WFH
WORLD FEDERATION OF HEMOPHILIA
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GTR
WFH GENE THERAPY REGISTRY

WFH Gene Therapy Registry

Basics of hemophilia, gene therapy, and long-term data collection

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About this Guide

This document is an introductory guide to the World Federation of Hemophilia (WFH) Gene Therapy Registry (GTR). It answers basic questions about the **registry**, its purpose, and what participants can expect. The guide is designed to help those who receive gene therapy for hemophilia and their care teams to decide if they should participate in the registry.

What is Gene Therapy?

The fundamentals

Like every other organism, humans are made up of **cells**. Within each cell is a set of instructions known as the **genome**. The genome is made of a chemical called deoxyribonucleic acid **(DNA)** and is organized in **chromosomes**, which contain **genes**.

Genes are sections of DNA that contain instructions to produce one specific molecule in the body, usually a protein. These proteins control how our body grows and works. They are also responsible for many of our characteristics, such as eye color, blood type, and height.

Why gene therapy for hemophilia?

People with hemophilia cannot clot blood properly because they do not have enough proteins, known as **clotting factors**. A segment of their DNA has incorrect information (known as a **mutation**) in either the *F8* (hemophilia A) or *F9* (hemophilia B) gene, which prevents their body from making the relevant clotting factor.

The current standard of care for all people living with severe hemophilia is regular therapy (**prophylaxis**) with clotting factor replacement therapy or non-factor replacement therapy to prevent bleeding.

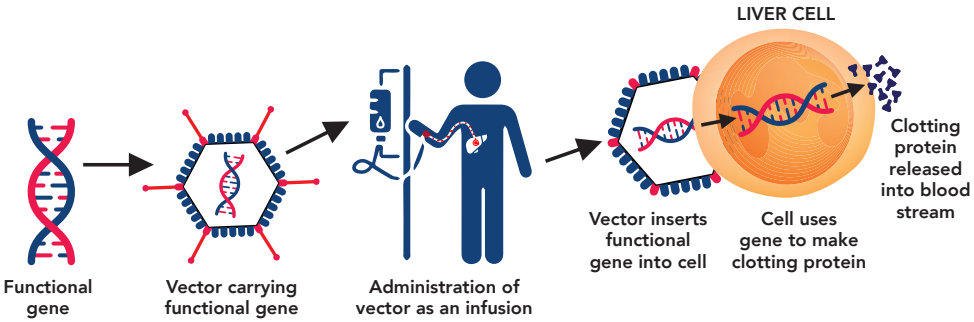
The goal of gene therapy is to provide sustained protection from bleeding over a longer duration of time through a one-time infusion, thereby reducing or removing the need for treatment regularly.

Gene therapy may make it possible for some people with hemophilia to achieve better health outcomes and quality of life than that possible with their currently available treatments.

Basic process of gene therapy

First-generation gene therapy involves inserting a functional copy of the faulty *F8* or *F9* gene (called a **transgene**) into a person through a one-time intravenous infusion. A modified virus is used as a vehicle (called a **vector**) to carry the corrected gene to liver cells (called **hepatocytes**). For gene therapy in hemophilia, **adeno-associated viruses (AAV)** are currently among the most frequently used viral vectors.

Once the transgene is inside the cells, two key steps in gene expression known as **transcription** and **translation** can occur. The cells will use the new transgene to produce functional clotting factor proteins and release them into the bloodstream.



Long-term outcomes of gene therapy

Like all new treatments, the safety and efficacy of gene therapy are tested in human clinical trials.

Different gene therapies have been investigated for more than two decades in hemophilia. Clinical trials have established the efficacy of gene therapy in decreasing bleeding and the need for regular treatment for up to 5-8 years post-infusion, for most patients.

However, many unresolved questions on the long-term safety, **variability**, and **durability** of **efficacy** will remain at the completion of clinical trial programs.

It is crucial to collect long-term information on its safety profile and the health and well-being of all people with hemophilia who receive gene therapy, whether as part of a clinical trial or as an approved treatment.

Long-term outcomes of gene therapy (cont.)

Collecting **data** over time will help clarify how well the gene therapy products perform over the long-term, if there are any new safety issues, and whether it improves clinical and lifestyle outcomes over a lifetime. As such, the WFH has developed the Gene Therapy Registry for all people with hemophilia receiving gene therapy across the globe.

SCAN QR CODE for information about hemophilia gene therapy or clinical trials.

What is the World Federation of Hemophilia Gene Therapy Registry?

The WFH GTR is a new online system that will collect uniform and standardized data on all recipients of gene therapy for hemophilia as part of a clinical trial or as an approved product. The WFH GTR aims to collect long-term data on the safety and efficacy of gene therapy, together with patient outcomes and experiences, to enhance understanding of the impact of gene therapy, and inform future research into gene-based technologies.

Why is the World Federation of Hemophilia Gene Therapy Registry Needed?

The WFH GTR can help researchers track the long-term outcomes of gene therapy

Gene therapy is a new treatment modality that works completely differently from other treatments used to prevent bleeding in people with hemophilia.

There are currently unanswered scientific questions, including how long the gene therapy will provide therapeutic levels of bleeding protection and whether any safety concerns may arise in the future. The WFH GTR will collect specific data over the lifespan of treated patients to help answer some of these questions.

The WFH GTR combines information from a large number of people with hemophilia

As the number of people with hemophilia who will receive gene therapy may be small at first, and dispersed globally, it will not be easy for researchers to see patterns and compare individual patient outcomes in a meaningful way. With international collaboration between centres and countries, registries are an effective way to pool enough data to enable robust evaluation of rare safety events and the durability of gene therapy.

A global system, such as the WFH GTR, will ensure that rare adverse events are detected, even in smaller and geographically dispersed populations.

Ultimately, researchers will be able to use this information to improve the design of gene therapies in the future.

Who is Eligible to Participate in the Registry?

People with hemophilia who have or will soon receive gene therapy can join the WFH GTR. Participation is entirely voluntary. The choice to join or not join the registry will not affect the treatment a patient receives at their Hemophilia Treatment Centre (HTC). Patients currently in a clinical trial can participate in the registry after the trial ends or earlier if permitted.

How can a Person with Hemophilia Participate?

People with hemophilia interested in participating in the WFH GTR should speak to their HTC health care team. They will need to read and sign a consent form before joining the WFH GTR. The HTC health care team or designated research lead will answer all questions, including questions on data protection. The HTC will enter participants' information into the registry at each scheduled gene therapy follow-up visit.

People with hemophilia participating in the registry will also be able to enter information on their quality of life using the WFH GTR mobile application at specific time points. A participant can withdraw consent and end their participation in the WFH GTR at any time.

The WFH has produced an in-depth user guide for participants of the GTR. **SCAN QR CODE** to find the *User Guide for People with Hemophilia*.

What Type of Information does the Registry Collect?

People with hemophilia who join the registry will have information collected at each clinic visit and entered into the registry. This will include:

- Medical history (eg, type and severity of hemophilia)
- Details of gene therapy received (eg, vector and transgene used)
- How well the treatment is working (eg, factor levels, bleeding events and the need for additional treatment, over time)
- Any adverse health events (side-effects) experienced after treatment

The WFH has produced an in-depth user guide for HTCs who have patients participating in the registry. **SCAN QR CODE** to find *User Guide for Hemophilia Treatment Centres (HTCs)*.

What are the Benefits of Being Involved in the Registry?

The WFH GTR will help people with hemophilia who receive gene therapy in the future by providing data and evidence on the safety and efficacy of these technologies. People participating in the registry will not receive direct benefits or any monetary compensation.

Where will the Data be Stored?

All data entered into the WFH GTR will be housed in a global **database**. All of the information that is entered in the GTR is coded and strictly confidential. Specific stakeholders may request access to anonymized and combined data for research and analysis. These groups may include regulatory bodies (such as the FDA and the EMA), pharmaceutical manufacturers of the gene therapy products, researchers, participating HTCs, and other groups that the WFH GTR Scientific Advisory Board approves.

All data requests will be governed by the WFH GTR Scientific Advisory Board. **SCAN QR CODE** for more information about the governance committees.

What are the Risks of Participating in the Registry?

Participating in the WFH GTR is very low risk. As with any online platform, there is a small chance of a data breach. However, all groups that work with the registry must follow strict data privacy standards to prevent a data breach. The registry will not contain participant names or any other identifying information. Participants will be assigned a unique registry-specific identification number for tracking purposes.

Can Someone Stop Participating in the Registry?

Yes, any participant can choose to stop participating in the registry at any time. You can request for any previously submitted information to be removed from the database. No new data will be added unless you rejoin the registry in the future.

Who do I Contact if I have Further Questions?

For more information, **SCAN QR CODE** to visit **www.wfh.org** or contact the WFH directly by email at **gtr@wfh.org**.

Glossary of Terms

AAV: An adeno-associated virus is a harmless virus used to deliver the DNA, including the correct factor gene, to liver cells during gene therapy infusion. It is also called the vector.

Adverse events: An adverse event is any side effect, or health problem that occurs during or after a person has received gene therapy. These can include anything from a rash to cancer. Adverse events are related to the timing of gene therapy but are not necessarily due to the gene therapy received. Tracking people with hemophilia (PWH) who receive gene therapy will help determine if there are specific health problems associated with gene therapy.

Cells: Tiny units or compartments that make up the body and are considered the building blocks of our bodies. The human body is composed of trillions of cells. Each cell contains 23 pairs of chromosomes and the body's hereditary material (DNA).

Chromosome: A chromosome is a thread-like structure found within the nucleus of every cell of our body and made up of DNA. We have 23 pairs of chromosomes in each cell.

Clotting factors: Clotting factors are proteins in blood that allow a clot to form. Without clotting factor, PWH do not stop bleeding efficiently. People with hemophilia A are missing clotting factor VIII and hemophilia B are missing clotting factor IX.

Data: Information collected during medical visits, including things such as the type of gene therapy or factor level.

Database: Electronic computer system which holds all the data collected on each participant of the registry or study.

DNA: DNA contains the genetic instructions for the creation and function of the body. It is material that people inherit from their parents.

Durability: Durability of gene therapy expression is a term used to describe how long the gene therapy treatment has a positive effect on a person's factor level.

Efficacy: Describes how efficient a gene therapy treatment is at elevating factor levels or reducing bleeding events.

Gene therapy: Treating a genetic disease by inserting a corrected copy of the disease-causing gene into a person.

Genes: On a long piece of DNA, instructions for each protein are in segments along the strand. These segments are called genes.

Genome: The entire set of DNA instructions in a human body.

Glossary of Terms (cont.)

Hepatocyte: The type of liver cell that will produce new clotting factor after gene therapy.

Mutation: A change in the DNA instructions of a gene.

Prophylaxis: The regular and continued use of a treatment to prevent bleeding events in a PWH.

Protein: Proteins are small molecules that cells make. Some proteins are building blocks that become things like muscle and bone. Other proteins make things happen in the body, such as forming a clot when needed.

Registry: A database where medical information on patients is stored. For example, the data of PWH who undergo gene therapy for hemophilia are kept in the WFH Gene Therapy Registry.

Transcription and translation: The processes that cells go through to read the DNA instructions of a gene and produce the protein.

Transgene: A corrected copy of a gene inserted during gene therapy.

Variability: How clotting factor production patterns change in a person over time or between people after gene therapy.

Vector: Delivery system of corrected genes into human cells during gene therapy.

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Notes

Notes

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