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# COMS Policy on Clinical Trial Studies

I. Purpose

Investigators must obtain approval from COMS before administering COMS Regulated Material (CRM) to human subjects.

II. Applicability

All investigators that conduct work or are employed by a COMS-affiliated institution must have approval from COMS for any clinical trial involving human gene transfer, human xenotransplantation or CRM.

III. Definitions

A. *Human Gene Transfer Studies*: Research involving the deliberate transfer of recombinant or synthetic nucleic acids into human subjects. NOTE: All human gene transfer studies must be submitted for evaluation to COMS. COMS will make a recommendation whether the study should be reviewed by the NIH Office of Science Policy, Recombinant DNA Advisory Committee (RAC).

B. *Human Xenotransplants and Xenografts*: Research and investigational therapeutic approaches involving the transfer of organs, tissue, or cells of animal origin into human subjects. Ex vivo use of animal tissue or cells for treating human subjects in a manner that may result in microorganisms being passed to human subjects.

C. *COMS-Regulated Materials ("CRM") as defined in the Policy Introduction in human subjects:* Investigational treatment of human subjects with biological agents, whether they are potentially pathogenic or not must be reviewed by COMS if they involve an Investigational New Drug (IND).

D. *Microorganisms*: An organism that is too small to be seen clearly with the naked eye. Some of these organisms may cause disease.

IV. Implementation Procedures

A. Clinical Trial documents for submittal to Committee:

1. Clinical Protocol
2. Investigator's Brochure
3. Informed Consent Form
4. COMS Clinical trial application form

5. *NIH Guidelines for Research Involving Recombinant DNA Molecules* (September 2009), Appendix M for gene transfer studies, "Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into the Genome of One or More Human Subjects."

B. Biosafety information:

   The Institutional Biosafety Officer will submit the above study documents with a risk assessment containing: i) study summary; ii) biosafety issues involved with the gene transfer product; iii) similar studies approved by COMS; and iv) a description of study adverse event reporting procedure (NIH, FDA, IRB, and COMS) and the presence of a Data Safety Monitoring Board (DSMB).

C. Review process:

1. All material relating to clinical studies must be submitted to the COMS Office of Biological Safety at least six weeks prior to the next COMS meeting. Local institutional deadlines vary. PIs/ Clinical Coordinators should consult with their institutional biosafety officer for their local institutional deadline.
2. All human gene therapy studies require two appointed scientific reviewers.
3. Non-recombinant or Synthetic nucleic acid COMS-Regulated Materials ("CRM"), as defined in the Policy Introduction, require a minimum of one appointed scientific reviewer. The COMS Chair may assign an additional reviewer.
4. At the COMS meeting, the application is reviewed by full committee and a vote is recorded.
5. For human gene therapy studies, the Committee will decide whether RAC review is warranted. If the Committee recommends the protocol be reviewed by the RAC, it is the PI's responsibility to send this recommendation, along with other necessary documentation, to the NIH. If the NIH agrees with the request for RAC review, COMS approval will be withheld until the RAC has concluded its review and COMS has considered the RAC's comments and recommendations. COMS's decision whether to recommend RAC review is made according to the following criteria:

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; or
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.

D. Approved Clinical Trials:

Clinical trials are approved by COMS for a period of one year, at which point they must undergo renewal. The following reporting is required for the duration of the protocol's approval:

1. Safety Reporting

a. Reporting to COMS Serious Adverse Events (SAE):

Principal Investigators must submit a written report on any serious adverse events that are both unexpected and associated with the use of gene transfer product. Investigators should also report events where there is a reasonable possibility that the product may have caused the event. Reporting is required for any finding from tests in laboratory animals that suggests a significant risk for human research participants including reports of mutagenicity, teratogenicity, or carcinogenicity. This report labeled "safety report" must be submitted to the NIH Office of Science Policy (OSP) as soon as possible, but not later than seven calendar days after the sponsor's initial receipt of the information for serious adverse events that result in death or considered life-threatening. Serious adverse events that do not result in death or considered life-threatening should be reported as soon as possible, but no later than 15 days after the sponsor's initial receipt of the information. It should be noted that the event must be reported concurrently to the FDA. Principal Investigators may delegate to another party, such as

the corporate sponsor, the reporting functions set forth in NIH Guidelines, Appendix M, with written notification to the NIH OSP. A copy of this written notification to NIH must be provided to COMS. The Principal Investigator is still responsible for notifying COMS of any serious adverse events through the institutional Biosafety Officer as described above. SAEs that do not require reporting are those that are considered un-related to the study drug or fall out of reporting requirements with the institutional review board(s) that are overseeing the study.

b. Reporting to other Committees and Regulatory Agencies:

Principal Investigators should adhere to any other serious adverse event reporting requirements in accordance with federal regulations, state laws, and local institutional policies and procedures, as applicable. Specific Institutional Review Boards may have additional requirements for adverse event reporting. Dana Farber /Harvard Cancer Institute (DF/HCC) studies (including multi-center trials) must report SAEs as soon as possible, but no later than 10 working days from notification of event on the DFCI IRB SAE Reporting form.

2. Annual Renewals

Clinical studies are approved for one year only. A renewal is necessary to proceed and may be submitted using the online application system, eCOMS. Renewals involve submittal of a renewal report form of the year's activities and results. Annual renewals are also required during the follow-up phase. The PI can adjust the renewal timing to correspond with annual reports to other Committees and Agencies (i.e. IRB and FDA). A current Data Safety Monitoring Board (DSMB) report can be substituted for a renewal report form. Renewal for the subsequent year will be required one year after the date of the DSMB report.

3. Clinical Holds

Investigators must immediately notify COMS of an FDA, DSMB or IRB-required hold. In general, the COMS-approved clinical study will automatically go on COMS hold as well. A release of the FDA hold does not automatically constitute a release by COMS. Rather, the circumstances necessitating the original hold and the extenuating information resulting in its release will be provided to the COMS Chair through the institutional Biosafety Officer. The Chair will determine whether the issues require committee discussion or if a release of the hold can go forward.

4. Amendments to Approved Clinical Protocols

   Clinical protocol amendments must be submitted electronically. The institutional Biosafety Officer then evaluates the changes and conducts a risk assessment. The Biosafety Officer generates a memorandum to the Committee Chair outlining the changes and recommending administrative (document updates, personnel changes) approval or full committee (scientific changes or PI change) review. Should the clinical trial site PI be changed, the new PI's CV must be submitted as part of the amendment.

5. Protocol Closures

   Clinical trials that are being closed require notification from the PI to COMS. A clinical trial is considered completed by COMS under the following circumstances:

   - Only data analysis is being conducted;
   - Study follow up is only to confirm long-term survival;
   - Patients are no longer receiving study drug or follow up;
   - There is no further study enrollment of new patients; and
   - Research samples from the patients are no longer being analyzed by laboratories.

V. Policy Authority

The Committee on Microbiological Safety shall enforce this policy.

VI. Related Policies to Clinical Trials

A. Principal Investigator Responsibilities:

The Principal Investigator for a clinical trial is solely responsible for its conduct. It is COMS policy that all materials, documents, and other formal communications relating to a proposed clinical trial come directly from the Principal Investigator, not the sponsor. It is the responsibility of the Principal Investigator to be fully informed about issues that pertain to the safe conductance of his/her study. Hence, all written responses to Committee queries must be submitted by the Principal Investigator, and all communications between a study sponsor and COMS must go through the Principal Investigator. Investigators must provide an annual renewal and reports to the COMS concerning the progress of clinical trials. Investigators are required to train clinical staff about the risks associated with the study, about safe procedures, and about the proper use safety equipment.

B. Multiple Clinical Sites

Many clinical studies involve multiple centers. When two (or more) centers fall under the COMS umbrella an application from a Principal Investigator at each institution is expected. However, identical protocols from different institutions can be considered together and approval for one will be approval for all. Each PI must submit a COMS application and they will reviewed as a group.

C. Tissue Processing Laboratories for Human Trials

It is COMS policy that processing eukaryotic cells or tissues modified with recombinant DNA and destined for human recipients must be carried out in a laboratory accredited, or, in special cases, actively seeking accreditation, by an independent, outside, clinical organization appropriate to the manipulations.

D. Laboratory Studies Closely Associated with Clinical Studies

Research laboratory studies in support of a clinical study carried out in a hospital setting on materials taken from a clinical study can be registered with COMS or, if the Biosafety Officer deems it appropriate, responsibility can be placed with the hospital's infection control unit. In the latter case the Infection Control Unit will take full responsibility for technician safety and training.

VII. References

- NIH Guidelines Appendix M