



Policy Name: Human Gene Transfer Studies Policy and Procedures		
Approved		
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Replaces Policy: Effective 12/01/2009		

I. POLICY

A. Introduction

Clinical trials involving the administration of recombinant nucleic acid molecules, biological toxin or microorganisms to humans must adhere to the same regulations, fulfill the same requirements, and follow the same guidelines as all other human research studies.

B. Regulations

Regulations and guidelines are set out in 45CFR46, 21CFR50, 21CFR56, and other documents from the Office for Human Research Protections (OHRP) and FDA. Additional institutional policies and procedures, local, and/or state laws and federal regulations and guidelines may also be applicable.

B. Specific Guidelines

1. In addition, human studies involving the transfer of genes must also follow the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)*. These Guidelines outline responsibilities of institutions, the Institutional Biosafety Committee (IBC), and principal investigators performing this research. If an institution receives NIH funds for recombinant nucleic acid molecules research, all human gene transfer trials at that institution are subject to these Guidelines regardless of the funding of the project.
2. Standards for research and clinical laboratories are published by the Centers for Disease Control, the Biosafety in Microbiological and Biomedical Laboratories (BMBL).

II. PROCEDURES

A. General Overview of the Submission and Approval Process

1. Research protocols involving the following agents require review and approval by the IBC: recombinant or synthetic nucleic acid molecules, gene transfer, infectious agents, select agents or microorganism. When a Principal Investigator proposes research

involving administration of one or more of such agents to human subjects, the PI must submit an application to the IBC and IRB for review.

2. The application checklist portion of the eIRB application has an entry for
 - a) "Recombinant or synthetic nucleic acid molecules, gene transfer, infectious agents, select agents or microorganism, or biological toxin (including Botulinum toxins) exposure to human subjects"
 - b) "Vaccine Trials"
 - c) "Transplantation"

If any of these boxes are checked, the IBC administrator is notified electronically that this study is available for examination. The purpose of the examination is to determine if IBC review and approval is needed for the study.

- (1) If humans are not being exposed to recombinant or synthetic nucleic acid molecules, gene transfer, infectious agents, select agents or microorganism, or biological toxin (including Botulinum toxins), then IRB approval is not contingent upon IBC approval. However, IBC approval may still be required for ex vivo use of these agents. IBC will issue Ancillary Approval and make a statement to this effect in the "Ancillary Committee Comment" textbox.
 - (2) If humans are being exposed to recombinant or synthetic nucleic acid molecules, gene transfer, infectious agents, select agents or microorganism (termed "Relevant Study"), IBC review will occur and no research participant shall be enrolled until IBC approval and IRB approval have been obtained.
3. The MUSC IBC application form has a question that requires PIs to indicate if humans will be exposed *in vivo* to the agents named in the application. The associated IRB protocol number can then be entered by the PI in the IBC form. The IBC administrator reviews IBC forms to see if the submission involves a potentially Relevant Study and can then coordinate review efforts with the IRB administrator for the human research application.

4. The IBC reviews Relevant Studies as an ancillary committee, according to the MUSC IBC Policies and Procedures. The IRB reviews Relevant Studies in accordance with the MUSC Human Research Protection Program IRB Policies and Procedures. Although the IRB may review an application prior to final IBC approval, IRB approval will not be granted without IBC approval. Through the eIRB system, the IBC provides ancillary approval or requests further information from the Principal Investigator. Applications may be submitted to IBC and IRB simultaneously for review.
5. The IRB will take into consideration the issues raised and recommendations made as a result of the IBC review and consideration of the Principal Investigator's response to the recommendations. If MUSC is an initial site, the IRB will provide a determination regarding their assessment of whether public RAC review is warranted pursuant to NIH *Guidelines* Appendix M-I-B. If, however, the IRB has already reviewed the Relevant Study and contingently approved pending IBC review and approval, the IRB Chair will determine if there are substantive changes to the Relevant Study based on IBC review. If changes are substantive, the Relevant Study will have to be returned to the full Board for review before final IRB approval is granted. No research participant shall be enrolled until IBC approval and IRB approval have been obtained.
5. The IBC administrator will issue Ancillary Approval in eIRB, once IBC approval has been released to the Principal Investigator. If requested, the IBC administrator will provide the IRB with a copy of the approval letter, the IBC registration form and any other materials that may be requested.
6. Human gene transfer studies need to be registered with the NIH Office of Science policy. Appendix M-III-A of the NIH Guidelines exempts certain types of vaccine trials from the requirements for submission of the protocol to the NIH Office of Science Policy (OSP) and subsequent reporting. Investigators shall submit the relevant information on the proposed human gene transfer experiment to the IRB and IBC.
 - I. MUSC as initial site: The IRB and IBC will each provide the PI with a statement regarding their assessment of whether public RAC review is warranted pursuant to *NIH Guidelines* Appendix M-I-B. Selection of Individual Protocols for Public RAC Review and Discussion). Per NIH Guidelines Appendix M-I-A, the PI is required to submit such statements to NIH OSP. In the event that public RAC review is requested, a justification that one or more of the NIH RAC review criteria (see NIH Guidelines Section III-C-1) are met shall be included in the statement.

- a. No public RAC review requested: If the IRB and IBC do not request public RAC review, then final IBC approval may be granted. However, no research participant shall be enrolled (see definition of enrollment in Section I-E-7) until receipt of the acknowledgement from the NIH that the protocol registration process is complete.
 - b. Request for RAC review: If either the IRB or IBC requests public RAC review, but the NIH does not concur, final IBC approval may then be granted upon receipt of the acknowledgement from the NIH that the protocol registration process is complete.
 - c. If either the IRB or IBC requests public RAC review, and the NIH concurs, the Principal Investigator shall then submit the documentation as outlined in Appendix M-I-A at least 8 weeks prior to the next scheduled RAC meeting in order to be reviewed at that RAC meeting. The IBC will continue review upon receipt of the letter summarizing the RAC's comments and recommendations (if any) regarding the protocol. The IBC will take into consideration the issues raised and recommendations made as a result of the RAC review and consideration of the Principal Investigator's response to the recommendations. Upon receipt of notification from the NIH that the NIH protocol registration process has been completed, the IBC may issue final approval.
- II. MUSC as add on site: Neither the IBC, nor the IRB, will provide the PI with a statement regarding their assessment of whether public RAC review is warranted pursuant to NIH Guidelines Appendix M-I-B. Selection of Individual Protocols for Public RAC Review and Discussion). The PI will be required to submit to the IRB and the IBC a copy of the acknowledgement from the NIH to the initial site that the protocol registration process is complete. Within 30 days of enrollment (see definition of enrollment in Section I-E-7) at a clinical trial site, the PI shall submit to NIH OSP the documentation as specified in NIH Guidelines Appendix M-I-C-2.

B. Amendments and Reporting Requirements

1. Reporting to MUSC IRB and IBC: The PI is responsible for dually reporting to the IRB and IBC unanticipated problems involving risks to research participants or others (UPIRSOs, see HRPP 4.7 - Unanticipated Problems and Adverse Events Policy and Procedures).

2. Reporting to MUSC IRB: The PI is responsible for submitting reports to the IRB in accordance with the MUSC Human Research Protection Program IRB Policies and Procedures. Such reports include, but are not limited to, continuing reviews (see HRPP 3.5 – Continuing Review Policies and Procedures), and changes to currently approved research (amendments, see HRPP 3.5 – Modifications to Approved Research Policies and Procedures).
3. Reporting to the MUSC IBC: The PI is responsible for submitting reports to the IBC in accordance with the MUSC IBC Policies and Procedures. Such reports include, but are not limited to, continuing reviews (see IBC P & P 6.3 – Continuing Reviews), and changes to currently approved research (amendments, see IBC P & P 6.2 – Amendments).
 - a. Human gene transfer studies: Investigators and study coordinators must be aware of the general responsibilities assigned by NIH Guidelines Section IV-B-7 to investigators conducting recombinant or synthetic DNA research. The Principal Investigator (or designee) has the responsibility of providing all mandated reports to the NIH OSP with copies to the Institutional Biosafety Committee per NIH Guidelines, Appendix M-I-C. Such reports include:
 - documents to be submitted at the time of Initiation of trials (Appendix M-I-C-1) or adding on additional trial sites (Appendix M-I-C-2),
 - Annual Reports (Appendix M-I-C-3), and
 - Safety Reporting (Appendix M-I-C-4).

A Principal Investigator engaged in human gene transfer research may delegate to another party, such as a corporate sponsor, the reporting functions set forth in NIH Guidelines Appendix M, with written notification to the IBC and NIH OSP of the delegation and of the name(s), address, telephone, and fax numbers of the contact. The Principal Investigator is responsible for ensuring that the reporting requirements are fulfilled and will be held accountable for any reporting lapses

C. Role of the Institutional Biosafety Officer

1. In accordance with the MUSC IBC Policies and Procedures Section 7, The institutional Biosafety Officer (BSO) will conduct an inspection of all areas to be used in the storage, processing, or administration of the materials to be used in the Relevant Study. A satisfactory laboratory inspection with correction of any deficiencies and submission of signed, satisfactory safety protocol are necessary for final approval and release of approval for the IBC submission.

2. Rooms and other areas to be used in the study as identified in the IBC application must be inspected at least every two years by the BSO. If the PI wants to use new space, it must be inspected and a satisfactory inspection achieved before it is used in the study. An amendment requesting addition of the new space must be approved by the IBC. It may also be necessary for equipment e.g. biosafety cabinets to be certified if they are new, have been moved, or possibly have been damaged.

D. Other relevant institutional policies and Procedures

1. There are two Medical Center Policies that specifically impact on gene transfer studies: C-120 (PC-74) -Management of Gene Therapy and C-153 (PC-90) - Management of HCT/P (Human Cells, Tissues, or Human Cell or Tissue-Based Products) Based Therapy. Portions of the policies including the IRB and IBC are summarized below.
2. Policy C-120 states that "All clinical trial protocols involving investigational gene therapy must be reviewed and approved by the Institutional Review Board (IRB) and the Institutional Biosafety Committee (IBC) before patient recruitment and protocol implementation. " Responsibility for education and training of the hospital personnel falls to the principal investigator "and will follow IBC policies". c) Policy C-153 states that, "All clinical trial products involving investigational HCT/P therapy must be reviewed and approved by the IRB before patient recruitment and protocol implementation. " Additionally, Appendix A must be applied to the policy if "one or more HCT/Ps containing or associated with recombinant DNA" are used. Likewise, Appendix B must be applied if HCT/P is combined with one or more infectious substances as part of the therapy. Responsibility for education and training of the hospital personnel falls to the principal investigator or designee and study coordinator and will follow Infection Prevention and Control recommendations.
3. For clinical trials that either policy applies to, Infection Prevention and Control (IPC) will be notified in writing by the Biosafety Officer about trials under review by the IBC. Either IPC or the BSO can stop any study in which infection control is not being performed according to recommendations of the IBC and Infection Control Committee.