

# RARE DISEASE

## Operationalizing Gene Therapy Trials



### ABSTRACT

Even measured against the vast scientific mystery that defines the biotech industry, gene therapy poses extraordinary challenges. To achieve operational excellence in gene therapy trials, sponsors must understand – and overcome – obstacles ranging from start-up regulations and site selection to patient recruitment and retention.

In these early days of gene therapy, many sponsors are seeking guidance on how to navigate the challenges of bringing these treatments from bench to bedside.



## Introduction

Gene therapy holds promise for treating a wide range of diseases, from cancer and diabetes to rare genetic disorders. It has also sparked great interest because it offers the possibility of a cure, particularly for single-gene diseases such as sickle cell anemia or hemophilia. This potentially revolutionary treatment modality is still in its infancy, the science is stunningly complex, and the regulatory terrain is constantly evolving. In these early days of gene therapy, many sponsors are seeking guidance on how to navigate the challenges of bringing these treatments from bench to bedside.

In this white paper, we will explore the history of gene therapy trials, as well as the types of gene therapy vectors and delivery strategies. We will also discuss the regulatory and operational challenges associated with gene therapy trials, including start-up regulations, site selection, recruitment, and retention. Of note, this white paper focuses on somatic cell gene transfer, rather than germ cell gene therapy.

## Background on gene therapy trials

Gene therapy is a powerful and innovative approach using genetic material such as DNA or mRNA to compensate for genetic mutations, confer the capability of producing potentially therapeutic substances, or elicit immune responses to fight disease. As such, gene therapy may be used to provide restorative, therapeutic, or even curative benefit.

When genes malfunction, there are typically three potential treatment approaches:

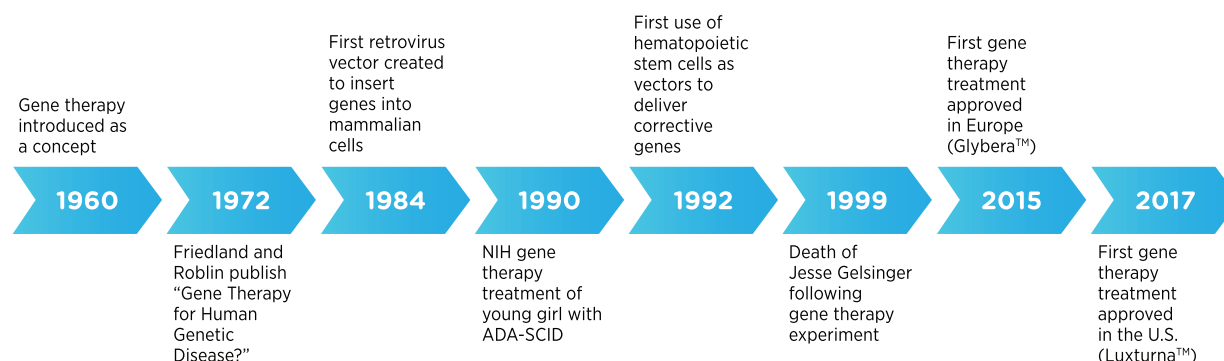
- Replacing the mutated, disease-causing gene with a healthy copy of the gene
- Inactivating or knocking out the mutated gene
- Introducing a new gene that creates the desired protein to help fight disease

## History of gene therapy research

The revolutionary concept of genes as a therapeutic approach arose in the 1960s, although attempts at gene transfer at that time were extremely inefficient. In 1990, the first gene therapy trial was initiated at the National Institutes of Health in Washington, DC, where a four-year-old girl with adenosine deaminase severe combined immunodeficiency (ADA-SCID) was given the gene she needed to make the enzyme she lacked. The defect was corrected only temporarily, but this was still the first successful gene therapy trial.

Since 1990, a number of studies and techniques for introducing genetic material into cells to address disease states have been tried. Among these is the well-published death of Jesse Gelsinger, an 18-year-old young man with partial ornithine transcarbamylase deficiency, a genetic liver disease often fatal at birth in more severe cases. Gelsinger died four days after receiving gene therapy due to what appears to have been a response to the adenoviral vector used to deliver the treatment. Since then, we have made tremendous strides in gene therapy. Most notably, in 2017, the U.S. Food and Drug Administration (FDA) approved voretigene neparvovec-rzyl (marketed as Luxturna™), making it the first in-vivo gene therapy approved in the U.S.! Luxturna™ is indicated for the treatment of inherited retinal dystrophy, a rare form of inherited vision loss that may result in blindness.

**Figure 1. A brief history of gene therapy research**



### Current state of gene therapy research

To date, more than 2400 gene therapy trials have been conducted across a variety of indications. While the majority of gene therapy trials have been in oncology indications, these promising therapies are applicable to a host of diseases, ranging from monogenic diseases such as hemophilia, Huntington’s disease, and cystic fibrosis to multi-factor diseases such as diabetes. Of note, many of the monogenic conditions being targeted in ongoing gene therapy trials are rare diseases such as lysosomal storage diseases and Duchenne muscular dystrophy.

### Gene therapy vectors and delivery systems

The majority of current gene therapy trials are using adenovirus, retrovirus, or a naked plasma DNA to introduce genes into cells. There are three main approaches to introducing genes into cells or editing genes:

1. **Viral vectors.** These are viruses that have been engineered to remove the part of their genetics that causes disease, but which retain the part of their genetics that drives them to reproduce once they have entered a cell.

*Examples:* adenoviruses, adeno-associated viruses, herpes viruses, lentiviruses, and retroviruses

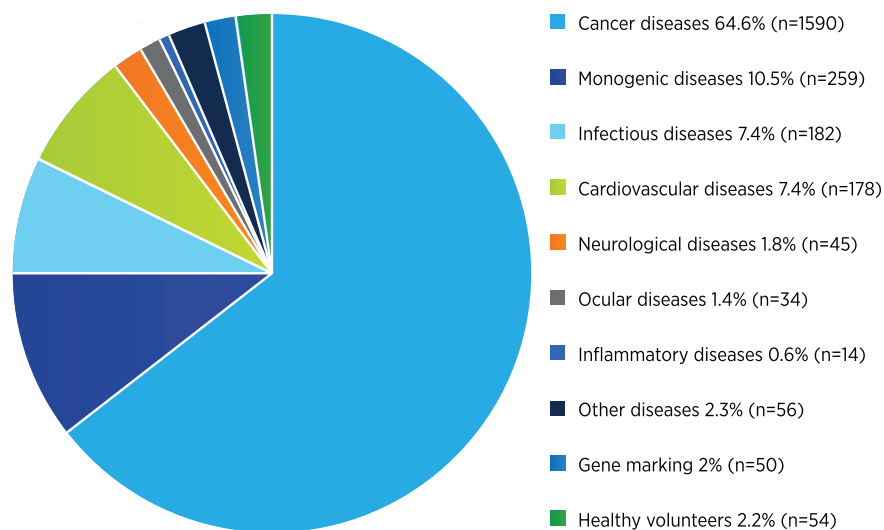
2. **Non-viral vectors.** These are naked DNA or DNA complexes that are not packaged with a virus to introduce genetic material into cells. These can include both vectors which have had genetic material completely removed (apart from the sequences that allow for packaging into vector particles to prevent replication) and vectors that retain partial coding information to allow replication. The advantage of non-viral vectors is that they can be used to transfer very large therapeutic genes.

*Examples:* naked DNA, oligonucleotides, lipoplexes, and polyplexes

3. **Engineered nucleases.** This is a type of genetic engineering in which DNA is inserted, deleted, or replaced in the genome of an organism using engineered nucleases, otherwise known as “molecular scissors.”

*Examples:* zinc finger nucleases, transcription activator-like effector nuclease (TALEN™), and CRISPR-associated protein-9 (CRISPR/Cas9)

Figure 2. Indications addressed by gene therapy clinical trials<sup>2</sup>



### A closer look at viral vectors

There are a variety of viral vectors (see Figure 3), and vector selection will depend on several factors, including:

- How well the virus transfers genes to the cells they recognize and are able to infect
- Whether the virus integrates with the host DNA or not
- Expectations for how long the introduced gene will be expressed by the host cell
- Size and structure of the virus

Figure 3. Common viral vectors for gene therapy<sup>3</sup>

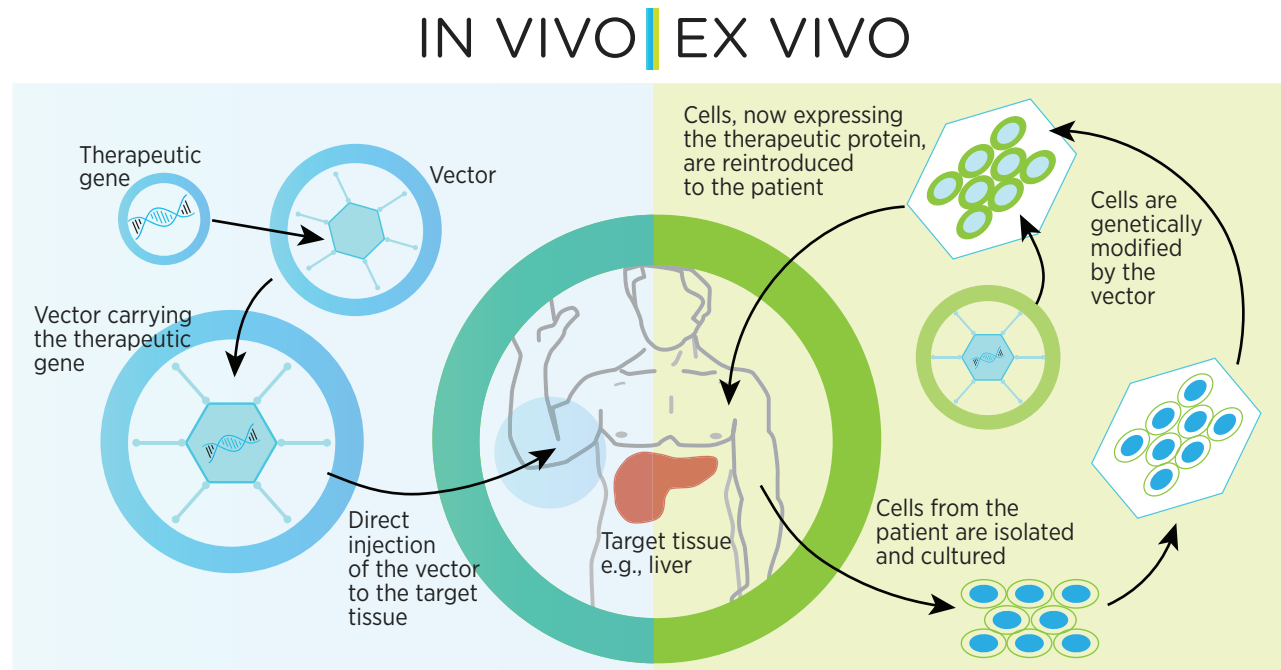
Particle Characteristics						
	Adenovirus	Adeno-associated virus	Alphavirus	Herpesvirus	Retrovirus/Lentivirus	Vaccinia virus
Genome	dsDNA	ssDNA	ssRNA (+)	dsDNA	ssRNA (+)	dsDNA
Capsid	Icosahedral	Icosahedral	Icosahedral	Icosahedral	Icosahedral	Complex
Coat	Naked	Naked	Enveloped	Enveloped	Enveloped	Enveloped
Virion polymerase	Negative	Negative	Negative	Negative	Positive	Positive
Virion diameter	70 - 90 nm	18 - 26 nm	60 - 70 nm	150 - 200 nm	80 - 130 nm	170 - 200 X 300 - 450 nm
Genome size	39 - 38 kb	5 kb	12 kb	120 - 200 kb	3 - 9 kb	130 - 280 kb



GeneTherapyNet.com	Adenoviridae	Parvoviridae	Togaviridae	Herpesviridae	Retroviridae	Poxviridae
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Gene Therapy Properties						
Family	Adenoviridae	Parvoviridae	Togaviridae	Herpesviridae	Retroviridae	Poxviridae
Infection/tropism	Dividing and non-dividing cells	Dividing and non-dividing cells	Dividing and non-dividing cells	Dividing and non-dividing cells	Dividing cells	Dividing and non-dividing cells
Host genome interaction	Non-integrating	Non-integrating	Non-integrating	Non-integrating	Integrating	Non-integrating
Transgene expression	Transient	Potential long lasting	Transient	Potential long lasting	Long lasting	Transient
Packaging capacity	7.5 kb	4.5 kb	7.5 kb	> 30 kb	8 kb	25 kb

Figure 4. Comparison of in-vivo and ex-vivo transduction<sup>4</sup>



There are two methodologies for somatic gene transfer:

1. **In-vivo transduction.** This method involves direct delivery of the vector carrying the therapeutic gene into the body of the patient. In-vivo transduction is useful when the targeted cells do not grow well in culture or when it is difficult to re-implant transduced cells.
2. **Ex-vivo transduction.** In this method, cells are removed from the patient and sent to a lab where they are exposed to the vector carrying the therapeutic gene. Once the cells have been modified, these now transduced cells are reintroduced to the patient. Ex-vivo gene therapy trials are extremely complex from an operational standpoint and require detailed planning and execution.

## Regulatory considerations in gene therapy trials

### GMO regulations and processes

Gene therapies containing genetically modified organisms (GMOs) fall under GMO regulations and processes.

In the EU, these regulations and processes include:

- **Directive 2001/18/EC** on the deliberate release of GMOs into the environment.<sup>5</sup> Deliberate release refers to any intentional introduction into the environment of a GMO or a combination of GMOs for which no specific containment measures are used to limit their contact with and to provide a high level of safety for the general population and the environment. This directive includes risk classifications from no or negligible risk to high risk. Of note, some countries, such as Spain and Germany, consider GMOs to be ‘deliberate release’ by default, even in the context of a clinical trial.
- **Directive 2009/41/EC** on contained use of genetically modified micro-organisms.<sup>6</sup> Contained use is defined as any activity involving GMOs that is carried out under containment to limit contact with the environment, including use, storage, transport, destruction, and disposal. To avoid adverse effects on human health and the environment, the user shall carry out an assessment of the contained uses as regards the risks to human health and the environment. This directive includes four risk classifications, ranging from Class 1 (covers activities of no or negligible risk) to Class 4 (covers activities of high risk). Investigational medicinal products (IMPs) tend to fall under Class 1 or 2.

- **Regulation (EC) 1829/2003** on genetically modified food and feed<sup>7</sup>
- **Directive (EU) 2015/412** amending Directive 2001/18/EC as it regards to the possibility for the Member States to restrict or prohibit the cultivation of GMOs in their territory<sup>8</sup>
- **Regulation (EC) 1830/2003** concerning the traceability and labeling of genetically modified organisms and the traceability of food and feed products produced from genetically modified organisms<sup>9</sup>
- **Regulation (EC) 1946/2003** on transboundary movements of GMOs<sup>10</sup>

In contrast to the EU, the U.S. does not have any federal legislation that is specific to GMOs. Instead, the approach to regulating GMOs is built on the assumptions that regulations should focus on the nature of the products, rather than the process by which they are produced. As such, GMOs are regulated under the Coordinated Framework for Regulation of Biotechnology which was first published in 1986. In 2017, this framework was updated with a comprehensive summary of the roles and responsibilities of the three principal regulatory agencies – the FDA, the Environmental Protection Agency, and the U.S. Department of Agriculture – with respect to regulating biotechnology products.<sup>11</sup>

Generally, the FDA holds regulatory authority over drugs, and companies interested in introducing a new drug into the U.S. market typically submit new drug applications (NDAs) to the FDA. Drugs developed through genetic engineering undergo the same NDA process as other types of drugs.

In the U.S., the approach to regulating GMOs is built on the assumptions that regulations should focus on the nature of the products, rather than the process by which they are produced.



### Site-specific requirements

Investigative sites that are involved in gene therapy trials may be subject to additional requirements, depending on the country:

- Certain Phase I studies may require sites to obtain an extra certification
- Extra documentation may need to be completed for submission to GMO authorities or competent authorities and requires coordination between the sponsor, the contract research organization (CRO), and/or participating sites
- Local submissions may be required by either the CRO or site staff
- Some competent authorities may require site-specific standard operating procedures (SOPs) related to GMO waste management.
- A specific storage room may be required and facilities may be inspected during site qualification visits (SQVs)
- Clear information from the sponsor on the responsibilities for drug importation may be required prior to site initiation

### Operational considerations

#### Planning

Planning a gene therapy trial is a complex undertaking. Initial considerations for study planning include:

- **Selecting the right vendors.** Sponsors require extensive support when planning or initiating a gene therapy trial. Selecting appropriate, experienced vendors – from consultants and CROs to shipping vendors – can facilitate the process.
- **Developing detailed support materials for all study team members.** Initiation and follow-up visits are often extensive and complex, with time-sensitive tasks. Providing detailed support materials and training will help all study team members execute their responsibilities smoothly and efficiently.
- **Creating back-up or mitigation plans for all components of the trial.** Given the complexity involved, creating back-up or risk mitigation plans for every aspect of the trial is critical.
- **Selecting the right sites.** In addition to identifying countries and sites where gene therapy is in accordance with local regulations and ethics, it is critical for sponsors to select sites that have the infrastructure necessary to support this type of trial. This infrastructure may include large, multi-disciplinary study teams; specialty laboratories; and a clean room with controlled airflow and highly-specialized, expensive equipment. It may also include access to specialized staff – such as a cultural mediator or other facilitator – who can assist with the logistical hurdles patients and their families may face as a result of study participation, such as medical travel visas or language barriers. Once sites have been selected, site-specific procedures will need to be generated regarding pharmacy policies and staffing, management of the investigational product (IP), exposure control, waste management, and IP administration.



- **Developing patient- or family-facing materials to explain all components of the study.** This includes working with regulatory and patient engagement experts to develop proper informed-consent language, or even informed-assent language for pediatric patients. If the trial involves young children, assent via video or cartoon characters may be a viable alternative. It is also important to provide support and education materials to siblings.
- **Working with site staff to monitor workload and resource allocation during periods of high complexity.** This can help to increase site engagement and data quality.

### Recruitment challenges

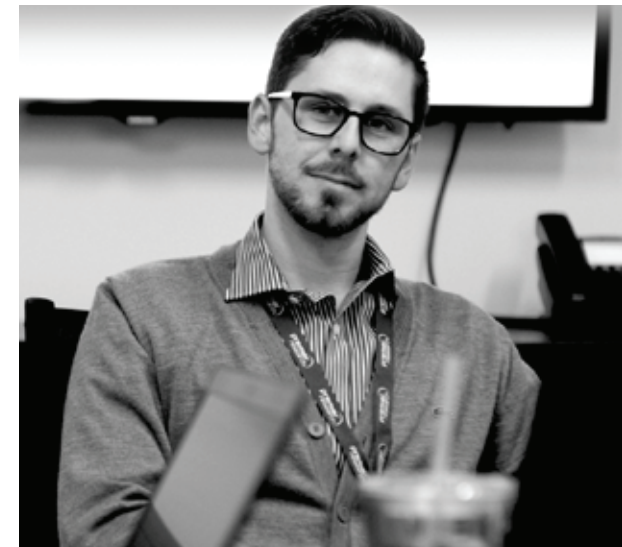
Often gene therapy trials focus on patients with rare genetic diseases and identifying patients and families to participate in a study can be challenging. Working with patient advocacy organizations and other stakeholders to understand the patient journey is critical to success, and the importance of adopting a patient-centric approach to recruitment cannot be overemphasized. Successful recruitment requires proper consideration of the concerns of not only the patient, but also the family. This may include managing expectations of a cure, assisting with planning for extended periods of time away from home, clarifying commitments regarding follow-up, and coordinating efforts between sites if administration and follow-up occur at two different locations. When developing a recruitment strategy, sponsors are encouraged to think creatively. For example, sponsors may consider providing access to genetic testing for siblings of participants who may have been undiagnosed or misdiagnosed.

### Retention challenges

Gene therapy trials often require a very long period of follow-up, making retention a critical barrier to overcome. Taking special measures to reduce the burden on these patients – such as using technology for remote data capture, including video or mobile apps – can help to improve retention. It is also important to educate patients and their families on the value and importance of staying in the trial, not only for themselves, but also for science and for future patients like them.

### Conclusion

Gene therapy offers incredible promise, and we have seen great strides in this space. Understanding, planning for, and overcoming the challenges of operationalizing gene therapy trials will help sponsors bring breakthrough treatments – and perhaps even cures – to patients.



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## Juliet M. Moritz, MPH | Executive Director, Patient Engagement and Strategic Development, Rare Disease and Pediatrics

Juliet Moritz has worked in clinical research for more than 30 years, and her extensive background covers the spectrum from single-site studies to large, multinational trials. She joined Premier Research in 2016 to specialize in rare diseases, supporting the strategic development of products that address unmet medical needs associated with rare and orphan afflictions. Prior to joining Premier Research, Juliet was Associate Director of Global Project Management at PPD, overseeing infectious and respiratory disease research, and prior to that was Associate Director of Clinical Research at Knopp Biosciences. She has held senior positions at Wyeth (now Pfizer), Theravance, and Medifacts International and began her career as a clinical research associate. Juliet holds a Master of Public Health degree from the Drexel University School of Public Health and a bachelor's degree in biology from the University of Pennsylvania. She is currently pursuing her doctorate in bioethics through the Alden March Bioethics Institute at Albany Medical College and is working toward a professional development certification in genetics and genomics from Stanford University.

## Nadia Zeini, MS | Senior Regulatory Start-Up Manager

Ms. Zeini has been with Premier Research since December 2016. She is responsible for all regulatory and start-up activities in EU and non-EU countries, as applicable. Ms. Zeini has a solid regulatory background where she grew from local start-up associate to global regulatory lead for ten years.

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