



April 2019 Amendment of the *NIH Guidelines*

1. Why is NIH making changes to its oversight of human gene transfer (HGT) research?

NIH and the Food and Drug Administration (FDA) are working together to ensure that the federal framework for oversight of HGT research keeps pace with this rapidly advancing and promising area of science. Federal and institutional oversight over HGT research has evolved since NIH first established the *NIH Guidelines*, resulting in a duplication in review and reporting not afforded to other areas of clinical research. Thus, NIH is eliminating unnecessary duplication in the oversight system to streamline areas of overlap among NIH, FDA, and the local oversight bodies (Institutional Review Boards and Institutional Biosafety Committees) regarding individual HGT protocols.

2. How can we be sure that there is adequate oversight for human gene transfer (HGT) research without the submission of protocols and reporting of adverse events to NIH's Office of Science Policy, and the transparent process afforded by the Recombinant DNA Advisory Committee public review?

It is important to note that while NIH is streamlining individual HGT protocol reporting requirements, robust oversight over HGT research will continue through both Federal and local oversight bodies. HGT research remains subject to Food and Drug Administration oversight. In addition, as with all NIH-supported research, HGT research will remain subject to NIH oversight, as well as applicable policies and regulations for the protection of human subjects in research—such as the Common Rule and the NIH policy on Certificates of Confidentiality—and rigorous local oversight will continue to be provided by Institutional Review Boards and Institutional Biosafety Committees.

3. How will Institutional Biosafety Committees (IBCs) be able to evaluate human gene transfer (HGT) protocols without the expertise that the Recombinant DNA Advisory Committee (RAC) and NIH provided?

IBCs are a cornerstone of institutional oversight of research involving recombinant and synthetic nucleic acid molecules, and they will continue to evaluate HGT protocols for important biosafety considerations. It is important to emphasize that review of the safety and ethical considerations for research participants has always been a shared responsibility of the Food and Drug Administration, Institutional Review Boards, and IBCs.



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Historically, only about 20% of HGT protocols submitted to IBCs underwent public RAC review. After the criteria for RAC review were amended in 2016, only 1% of HGT protocols were assessed by NIH to meet the revised criteria, reinforcing the important role IBCs have had in independently reviewing HGT research.

4. What is the future of the Recombinant DNA Advisory Committee (RAC)?

NIH recognizes the role the RAC has played in advancing human gene transfer (HGT) research into clinical studies and avenues for treatment. Thus, the agency looks to harness the convening power of the RAC to apply this successful forum for the transparent discussion of science, safety, and ethics to areas of emerging biotechnologies, which include, but are not restricted to, technologies surrounding advances in recombinant or synthetic nucleic acid research such as HGT. Effective immediately, NIH has renamed the RAC the Novel and Exceptional Technology and Research Advisory Committee (NExTRAC) to reflect this expanded focus.

5. What specific changes have been made to the *NIH Guidelines* regarding human gene transfer (HGT) protocol submission and reporting requirements to NIH's Office of Science Policy (OSP)?

Under the *NIH Guidelines*, individual HGT protocol submission and reporting to NIH/OSP are no longer required. Specifically, NIH/OSP will not:

- accept or register new HGT protocols
- convene the Recombinant DNA Advisory Committee (RAC) to review individual HGT protocols
- accept annual reports, safety reports, amendments or other documentation for any HGT protocols previously registered under the *NIH Guidelines* (formerly, Appendix M-I-C)

6. What changes have been made to the *NIH Guidelines* regarding the roles and responsibilities of relevant entities?

It is important to note that while NIH is streamlining individual human gene transfer (HGT)



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protocol reporting requirements, robust oversight over HGT research will continue through both Federal and local oversight bodies. The roles and responsibilities of investigators, institutions, and oversight bodies involved in HGT research remain the same, except:

- The roles of Institutional Biosafety Committees in reviewing HGT research have been modified to be consistent with the review of other research covered by the *NIH Guidelines*.
- Principal Investigators (PIs) will no longer be responsible for ensuring requirements for protocol submission, review, and reporting for HGT protocols to NIH's Office of Science Policy are addressed, since these responsibilities have been eliminated. All other roles and responsibilities for PIs will remain the same.
- Because the Novel and Exceptional Technology and Research Advisory Committee (NExTRAC) will now focus on advising the NIH Director on scientific, safety, and ethical issues associated with emerging biotechnologies (which is not necessarily limited to recombinant or synthetic nucleic acid molecule research), non-historical references to the Recombinant DNA Advisory Committee will be removed from the *NIH Guidelines*. The roles and responsibilities will be delineated in the charter, as is typical for such committees.

7. Is human gene transfer (HGT) research still covered under the *NIH Guidelines*? What is required before a Principal Investigator or sponsor can initiate HGT research and begin enrollment/recruitment/accrual?

Yes. When conducted by an entity subject to the *NIH Guidelines* (see Section I-C), HGT research (see Section III-C) is still covered, as protocols must still be reviewed and approved by Institutional Biosafety Committees to assess biosafety considerations at the clinical trial site. In addition, all other applicable institutional and regulatory authorization(s) and approvals must be obtained before any research with human participants can be initiated.

8. If human gene transfer (HGT) protocols are no longer registered with NIH's Office of Science Policy (OSP), will sites conducting only HGT research still need to register their Institutional Biosafety Committees (IBCs) with NIH/OSP?

Yes. All entities conducting research subject to the *NIH Guidelines*, including HGT research, must have an appropriately constituted IBC registered with NIH/OSP. For additional information on registering an IBC, see Section IV-B-2 of the *NIH Guidelines* and on the



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NIH/OSP website: <https://osp.od.nih.gov/biotechnology/faqs-on-ibc-administration/>.

9. Is human gene transfer research conducted under Food and Drug Administration (FDA)-regulated individual patient expanded access Investigational New Drug (IND) applications subject to the *NIH Guidelines*?

No. The deliberate transfer of recombinant or synthetic nucleic acids into one human research participant, conducted under an FDA-regulated individual patient expanded access IND or protocol, including for emergency use, is not research subject to the *NIH Guidelines* and thus does not need to be submitted to an Institutional Biosafety Committee for review and approval. Specific guidance regarding FDA requirements is provided at: <https://www.fda.gov/downloads/drugs/guidances/ucm351261.pdf>.

10. Will Institutional Biosafety Committees (IBCs) be required to change their review processes? What aspects of human gene transfer (HGT) research should IBCs focus on?

The focus of the IBC review of HGT research should be equivalent to their review of the biosafety aspects of other covered research, e.g.:

- required containment levels
- potential for shedding
- safety and training of laboratory/technical personnel involved in the clinical protocol
- details of the facilities
- adequacy and maintenance of safety equipment that may be used in support of the clinical protocol
- safety procedures and practices when working with the product and during administration to a protocol participant
- reporting of biosafety accidents and incidents occurring during conduct of the protocol
- approving emergency response plans for accidental spills and personnel contamination

As with other research reviewed by IBCs, IBCs should determine what information they require to complete their biosafety review of HGT protocols.

IBC oversight may conclude after the last participant is administered the final dose of product. However, IBCs may choose to establish other end points for oversight, based on



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their biosafety assessment of the proposed research.

Other aspects of HGT research, such as review of informed consent, are under the purview of the Food and Drug Administration and Institutional Review Boards.

11. Should biosafety incidents occurring during the conduct of human gene transfer (HGT) research still be reported to NIH's Office of Science Policy (OSP)?

Yes. The *NIH Guidelines* require that "...any significant problems, violations of the *NIH Guidelines*, or any significant research-related accidents and illnesses" be reported to NIH. Reports of incidents can be emailed to NIHguidelines@od.nih.gov. Relevant incidents would include spills and accidents that result in overt exposures to organisms containing recombinant or synthetic nucleic acid molecules in the laboratory, rather than serious adverse events that may occur in the conduct of HGT research. Additional information on incident reporting and a reporting template are available on the NIH/OSP website at <https://osp.od.nih.gov/biotechnology/nih-guidelines/>.

12. Since oversight bodies can no longer request Recombinant DNA Advisory Committee (RAC) review of protocols, what resources are available for Institutional Biosafety Committees (IBCs) that need assistance with their review of human gene transfer (HGT) protocols?

As always, the IBC may augment the expertise of its members with HGT subject matter experts, as necessary. The parts of the former Appendix M-I-A that are still relevant, in light of the final changes to the *NIH Guidelines*, are available [as a separate resource](#) for institutions, IBCs, and Principal Investigators (PIs) on the types of information that institutions and IBCs may wish to consider in the review of HGT protocols. Other resources are accessible on NIH's Office of Science Policy (OSP) website, including webcasts and minutes of previous RAC public meetings and workshops. In addition, ClinicalTrials.gov is a publicly available resource. NIH/OSP continues to serve as a resource for questions from institutions, IBCs, and PIs regarding the applicability of the *NIH Guidelines*.

For more information about the *NIH Guidelines*, please email NIH/OSP at NIHGuidelines@od.nih.gov or call 301-496-9838.



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