



Policy Name: Human Gene Transfer Studies Policy and Procedures			
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I. POLICY

A. Introduction

Clinical trials involving the transfer of genes into 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.

C. 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 DNA (rDNA) research, all human gene transfer trials at that institution are subject to these Guidelines regardless of the funding of the project.
2. Section III-C of the *NIH Guidelines* covers the basics regarding "Experiments that Require Institutional Biosafety Committee and Institutional Review Board Approvals and RAC Review before Research Participant Enrollment". Appendix M, added in 1990, includes additional information on considerations for the design of these protocols and their submission to the Recombinant DNA Advisory Committee (RAC) of the NIH Office of Biotechnology Activities (OBA). Section IV IV-B-7-c and -e describe aspects of the responsible conduct of research involving rDNA molecules that must be followed by both basic and clinical researchers.
3. The RAC page on the NIH/OBA web-site provides further assistance with these protocols in which recombinant DNA molecules are transferred into one or more human research participants. Included are links to:

- a) NIH Guidance on Informed Consent for Gene Transfer Research that can be used by both investigators and the Institutional Review Board for Human Research (IRB);
- b) FAQs on the NIH review process for these trials that includes sections on the NIH, RAC, and submission of protocols; and
- c) May 28, 2002 reminder re: compliance with the *NIH Guidelines*. All of these divisions are available for consultation on design, methodology, statistics, and ethical issues.

II. PROCEDURES

A. General Overview of the Submission and Approval Process

1. The principal investigator (PI) for a human gene transfer protocol submits Appendix M and other supportive documentation to the RAC for a determination. After review the RAC may notify the PI either that the trial may proceed without additional review or that it will need to be reviewed at a public session. In the first case any feedback sent to the PI is also available to other investigators, sponsors, the IRB, and the IBC upon request. If there is a public review, a summary letter is sent to the PI, IRB, IBC, and FDA.
2. At the principal investigator's institution, IBC and IRB applications may be submitted for review either before or after RAC review. No final decision may be made on IBC submissions until the RAC recommendations are received. Likewise, no final approval may be made on IRB submissions until approval from the institutional IBC is received. The IRB may review the protocol before or after RAC review.

B. Initiation of the Human Gene Transfer Trial

1. In the cover letter to NIH/OBA that accompanies Appendix M, the principal investigator(s) must identify the IBC and IRB at the proposed clinical trial site(s) that are responsible for local review and approval of the protocol.
2. According to the *NIH Guidelines*, participants cannot be enrolled in the trial until RAC review is complete and IBC, IRB, FDA, and other applicable regulatory authorizations are obtained.
3. If a clinical site is added to a trial that has already been approved by the RAC, the necessary approvals must be obtained from the

institutional IBC and IRB at the additional site before enrollment may occur.

C. Reporting Requirements

1. Appendix M of the *NIH Guidelines* specifies reporting requirements that must be fulfilled by the primary investigator, the individual who originally submitted the study to the RAC for review, as well as any secondary investigators who are responsible for the conduct of the trial at any additional clinical sites. A secondary investigator may designate another individual e.g. the primary investigator to complete some of the reporting requirements.
2. With respect to the IRB, the principal investigator(s) must submit a copy of the approved protocol, a copy of the approval, and a copy of the informed consent document to the NIH/OBA no later than 20 days after enrollment of the first participant.
3. Within the same time frame, a copy of the IBC approval must also be submitted to the NIH/OBA.

D. Roles of Institutional Entities in Gene Transfer Trials at MUSC

1. MUSC Office of Research and Sponsored Programs (ORSP)
 - a) Principal investigators record the proposed involvement of human participants in section 7 of the Proposal Data Sheet (PDS). They record use of microorganisms, recombinant DNA, biotoxins, and Select Agents in section 9. The IBC administrator is able to access these sheets and the associated proposals for review in conjunction with the processing of applications associated with gene transfer clinical trials.
 - b) The ORSP Policies and Procedures Manual includes the roles and responsibilities of PIs including the need to obtain IBC approval for research involving recombinant DNA.
2. MUSC Office of Research Integrity - Institutional Review Board for Human Research (IRB)
 - a) Section IV. Special concern areas of the Human Research Application includes checkboxes for both Vaccine Trials and Gene Therapy/Recombinant DNA as well as an Investigational New Drug box with a request to attach the Investigators Drug Brochure. The Gene Therapy box has a note that IBC approval should be attached. Administrators are thereby alerted to follow up with the IBC administrator

regarding status of the IBC application for approval if it is not attached and with any questions that they or the Board itself may have regarding biosafety issues. They may request that a representative of the IBC attend the IRB meeting at which the human research application is discussed to address any questions and concerns.

- b) Gene transfer trials are subject to the same human research regulations and guidelines as any other clinical trials. Continuing reviews must be submitted at least annually. Adverse events and other safety reports must be submitted according to institutional (includes federal) requirements. Amendments must be filed as indicated. The IRB administrator will notify the IBC administrator if any amendments are submitted that are pertinent to biosafety issues e.g. change of personnel and change of rooms.

3. MUSC Office of Research Integrity - Institutional Biosafety Committee (IBC)

- a) According to the *NIH Guidelines*, Section IV-B-6, when an institution participates in or sponsors rDNA research, the institution must ensure that: (i) the IBC has adequate expertise and training (using *ad hoc* consultants as deemed necessary) and (ii) all aspects of Appendix M have been appropriately addressed by the PI before it's submitted to NIH/OBA.
- b) Approval must be obtained from the IBC at each institution at which the recombinant DNA material will be administered to humans. This includes those institutions at which the primary investigator will be heading the clinical trial and those additional clinical sites at which secondary investigators will be overseeing the trial.
- c) The IBC is responsible for reviewing the application to use materials that are proposed for use in a clinical trial according to the directives in the *NIH Guidelines*. In addition, the IBC must perform continuing reviews of the use of these materials.
- d) Section 4 Recombinant DNA of the MUSC IBC application inquires in section 4h1 if humans will be exposed *in vivo* to the recombinants named in the application. A text box is available in section 4h4 to record the HR# of the study. At this point on the form, the investigator is advised to refer to the *NIH Guidelines* especially Appendix M and links

available at the NIH/OBA web-site. The IBC administrator is alerted if section 4h1 and/or 4h4 indicates that clinical trials are planned and can then coordinate review efforts with the IRB administrator for the human research application. The IBC administrator will notify the IRB administrator for the human research application when IBC approval has been obtained will provide the IRB with a copy of the approval letter and, if requested, a copy of that IBC application.

- e) For continuing review, the IBC requires completion of the continuing review form and submission of the same annual reports and other safety reports that are submitted to the IBC for their continuing review process. In addition, the IBC may request that additional information be submitted.
- f) The IBC will review the IBC Termination Form to be submitted by the principal investigator at the conclusion of the clinical trial for proper disposal or transfer of any recombinant DNA materials remaining.

4. MUSC University Risk Management/Occupational Safety and Health (OSH)

- a) 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 clinical trial. If there are any deficiencies, s/he will inform the PI so that they can be corrected. In addition, the BSO will review the safety protocol to be used for this study and request revisions as needed. Once the safety protocol is satisfactory, the BSO will request that it be signed by all individuals who will come in contact with the recombinant material to be used and submitted to OSH. A satisfactory laboratory inspection with correction of any deficiencies and submission of signed, satisfactory safety protocol are necessary for final approval and release of the IBC submission. The BSO will provide written documentation to the IBC administrator when these requirements have been achieved.
- b) Rooms and other areas to be used in the study 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. It may also be necessary for new equipment e.g. biosafety cabinets to be certified.

5. MUSC Medical Center

- a) There are two Medical Center Policies that specifically impact on gene transfer studies: C-120 –Management of Gene Therapy and C-153- 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.
- b) 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”. The Infection Control Department (ICD) is responsible to establish guidelines and provide or monitor surveillance studies as recommended by the IBC and Infection Control Committee. Either the ICD or BSO can stop any study in which infection control is not being done according to recommendations of the IBC and Infection Control Committee.
- c) Policy C-153 includes the two responsibilities of the ICD and BSO noted above for policy C-120. It 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.

III. REFERENCES

- A. [45CFR46](#)
- B. [21CFR50](#)
- C. [21CFR56](#)
- D. [NIH Guidelines for Research Involving Recombinant DNA Molecules \(NIH Guidelines\)](#)
- E. [Recombinant DNA Advisory Committee \(RAC\) of the NIH Office of Biotechnology Activities \(OBA\) web-site](#)
- F. Medical University of South Carolina Policies
 1. [PC-74 \(New\) C-120 \(Prior\) –Management of Gene Therapy](#)
 2. [PC-90 \(New\) C-153 \(Prior\) - Management of HCT/P \(Human Cells, Tissues, or Human Cell or Tissue-Based Products\) Based Therapy](#)