

enrolling in a
**gene
therapy
trial**

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enrolling in a gene therapy trial for hemophilia can be an exciting thing to do, because you become a crucial part of the advancement of therapy for the next generation. On the other hand, volunteering can be a scary and confusing thing to do if you do not completely understand all aspects of the clinical trial.

If you are a man with severe hemophilia, you may be eligible to participate in one of the ongoing gene therapy clinical trials. If you or someone you know is even thinking about being part of gene therapy research, the first step is gathering information and asking questions.

Gene Therapy 101 Before delving into clinical trial specifics, familiarize yourself with the basics of gene therapy (See Glossary/Acronyms on page 30). Gene therapy is easily broken down into four puzzle pieces: the gene, the vector, the target cell and the delivery method. The **gene** (also called the transgene) is the healthy gene your body is missing; the gene the researchers are trying replace. The **vector** is the package or cassette that carries the gene into the **target cell**

of the body. A vector is often a virus that has been altered so that it does not cause disease. Finally, the last puzzle piece is the method in which the vector will be delivered to the target cell. The two main **delivery methods** are *in vivo* and *ex vivo*. “*In vivo*” or “into the body” means that the vector will be delivered directly to the target cell while “*ex vivo*” or “out of the body” means that the target cell will be taken out of the body, infected with the vector and then reinserted back into the body.

When these four puzzle pieces are put together successfully, **gene transfer** will occur. Technically, current trials for hemophilia are gene transfer trials, not gene therapy. Gene transfer literally means the transport of the gene into the target cell. Gene therapy takes gene transfer to the next level of success only when the transgene begins to reproduce and therapeutic levels of factor VII or IX are achieved (transgene expression).

Laboratory Testing

All gene therapy research begins in the laboratory. Once the genes for factor VIII and factor IX were identified, scientists began to experiment with ways to reproduce and package the genes for gene transfer. Tests are first performed to determine if the reproduced genes work to make factor VIII or IX. Then, a great deal of research is conducted to find the best way to deliver the gene therapy package to the body.

Pre-Clinical Studies

After laboratory studies, the next step in the process is animal testing. All vectors and delivery methods are tested on animals. Researchers must prove that the vector and method are safe and



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effective in animals before using it on human subjects. Most animal testing begins on small animals, such as mice and rats. If successful, the studies using the same vector and delivery method are “scaled-up” to larger animals, such as hemophilic dogs, to better predict an outcome in a human body.

Scientists collect three types of data from animal studies: toxicology, biodistribution and efficacy. Toxicology studies test a wide range of doses over a period of time to see which ones might produce harmful or adverse effects. Biodistribution studies test all organs of the body to see if the vector is found on any other cells besides the target cell. Efficacy studies try to find the best possible combination of the vector, target cell and delivery method, so that a therapeutic effect is achieved (ie, an increase in the level of factor VIII or factor IX) for the longest time possible. After safety and efficacy are proven in larger animals, researchers can then begin to request approval to begin human testing in a clinical trial.

Clinical Trials

Studies on human patients that examine the safety and efficacy of a new medical treatment are called **clinical trials**. Clinical trials are not new to persons with hemophilia. All current hemophilia treatment materials have been used first in clinical trials before becoming licensed and widely available for use. There are four phases of clinical trials. Each phase is designed to answer a different question. It is important for you to know the goals of each phase and clearly understand the phase in which you are being asked to participate in.

**PHASE I
SAFETY PHASE**

“Is the treatment safe?”

All current hemophilia gene therapy trials are phase I trials. Participants in phase I trials are the first humans to receive a new treatment. The goal of this phase is to see if the method and doses utilized are safe in humans. People who volunteer for a phase I trial are, in general, altruistic; they do not expect any personal gain, but volunteer so that treatment may be advanced for future generations. Enrollment in this phase is only offered to those with a severe form of the disease.

**PHASE II
EFFICACY PHASE**

“Does the treatment work?”

Once a vector and its delivery method are found to be safe, phase II of the clinical trial process can begin. The purpose of this phase is to measure how well the treatment works in human subjects. In this phase, treatments are given in doses that are expected to have some positive or therapeutic results for the subject. Participants are carefully monitored for long periods of time (perhaps for several years to a lifetime) to measure the level and duration of effectiveness and to observe any side effects of the treatment.

**PHASE III
COMPARISON PHASE**

“How does gene therapy compare to standard hemophilia treatment?”

In this phase, a gene therapy treatment that has already been shown to be safe and effective is administered to large numbers of volunteers. These participants are monitored closely to evaluate the benefits of gene therapy compared to traditional hemophilia treatment. The

frequency and severity of bleeding episodes, baseline factor levels and complications of bleeding will be observed closely and reported. This data will be evaluated to determine differences between these results and those of the patient prior to gene therapy. Comparisons will also be made between the groups of gene therapy recipients

and the historical published averages for patients with severe hemophilia treated with traditional methods.

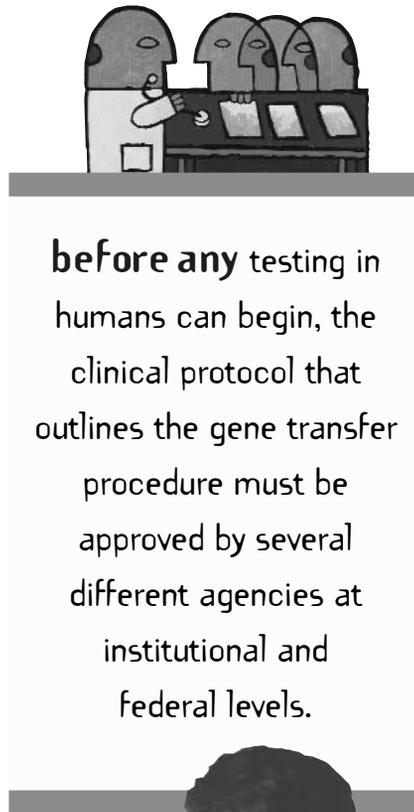
**PHASE IV
POST-MARKETING PHASE**

“Can the product be used in additional ways ?”

In phase IV trials, volunteers are treated with methods or drugs that are already approved and used widely. These trials continue to track any possible side effects and help providers identify new uses for the treatment.

Regulatory Approval

Before any testing in humans can begin, the clinical protocol that outlines the gene transfer procedure must be approved by several different agencies at institutional (hospital-based) and federal (governmental) levels. Institutional Review Boards (IRBs) and Institutional Biosafety Committees (IBCs) first approve the protocol at the hospital level. An IRB is composed of a variety of people, from consumers to pharmacists to physicians, whose foremost concern is the protection and well being of research subjects. After institutional approval, the protocol is reviewed in a public forum by a special committee of the National Institutes of Health (NIH) called the Recombinant DNA Advisory Committee (RAC). The RAC was formed to deliberate on the current state of knowledge regarding recombinant DNA gene transfer. To achieve this goal, the RAC reviews all human gene transfer trials and provides recommendations to the clinical protocol. (Discussion and the specific recommendations of each RAC review can be read on The Office of Biotechnology Activity’s (OBA) Web site www4.od.nih.gov/oba/about-oba.htm.) Finally, the clinical protocol is reviewed by the Food and Drug Administration (FDA). Once ▶



► FDA has given clearance to the protocol, the human trial can finally begin.

Informed Consent Procedure

Before a patient becomes a subject in a clinical trial, he or she is informed by the principal investigator (PI) as to the goal of the trial, the details of the procedure, the risks and the possible benefits (if any). This process, called the informed consent procedure, is the patient's time to ask any and all questions that he or she may have regarding enrollment in the trial. However, this *should not* be the patient's first contact with the investigator for a question and answer session. If you are interested in enrolling in a trial, you should review the informed consent document long before you arrive at the hospital to enroll. It should be reviewed with a significant other (who may be affected by your enrollment) and by your own hemophilia treater who can offer insight and direction.

Categories within an informed consent document are governed by the hospital's IRB. Most informed consent documents outline the following topics: purpose of the research study, background of the disease and research, description of the research procedures, risks, potential benefits, alternative procedures, injury compensation and confidentiality. We have provided a very specific list of questions on page 30 that you can use when researching a gene therapy trial. Be comfortable with the investigator and ask as many questions as possible before signing your name to the consent form.

Participating in gene therapy clinical trial is a great commitment. Knowing what to expect will help you make an informed decision and guide you through the enrollment process. As an informed subject, you have the opportunity to play a crucial role in the advancement of hemophilia therapy for the next generation.

Acronyms/Glossary

AE: Adverse Event: any untoward medical occurrence in a subject that may or may not be related to the treatment procedure.

GCRC: General Clinical Research Center: an NIH-funded hospital unit where clinical research takes place.

GCP: Good Clinical Practice: a standard for conducting human clinical trials.

Horizontal transmission: spreading of the vector to another person with whom the subject comes in contact.

Knockout mice: laboratory mice that have had their factor-producing genes "knocked out" so that they do not produce factor and resemble having hemophilia.

OBA: The Office of Biotechnology Activities.

SAE: Serious Adverse Event: any untoward medical occurrence that results in death, is life threatening, requires unexpected hospitalization or causes a persistent disability.

Sponsor: a person, company or institution that takes responsibility for all aspects of the clinical trial.

Subject: the person (patient) who volunteers for an experimental therapy.

Target Cell: the cell into which the new gene is inserted.

Transgene expression: measurable factor VII or IX in the blood or organs of the subject after treatment.

Vector Shedding: the presence of vector in the body fluids of the patient after therapy.

Vertical transmission: (germline transmission): transmission of the vector to offspring through reproduction. ►

The image shows a screenshot of the website www.hemophilia.org. The page features a navigation menu with three main sections:

- 1 COMPREHENSIVE INFORMATION**: Detailed material on hemophilia, von Willebrand and other bleeding disorders for patients, families and clinicians. Presented in a format that is complete and easy to understand, this information is essential. Plus, there are links to obtaining more in-depth information from NHF.
- 2 PARENT'S GUIDE**: This section is designed for the parents of a child newly diagnosed with a bleeding disorder. It gives pertinent information and advice, walking the parent through each step they need to take. There are also links to hemophilia treatment centers in your area.
- 3 NEWS**: Up-to-date news in the field of research, as well as events of interest to members of the bleeding disorders community. Use this section as a resource to the search for a cure.

The background of the screenshot shows a grid pattern and the text "features" repeated vertically on the right side.



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CHECKLIST OF QUESTIONS

Pre-clinical

- What toxicology studies were performed?
- At what timepoints were data collected (short/long-term)?
- Were there adverse events? If so, what has been done to avoid similar problems in humans?
- Were biodistribution studies performed?
- Was the vector seen in the germline cells(eggs and sperm)?
- What efficacy studies were performed? In what animals?
- How does that dose compare to the one I will receive? How long did it last?

Regulatory Review

- Was this protocol approved by the hospital's IRB and IBC?
- Was this protocol reviewed by RAC and what were the recommendations of the committee?
- Was this protocol reviewed by FDA?

Informed consent

- Can I be given a copy of the informed consent and/or protocol to review with my physician?
- Can I have someone present with me during informed consent?

Human Administration

- Has this vector ever been administered to humans before? If so, how many?
- What was the outcome? Were there any adverse events?
- How long have they been followed?

Gene Transfer Protocol

- What is the goal of the trial? What phase is the trial?
- How long will I have to stay in the hospital?
- Will I have to receive general anesthesia?
- How long will I be followed?
- What testing will be done? How frequently?
- Will I need to provide semen samples? How frequently?
- Who will pay for my travel?
- Will I be reimbursed for time missed at work?
- Will the factor that I use directly for the study be paid for?
- Will I be offered the possibility to bank sperm? If so, will it be paid for and for how long?
- Will any restrictions be placed on my activity or future treatment?
- Will I be asked to consent for an autopsy at the time of my death (from any cause)?

Risks

- Are there any problems or risks that you expect to encounter in the clinical trial?
- What are the risks of this particular vector when compared to other vectors?
- Have studies examining germline transmission been completed in animals?
- Have any inhibitors developed in the animals tested?
- Is there any long-term data in animals supporting a lack of tumor or cancer formation?
- What are the bleeding risks of the actual gene transfer procedure?
- If I have any side effects, where and by whom will my medical care be provided? Who will pay for it?

Confidentiality

- Who will have access to my medical records?
- What type of identifying information may be used in scientific journals or public presentations (ie, hemophilia treatment center location, age, viral status)?
- Will I be asked to consent that pictures be taken during the procedure?
- Will I be asked to participate in any media-related events regarding my enrollment?

Conflict of Interest

- Is the sponsor of the trial a person or the company that makes the vector?
- Does anyone involved in my care have financial interest in the outcome of the trial?
- Who will financially benefit if the therapy is successful?

Readministration

- If I participate early in the trial, will I be able to be re-administered a dose if the treatment eventually becomes successful?
- Are there any studies being conducted to allow me to receive another dose?

Additional Resources

- Have I checked the manufacturer/sponsor Web site for a detailed explanation of the vector?
- Have I checked the RAC's Web site for the minutes and recommendations of their review?
- Have I discussed the protocol with my hemophilia treater?
- Have I e-mailed the PI a list of questions?
- Do I know who the clinical coordinator is? 