

Appendix M-II-B-2-d. Non-Retrovirus Delivery/Expression Systems

If a non-retroviral delivery system is used, what animal studies have been conducted to determine if there are pathological or other undesirable consequences of the protocol (including insertion of DNA into cells other than those treated, particularly germ-line cells)? How long have the animals been studied after treatment? What safety studies have been conducted? (Include data about the level of sensitivity of such assays.)

Appendix M-II-B-3. Clinical Procedures, Including Patient Monitoring

Describe the treatment that will be administered to patients and the diagnostic methods that will be used to monitor the success or failure of the treatment. If previous clinical studies using similar methods have been performed by yourself or others, indicate their relevance to the proposed study. Specifically:

Appendix M-II-B-3-a. Will cells (e.g., bone marrow cells) be removed from patients and treated *ex vivo*? If so, describe the type, number, and intervals at which these cells will be removed.

Appendix M-II-B-3-b. Will patients be treated to eliminate or reduce the number of cells containing malfunctioning genes (e.g., through radiation or chemotherapy)?

Appendix M-II-B-3-c. What treated cells (or vector/DNA combination) will be given to patients? How will the treated cells be administered? What volume of cells will be used? Will there be single or multiple treatments? If so, over what period of time?

Appendix M-II-B-3-d. How will it be determined that new gene sequences have been inserted into the patient's cells and if these sequences are being expressed? Are these cells limited to the intended target cell populations? How sensitive are these analyses?

Appendix M-II-B-3-e. What studies will be conducted to assess the presence and effects of the contaminants?

Appendix M-II-B-3-f. What are the clinical endpoints of the study? Are there objectives and quantitative measurements to assess the natural history of the disease? Will such measurements be used in patient follow-up? How will patients be monitored to assess specific effects of the treatment on the disease? What is the sensitivity of the analyses? How frequently will follow-up studies be conducted? How long will patient follow-up continue?

Appendix M-II-B-3-g. What are the major beneficial and adverse effects of

treatment that you anticipate? What measures will be taken in an attempt to control or reverse these adverse effects if they occur? Compare the probability and magnitude of deleterious consequences from the disease if recombinant DNA transfer is not used.

Appendix M-II-B-3-h. If a treated patient dies, what special post-mortem studies will be performed?

Appendix M-II-B-4. Public Health Considerations

Describe any potential benefits and hazards of the proposed therapy to persons other than the patients being treated. Specifically:

Appendix M-II-B-4-a. On what basis are potential public health benefits or hazards postulated?

Appendix M-II-B-4-b. Is there a significant possibility that the added DNA will spread from the patient to other persons or to the environment?

Appendix M-II-B-4-c. What precautions will be taken against such spread (e.g., patients sharing a room, health-care workers, or family members)?

Appendix M-II-B-4-d. What measures will be undertaken to mitigate the risks, if any, to public health?

Appendix M-II-B-4-e. In light of possible risks to offspring, including vertical transmission, will birth control measures be recommended to patients? Are such concerns applicable to health care personnel?

Appendix M-II-B-5. Qualifications of Investigators and Adequacy of Laboratory and Clinical Facilities

Indicate the relevant training and experience of the personnel who will be involved in the preclinical studies and clinical administration of recombinant DNA. Describe the laboratory and clinical facilities where the proposed study will be performed. Specifically:

Appendix M-II-B-5-a. What professional personnel (medical and nonmedical) will be involved in the proposed study and what is their relevant expertise? Provide a two-page curriculum vitae for each key professional person in biographical sketch format (see Appendix M-I, *Submission Requirements*).

Appendix M-II-B-5-b. At what hospital or clinic will the treatment be given? Which facilities of the hospital or clinic will be especially important for the proposed study? Will patients occupy regular hospital beds or clinical research center beds? Where will patients reside during the followup period? What special arrangements will be made for the comfort and consideration of the patients. Will the research institution designate an ombudsman, patient care representative,

or other individual to help protect the rights and welfare of the patient?

Appendix M-II-C. Selection of the Patients

Estimate the number of patients to be involved in the proposed study.

Describe recruitment procedures and patient eligibility requirements, paying particular attention to whether these procedures and requirements are fair and equitable. Specifically:

Appendix M-II-C-1. How many patients do you plan to involve in the proposed study?

Appendix M-II-C-2. How many eligible patients do you anticipate being able to identify each year?

Appendix M-II-C-3. What recruitment procedures do you plan to use?

Appendix M-II-C-4. What selection criteria do you plan to employ? What are the exclusion and inclusion criteria for the study?

Appendix M-II-C-5. How will patients be selected if it is not possible to include all who desire to participate?

Appendix M-III. Informed Consent

In accordance with the Protection of Human Subjects (45 CFR Part 46), investigators should indicate how subjects will be informed about the proposed study and the manner in which their consent will be solicited. They should indicate how the Informed Consent document makes clear the special requirements of gene transfer research. If a proposal involves children, special attention should be paid to the Protection of Human Subjects (45 CFR Part 46), Subpart D, Additional Protections for Children Involved as Subjects in Research.

Appendix M-III-A. Communication About the Study to Potential Participants

Appendix M-III-A-1. Which members of the research group and/or institution will be responsible for contacting potential participants and for describing the study to them? What procedures will be used to avoid possible conflicts of interest if the investigator is also providing medical care to potential subjects?

Appendix M-III-A-2. How will the major points covered in Appendix M-II, *Description of Proposal*, be disclosed to potential participants and/or their parents or guardians in language that is understandable to them?

Appendix M-III-A-3. What is the length of time that potential participants will have to make a decision about their participation in the study?