Approved 4-29-2011

COMS Policy on Clinical Trial Studies

I. Purpose:
Investigators must obtain approval from COMS before administering recombinant DNA, xenotransplantation materials or biological agents 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 xenotransplant, xenograft, or biological agents.

III. Definitions:
1. Human Gene Transfer Studies
Research involving the deliberate transfer of recombinant DNA or RNA derived from recombinant DNA into human subjects. NOTE: All human gene transfer studies must be submitted for evaluation to the NIH Office of Biotechnology Activities, Recombinant Advisory Committee (RAC). COMS cannot approve a Human Gene Transfer study until the RAC has made a determination.

2. 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 infectious agents being passed to human subjects.

3. Biological Agents in Human Subjects
Investigational treatment of human subjects with biological agents, whether they are potentially pathogenic or not must be reviewed by COMS.

IV. Implementation Procedures

1. Clinical Trial documents for submittal to Committee:

a. Clinical Protocol
b. Investigator's Brochure
c. Informed Consent Form
d. COMS Clinical trial application form
e. *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."

f. NIH/OBA RAC letter of review and comments

NIH regulations require Institutional Biosafety Committees await action by the NIH Recombinant DNA Advisory Committee (RAC) before approving and human study involving DNA transfer. The RAC can simply pass the protocol to the FDA or it can decide to evaluate the proposal at its next quarterly meeting. This procedure can delay study approval by as much as six months. However, if an investigator sends a Gene Transfer protocol to COMS at the same time as it is sent to the RAC, local approval can come immediately after the RAC acts.

The Institutional Biosafety Officer will submit the above study documents with a memo table with the following items: **a)** summarizing the study, **b)** outlining the biosafety issues involved with the gene transfer product, **c)** listing any similar studies approved by COMS **d)** description of study adverse event reporting procedure (NIH, FDA, IRB, and COMS) and the presence of a Data Safety Monitoring Board (DSMB).

2. Review process

In consultation with the institutional Biosafety Officer the Associate Director of the Office of Biological Safety/COMS Chair decides on one of three courses of action:

1) For completely novel procedures the application material is sent to every COMS member. Two members are selected to review the material in depth and report to the committee at its next meeting. At the COMS meeting a decision is taken as to approval, approval with stipulations, decline, or reject.

2) For studies with ample precedent faster approval is likely. One COMS member is assigned to review the study. The recommendation can be for initial approval, further review or discussion by COMS at its next meeting. In all cases the COMS chair has the responsibility of accepting the recommendation or choosing another path.

3) Finally, studies deemed to have low risk and some (but not “ample”) precedent will be sent to two COMS members for their recommendations.

All material relating to clinical studies must be submitted to the Office of Biological Safety 6 weeks prior to the next COMS meeting

3.Approved Clinical Trials

No research participant shall be enrolled at a clinical trial site until the following documentation is provided below. Human trials involving gene transfer or xenotransplantation are approved for one year.

a. Safety Reporting

i. Reporting to COMS Serious Adverse Events (SAE)

Principal Investigators must submit a written report on any serious adverse events that is 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 NIH OBA as soon as possible, but not later than after the sponsor's initial receipt of the information7 days 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 concurrent 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 OBA. 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.

ii. 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 Board 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.

b. Annual Renewals

Clinical studies are approved for one year only. A renewal is necessary to proceed. Renewals involve submittal of renewal report form of the year's activities and results. Renewals are required during the follow-up phase. The form can be found at http://www.hms.harvard.edu/orsp/coms/forms.htm. 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.

c. Clinical Holds

Investigators must immediately notify COMS of an FDA 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.

d. Amendments to approved clinical protocols

Clinical protocol amendments are processed much in the same way as original submissions, without the necessity of submitting a formal application. A short letter or e-mail describing the additions and changes is usually all that is necessary. The institutional Biosafety Officer then evaluates the changes and decides whether the changes require a new application. If not, the Biosafety Officer generates a memorandum to the Committee Chair outlining the changes and recommending initial approval or full committee action

e. 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 and
- There is no further study enrollment of new patients
- Research samples from the patients are no longer being analyzed by laboratories

V. Policy Authority

VI. Related Policies to Clinical Trials

A. Principal Investigator Responsibilities:

The Principal Investigator for a clinical trial is solely responsibility for its conduct. It is COMS policy that all materials, documents and other formal communications relating to a proposed human gene transfer or xenotransplantation study come 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 on the Principal Investigator's letter head and must be signed and dated by the Investigator. Signature stamps and signatures by others in the Investigator's name are not acceptable. All communications between a study sponsor and COMS must go through the Principal Investigator. The sponsor may not communicate directly with COMS. Investigators must provide annual updates 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 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 should submit a COMS application and they will be assigned a related protocol number (e.g. 11-100a, 11-100b…) and will be reviewed as a group.

C. Referrals to Human Gene Transfer and Xenotransplantation Trials at External Institution:

For human gene transfer and human xenotransplantation studies in which investigators associated with Harvard affiliated institutions recruit and follow participants but do not administer the test article will be fully reviewed by COMS. This means the Harvard institution must submit: a copy of the remote site IBC and IRB approvals, a completed COMS application form covering the entire study, a completed NIH recombinant DNA Guideline Appendix M (if required by the NIH), a completed FDA protocol, an FDA investigator s brochure, informed consent forms for both sites, NIH biosketches of investigators at the non-Harvard institution, and a description of the facilities involved. COMS will defer or reject the application, if deficient. In a mirror situation, one in which the drug or tissue is administered in a Harvard Institution but recruitment and follow-up are done elsewhere, COMS will not require NIH biosketches of investigators at the non-Harvard institution or a description of the facilities involved.

D. Tissue Processing Laboratories for Human Trials
It is COMS policy that processing of 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, is actively seeking accreditation, by an independent, outside, clinical organization appropriate to the manipulations.

E. 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.

F. Cooperative Arrangement with Dana-Farber Cancer Institute
The Dana-Farber Cancer Institute (DFCI) is not covered by COMS. DFCI has its own Biosafety Committee - the Biohazard Control Committee (BCC). On occasion COMS and the BCC are asked to approve the same gene transfer protocol. Principal Investigators will have submitted applications to the IBC serving their institution that include an identical IRB protocol, Investigator's Brochure and Appendix M plus an institution specific application form.

VII. References

NIH Guidelines Appendix M

GUIDELINES FOR MICROBIOLOGIC SAFETY IN CLINICAL TRIALS INVOLVING XENOTRANSPLANTATION

Note: Adopted by COMS on September 28, 2001

I. **Purpose**

The goals of the Xenotransplantation Advisory Committee (XTAC) include the protection of subjects in clinical trials of xenotransplantation (XT), protection of the community at large, and the facilitation of such studies whenever possible. These goals are not contradictory. However, adherence to optimal safety practices will always take precedence when these goals come into conflict.

II. **Applicability**

III. **Definitions**

Xenotransplantation: any study in which human tissues (including blood) come into contact (in vivo or ex vivo) with non-human fluids, cells, tissues, or organs. This includes cells or tissues intended for human uses that contact nonhuman cells in vitro (e.g., stem cells cultured with murine feeder cells).

Porcine endogenous retrovirus (PERV-A, B, and C): a family of C type retroviruses with some infectivity for human cell lines. No active infection of humans exposed to porcine tissues has been identified to date.

Porcine cytomegalovirus (PCMV): a herpes virus without known infectivity for human cells

Porcine gammaherpesvirus: (PGHV) an agent associated with post-transplant lymphoma in immunosuppressed swine.

Porcine circovirus: of unknown infectivity

IV. **Implementation Procedures**

A. General Concerns:

A central concern for any human study of XT is the possible introduction of novel infectious agents into the subjects and, subsequently, into their sexual and social contacts. This possibility has been reviewed extensively in the literature. For example, a number of potential pathogens have been described in swine including, but not limited to:

1. Porcine endogenous retrovirus (PERV-A, B, and C): a family of C type retroviruses with some infectivity for human cell lines. No active infection of humans exposed to porcine tissues has been identified to date.
2. Porcine cytomegalovirus (PCMV): a herpes virus without known infectivity for human cells
3. Porcine gammaherpesvirus: (PGHV) an agent associated with post-transplant lymphoma in immunosuppressed swine.
4. Porcine circovirus: of unknown infectivity

Many common pathogens of humans including mycobacteria, common bacteria (e.g., *S. suis* and S*almonella spp*.), parasites (*Toxoplasma gondii*), fungi (*Aspergillus spp*.) The risk of infection due to each of these organisms is unknown and immeasurable for XT procedures. Thus, the FDA has developed guidelines and restrictions for the performance of such trials including sample archiving from donor animals and recipients, testing for a variety of infectious agents, and lifelong- surveillance of recipients of xenogenic tissues (http://www.cdc.gov/mmwr/PDF/rr/rr5015.pdf). It is the responsibility of each investigator to become familiar with relevant regulations and background materials and to assure that each protocol will adhere to these guidelines.

B. Specific Concerns:

1. The sponsor must ensure that appropriate counseling is provided to subjects and their close contacts (family and or sexual partners) to minimize the potential risk of transmission of infectious agents to social and sexual contacts (see pages 5, 17 and 18 of guidance document). Subjects must be required to agree to barrier protection during sexual contacts and to report unexplained illnesses after XT. Subjects must also educate close contacts and relatives regarding potential risks. Pregnancy and unprotected sexual contacts are central concerns regarding the possible transmission of pathogens to a fetus (potentially via germ line transmission), to sexual contacts, and to society.

2. Informational materials regarding potential hazards should be developed for staff and participants.

3. Corporate sponsors are required to test donor animals and tissues for infectious agents (see pages 6-8, 16, 19-29 of guidance document) and to maintain archived blood and tissue samples. They must also report adverse events in clinical trials, and insure that appropriate and up-to-date microbiologic assays are in place for known and potential human pathogens. The sponsor of each study must maintain these records for 50 years. Surveillance samples are required from subjects, source animals, and health care workers (see pages 16, 27, 29, 33 of guidance document).

4. Clinical centers performing XT trials should have the capability to culture and identify potential pathogens on site or through collaborators.

5. Most clinical trials to date have tested blood cells or serum samples to ascertain the presence of potential infection during XT trials. Given that pathogens, including most viruses, have preferred tropism for specific tissues (e.g., brain, lymphocytes, liver); it is

likely that such testing is not adequate to detect sub-clinical infection. Thus, it is reasonable to test multiple tissues during the course of each study (e.g., biopsies, blood samples, autopsy samples) using the most sensitive assays available. The development of new assays will necessitate the re-testing of stored samples. The absence of appropriate assays will necessitate the utilization of resources to develop such assays. Thus, for example, if a study involves xenotransplantation of porcine tissues into the brain, it is reasonable to test any brain tissue samples for PERV DNA and RNA. Other clinical compartments available for testing (i.e., blood) can be used for serial testing of cells and sera for PERV DNA and RNA. The risk for infection may be increased in some trials by the need for immune suppression to prevent graft rejection. COMS considers the investigator responsible for all aspects of each XT trial. These responsibilities include, but are not limited to:

a) Data regarding microbiologic risks are to be provided by corporate sponsors to the investigator. The investigator will provide such information to both COMS and the relevant IRB as part of, or as an amendment to, each XT proposal.

b) The FDA requires that each XT trial includes appropriate infectious disease and epidemiological support to assure appropriate protection of subjects and their contacts throughout the trial and to assist in the evaluation of infectious syndromes if such occur.

c) Annual reports of XT trials must be provided to COMS for review as a condition of trial continuation. As studies progress, it is reasonable to ask investigators to obtain and provide data obtained from earlier clinical trial subjects and from other participating centers. Corporate sponsors and/or investigators must assure that the maximum possible effort (up-to-date assay systems) has been made to identify any infection due to known or unknown infectious agents.

d) The potential benefit to the patient and/or the scientific merit of the proposed trial must outweigh the perceived risks to the subject associated with XT procedures.

e) Administrative review or approval of XT trials will not be available.

f) Significant adverse events will be reported to the IRB and to COMS even if not considered related to the exposure to xenogenic tissues. SAE's from other centers performing clinical trial must also be reported to COMS in a timely fashion. Any adverse event which may have implications for microbiologic safety must also be reported to COMS. SAEs that do not require reporting are those that are considered un-related to the study drug or fall out of reporting requirements of the institutional review board(s) that are overseeing the study.

g) Life-long monitoring of all subjects is required. Assurance of such monitoring is the responsibility of the investigator and trial sponsors. Subjects unable to comply with this or other aspects of the trial should not be included as trial subjects.

h) Investigators should consider that review of complex XT trials is a time consuming process. The timely submission of materials will expedite the review process.

i) Protocol Closures

Clinical trials that are being closed require notification from the PI to COMS. All filings shall be distributed through the Biosafety officer at each respective institution. A clinical trial is considered completed by COMS under the following circumstances:

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

IV. Policy Authority

V. Related Policies

VI. References

NIH Guidelines Appendix M