

NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (*NIH Guidelines*)

Frequently Asked Questions about the Registration and Review Process for Human Gene Transfer Protocols

What is the process for initiating review of individual human gene transfer protocols by the NIH Recombinant DNA Advisory Committee (RAC)?

In April 2016, the NIH streamlined the review process for human gene transfer protocols subject to the *NIH Guidelines*. RAC review of individual human gene transfer protocols will be performed only in exceptional cases that meet the following specified criteria (criteria listed in both items 1 and 2 must be met):

1. An oversight body (e.g., Institutional Biosafety Committee (IBC) or 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.

Does the NIH need to concur that both criteria listed above are met in order for RAC review to proceed?

The NIH must concur that both criteria listed in items 1 and 2 above are met in order to initiate RAC review. If one or more oversight bodies requests RAC review but the NIH does not concur that both criteria are met, then the NIH will inform the submitter within 10 working days that RAC review is not warranted.

As a note, even if a protocol does not meet the criteria listed above, the NIH Director, in consultation (if needed) with appropriate regulatory authorities (e.g., the Office for Human Research Protections, the FDA), can select a protocol for review that may present significant scientific, societal, or ethical concerns.

Who can request RAC review?

The chair of an oversight body (e.g., IBC or IRB) or an institutionally authorized representative may submit a request for RAC review by sending the request to the NIH as part of the submission materials provided by the principal investigator. Requests for RAC review must originate from oversight bodies involved in the initial site(s) review, and must include the rationale for why the protocol satisfies both criteria for initiating RAC review. The NIH will review the request and notify the submitter as to whether it concurs with its assessment within 10 working days. Oversight bodies reviewing protocols at sites added after the initial registration process has been completed may not request RAC review.

Do all of the oversight bodies at all of the sites that are identified as an initial trial site have to provide documentation as to whether or not they are requesting RAC review?

The submission to NIH must include documentation regarding whether or not all oversight bodies at each initial trial site are requesting RAC review. If RAC review is requested, the submission to NIH must include an assessment as to how the protocol meets the criteria for RAC review. A request for RAC review from any of the oversight bodies at an initial trial site will be sufficient to trigger RAC review if NIH concurs that the criteria for review are met.

Does the IRB at each initial clinical trial site have to submit documentation regarding whether or not they are requesting RAC review?

An assessment must originate from all oversight bodies involved in the review at initial sites(s). The IRB may, however, defer its assessment to the IBC or abstain from making this assessment. The decision of an IRB to defer or abstain must be provided to NIH in writing.

Does the entire oversight body need to meet to decide whether RAC review should be requested, and if so, that the protocol meets the criteria for RAC review?

The entire oversight body does not need to hold a convened meeting to determine whether RAC review will be requested. The chair of an oversight body (e.g., IBC or IRB) or an institutionally authorized representative may submit a request for RAC review. The process by which the oversight body makes such a determination is left to the discretion of the institution.

Will oversight bodies have to change the way they review human gene transfer protocols?

It is expected that oversight bodies will continue to review protocols in the same manner they always have. In cases where an oversight body feels additional expertise is required, they are encouraged to augment the committee with appropriate ad hoc members. NIH can also assist oversight bodies upon request, by providing them with publicly available information, including data from its Genetic Modification Clinical Research Information System (GeMCRIS®): <https://www.gemcris.od.nih.gov/>.

Do all human gene transfer protocols still need to be registered with the NIH?

As previously, all human gene transfer protocols subject to the *NIH Guidelines* must be registered with the NIH.

Have the submission requirements for the human gene transfer protocol registration process changed?

The information required to be submitted by investigators is listed in Appendix M-I-A. As part of the submission, the principal investigator will be required to include written assessments from all oversight bodies (e.g., IBCs and IRBs) involved in the review of the protocol at the initial trial site(s) as to whether review by the RAC is warranted.

The IBC at each trial site, regardless of whether the site is the initial or a subsequent site, is charged with ensuring that all aspects of Appendix M are appropriately addressed prior to granting approval (see Section IV-B-2-b-(1)). A review of all documents submitted under Appendix M-I-A is expected. This includes review of the informed consent document.

When is an IBC permitted to approve a human gene transfer protocol?

The IBC is permitted to approve the protocol upon confirmation from the NIH that the protocol registration process is complete. In the event that RAC review is requested and the NIH concurs, the protocol registration process cannot be completed until RAC review has taken place.

When may an investigator start enrolling participants in a human gene transfer protocol?

Under the *NIH Guidelines*, participant enrollment begins with the process of obtaining informed consent from prospective participants. For an initial clinical trial site(s), enrollment cannot begin until: (1) All documentation described in Appendix M-I-A has been submitted, and the NIH has informed the investigator that the protocol registration process/RAC review (if applicable) has been completed; and (2) IBC approval as well as all applicable regulatory authorization(s) have been obtained. All documentation described in Appendix M-I-C-1 of the *NIH Guidelines* must then be provided no later than 30 days after enrollment of the first participant.

For a clinical trial site that is added after the completion of the NIH protocol registration process, no research participant shall be enrolled at the clinical trial site until IBC approval and IRB approval from that site have been obtained. Within 30 days of enrollment at a clinical trial site, the following documentation shall be submitted to NIH: (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.

Are investigators still required to submit follow-up information to the NIH after the human gene transfer protocol registration process is complete?

Principal investigators remain responsible for submitting appropriate and timely follow-up data including protocol amendments, serious adverse events, and annual reports with cumulative safety data for all protocols subject to the *NIH Guidelines*. Safety information such as adverse events occurring on human gene transfer trials and annual reports may be reported directly to NIH using GeMCRIS[®] (<https://www.gemcris.od.nih.gov/>) or via email at HGTprotocols@mail.nih.gov.

Is information regarding human gene transfer protocols submitted to NIH confidential?

Documents submitted to NIH should not contain information considered confidential, and a document such as a clinical protocol cannot be classified as “confidential” in its entirety. Should a submitter choose to provide information that is considered to be trade secret, commercial confidential, or financial in nature, it is incumbent on the submitter to clearly identify those portions of the document and to justify with specificity how the release of that information could cause financial or competitive harm. All records submitted to NIH, including human gene transfer clinical trial information, are subject to the Freedom of Information Act (FOIA – 5 U.S.C. 552) and the Department of Health and Human Services FOIA regulations (45 CFR part 5).

Where can individuals obtain more information about the requirements for human gene transfer protocol registration and review under the *NIH Guidelines*?

For more information about the registration and review process for human gene transfer trials under the *NIH Guidelines*, please email OSP at HGTprotocols@mail.nih.gov or call 301-496-9838.