

Proposal for Long-term Follow-up of Participants in Gene Transfer Clinical Trials

This document provides the rationale and the specific proposals CBER is considering for long-term follow-up (LTFU) of participants in gene transfer clinical trials so that the BRMAC may advise CBER as to the suitability of this proposal (specific questions for the committee are at the end of this document). For the purpose of this proposal, "long-term follow-up"(LTFU) is defined as the follow-up of study participants that occurs at least one year or longer after the treatment period of the clinical trial. The recommended follow-up of participants in gene transfer clinical protocols during the first year post-treatment is not included in this proposal.

The issue of LTFU was discussed with the BRMAC during a half-day session on November 17, 2000 (please review briefing documents for session III of Nov 16-17 meeting; transcripts available at <http://www.fda.gov/ohrms/dockets/ac/cber00.htm>). The committee generally agreed that LTFU of participants in some gene transfer clinical trials is important to obtain data regarding the long-term risks of exposure to certain categories of gene transfer vectors. Some vector characteristics were considered to pose higher degrees of long-term risk. As one example, integrating vectors have the potential to initiate neoplastic processes depending upon the site of integration and presence of strong promoter/enhancer elements present in the gene transfer vector. CBER staff have reviewed the transcripts of the November, 2000, BRMAC session on LTFU and have attempted to distill the advice and comments from the committee into a proposal. The CBER proposal is based on vector properties and recommends types of LTFU and how LTFU should be achieved. CBER is proposing a three-tier system of LTFU based on certain properties of gene transfer vectors. CBER recognizes that in certain instances a sponsor may have data that may be useful for determining exceptions to the tier categorization described below. The proposal assumes that LTFU of participants in gene transfer clinical trials will be performed by sponsors, the data will be reported to FDA, maintained in a database, and reviewed periodically for trends and adverse events.

A summary of the proposed three-tier system is found in Table 1. CBER's proposal classifies LTFU based on characteristics of gene transfer vectors, rather than on current vector classes, in recognition of the fact that meaningful distinctions between gene transfer vector classes are rapidly blurring (note, for example, the recent report of a novel adenovirus vector carrying an insertion of retroviral elements to increase integration frequency, [1]). A more detailed description of each tier is provided below.

Table 1. Proposed Three-Tier System

Tier	Vector Characteristics	Study Participant Follow-up (Past 1 st Year)
1	◇ Ex vivo gene transfer with non-replicating vector into cells with demonstrated limited survival of ≤ 2 weeks in vivo	◇ None
2	◇ All gene transfer products that are not in tiers 1 or 3	◇ During enrollment, subject education for need for LTFU ◇ 1-20 years: data collection by sponsor
3	◇ Replicating or potential to replicate, except poxvirus and adenovirus ◇ High integration potential ◇ Altered receptor tropism ◇ Latency potential	◇ During enrollment, subject education for need for LTFU ◇ 1-5 years: annual physical exam by treatment center, obtain appropriate samples for archive ◇ 6-20 years: data collection by sponsor

Tier 1

The BRMAC consensus from the 11/17/00 meeting was that one group of gene transfer clinical trials should be exempt from any long-term follow-up. BRMAC recommended that follow-up would not be needed past the acute period as defined in the study when gene transfer is performed *ex vivo* into cells meeting each of the following conditions: 1) cells are no longer replicating or able to survive past two weeks (*i.e.*, irradiated cells), 2) the gene transfer vector is a non-replicating vector, and 3) the gene transfer vector does not have the potential for contamination with a replicating virus. In order for a gene transfer product to qualify for tier 1, the sponsor should provide data demonstrating the limited survival of the cells in an animal model.

Tier 2

The second tier includes protocols for all gene transfer products not having the characteristics described for tiers 1 or 3 (Table 1). Tier 2, for example, would capture clinical protocols using adenovirus and poxvirus vectors, and plasmids (see Table 2). Clinical protocols using cells known to have a long life-span or replication potential that are exposed *ex vivo* to tier 2 gene transfer vectors would also qualify for tier 2 LTFU. CBER has exempted the poxvirus and adenovirus vectors from tier 3 because of evidence for lack of persistence or latency when subjects are exposed to replicating viruses or vectors derived from poxvirus [2] or adenovirus. For example, a study using DNA PCR for detection of adenovirus sequences in peripheral blood mononuclear cells did not find evidence of persistence [3].

Clinical trial participants treated with gene transfer products in tier 2 would be subject to protocol-specific follow-up during the first year, including, at a minimum, a baseline sample of serum and PBMC obtained for archiving. During enrollment, study participants should be educated as to the need to participate in long-term follow-up, for at least 20 years post-treatment. During the period from years 1-20 post-treatment, the sponsor would collect updated subject information (described in more detail below) and report some of the data to the FDA in annual reports.

Tier 3

Clinical protocols using gene transfer products with one or more of the following characteristics would be placed in tier 3 (see Table 1): 1) replication-competent or potential to replicate (with the exception of poxvirus and adenovirus vectors, see above for explanation), 2) high integration potential, altered receptor tropism, 3) and potential for latency followed by reactivation. Of particular relevance to this tier, is the recent FDA/NIH Gene Transfer Safety Symposium on adenovirus-associated virus vectors (AAV): "Safety Considerations in the Use of AAV Vectors in Gene Transfer Clinical Trials" (March 7, 2001). The Safety Symposium focussed on recent safety data on vector integration and the need for long-term safety assessment in clinical trials using AAV.

The study participants treated with gene transfer products in this category would be subject to protocol-specific follow-up during the first year, including, at a minimum, a baseline sample of serum and PBMC obtained for archiving. During enrollment, subjects should be educated as to the need to participate in long-term follow-up for at least 20 years post-treatment. What differentiates the follow-up recommended for tier 3 is the 1-5 year post-treatment period. CBER is proposing that subjects in gene transfer clinical trials using tier 3 gene transfer products would be expected to have an annual physical examination by the treatment center at which time appropriate samples would be obtained for archiving. During the next 6-20 year post-treatment period, the sponsor would collect updated subject information (described in more detail below) and report some of the data to the FDA in annual reports.

Data Collection by Sponsor

CBER's proposal recommends that the responsibility for LTFU data collection be with the investigator and the sponsor. As with all regulated clinical research, investigators and sponsors have responsibility for collecting protocol mandated safety data. We recommend that sponsors ensure that other parties, *e.g.* the treatment institution, are willing and able to complete LTFU should the investigator and sponsor be unable to do so.

The proposal recommends clinical data collection consisting of two types. One category of data is confidential subject information maintained by the sponsor and not routinely reported to the government. This category includes updated subject contact information (name, address, telephone number), study site information, date of subject's last visit to the study site, and the subject's current primary health care provider and contact information for the primary health care provider. The second category of data proposed is the information the sponsor should submit to FDA in the annual report. For each subject, the sponsor should report subject status (alive, dead, lost to follow-up). If the subject is dead, the sponsor should report whether an autopsy was performed, and, if so, attach the report. If the subject is alive, the sponsor should report any changes in clinical status, focusing on new malignancies, hematologic disorders, neurologic disorders, autoimmune disease, or, in some cases, reactivation of vector (for example, for herpes).

CBER's proposal recommends that sponsors of clinical trials in tier 3 obtain laboratory specimens for testing and archival purposes in addition to clinical data collection. The laboratory specimen for LTFU should be collected at one year post-treatment and then annually for a total of 5 years.

Comparison to Current Recommendations

Current recommendations for long-term follow-up of subjects in gene transfer clinical protocols using retroviral vectors recommend life-long follow-up. At this time, CBER has no written guidance for LTFU of participants in clinical trials using any other class of gene transfer product. CBER proposes changing our current recommendations to a maximum of 20 years for subjects treated with gene transfer products in tiers 2 and 3. The proposed recommendations are a reduction in the time for follow-up for subjects treated with retroviral vectors, while the proposed recommendations are an increase in the burden for follow-up for all other categories of gene transfer clinical protocols.

A population-based LTFU of gene transfer study participants that allows for the detection of rare clinical events was suggested by BRMAC. Proposed was a database containing pre-defined clinical information on all gene therapy study participants followed over an extended period of time. BRMAC discussed LTFU periods ranging from a minimum of 5 years to a maximum period defined as a study participant's lifetime. A life-long monitoring program provides an advantage for the detection of events that occur years, sometimes decades following protocol therapy. For example, the excess risk of leukemia attributable to treatment for Hodgkin's disease peaks 5 to 9 years following initial therapy and reaches a plateau after 15 years. The relative risk of lung cancer increases steadily with increasing follow-up time and the risk for breast and thyroid cancer does not become apparent until after 10-15 years of observation [4]. Practical considerations lead the Committee to suggest that a time limit for LTFU be defined. An arbitrary period of twenty years was suggested. CBER has adopted the 20-year LTFU period in the current recommendations but recognizes that future clinical knowledge may warrant longer clinical follow-up periods not excluding lifelong monitoring.

The CBER proposal not only differs from current recommendations for LTFU of participants in clinical trials with respect to the length of time for clinical follow-up but also for the length of time that laboratory specimens should be obtained and archived. Currently, CBER requests that sponsors should obtain archival specimens annually from subjects in gene transfer clinical protocols using retroviral vectors for the life-time of the subject. No formal guidance regarding archival specimens currently exists for all other categories of gene transfer clinical trials. CBER is now proposing that for clinical trials in tier 3, sponsors should obtain and archive subject's specimens for years 1-5 of the post-treatment period.

References

1. Zheng, C., et al., *Genomic integration and gene expression by a modified adenoviral vector*. *Nature Biotechnology*, 2000. **18**: p. 176-180.
2. Fenner, F., *Poxviruses*, in *Virology*, B.N. Fields, D.M. Knipe, and P.M. Howley, Editors. 1996, Lipincott-Raven: Philadelphia. p. 2673-2678.
3. Flomenberg, P., et al., *Detection of adenovirus DNA in peripheral blood mononuclear cells by polymerase chain reaction assay*. *J. Med. Virol.*, 1997. **51**: p. 182-188.
4. Van Leewen, FE, et al., Long-term risk of second malignancy in survivors of Hodgkin's disease treated during adolescence or young adulthood. *J Clin Oncol*, 2000, **18**: p. 487-497.

Table 2. Comparison of LTFU for Vector Classes: Current vs. Proposed 3-Tier System

Vector Class	Integration Potential	Replicating/ Defective	Latency Potential	Current LTFU	Tier for LTFU
Retroviral Vector	Reliably high	Defective	High	Life-long	3
Adeno-associated Virus Vector	Varies, depending on tissue	Defective	Varies	Varies	3
Herpesvirus Vector	None reported	Replicating or Defective	High	None	3
Plasmid	Low, may vary depending on method	None	None	None	2
Adenovirus Vector	Low	Replicating or Defective	None	None	2
Poxvirus Vector	None reported	Replicating	None	None	2

DRAFT Questions for the Committee

1. Please comment on the appropriateness of the vector characteristics chosen for tier 3. Are there any vector characteristics that should be added to or deleted from tier 3?
2. Although there are gene transfer products derived from adenovirus and poxvirus that are replication-competent, we have exempted them from tier 3. Please comment.
3. CBER is proposing that LTFU should be performed for a total of 20 years post-treatment for all subjects treated with gene transfer products in tiers 2 and 3. Please comment on the appropriateness of that time-frame for LTFU.
4. CBER is proposing that samples should be obtained and archived from all subjects treated with gene transfer products in tier 3. In the current proposal, the specimens would be obtained on a yearly basis from one through five years post-treatment. Please comment on whether it is necessary to obtain specimens for archival purposes each year, or whether fewer sampling time points may be appropriate.