WFH
WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

Clinical trials for hemophilia

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What is a clinical trial?

Clinical studies typically involve human volunteers, participants, or samples (blood or other tissues) from humans with the intent of advancing medical knowledge. There are two main types of clinical studies: **clinical trials** (also called **interventional studies**) and **observational studies**.

A **clinical trial** is a type of research study in which researchers test new ways to prevent, detect, or treat diseases. Participants in a clinical trial receive specific **interventions** according to a detailed protocol for that clinical trial. Such interventions may be medical products, such as drugs or devices, surgical procedures, or changes to behavior, such as a participant's diet.

Clinical trials may compare a new treatment method to a standard one that is already available, to a placebo, or to no intervention. Clinical trials are the main method that researchers use to find out if a new treatment is safe and efficacious. For a drug to become a medicine that doctors can prescribe, it must first be tested in a series of clinical trials, known as Phase 1, Phase 2, and Phase 3. Following Phase 3 clinical trials, data from the clinical trials is submitted to a regulatory agency who then determines if this drug should be approved for use.

Content

THERE ARE DIFFERENT TYPES OF CLINICAL TRIALS:

- **Prevention trials**: Designed to find better ways to prevent a disease in people who have never had the disease or to prevent a disease from returning in people who have had the disease. Interventions in prevention trials may include medicines, vitamins, vaccines, or lifestyle changes.
- **Screening trials**: Test new ways for detecting diseases or health conditions in a population.
- **Diagnostic trials**: Research on comparing tests or procedures for diagnosing a particular disease or condition.
- **Treatment trials**: Test new treatments such as medication, new devices, and new ways of doing surgery or radiation therapy.
- **Quality of life trials**: Explore ways to assess or improve the quality of life for persons with an illness or condition.

THE FOLLOWING TERMS ARE OFTEN USED IN DESCRIBING CLINICAL TRIALS:

- **Randomization**: The process by which treatments are assigned to participants in a clinical trial by chance rather than by choice. Neither the researcher nor the participant selects which treatment a given participant will receive.
- **Placebo-controlled clinical trial**: A clinical trial in which the treatment of interest is compared to a control group who receive a placebo (a treatment that looks like the investigational treatment but does not have any active ingredients).
- **Open-label clinical trial**: A type of clinical trial in which both the participants and the researchers know what treatment is being administered to the participants.
- **Single-blind clinical trial**: A clinical trial in which the clinical trial research team is aware of the treatment a participant is taking but the study participants do not know which medicine or treatment they are receiving.
- **Double-blind clinical trial**: A type of clinical trial in which neither the study participants nor the researchers know what treatment the participants are receiving until the study is complete. The pharmacist does know which treatment the participants are given. Such blinding is designed to prevent members of the research team and study participants from influencing results.
- **Study endpoints**: In a clinical trial protocol, the primary endpoint is the planned outcome measure that is the most important for evaluating the effect of an intervention or treatment.

What is an observational study?

An **observational study** is a type of research study in which researchers **observe** the effects of an intervention in a group of participants, without intervening. Participants are not assigned to specific interventions by the investigator, as in a clinical trial, but may be receiving a treatment that is already part of their routine medical care. Researchers can then assess associations between interventions and health outcomes, among people taking it as part of standard care. Such findings may lead to further investigation in a clinical trial. There are several different types of observational studies. A **patient registry** is one type of observational study.

A patient registry is an organized system that uses observational study methods to collect data on treatments, clinical outcomes, and the well-being of a population defined by a particular disease, condition, or exposure.

For the hemophilia community, two important patient registries are:

WORLD BLEEDING DISORDERS REGISTRY

The World Bleeding Disorders Registry (WBDR) is a web-based data entry system that provides a platform for a network of hemophilia treatment centers around the world to collect uniform and standardized patient data, and to guide clinical practice. With informed consent from the patient, the WBDR stores de-identified data about the person's disease, such as hemophilia type and severity, symptoms, treatment and health outcomes.

Health care professionals participating in the WBDR can use the WBDR to track and monitor their patient's progress and guide their clinical care. These de-identified and confidential data can also be used to help researchers answer important questions about disparities in care globally and help advance advocacy/health policy initiatives.

WORLD FEDERATION OF HEMOPHILIA GENE THERAPY REGISTRY

Through an international collaborative effort, the WFH has developed a global gene therapy patient registry, the WFH Gene Therapy Registry (GTR). The aim of the GTR is to provide a robust, scientifically valid database, available to all healthcare providers treating people with hemophilia who receive gene therapy, anywhere in the world. The data collected through the WFH GTR will be used to assess the long-term safety and efficacy of gene therapy in people with hemophilia.

The following table can be helpful to see how clinical research is different from a medical treatment.

CLINICAL RESEARCH	VS.	MEDICAL TREATMENT
Answers specific questions through research involving numerous research volunteers	INTENT	Address the needs of individual patients
Generally designed and intended to benefit future patients	INTENDED BENEFIT	Intended to benefit the individual patient
Paid for by drug developers and government agencies	FUNDING	Funded by individual patients and their health plans
Depends on the research protocol	TIMEFRAME	Requires real-time decisions
Requires written informed consent	CONSENT	May or may not require informed consent
Involves periodic and systematic assessment of patient data	ASSESSMENT	Based on as-needed patient assessment
Protected by government, agencies, institutional review boards, profession standards, informed consent, and legal standards	PROTECTIONS	Guided by state boards of medical practice, professional standards, peer review, informed consent, and legal standards
Test products and procedures of unproven benefit to the patient	CERTAINTY	Uses products and procedures accepted by the medical community as safe and effective
Considered confidential intellectual property	ACCESS TO INFORMATION	Available to the general public through product labeling
Published in medical journals, after clinical research ends	RELEASE OF FINDINGS	Individual medical records are not released to the general public

Why are clinical trials needed?

Clinical trials are designed and conducted to find better ways to diagnose, treat, and prevent diseases or conditions. Before a medical intervention or treatment is approved by a regulatory agency (such as the European Medicines Agency (EMA) or U.S. Food and Drug Administration (FDA)) for use in patients, it must be tested in a clinical trial to ensure it is safe and effective. Some common reasons for conducting clinical trials include:

To evaluate treatment of a disease, syndrome, or condition:

- Is a new treatment safe and effective?
- How does a new formulation of a medicine compare with an existing treatment?
- Is an existing treatment safe and effective in a new patient population (such as children)?

For example, there are many ongoing clinical trials, in various phases of development, assessing how safe and efficacious gene therapy is for people with hemophilia.

How are clinical trials conducted?

THE CLINICAL TRIAL PROCESS

For a drug to become a treatment that doctors can prescribe, it must first be tested in a series of clinical trial phases, and then assessed and approved by a regulatory agency. Each clinical trial phase has a purpose, and the phases progress in order from Phase 1 to Phase 4.

PHASE 1

This is the first time a new investigational treatment is tested in people. The purpose of Phase 1 clinical trials is to assess the safety and side effects associated with the treatment. They are often conducted in a small group of healthy volunteers. However, in rare diseases, such as hemophilia, Phase I trials are usually conducted in people with hemophilia. Phase 1 clinical trials are typically several months long and approximately 70% of therapies tested in Phase 1 trials move to the next phase. Clinical development does not proceed beyond Phase 1 for the other 30% of therapies that are not shown to be safe in Phase 1.

Phase 1 hemophilia gene therapy clinical trials enroll between 10-30 persons with hemophilia.

PHASE 2

The purpose of Phase 2 clinical trials is to continue to test the safety and side effects associated with the treatment, but also test the efficacy and determine the most effective dosages. Phase 2 trials are usually conducted in more participants than a Phase 1 trial, and include people who have the disease. In some situations, Phase 1 and Phase 2 trials are combined and referred to as Phase 1/2. Phase 2 clinical trials are typically several months to 2 years long. It is estimated that 30% of therapies tested in Phase 2 trials move to the next phase. Clinical development does not proceed beyond Phase 2 if the treatment is not shown to be efficacious or there are safety concerns.

Phase 2 hemophilia gene therapy clinical trials enroll between 10-50 persons with hemophilia. This number is smaller than in other disease states because hemophilia is a rare disease. Phase 1 and 2 clinical trials are often combined for rare diseases such as hemophilia. By combining trial phases, drug manufacturers hope to speed up the development timelines for new drugs.

PHASE 3

The purpose of Phase 3 clinical trials is to confirm efficacy of the treatment, monitor side effects, and compare the new treatment with standard or similar treatments. Phase 3 trials, sometimes called a 'pivotal trial,' are conducted on a large number of people with the disease and in many different study locations (national and international, depending on the study). Phase 3 clinical trials are sometimes randomized and often double-blinded. Phase 3 clinical trials are typically 1 to 4 years long and are the last step before submitting an application to a regulatory agency for approval. An estimated 25% of Phase 3 trials move to Phase 4 studies.

Data from the Phase 3 pivotal study, and sometimes data from Phase 1 and 2 clinical trials, are submitted to a regulatory agency for review. The regulatory agency conducts independent analyses on the safety and efficacy of the treatment and makes a decision on whether a treatment is approved for use by patients or not.

Phase 3 hemophilia gene therapy clinical trials enroll between 50-150 persons with hemophilia and are conducted in study locations around the world.

PHASE 4

Phase 4, sometimes called post-marketing trials, are conducted after a new treatment has received regulatory approval and is available to patients. These studies allow researchers to gather additional information about the longer-term risks (including rare side effects) and benefits of the treatment, as well as optimal use in 'real-world' situations.

How new therapies get tested in clinical trials

CLINICAL TRIALS PHASES	DURATION OF STUDY	NUMBER OF PEOPLE ENROLLED*	STUDY PURPOSE	PERCENT OF TREATMENTS MOVING TO NEXT PHASE
PHASE 1	SEVERAL MONTHS	~10-30 SMALL NUMBER of people with hemophilia	SAFETY DOSE RANGE	±70% OF STUDIES ARE SUCCESSFUL and move to Phase 2
PHASE 2	SEVERAL MONTHS TO 2 YEARS	~10-50 SLIGHTLY MORE people with hemophilia	SAFETY EFFICACY DOSE SELECTION	±30% OF STUDIES ARE SUCCESSFUL and move to Phase 3
PHASE 3	1 TO 4 YEARS	~50-150 LARGER GROUP of people with hemophilia	SAFETY EFFICACY	±25% OF STUDIES ARE SUCCESSFUL and move to Phase 4
IF SUCCESSFUL		DATA FROM CLINICAL TRIAL SUBMITTED TO REGULATORY AGENCY (e.g., FDA, EMA)		REGULATORY APPROVAL
PHASE 4	SEVERAL YEARS	MORE THAN 100 People with hemophilia enrolled	LONG TERM FOLLOW-UP	NEW THERAPY available to people with hemophilia

*The number of people with hemophilia enrolled in clinical trials is smaller than in other disease states because hemophilia is a rare disease.

CLINICAL TRIAL PROTOCOL

Each clinical trial has a detailed, comprehensive plan for conducting the trial called the **protocol**. The clinical trial protocol is developed to answer specific research questions and to protect the health of the study participants. The protocol is reviewed and approved by a regulatory agency before a clinical trial can begin. Information contained in a clinical trial protocol includes:

- The reason for conducting the study
- The study population. Who may participate is determined by **eligibility** criteria
  - Reminder: Eligibility refers to the key requirements that must be met for people to participate in a clinical trial. Eligibility includes **inclusion criteria** (that are required for participation) and **exclusion criteria** (that prevent a person from participation). See example on page 15.
- The number of participants that will be enrolled in the trials
- Information about the drugs/treatments that will be used, including the name and dosage(s)
- The study endpoints
- The clinic visits, tests and procedures that the participants will need to do during the study and how often
- How long the study will last
- The information that will be gathered about the participants
- Protections that are part of the study to guard against risk to study participants

STUDY ENDPOINTS

The clinical development program of a new therapy or intervention determines if the new therapy is effective and safe. In a clinical trial protocol, the primary endpoint is the planned outcome measure that is the most important for evaluating the intervention or treatment. Depending on the phase of the clinical trial, the primary endpoint may be focused on safety, such as treatment-related adverse events and/or changes from baseline in clinical laboratory evaluations; or efficacy, such as annualized bleeding rate or factor level.

Examples of safety and efficacy endpoints in hemophilia clinical trials (including gene therapy trials):

SAFETY ENDPOINTS	EFFICACY ENDPOINTS
Adverse events; treatment-emergent adverse events; serious adverse events	Annualized bleeding rate
Changes from baseline in clinical laboratory evaluations	Annualized joint bleeding rate
Thromboembolic events	Spontaneous and traumatic bleeding episodes
Hypersensitivity type reactions	Factor levels/activity
Inhibitor development	Factor utilization
Immune response/antibody development	Quality of life (questionnaire)
Vector genomes in blood, urine, saliva, stool, and semen	

Participating in clinical trials

The decision to participate in a clinical trial is one that you need to consider carefully and discuss with your doctor and family. With help from your doctor, you should weigh the benefits and risks of participating as well as the time commitment required to participate.

BENEFITS AND RISKS

It is critical to understand the potential benefits and risks of participating in a clinical trial.

POTENTIAL BENEFITS	POTENTIAL RISKS
You may have access to a new treatment before it is available and could be among the first to benefit	You may experience unwanted side effects of the new treatment
You will have the support of an expert hemophilia care team who will monitor your health closely	The new therapy may not work for you or you may receive placebo if it is a placebo-controlled study
You will have an opportunity to play an active role in your health and improve your own hemophilia management	The new therapy being studied may not be better than your current standard of care
You may help future people diagnosed with hemophilia by contributing to the development of a potential therapy	The trial could take more of your time than your usual treatment; you may have more doctor visits and tests

IMPORTANCE OF EXPECTATIONS

Potential clinical trial participants need to remember that the purpose of the clinical trial is to study a new treatment or intervention.

- This means that it is **not known in advance** if an individual study participant will or will not benefit from participating
- Treatment received during a clinical trial may be very different from a person's routine hemophilia treatment practices
- There may be unknown risks associated with study participation

WHO CAN PARTICIPATE IN A CLINICAL TRIAL?

Patients are invited to join clinical trials through their health care team, based on the eligibility criteria of the study. **Eligibility** refers to the key requirements that must be met for people to participate in a clinical trial. These criteria help to ensure the safety of participants and ensure that the specific research questions being studied in the clinical trial may be answered accurately.

Each study has both inclusion criteria and exclusion criteria.

- **Inclusion criteria**: These are the conditions that *must be met* and allow a person to participate in a clinical trial
- **Exclusion criteria**: These are reasons that a person is not allowed to participate in a clinical study

For hemophilia clinical trials, severity and type of hemophilia, age, inhibitor status, and history of prophylaxis are common factors determining eligibility. Each clinical trial is unique and eligibility criteria vary from study to study. Many clinical trials start in adults first, before studying the new treatment in children. For this reason, it is very common to see age listed as an inclusion criterion.

WANT TO KNOW MORE ABOUT ELIGIBILITY CRITERIA?

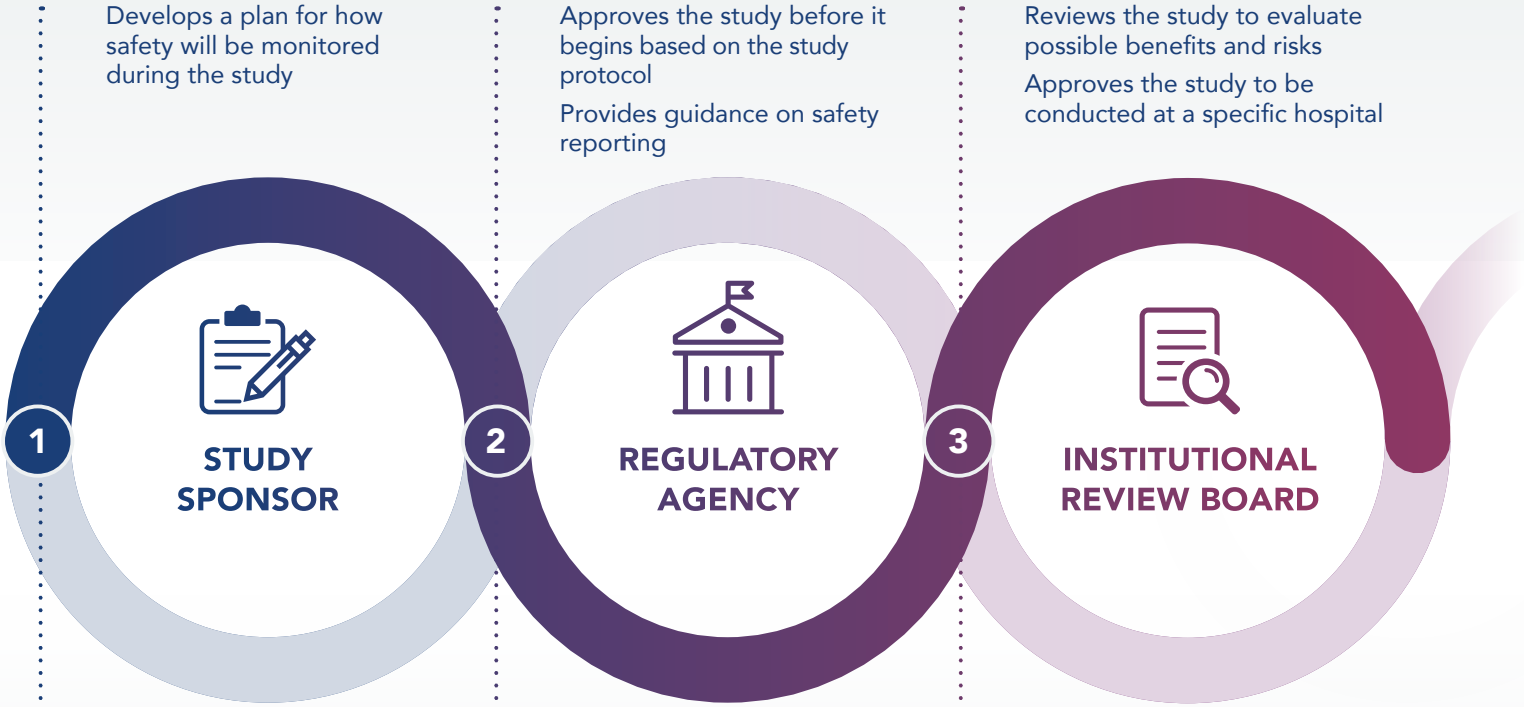
People with hemophilia who are interested in participating in a clinical trial will go through a "screening process" where the research team will determine if that person meets the eligibility criteria of the study. The screening process will include a review of the people with hemophilia's medical history and current medical status, as well as discussions on the roles and responsibilities of participants, and the potential risks and benefits of participating.

It is important to understand that not everyone who has an interest in a clinical trial will have the opportunity to participate. This can happen because some aspect of a person's medical history does not meet the inclusion criteria for the trial (for example, a study may only be enrolling people with hemophilia of a certain age). Further, each clinical trial will have an estimated number of participants for planned enrollment, when a clinical trial has the required number of people enrolled they will stop accepting additional study participants.

Review a (fictional) example of eligibility criteria for hemophilia clinical trials on page 15.

Monitoring patient safety in clinical trials*

*BEFORE THE TRIAL BEGINS



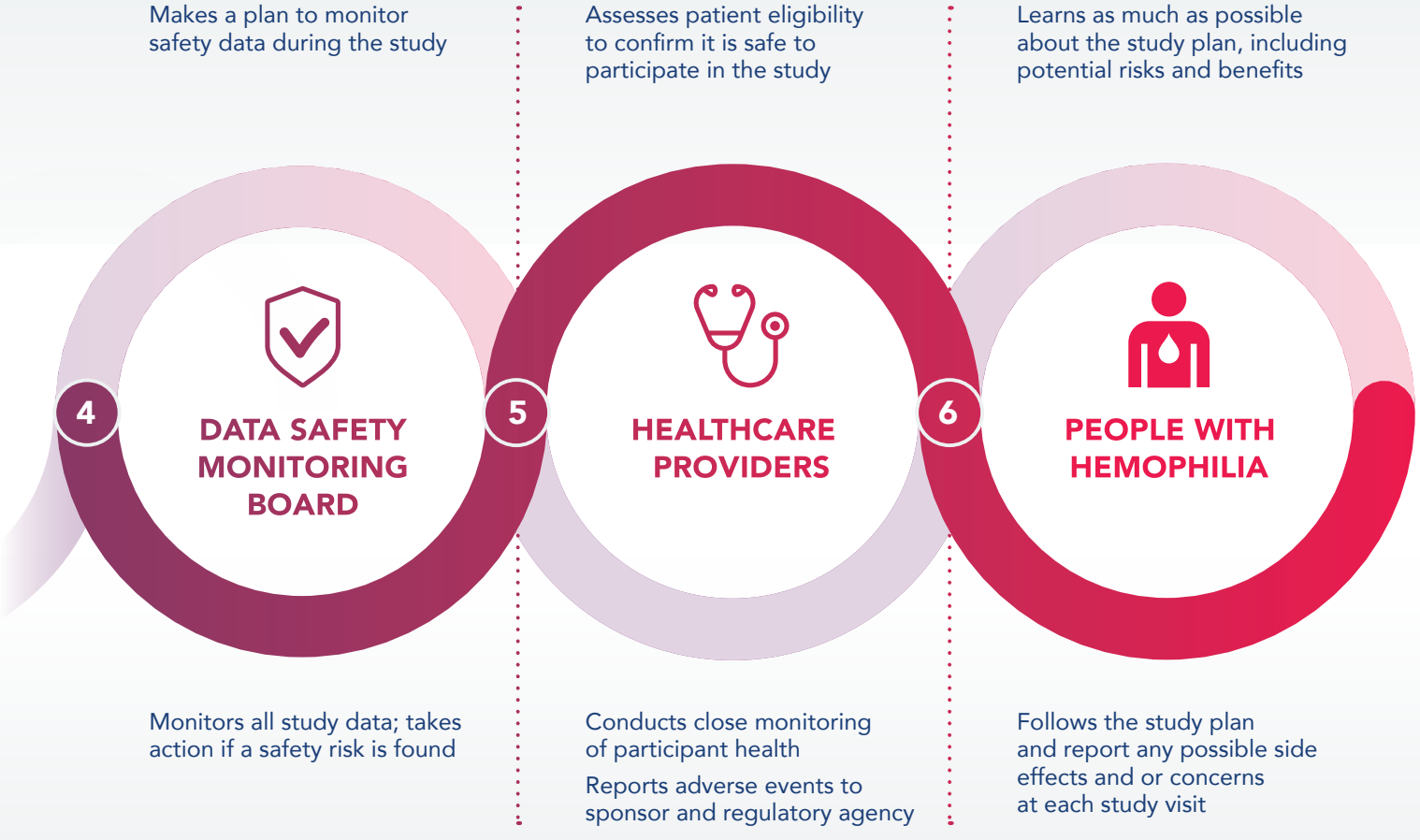
*DURING THE TRIAL

PROTECTING PATIENTS IN A CLINICAL TRIAL

Ensuring patient safety is of paramount importance during the clinical trial process. There are many levels of study approval and monitoring to protect the safety of participants in clinical trials, and a system in place for collecting and reporting safety outcomes during a study.

Regardless of the phase of a clinical trial, each study must be reviewed and approved by a regulatory agency before patients can be enrolled. The study sponsor, often the manufacturer of the treatment under study, develops a study protocol that includes a section on how the safety of the treatment will be monitored throughout the study. The study protocol must then be approved by a regulatory agency, such as the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA). Once a study is approved and study sites are identified, participating sites must submit and receive approval of the study protocol to the Institutional Review Board used by the hospital or hemophilia treatment center where it will be carried out.

Once a study is approved, the safety of patients participating is monitored throughout the study by a Data Safety Monitoring Board, the sponsor or the company manufacturing the study treatment, and by the healthcare professionals involved. The people with hemophilia enrolled in a study also have a role to play. People with hemophilia participating in trials need to inform the study team at their treatment center if they experience any side effects or safety events.



INFORMED CONSENT

Every participant who volunteers to participate in a clinical trial must sign an informed consent form prior to being enrolled in the study (or a parent can sign an assent form for their child in the case of minor participants). An informed consent provides potential participants information about the trial and explains the potential risks and benefits associated with participating before a person decides to participate. The process of obtaining informed consent involves a discussion with the study team prior to signing the form:

In general, the **informed consent** process involves the following:

- Providing the potential study participant with enough information to allow for an informed decision about participation in the clinical investigation
- Making sure the potential participant has a full understanding of the information provided
- Ensuring that there is an appropriate amount of time (perhaps multiple visits) to ask questions and to discuss the research protocol with family and friends to decide about participation
- Obtaining the potential participant's voluntary agreement to participate
- Providing information on an ongoing basis as the clinical investigation progresses or as the subject or situation requires

The following is a detailed list from a regulatory agency, in this example the U.S. FDA. As part of the informed consent process, this information must be given to each potential research subject *before* enrolling in a clinical trial:

- A statement explaining that the study involves research
- An explanation of the purposes of the research
- The expected length of time for participation
- A description of all the procedures that will be completed during enrollment on the clinical trial
- Information about all experimental procedures that will be completed during the clinical trial
- A description of any predictable risks
- Any possible discomforts (e.g., injections, frequency of blood test etc.) that could occur as a result of the research
- Any possible benefits that may be expected from the research
- Information about any alternative procedures or treatment (if any) that might benefit the research subject
- A statement describing:
  - The confidentiality of information collected during the clinical trial
  - How records that identify the subject will be kept
  - The possibility that the FDA may inspect the records
- For research involving more than minimal risk, information including an explanation as to whether any compensation or medical treatments are available if injury occurs, what they consist of, or where more information may be found
- Research subject participation is voluntary
- Research subjects have the right to refuse treatment and will not lose any benefits for which they are entitled
- Research subjects may choose to stop participation in the clinical trial at any time without losing benefits for which they are entitled

Questions to ask before participating in a clinical trial

For people considering participation in a clinical trial, it is extremely important to learn as much as possible about the clinical trial, the risks and benefits to the participants, the responsibilities of participants, the care expected, and the team that will be conducting the trial. It is expected that you will have questions, and essential that your questions are answered. It may be helpful to write down a list of questions to ask before meeting with a clinical trial research team.

HERE ARE SOME EXAMPLES:

Purpose & procedures

- ◯ What is the purpose of the clinical trial?
- ◯ If researchers are studying an investigational drug or treatment, why do they believe it will be effective for me?
- ◯ Who has reviewed and approved the study?
- ◯ How many people will be included in the study?
- ◯ Can I talk to other people who are participating in the study?
- ◯ What types of tests and medical procedures will be performed?
- ◯ Will the tests and procedures be the same for each study visit or will it change over time?
- ◯ How often will I have to visit the hospital or clinic? Will any of these visits require an overnight stay?
- ◯ Is there a chance of receiving a placebo?
- ◯ If the trial is successful, what will the results show?

Potential risks and benefits

- ◯ What are the possible risks and benefits of participation?
- ◯ What are potential short-term and long-term side effects of this treatment?
- ◯ What steps will be taken to monitor my safety?
- ◯ Who will oversee my healthcare while participating?
- ◯ Will my healthcare records and study results be confidential?
- ◯ If the treatment works for me, can I keep using it after the trial ends?

Practical concerns

- ◯ Where will I receive my medical care?
- ◯ Will I be able to see my own health care team?
- ◯ Whom do I contact if I have questions during the trial?
- ◯ Will my treatment and care change if I join this study? If yes, how?
- ◯ Will the results of the clinical trial be available to participants?
- ◯ Who is paying for and supporting the study?
- ◯ Are there any costs associated with participation?
- ◯ If I participate in this clinical trial, will it prevent me from being part of another clinical trial in the future?

Members of the healthcare team have a vital role in ensuring that potential study participants fully understand what it will mean to be part of a clinical trial.

COMPONENTS OF THE INFORMED CONSENT PROCESS	MEETING THE NEEDS OF POTENTIAL CLINICAL TRIAL PARTICIPANTS
Providing the potential study participant with enough **information** to allow for an informed decision about participation in the clinical investigation	Has comprehensive information about the clinical trial been provided in a **format**, at an **appropriate level**, and with **language** that is best for the individual?
Making sure the potential participant has a **full understanding** of the information provided	Is there a process is in place (for example, 'teach back') to **confirm understanding** of the clinical trial, including: the patient's role, how the trial will work, frequency of study visits, what will happen at study visits, the overall time commitment, potential risks, and benefits of participation?
Ensuring that there is an appropriate amount of time to ask **questions** and to discuss the research protocol with family and friends to decide about participation	Has sufficient **time** been devoted to encouraging and answering questions? Has contact information been provided for follow-up discussions or questions? Have potential participants been encouraged to discuss the clinical trial with loved ones/get additional input prior to deciding about participation?
Obtaining the potential participant's **voluntary** agreement to participate	Is it clearly communicated and understood that participation in a clinical trial is the **individual's choice**, and they are not obligated to their healthcare team or anyone else to participate?
Providing information on an **ongoing** basis as the clinical investigation progresses or as the subject or situation requires	Is there a **plan** for communicating updates and additional information to participants during the clinical trial? Has this plan and **point person** for updates been shared with participants?

A NOTE ABOUT CONFIDENTIALITY

Individuals who are considering participation in a clinical trial may have questions about their health care information and privacy. **Confidentiality** refers to maintaining privacy with individually identifiable health-related information for persons who participate in clinical trials. This includes research records related to identification (such as name), diagnosis, prognosis, treatment, or any other information that could be linked to a participant. In situations in which results of a clinical trial are published in a peer-reviewed journal, patient related information is de-identified, and privacy is maintained in such reporting.

WHO IS INVOLVED IN CLINICAL TRIALS?

Many different groups of people are involved in the clinical trial process, and they all have different responsibilities and roles. Participants and health care providers play an important role throughout the duration of the clinical trial process. It is important that both participants and health care providers fully understand their roles.

Patient and healthcare provider roles in clinical trials

PARTICIPANT/ PATIENT	CLINICAL TRIAL PROCESS	HEALTHCARE PROVIDER
Learn about the clinical trial process Ask your healthcare team about clinical trial opportunities Look on clinical trial sites for opportunities (clinicaltrials.gov)	**ACCESS TO CLINICAL TRIALS**	Educate/provide resources to participants about clinical trials in general Share information about potential clinical trial opportunities
Become well informed about details of a study	**RECRUITMENT**	Be well informed of the study plan and objectives Answer questions about the study protocol
Participate in the screening process, including any tests and evaluations, and participate in discussions with members of the research team	**CLINICAL TRIAL PROTOCOL**	Identify potential participants based on eligibility criteria Review medical history, perform tests, and evaluations as part of the screening process Participate in discussions with potential participants
Review all information related to the clinical trial including how the trial will work, the location and frequency for study visits, the overall time commitment, potential risks, and benefits of participation Make a list of questions and be sure that all questions are answered Discuss the opportunity to participate in a clinical trial with a loved one or trusted advisor	**INFORMED CONSENT PROCESS**	Provide comprehensive information about the clinical trial in the appropriate format, level, and language of the participant Ensure the participant understands all aspects of the clinical trial process Devote sufficient time for encouraging and answering questions Establish a contact person for follow-up questions Use a Shared Decision Making tool to guide the discussions between participant and health care team if possible
Attend all study visits Undergo tests and assessments per protocol Communicate with research team about potential side effects or concerns Ask questions	**STUDY VISITS**	Conduct all study assessments/measurements to evaluate safety and efficacy as per study protocol Provide opportunities for participants to report potential side effects, share concerns, and ask questions
Learn about the results of the study, and how this may impact future studies or hemophilia care	**STUDY RESULTS**	Summarize the study results in a preferred format and language for participants Provide participants with a summary of the study results
Participate in long-term follow-up and/ or a patient registry as applicable	**LONG-TERM MONITORING**	Reinforce the importance of long-term follow-up and or participation in a patient registry as applicable

Please see the roles and responsibilities of each of these groups below.

REGULATORY AUTHORITIES: Each country has its own regulatory authority with its own regulations, or laws, for conducting clinical trials. The regulatory authority reviews and approves clinical trial protocols before studies begin and ensures that all clinical trials follow national regulations. The regulatory agency interacts with researchers throughout the clinical trial process, and ultimately reviews all of the safety and efficacy data from a clinical development program in order to determine if the new treatment/intervention should be approved and publicly available.

SPONSOR/FUNDER: A person, company, institution, group, or organization that takes responsibility for initiation, management, and/or financing of a clinical trial.

INSTITUTIONAL REVIEW BOARD (IRB): A group of scientists, doctors, non-scientists, and patient advocates that reviews and approves the detailed plan for a clinical trial. IRBs are meant to protect the people who take part in a clinical trial. In countries outside of the United States, this group is called an Ethics Committee.

DATA SAFETY MONITORING BOARD: A group of independent scientists who monitor the safety and integrity of a clinical trial.

PRINCIPAL INVESTIGATOR: The person(s) in charge of a clinical trial. The principal investigator, or 'PI,' is often a medical doctor.

RESEARCH COORDINATOR: A person responsible for conducting clinical trials according to principles of good laboratory practice (GLP) and under the guidance of a principal investigator.

CLINICAL RESEARCH TEAM: Members of the health care team involved in conducting a clinical trial. This includes medical doctors, nurses, physician assistants, pharmacists, scientists, and others who support trial participants throughout the clinical trial process, perform tests, evaluations/assessments at study visits, collect data, and carry out all aspects of the clinical trial protocol.

PATIENTS: Individuals who meet the eligibility criteria and participate in a clinical trial.

Gene therapy for hemophilia clinical trials pipeline tool

Follow the progress of hemophilia gene therapy clinicals with the **WFH Gene Therapy for Hemophilia Pipeline** tool to track clinical trials and stay informed about current research.

SCAN AND SEE

Appendix

Example 1

Example of eligibility criteria in a gene therapy clinical trial (fictional)

OPEN-LABEL SINGLE ASCENDING DOSE OF GENE THERAPY XYZ IN ADULTS WITH HEMOPHILIA B

INCLUSION CRITERIA	EXCLUSION CRITERIA
Males age 18-75 years, inclusive	Family history of inhibitor to FIX protein or personal laboratory evidence of having developed inhibitors to FIX protein at any time (> 0.6 Bethesda Units on any single test)
Established hemophilia B with ≥ 3 hemorrhages per year requiring treatment with exogenous FIX OR use of FIX prophylaxis because of history of frequent bleeding episodes	Documented prior allergic reaction to any FIX product
Plasma FIX activity ≤ 2%	Detectable Gene Therapy XYZ neutralizing antibodies
Negative for active Hepatitis C virus (HCV), defined as Hepatitis C virus antibody negative and negative (undetectable) PCR test for plasma Hepatitis C virus ribonucleic acid (RNA), OR if Hepatitis C virus antibody positive must have ≥ 2 consecutive negative (undetectable) PCR tests for plasma HCV RNA at least 3 months apart, and negative at screening	Markers of hepatic inflammation or overt or occult cirrhosis as evidenced by one or more of the following: • Platelet count < 175,000/μL • Albumin ≤ 3.5 g/dL • Total bilirubin > 1.5 x ULN and direct bilirubin ≥ 0.5 mg/dL • Alkaline phosphatase > 2.0 x ULN • ALT or AST > 2.0 x ULN (except for subjects who are HIV infected) • Liver biopsy in the past indicating moderate or severe fibrosis (METAVIR staging of 2 or greater) • History of ascites, varices, variceal hemorrhage or hepatic encephalopathy

Glossary

ADMINISTRATION: In clinical trials, the act of giving a treatment (such as a drug) to a patient. It can also refer to the way a treatment is given (for example, oral, intravenous, by inhalation, intramuscular, etc), the dose, or how often the treatment is given.

ADVERSE EVENT: A medical problem, including abnormal laboratory findings that occurs during treatment with a drug or other therapy. Adverse events may be mild, moderate, or severe. In a clinical trial, an adverse event may be caused by something other than the treatment being investigated.

ARM (STUDY ARM): In clinical trials, participants are often divided into groups. 'Arm' refers to each group or subgroup of participants in a clinical trial that receives specific interventions (or no intervention) according to the study protocol.

BASELINE CHARACTERISTICS: Demographic, clinical, and other data collected at the start of a clinical trial before intervention that may be used for comparison over time to look for changes.

BLINDED STUDY: A type of study in which the participants do not know what treatment they are receiving. In a single-blind study, the patients/volunteers do not know what treatment they are receiving but the research team is aware of their treatment. In a double-blind study, neither the patients nor the investigators are aware of the treatment assignments (only the pharmacist knows). Blinding helps to reduce any bias in the study results.

CLINICAL RESEARCH: Medical research in which human volunteers (including people with certain health conditions), data, or samples of tissue from people are studied to better understand health and disease. There are two main types of clinical research or studies: clinical trials and observational studies.

CLINICAL RESEARCH COORDINATOR (STUDY COORDINATOR): A person responsible for conducting clinical trials according to principles of good laboratory practice (GLP) and under the guidance of a principal investigator.

CLINICAL TRIAL: A type of research study in which researchers test new ways to prevent, detect, or treat disease. Participants in a clinical trial may receive specific interventions according to a detailed protocol for that clinical trial. Such interventions may be medical products, such as drugs or devices, surgical procedures, or changes to behavior, such as a participant's diet. Clinical trials may compare a new medical approach to a standard one that is already available, to a placebo, or to no intervention. Clinical trials are the main method that researchers use to find out if a new treatment is safe and effective in people.

CONFIDENTIALITY: Maintaining privacy with individually identifiable health-related information for persons who participate in clinical trials. This includes research records related to identify (such as name), diagnosis, prognosis, treatment, or any other information that could be linked to a participant. In situations in which results of a clinical trial are published in a peer-reviewed journal, patient related information is de-identified, and privacy is maintained in such reporting.

CONTROL GROUP: The group in a clinical trial that does *not* receive the new treatment being studied.

CONTROLLED CLINICAL TRIAL: A clinical trial that includes a comparison group. This comparison group may receive a placebo, another treatment, or no treatment at all.

DATA SAFETY MONITORING BOARD: A group of independent scientists who monitor the safety and integrity of a clinical trial.

DATA SAFETY MONITORING PLAN: A written plan that prospectively identifies and documents monitoring activities designed to protect the safety of participants in a clinical trial, the validity of the data collected, and the integrity of the research study.

DOSE ESCALATION: A progressive, increase in the dose or strength of a treatment to maximize effect while improving or maintaining tolerability, and avoiding harmful side effects.

DOSE ESCALATION STUDY: A type of study that helps to determine the best dose of a new drug or treatment. This type of study usually involves a small number of people, and the dose of the new treatment is increased a little at a time in different groups of participants, carefully monitoring for harmful side effects.

DOUBLE-BLIND CLINICAL TRIAL: A type of clinical trial in which neither the study participants nor the researchers know what treatment the participants are receiving until the study is complete.

EFFICACY: The ability of a treatment or intervention to produce the desired beneficial effect.

ELIGIBILITY: The key requirements that must be met for people to participate in a clinical trial. Eligibility includes inclusion criteria (that are required for participation) and exclusion criteria (that prevent a person from participation).

ENROLLMENT: The number of participants in a clinical study.

EXCLUSION CRITERIA: A type of eligibility criteria. These are reasons that a person is *not* allowed to participate in a clinical study.

EXPERIMENTAL ARM: The study group of participants who receive an intervention or treatment that is the focus for the clinical trial (in contrast to a placebo arm or control group).

EXTENSION STUDY: Often termed open-label extension study or long-term extension study, this is a type of clinical trial that enrolls participants in a previous clinical trial and is designed to collect additional safety and tolerability data on a potential new treatment or intervention over a longer time period than the original/main clinical trial.

GOOD CLINICAL PRACTICE: An international set of guidelines covering the way a clinical trial is designed, conducted, performed, monitored, audited, recorded, analyzed, and reported; with the goal to ensure that participants are protected, and results are reliable.

HEALTHY VOLUNTEER: A person with no known significant health conditions who participates in clinical research.

HUMAN SUBJECT: A participant in a research study.

INCLUSION CRITERIA: A type of eligibility criteria for a clinical trial. These are the conditions that *must be met* and allow a person to participate in a clinical trial.

INFORMED CONSENT: A process used by researchers to provide comprehensive information and explain risks and potential benefits about a clinical trial before a person decides if they want to participate.

INSTITUTIONAL REVIEW BOARD (IRB): A group of scientists, doctors, non-scientists, and patient advocates that reviews and approves the detailed plan for a clinical trial. IRBs are meant to protect the people who take part in a clinical trial. In countries outside of the United States, this group is called an Ethics Committee.

INTERIM ANALYSIS: Analysis of data collected in a clinical trial before the formal completion of the study.

INTERVENTION: A treatment, procedure, or other action to prevent or treat disease or improve health that is the focus of a clinical study.

INVESTIGATOR: A person involved in running a clinical trial or research study. Investigators can include doctors, scientists, nurses, social workers, and other health care professionals.

LONG-TERM FOLLOW-UP: Extended assessments that continue some of the scheduled observations of a clinical trial past the active follow-up period. In the case of human gene therapy trials, this may be for 5–15 years.

MASKING: The same as 'blinding' in a clinical trial. Masked studies are designed to prevent the participants and members of the research team from influencing study results.

MECHANISM OF ACTION: A term used to describe how a drug or other treatment produces an effect in the body.

MULTICENTER TRIAL: A clinical trial that is conducted at more than one medical institution.

OBSERVATIONAL STUDY: In an observational study, researchers measure certain health outcomes in groups of participants according to a research plan or protocol. Participants are not assigned to specific interventions by the investigator (as in a clinical trial) but may be receiving a treatment that is already part of their routine medical care.

OPEN-LABEL CLINICAL TRIAL: A type of clinical trial in which both the participants and the researchers know what treatment is being administered to the participants.

OUTCOME MEASURE: Measure selected to assess the impact of a treatment or intervention in a clinical trial.

PHASE: Clinical trials are conducted in phases or a stepwise process. The trials at each phase have a specific purpose, and help the investigators answer different questions.

PLACEBO: A treatment that looks like a new treatment being tested in a clinical trial but does not have any active ingredients.

PLACEBO-CONTROLLED TRIAL: A clinical study in which the treatment of interest is compared to a control group who receive a placebo (a treatment that looks like the investigational treatment but does not have any active ingredients).

PRIMARY ENDPOINT: In a clinical study protocol, the planned outcome measure that is the most important for evaluating the effect of an intervention/treatment.

PRINCIPAL INVESTIGATOR: The person(s) in charge of a clinical trial. The principal investigator or 'PI,' is often a medical doctor.

PROTOCOL: The detailed plan that a clinical trial follows, including the goal of the study, who is eligible to participate, how many participants are needed, protections against risks to study participants, details about tests, procedures, treatments, how long the trial is anticipated to last, and what information will be collected.

RANDOMIZATION: The process by which treatments are assigned to participants in a clinical trial by chance rather than by choice. Neither the researcher nor the participant selects which treatment a given participant will receive.

RECRUITMENT STATUS: The enrollment status of the number of participants for a clinical trial. Each clinical trial will have an estimated number of participants for planned enrollment at the start of the study. A variety of terms are used to describe recruitment status, such as 'not yet recruiting' [the study has not yet started recruiting participants], 'recruiting' [the study is currently recruiting participants], 'enrolling by invitation' [the study is selecting its participants from a population, or group of people, decided on by the researchers in advance], 'active, not recruiting' [the study is ongoing, and participants are receiving an intervention or being examined, but potential participants are not currently being recruited or enrolled], etc.

REGISTRY: An organized system that uses observational study methods to collect data about treatment, outcomes, and well-being of a population defined by a particular disease, condition, or exposure.

SECONDARY ENDPOINT: In a clinical study protocol, a planned outcome measure (or measures) that is not as important as the primary outcome measure for evaluating the effect of an intervention or treatment, but still of interest.

SERIOUS ADVERSE EVENT: An adverse event or suspected adverse reaction is considered "serious" if in the view of the investigator it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a significant incapacity of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

SINGLE-BLIND CLINICAL TRIAL: A clinical trial in which the study participants do not know which medicine or treatment they are receiving.

SPONSOR: A person, company, institution, group, or organization that takes responsibility for initiation, management, and/or financing of a clinical trial.

TITRATION: Titration is the process of adjusting the dose of a medical treatment for the maximum benefit (efficacy) without adverse effects.

TOLERABILITY: The degree to which a treatment side effect can be tolerated or endured by a study participant. This is different from the 'safety' of treatment, which refers to the medical risk to a person who receives such treatment.

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