IBC Human Gene Transfer (HGT) Trials Serious Adverse Event (SAE) Reporting Policy

(Adopted 11/21/2013)

1.0 Purpose

The purpose of this Institutional Biosafety Committee (IBC) policy is to provide an explanation of how the MU IBC will notify NIH OBA of Serious Adverse Events (SAE) associated with Human Gene Transfer (HGT) trials being conducted at the University of Missouri. This policy will also explain how the IBC will complete annual adverse events (AE) reporting to NIH OBA. This applies to the MU IBC as well as other institutions identifying the MU IBC as their externally administered IBC (as per the *NIH Guidelines).*

2.0 Scope

This policy applies to all SAE reporting and annual AE reports reviewed by the IBC and sent to NIH OBA. Safety Reporting and Annual Reporting for HGT trials are required under Appendix M of the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules.*

3.0 Related Documents

- University of Missouri Institutional Biosafety Committee (IBC) Resource Book
- U.S. Department of Health and Human Services, National Institutes of Health (NIH) - *NIH Guidelines* Appendix M: Appendix M-I-C-4 Reporting and Appendix M-I-C-3 Anhnual Reports

4.0 Safety Reporting (*NIH Guidelines* Appendix M-I-C-4)

- 4.1. The Principal Investigator is required to notify the Manager of Biosafety or other Biosafety staff member of any serious adverse event or any finding from tests in laboratory animals that suggests a significant risk to human research participants. This will allow the Biosafety Staff to assist the Principal Investigator with required NIH OBA safety reporting requirements as well as assure the Institutional Biosafety Committee members are advised of the safety concern.
- The MU IRB electronic Unanticipated Event Form will include two questions:
    - Is this even unexpected?
    - Is this event associated with the use of gene transfer project? (even a reasonable possibility should be marked yes).

If the answer to both questions is "Yes", the investigator will immediately be notified that he/she must immediately contact the MU Biosafety Office. The MU Biosafety Office Staff will work with the investigator to complete a 'safety report' (SAE report) that will be submitted to the IBC, IRB, and NIH OBA.

- The IBC Protocol Approval/Renewal letter to the Principal Investigator will include the following paragraph:

"*The Principal Investigator is required under Appendix M-I-C-4 of the NIH Guidelines to complete Safety Reporting. The Principal Investigator must notify the Biosafety Manager* ***IMMEDIATELY*** *of (1) any serious adverse event that is both unexpected and associated with the use of the gene transfer product (i.e., there is reasonable possibility that the event may have been caused by the use of the product; investigators should not await definitive proof of association before reporting such events); and (2) any finding from tests in laboratory animals that suggests a significant risk of human research participants including reports of mutagenicity, teratogenicity, or carcinogenicity.*"
4.2. The IBC Chair will work with the Manager of Biosafety and the Biosafety Professional to prepare an SAE report which will include the following items:

- date of the event;

- designation of the report as an initial report or a follow-up report, identification of all safety reports previously filed for the clinical protocol concerning a similar adverse event, and any analysis of the significance of the adverse event in light of previous similar reports;
- clinical site;
- Principal Investigator;
- NIH protocol number;
- FDA's Investigation New Drug (IND) Application number;
- vector type, e.g., adenovirus;
- vector subtype, e.g., type 5, relevant deletions;
- gene delivery method, e.g., *in vivo*, *ex vivo* transduction;
- route of administration, e.g., intrtumoral, intravenous;
- doing schedule;
- a complete description of the event;
- relevant clinical observations;
- relevant clinical history;
- relevant tests that were or are planned to be conducted;
- date of any treatment of the event;
- the suspected cause of the event;

4.3. Any serious adverse event that is fatal or life-threatening, that is unexpected, and associated with the use of the gene transfer product must be reported to the NIH OBA as soon as possible, but not 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).

4.4. 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 OBA as soon as possible, but not 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).

4.5. Changes in this schedule are permitted only where, under the FDA investigation new drug (IND) regulation [21 CFR 312(c)(3)], changes in this

reporting schedule have been approved by the DFA and are reflected in the protocol.

4.6. If, after further evaluation, an adverse event initially considered not to be associated with the use of the gene transfer product is subsequently determined to be associated, then the event must be reported to the NH OBA within 15 days of the determination.

4.7. Relevant, additional clinical and laboratory data may become available following the initial serious adverse event report. Any follow-up information relevant to a serious adverse event must be reported within 15 calendar days of the sponsor's receipt of the information. If a serious adverse event occurs after the end of a clinical trial and is determined to be associated with the use of the gene transfer product, that event shall be reported cot the NIH OBA within 15 calendar days of the determination.

4.8. Any finding from tests in laboratory animals that suggests a significant risk of human research participants including reports of mutagenicity, teratogenicity, or carcinogenicity must be reported as soon as possibile, but not 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).

4.9. The completed SAE report will be submitted to NIH OBA by either e-mail to oba@od.nih.gov; or by fax to 301-496-9839; or by mail to Office of Biotechnology Activities, National Institutes of Health, MSC 7985, 6705 Rockledge Drive, Suite 750, Bethesda, Maryland 20892-7985. The SAE report will be submitted within the reporting date requirements listed above in 4.3 through 4.8 (above). The completed SAE report will also be submitted for review and discussion during the next scheduled Institutional Biosafety Committee Meeting.

5.0 Annual Reports (*NIH Guidelines* Appendix M-I-C-3)

- 5.1. 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 complete, the PI (or delegate) shall submit the information set forth in (a), (b), and (c) to the Manager of Biosafety (or designee). The Manager of Biosafety (or designee) will review the information with the IBC Chairman and then forward the annual report on to the full IBC for review prior to submission to NIH OBA via the options noted in 4.9 (above).

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 on each trial:

- the title and purpose of the trial;
- clinical site;
- the Principal Investigator;
- clinical protocol identifiers, including the assigned MU IBC protocol number, the NIH OBA protocol number, NIH grant number(s) (if applicable), and the FDA IND application number.
- participant population (such as disease indication and general age group, e.g., adult or pediatric);
- the total number of participants planned for including in the trial; the number entered into the trial 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 hte reasons; the status of the trial, e.g., open to accrual of subjects, closed but data collection ongoing, or fully completed;
- if the trial has been completed, a brief description of any study results.

b) Progress Report and Data Analysis: Information obtained during the previous year's clinical and non-clinical investigations, including:

- narrative or tabular summary showing the most frequent and most serious adverse experiments by body system;
- summary of all serious adverse events submitted during the past year;
- 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 medication;
- if any deaths have occurred, the number of participants who dies during participation in the investigation and causes of death;

- 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 and non-technical abstract.