



NATIONAL HEMOPHILIA FOUNDATION
for all bleeding disorders

MASAC Document #254
(Replaces MASAC Document #212)

MASAC DOCUMENT REGARDING RISKS OF GENE THERAPY TRIALS FOR HEMOPHILIA

The document was approved by the Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation (NHF) on November 21, 2018, and adopted by the NHF Board of Directors on December 6, 2018.

The National Hemophilia Foundation (NHF) has recognized the importance of the development of gene transfer and stem cell research to cure bleeding disorders. To this end, NHF has supported collaborative relationships between gene and stem cell researchers, the National Institutes of Health (NIH), and individuals with bleeding disorders. Additionally, this support has been funded by generous donations from the bleeding disorders community, which has resulted in numerous research grant awards to advance gene and cell cures. The knowledge gained from preclinical and clinical research has contributed to an iterative process that has incorporated sequential changes as new data are obtained and are integrated into new solutions to overcome existing hurdles.

Numerous human Phase 1/2 clinical trials for hemophilia B and A have been conducted over the past decade (1-6). These trials have incorporated modifications of promoters, transgenes, and adeno-associated virus (AAV) vector serotypes, resulting in varying adverse events and levels of Factor IX or Factor VIII. More Phase 1/2 trials are in planning stages, including with different transgene delivery systems (eg, lentiviral vectors). Further, four Phase 3 trials, 2 each in Hemophilia B and A are underway. While the initial results are tremendously exciting, and offer the prospect of a potential cure for hemophilia, many questions regarding efficacy and safety remain (7-10).

Most ongoing trials have shown transient hepatic enzyme elevations, signifying toxicity, in at least a subset of clinical trial participants. The mechanisms behind this toxicity are not fully understood, but include an immune response to vector capsid; possible direct cellular toxicity due to stress from catabolizing the AAV capsid; a cellular stress response due to high transgene protein synthesis burden; and/or hepatotoxicity resulting from interaction of vector and co-administered potentially hepatotoxic medications, e.g. efavirenz a component of a HAART regimen for HIV infection(11, 12). While the mechanisms are not all understood, these adverse events support the need to counsel patients receiving gene therapy to avoid potentially hepatotoxic therapies such as within HAART, and support the need for more studies to determine the mechanisms of liver toxicity complicating gene therapy.

The Medical and Scientific Advisory Council (MASAC) of NHF continues to emphasize the careful consideration of advances in gene therapy to quantify and mitigate the risks to patients and others, including evaluation in informative animal models (e.g. primates). MASAC supports human clinical trials that proceed with appropriate risk/benefit analysis and risk reduction. MASAC encourages iterative research efforts to pursue adequate gene expression to achieve an absence of bleeding events without concern for hepatic and other injury. We strongly suggest the sponsors of gene therapy clinical trials address the relevant unknowns during the clinical trial process, including but not limited to: opportunities to treat subjects with pre-existing capsid antibodies; develop strategies to re-treat clinical trial participants; address potential liver damage short term and long term, including biopsy of treated livers; durability of response; clotting factor activity discrepancies; genomic integration events; strategies to treat children; and confounders unique to the hemophilia population, including HIV, hepatitis, and the drugs used for treatment of these disorders. Use of other hepatotoxic agents, such as alcohol and acetaminophen should be carefully evaluated, especially during early timepoints following administration of AAV.

Thus, MASAC recommends that existing NHF and other resources leverage communications that document the existing positive results in hemophilia gene therapy and support continued momentum and options for clinical trial participation.

Effective communication should continue to be provided to the bleeding disorders community through relevant NHF workstreams as well as taking advantage of resources from other non-profit and for-profit organizations.

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