New IV-C-2 OSP Includes multiple revisions and deletions
IV-D -5	Voluntary compliance	... Members of RAC ...	Reference to RAC was removed
V-A	Footnotes and references of sections I-IV	... with the advice of the RAC ...	Reference to RAC was removed
V-B	Section III- judgment call	NIH OSP may request advice from the RAC ...	Reference to RAC was removed
Appendix A	Exemptions under section III-F-6	Advice of RAC	Reference to RAC was removed
Appendix C-IX-A	Footnotes and references of Appendix C	Advice of RAC	Reference to RAC was removed
Appendix D	Major actions	Reference to RAC	Reference to RAC was removed
Appendix I-II	Biological containment (Appendix E, certified host-vector systems)	Multiple references to RAC review	Reference to RAC was removed; added deference to NIH OSP
Appendix L	Gene therapy policy conferences	Gene therapy policy conferences	Gene therapy policy conferences has been deleted in its entirety New Appendix L: Physical and biological containment for recombinant or synthetic nucleic acid molecule research involving plants (formerly Appendix P)
Appendix M	Protocols for transfer of recombinant or synthetic nucleic acid molecule into human participant	Points to consider in the design and submission of protocols for the transfer of recombinant or synthetic nucleic acid molecules into 1 or more human research participants (points to consider)	Points to consider has been deleted in its entirety; it is now a document found on the NIH OSP web page "NIH Guidelines Frequently Asked Questions" New Appendix M: Physical and biological containment for recombinant or synthetic nucleic acid molecule research involving animals (formerly Appendix Q)

Abbreviations: HGT, human gene transfer; IBC, institutional biosafety committee; NIH, National Institutes of Health; OSP, Office of Science Policy; PI, principal investigator; RAC, Recombinant DNA Advisory Committee.

Inquiries can be directed to the NIH OSP at SciencePolicy@od.nih.gov.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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1. Federal Register Department of Health and Human Services Office of Science Policy National Institutes of Health. Final action under the NIH guidelines for research involving recombinant or synthetic nucleic acid molecules (NIH Guidelines). 84 FR 17858. <https://www.federalregister.gov/documents/2019/04/26/2019-08462/final-action-under-the-nih-guidelines-for-research-involving-recombinant-or-synthetic-nucleic-acid> April 26, 2019. Accessed June 9, 2019.
2. Federal Register Department of Health and Human Services National Institutes of Health Office of Science Policy. Notice - Proposed Changes to the Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules. <https://www.govinfo.gov/content/pkg/FR-2018-08-17/pdf/2018-17760.pdf> August 17, 2018. Accessed June 9, 2019.