The Gene Therapy Development Process

Gene Therapy *is the use of genetic material in the treatment or prevention of a condition*[1]

Before a gene therapy can be prescribed by a healthcare provider, it must be shown that the potential benefits outweigh the possible risks. This is the development process, which involves many studies that can last years, even decades.

PRECLINICAL RESEARCH: BEFORE STUDIES IN PEOPLE

1

- In the lab, multiple potential gene therapies are designed and tested
- Only the most promising potential therapies continue in the development process

2

- Testing of the most promising potential gene therapies, sometimes in models of a specific condition, involves gathering information on
  - Best way to give the potential gene therapy *(also called **route of administration**)*
  - Potential benefits
  - Possible safety risks and side effects
  - How much to give *(also called **dose**)* that balances risks and benefits
- Studies are used to refine the potential gene therapy to make sure it is safe and ready to continue into clinical studies with people

For definitions of **key terms** *see information boxes like this one;* **key people/groups** *are defined on the inside back page*

Consultation with Healthcare Providers and the Patient Community

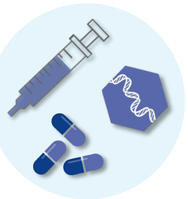
Sponsors work with many groups to focus upcoming clinical studies on research questions that are meaningful to people living with the condition

CLINICAL STUDIES: RESEARCH WITH PEOPLE

Request to start clinical trials

3

- **Sponsors** need permission from country or regional **regulatory agencies** and local **ethics committees** to start a clinical trial
- **Regulatory agencies** and local **ethics committees** decide if the gene therapy's potential benefits outweigh the possible risks and if it is safe to move forward with the proposed clinical trials by reviewing:
  - What the early, preclinical studies showed
  - How the potential gene therapy will be studied in people *(also called **trial protocol**)*
  - How the potential gene therapy is made *(also called **manufacturing**)*



There are two main types of clinical studies: Observational Studies and Clinical Trials

OBSERVATIONAL STUDIES (which include **registries** and **natural history studies**) collect health information about individuals living with a specific condition without changing their usual medical care

CLINICAL TRIALS *(also called **interventional trials**)* provide the potential gene therapy to people to determine if it is safe and how it may benefit those living with a specific condition

Observational Studies

- Health information collected from individuals living with a specific condition in a **natural history study (NHS)** or **registry** helps to
  - Understand how the condition affects people and their bodies over time
  - Inform how the potential gene therapy will be studied in people
  - Identify ways to measure if the potential gene therapy is making a difference *(also called **endpoints** or **outcomes**)*

Information from an observational study may be used as a control group for clinical trials

Clinical Trials

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- Drugs and other medicines are studied through a series of trials that build upon one another
- Each phase in the series has slightly different research questions and an increasing number of **study participants** as more is learned about the medicine being studied[2]

Study participants in the **control group** *(also called a **comparison group**)* do not receive the medicine but may receive something inactive *(also called **placebo**)* that looks like the potential medicine

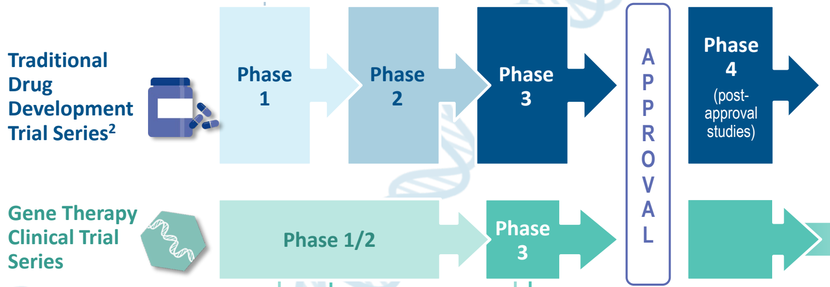
Study participants in the **treatment group** receive the medicine being studied

Throughout clinical studies, **regulatory agencies**, **oversight committees**, and other groups continually review data and results as they are being collected to make sure the health and wellbeing of the **study participants** is maintained. This information is sometimes shared with the public in accordance with regulatory and other requirements.

Gene Therapy Clinical Trials are different than traditional clinical trials and may be different for each gene therapy

- Typically involve fewer **study participants**
- Are typically longer in length, possibly span several years – the number of visits may decrease over time
- Sometimes do not include a control group or include a control group that receives the potential gene therapy after a period of being observed without it *(also called **delayed-treatment control group**)*

*Some Phase 1 studies include **study participants** that do not have the condition being studied, to test the medicine's safety and distribution in the body*



Phase 1/2 Trials aim to answer:

- *What is the best dose to deliver the greatest benefit while also ensuring safety?*
- *Is there enough information to support continuing trials with more study participants?*

A **Phase 3 Trial** aims to answer:

- *Do the possible benefits of the potential gene therapy outweigh the possible risks?*
- *Is the potential gene therapy better than currently available care and treatments?*

Long-term Follow-up

- Regulatory agencies may ask for longer-term monitoring of **study participants**, resulting in **5 to 15 years** of total participation
- This is to help understand if what was seen in the initial studies continues or if anything new appears over time

GENE THERAPY APPROVAL

Approval means a **healthcare provider** can prescribe the gene therapy to people living with the specific condition for which it was studied

Regulatory Review and Approval

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- Once the clinical trials are complete or there is enough data in support of the gene therapy's benefit and risks and potential use in routine medical treatment, a **sponsor** formally asks a **regulatory agency** to review and consider approving the potential gene therapy
- This regulatory review is a rigorous process looking at
  - What the early, preclinical studies showed
  - What the clinical studies showed in people (both observational studies and clinical trials)
  - How the gene therapy is made
  - Preferences of the **patient community**
  - Opinions from **healthcare providers** and **other groups**
- After a gene therapy is approved by a **regulatory agency**, health insurance companies and national healthcare systems decide on pricing and reimbursement

Each country or region has a different **regulatory agency** and process for review and approval

Post-approval Studies

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Sometimes additional studies may be required to collect more information, such as

- To assess the long-term benefits and risks of the gene therapy
- To test if the gene therapy would be beneficial for other people who were not eligible to participate in the original trials
- To inform pricing and reimbursement discussions

KEY PEOPLE/GROUPS INVOLVED

Ethics committees – Independent groups responsible for ensuring the protection of the rights, safety, and wellbeing of study participants
Examples: Institutional Review Boards (IRB), Ethics Committees (EC), Research Ethics Boards (REB), Independent Ethics Committees (IEC)

Healthcare provider – An individual medical professional or a health facility organization licensed to provide health diagnosis and care services including medication, surgery, and medical devices

Investigator – Healthcare provider carrying out a clinical study at a specific hospital or research institute *(also called a **trial site** or **study site**)*

Other oversight committees – Independent groups of experts that advise sponsors and ensure the protection of study participants and the integrity of the clinical study data. *Examples:* Data Monitoring Committees (DMC), Institutional Biosafety Committees (IBC), Scientific Review Committees (SRC), Endpoint Adjudication Committees (EAC)

Patient community – Collection of individuals, groups, and organizations with personal experience living with a condition, caring for someone living with a condition, or advocating for someone living with a condition

Regulatory agency – An independent government authority that oversees and protects public health in areas such as medicines, including gene therapies

Sponsor – A biopharmaceutical company or research institute that is the developer of the gene therapy and responsible for the initiation and management of each clinical study

Study participants – Individuals who meet eligibility criteria and volunteer to take part in a clinical study through informed consent

NOTES

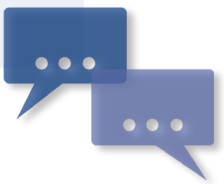
References:
1. American Society of Gene & Cell Therapy (ASGCT). Available at https://patienteducation.asgct.org/gene-therapy-101/gene-therapy-basics
2. US Food and Drug Administration (FDA) Drug Approval Process Infographic. Available at: https://www.fda.gov/drugs/information-consumers-and-patients-drugs/fda-drug-approval-process-infographic-horizontal

Additional reading: Courageous Parents Network, 2020. Evaluating the Clinical Trial Option: Understanding clinical trial terms. Available at: https://api.courageousparentsnetwork.org/app/uploads/2020/02/CPN-Clinical-Trial_Terms.pdf;
Questions to consider. Available at: https://api.courageousparentsnetwork.org/app/uploads/2020/02/CPN-Clinical-Trial_Questions.pdf

SELECT CONSIDERATIONS
WHEN THINKING ABOUT PARTICIPATING IN A GENE THERAPY CLINICAL TRIAL

- There are many unknowns about gene therapies, which clinical trials are trying to answer
- There are several ways to give the gene therapy, each with its own risks and benefits
- Viral vector-based gene therapies may require use of **immunosuppressants**. These are medicines that decrease the activity of the immune system
- Many gene therapies are **one-time treatments** that cannot be removed once given and currently cannot be given twice. Receiving one gene therapy may limit the ability to receive a different gene therapy
- Participation in a gene therapy trial may
  - **Disrupt routines** and normal daily activities
  - Involve **multiple study visits**, each possibly being full days to multiple days long
  - Last for years, potentially 5 to 15 years when including the **long-term follow up**
  - Require **traveling** long distances
  - Involve **costs** that are not be covered, such as childcare or missed work
- Each study has specific **eligibility criteria** *(also called **inclusion/exclusion criteria**),* which is a list of requirements participants must meet to make sure the clinical study can answer its research questions
  - These criteria are based on what is known about the condition and how the potential gene therapy may work
  - In some cases, this means not everyone living with a specific condition may be eligible for the study
- Before someone can participate in a study, and whenever information about the study significantly changes, there is an ongoing conversation between the investigator and study participant, with written acknowledgement
  - This is known as **informed consent** and includes the details of a study, what it means to participate, the potential benefits and possible risks, and the rights study participants have

Due to the complexity of this decision-making process, it is recommended that all available treatments are discussed with a **healthcare provider**



Thank you

Participating in a clinical study when you do not know whether you will get direct personal benefit is a brave and selfless act, one that advances medical knowledge and benefits public health. Thank you to all who participate, advise, and support the development of gene therapies. It is only together that we can achieve transformational changes.