

MASAC RECOMMENDATIONS FOR CONDUCTING GENE TRANSFER  
CLINICAL TRIALS IN PERSONS WITH BLEEDING DISORDERS  
(Revised November 2002)

The following recommendations were approved by the Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation on November 2, 2002, and adopted by the NHF Board of Directors on November 3, 2002.

Administration of normal coagulation factor genes to individuals with hemophilia, von Willebrand disease, and other rarer coagulation factor deficiencies represents the best hope for preventing bleeding episodes and their associated morbidity and mortality. Results in mouse and canine hemophilia models have shown long-term, sustained therapeutic levels of clotting factors and have led to clinical testing in human subjects. Since hemophilia is treated with recombinant and human-derived clotting factor replacement therapies, proof of the principle that delivery of the gene product will work is well established. While we recognize that early Phase 1 studies are not designed to demonstrate efficacy, we believe that consideration of the choice of delivery system coupled with an understanding of the clinical diseases will offer maximal chances for success. This patient population is a precious resource, and clinical trials must be based upon good science with a reasonable possibility for success during dose escalation. Human trials should only be initiated after solid preclinical efficacy and safety data have been established. As clinical trials are developed, the following recommendations should be considered:

1. The therapeutic window for the vector transgene should be well established in mouse and canine models of factor VIII and factor IX deficiencies, unless vector safety and efficacy have been well established in other preclinical/clinical systems. Investigators are strongly encouraged to publish their data in peer-reviewed literature.
2. Ideally, a species-specific transgene or a tolerized animal model should be used to establish (1) the duration of the response and (2) the potential for humoral immune responses to the transgene and for cellular immune responses to the genetically modified cells.
3. Predictable levels of activity should be achievable in animal models including a large animal model before consideration of human trials.
4. The impact of gene transfer on liver disease should be assessed by critical examination of the effect on liver function in preclinical models and on liver function and the course of chronic liver disease in clinical trials. The latter should include measurement of liver function and viral markers but may also include examination of hepatic histology in view of the known lack of noninvasive markers to reflect progression of chronic liver disease. Subjects with chronic liver disease should be included in initial phase 1 clinical trials only if hepatic safety has been established in preclinical models.
5. Children should not be included in clinical trials until safety has been established in adults.

6. Preference should be given to vectors requiring infrequent administration, those given relatively noninvasively, those remaining episomal, those with specific sites of integration, those with tissue-specific promoters, and those containing few to no foreign antigenic proteins capable of eliciting cell-mediated immune responses.
7. Careful immunologic monitoring of potential immune responses to the vector and to the transgene should be included in the study design.
8. The informed consent process should clearly spell out the risks associated with early clinical testing, including the potential for inhibitor formation, vector toxicities in preclinical studies and in unrelated clinical studies, and likely exclusion from enrollment in other early-stage gene therapy clinical trials.
9. As part of the informed consent process, investigators must inform subjects of other gene transfer protocols for which they may qualify in accordance with federal regulations.
10. The principal investigator (PI) is essential to the conduct of the study, from involvement in initial study design to understanding the potential for therapy-related toxicities to the recruitment of patients. PIs and referring physicians must be given sufficient access to vector-related molecular, biochemical, manufacturing, preclinical, and clinical data to make informed decisions based on the primary and secondary disease processes in the bleeding disorders community.
11. Serious adverse events must be promptly reported to all appropriate regulatory and review bodies including the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health, the FDA, and local institutional review boards.
12. Full disclosure must be made by principal investigators, scientists, clinicians, and their institutions of any conflict of interest, consistent with MASAC Document #1361, which endorses the Association of American Medical Colleges' Conflict of Interest Guidelines and the requirements of the Office for Human Research Protections.
13. In order to maximize information derived from these trials, we urge that genotyping be carried out on all participants in these trials.

References:

1. National Hemophilia Foundation. Medical and Scientific Advisory Council Document #136: MASAC Standard on Disclosing Conflicts of Interest for Individuals Conducting Clinical Bleeding and Clotting Disorder Research. New York: November 2002.