

Guide to Conduct Human Gene Transfer (HGT) Research at Weill Cornell Medicine (WCM)

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1.0 Overview

The following guide has been prepared to assist Principal Investigators (PI) and supporting staff with the submission and review process for clinical research studies that involve the use of recombinant or synthetic nucleic acid molecules into human research participants, Human Gene Transfer (HGT) at Weill Cornell Medicine (WCM). Although the guide provides assistance with the submission, registration process and ongoing requirements after initiation of a human gene transfer protocol at WCM, it may not cover every question that may arise. If you have any questions please contact the EHS office at 646-962-7233 and ask to speak to the Regulatory Coordinator or email the IBC at ibc@med.cornell.edu.



Institutional Biosafety Committee

TEL 646-962-7233 EMAIL ibc@med.cornell.edu

WEB http://researchintegrity.weill.cornell.edu/institutional_biosafety_committee/index.html

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2.0 2016 Changes to Appendix M of the NIH Guidelines

In April 2016, the National Institute of Health (NIH) Office of Science Policy (OSP) revised Appendix M of the NIH Guidelines, which addressed the review and management of HGT protocols.

Significant changes to the NIH review process include:

- Initial review of HGT research protocols will be performed by an organizational oversight body, such as an Institutional Biosafety Committee (IBC) or an Institutional Review Board (IRB). This local commission will determine if the protocol requires further review by the NIH Recombinant DNA Advisory Committee (RAC). Please note that additional clinical trial sites added to the protocol at a later date must ensure and document that RAC review determination was made by the initial site.
- The M-I-A Requirements for Protocol Submission have been updated to simplify and consolidate the responses provided by the Principal Investigator, as well as clarify what constitutes a trade secret.
- Appendices M-II, M-III, M-IV, and M-V have been removed (except Section M-III-B-2-b Long Term Follow up). Long-Term Follow up was updated with information from the FDA. Long-Term Follow up is the subject of the new Section M-II.

3.0 Human Subjects Research Requiring IBC Approval

For experiments involving deliberate transfer of recombinant or synthetic nucleic acid molecules or DNA or RNA derived from recombinant or synthetic nucleic acid molecules, into human research participants (Human Gene Transfer) that meet any of the listed below criteria no research participant shall be enrolled until the NIH protocol registration process has been completed.

- Contain more than 100 nucleotides;
- Possess biological properties that enable integration into the genome (e.g., cis elements involved in integration);
- Have the potential to replicate in a cell; or
- Can be translated or transcribed.

4.0 Definitions

Enrollment is defined as the process of obtaining informed consent from a potential research participant, or a designated legal guardian of the participant, to undergo a test or procedure associated with the gene transfer experiment.

Recombinant and synthetic nucleic acids are:

- i. Molecules that a) are constructed by joining nucleic acid molecules and b) that can replicate in a living cell, i.e., recombinant nucleic acids;
- ii. Nucleic acid molecules that are synthesized or amplified chemically or by other means, including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules, i.e., synthetic nucleic acids, or
- iii. Molecules that result from the replication of those described in (i) or (ii) above.

5.0 IBC Submission Process

The IBC and IRB submission process varies depending on whether the study is single-site or multi-site. The process will also vary depending on whether review by the NIH RAC is needed.

5.1 WCM AS THE INITIAL OR ONLY SITE FOR THE STUDY

If WCM is the initial or only site for the study, no research participant shall be enrolled in the study until:

- An assessment has been performed by the Institutional Biosafety Committee (IBC) and Institutional Review Board (IRB) to determine whether NIH RAC review is needed;



- NIH RAC review has been completed, when applicable;
- IBC approval has been obtained;
- IRB approval has been obtained;
- NIH protocol registration process has been completed; and
- All applicable regulatory authorization(s) have been obtained.

5.2 WCM AS AN ADDITIONAL CLINICAL TRIAL SITE

If WCM is added as a clinical trial site after the NIH protocol registration process (for multi-site studies), no research participant shall be enrolled at WCM until approvals from the WCM IBC and IRB are in place.

6.0 Institutional Assessment for NIH RAC Submission and Review

Public RAC review and discussion of a human gene transfer experiment will be initiated in two exceptional circumstances:

1. The NIH Director determines it is necessary, or
2. The IRB or IBC at any initial site(s) determine that a protocol would significantly benefit from RAC review AND meets any of the following criteria:
 - The protocol uses a new vector, genetic material, or delivery methodology that represents a first-in-human experience, thus presenting an unknown risk;
 - The protocol relies on preclinical safety data that were obtained using a new preclinical model system of unknown and unconfirmed value; or
 - 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 oversight bodies involved to evaluate the protocol rigorously.

For HGT Clinical Trials where WCM is the initial trial site, the WCM IBC and the WCM IRB will jointly assess whether the protocol requires RAC review.

7.0 WCM IBC Review Process

7.1 WCM AS THE INITIAL OR ONLY SITE FOR THE STUDY

Only one determination type (**either A or B**) will apply to each protocol. Steps for both processes are detailed below.

7.1.1 Process A: IRB and/or IBC requests public RAC review

1. PI completes the WCM HGT Application and submits with supporting documentation to IBC via email submit2ibc@med.cornell.edu
2. IBC provides the IRB with the completed RAC Review Assessment Form and any supporting documentation.
3. IBC and IRB perform RAC assessment simultaneously, **conclude that RAC review is needed**.
4. IBC/IRB provide joint assessment determination letter to the PI via email.
5. PI submits documents listed in Appendix M-I-A to the RAC.
6. RAC proceeds with public review. A determination letter is mailed from the NIH to the PI within 10 business days after RAC meeting. Receipt of this letter concludes the protocol registration process.
7. PI submits to IRB for initial review. The submission must include the RAC determination letter and response to RAC's recommendations on the protocol (if applicable).
8. IRB proceeds with the review and once all IRB requirements are met, issues approval pending letter.
9. PI submits the protocol to IBC for review
10. IBC proceeds with the review and once all IBC requirements are met, issues approval.
11. PI provides the final IBC approval to the IRB.
12. IRB final approval is issued.



13. Initiation of the Clinical Investigation: PI submits the documents listed in Appendix M-I-C-1 to the NIH via email at HGTprotocols@mail.nih.gov **within 30 days of enrollment of the first research participant.**

7.1.2 Process B: No public RAC review requested

1. PI completes the WCM HGT Application and submits with supporting documentation to IBC.
2. IBC staff provide the IRB staff with the completed RAC Review Assessment Form and any supporting documentation.
3. IBC and IRB perform RAC assessment simultaneously, **conclude that RAC review is not needed.**
4. IBC/IRB provide joint assessment determination letter to the PI via email.
5. PI submits to IRB for initial review, IRB proceeds with the review, once all IRB requirements are met, issues approval pending letter.
6. PI submits the protocol to IBC for review.
7. IBC proceeds with the review and once all IBC requirements are met, issues approval.
8. PI provides the final IBC approval to the IRB.
9. IRB final approval is issued.
10. PI submits the required documents listed in Appendix M-I-A to register the protocol with NIH **but no less than 10 working days prior to the anticipated date of enrollment of the first research participant.** PI must submit to IBC the NIH the acknowledgment that the protocol registration is complete.
11. Initiation of the Clinical Investigation: PI submits the documents listed in Appendix M-I-C-1 to the NIH via email at HGTprotocols@mail.nih.gov **but no later than 30 days after enrollment of the first research participant.**

NOTE: Additional WCM approvals may be needed before study initiation, e.g., Radiation Safety Committee approval (if applicable), Investigational Pharmacy and Pathology approval.

7.2 WCM AS AN ADDITIONAL CLINICAL TRIAL SITE

If WCM is not the initial study site, the initial site will perform the assessment and determine whether the study needs to be submitted to NIH RAC. This evaluation should be done prior to submitting the study to the WCM IBC for review; so that the RAC determination (if applicable) or confirmation that the protocol registration process was completed can be included in the submission. WCM is not responsible for making this assessment.

1. PI submits the protocol with supporting documentation to IRB for review, IRB proceeds with the review, once all IRB requirements are met, issues approval pending letter.
2. PI submits the protocol to IBC for review.
3. IBC proceeds with the review and once all IBC requirements are met, issues approval.
4. PI provides the IBC approval to the IRB.
5. IRB approval is issued.
6. NIH registration is updated to include the WCM trial site. PI submits the documents listed in Appendix M-I-C-2 (IBC approval, IRB approval, IRB-approved informed consent documentation and NIH grant number, if applicable) to the NIH via email at HGTprotocols@mail.nih.gov **within 30 days of enrollment of the first participant.**
7. PI provides notification to IBC once registration of the WCM site is complete.

NOTE: Additional WCM approvals may be needed before study initiation, e.g., Radiation Safety Committee approval (if applicable), Investigational Pharmacy and Pathology approval.

8.0 Initiation of the Clinical Trial, Annual Reports, and Safety Reporting Requirements

Appendix M-I-C of the NIH Guidelines describes the criteria, timing, and process for reporting in human gene transfer trials/protocols.

THE PRINCIPAL INVESTIGATOR IS RESPONSIBLE FOR ENSURING THAT THE REPORTING REQUIREMENTS ARE FULFILLED AND WILL BE HELD ACCOUNTABLE FOR ANY REPORTING LAPSES.



Report	NIH-OSP	IRB	IBC
INITIATION OF STUDY NOTE: No research participant shall be enrolled until the NIH protocol registration process has been completed.			
Initiation of the Clinical Investigation: After enrollment of the first research participant in a human gene transfer experiment, the Principal Investigator shall submit documents listed in Appendix M-I-C-1 to NIH.	No later than 30 days after enrollment of the first research participant.	No submission required.	PI provides notification to IBC via submit2ibc@med.cornell.edu
Addition of Clinical Trial Site: For a clinical trial site that is added after the completion of the NIH protocol registration process, no research participant shall be enrolled at that clinical trial site until site IBC and IRB approvals have been obtained.	Within 30 days of participant enrollment, the Principal Investigator shall submit documents listed in Appendix M-I-C-2 to NIH.	No submission required.	When registration of the WCM site is complete, PI provides notification to IBC via submit2ibc@med.cornell.edu
Annual Reports (Appendix M-I-C-3)	Within 60 days after the one-year anniversary of the date on which the investigational new drug (IND) application went into effect, and after each subsequent anniversary until the trial is completed.	Submit your Continuing Review ("Annual Review") to the IRB 6 to 8 weeks before your IRB study expiration date.	Same timeline as reporting to IRB.
APPENDIX M-I-C-4-B: SAFETY REPORTING			
Any serious adverse event that is fatal, life-threatening, or unexpected , and associated with the use of the gene transfer product must be reported to the NIH.	No later than 7 calendar days after the sponsor's initial receipt of the information (i.e., at the same time the event must be reported to the FDA).	According to IRB Immediate Reporting Policy, submit the Immediate Report within 7 calendar days of PI awareness.	According to IRB Immediate Reporting Policy.



Serious adverse events that are unexpected and associated with the use of the gene transfer product, but are not fatal or life-threatening, must be reported to the NIH.	As soon as possible, no later than 15 calendar days after the sponsor's initial receipt of the information (i.e., at the same time the event must be reported to the FDA).	According to IRB Immediate Reporting Policy	According to IRB Immediate Reporting Policy.
<i>See Appendix M-I-C-4-a for Safety Reporting content and format.</i>			

Note: Adverse events meeting certain criteria within HGT clinical trials at WCM must be reported to the NIH/OSP, IRB, IBC and other oversight bodies involved in the review (if applicable), within specific timeframes.

WCM IBC: submit2ibc@med.cornell.edu

WCM IRB: irb@med.cornell.edu

NIH OSP: HGTprotocols@mail.nih.gov

Please use the [Adverse Event Reporting Template](#) available at NIH OSP's website.

9.0 HGT Protocol Closeout

The PI must notify NIH, the IRB and the IBC when clinical HGT protocol is closed.

10.0 List of Documents

APPENDIX M-I-A DOCUMENTS

1. Scientific abstract.
2. 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. Description of the product, including:
 - a. 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. 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). Regulatory elements contained in the construct must be specified.
 - c. 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. Methods for replication-competent virus testing, if applicable.
 - e. Intended ex vivo or in vivo target cells and transduction efficiency.
 - f. Gene transfer agent delivery method.
5. Informed consent document(s) proposed.

APPENDIX M-I-C-1 DOCUMENTS

1. Copy of the informed consent document(s) approved by the WCM IRB
2. Copy of the protocol approved by the IBC and IRB.
3. Copy of the final WCM IBC approval.



4. Copy of the final IRB approval.
5. A brief written report that includes the following information:
 - How the investigator(s) responded to each of the RAC's recommendations on the protocol (if applicable), and
 - Any modifications to the protocol as required by FDA.
6. Applicable NIH grant number(s).
7. FDA Investigational New Drug Application (IND) number.
8. Date of the initiation of the trial.

APPENDIX M-I-C-2 DOCUMENTS

1. WCM IBC approval
2. WCM IRB approval,
3. WCM IRB approved informed consent document(s), and
4. NIH grant number(s) if applicable.

APPENDIX M-I-C-3 ANNUAL REPORT DOCUMENTS

Within 60 days after the one-year anniversary of the date on which the investigational new drug (IND) application went into effect, and after each subsequent anniversary until the trial is completed, the Principal Investigator (or delegate) shall submit the information set forth in (a), (b), and (c). When multiple studies are conducted under the single IND, the Principal Investigator (or delegate) may choose to submit a single annual report covering all studies, provided that each study is identified by its NIH protocol number.

A. Clinical Trial Information

A brief summary of the status of each trial in progress and each trial completed during the previous year. The summary is required to include the following information for each trial:

1. The title and purpose of the trial.
2. Clinical site.
3. Principal Investigator Information.
4. Clinical protocol identifiers; including the NIH protocol number, NIH grant number(s) (if applicable), and the FDA IND application number.
5. Participant population (such as disease indication and general age group, e.g., adult or pediatric).
6. Total number of participants planned for inclusion in the trial, the number of participants enrolled to date, the number whose participation in the trial was completed, and the number who dropped out of the trial with a brief description of the reasons.
7. The status of the trial, e.g., open to accrual of subjects, closed but data collection ongoing, or fully completed.
8. If the trial has been completed, a brief description of any study results.

B. Progress Report and Data Analysis

The progress report and data analysis must provide information obtained during the previous year's clinical and non-clinical investigations, including:

1. A narrative or tabular summary showing the most frequent and most serious adverse experiences by body system.
2. A summary of all serious adverse events submitted during the past year.
3. A summary of serious adverse events that were expected or considered to have causes not associated with the use of the gene transfer product, such as disease progression or concurrent medications.
4. If any deaths have occurred, the number of participants who died during participation in the investigation and causes of decease.
5. A brief description of any information obtained that is pertinent to an understanding of the gene transfer product's actions; including, for example, information about dose-response, information from controlled trials, and information about bioavailability.

C. A copy of the updated clinical protocol including a technical abstract.

