Insight Brief

Long-term Follow-up for Gene Therapies – Innovative, Patient-centered Approaches

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Introduction

It is mandatory to monitor patients who receive a gene therapy product over extended periods to assess for delayed adverse events and also to potentially evaluate for sustained efficacy. Many regulatory agencies, including the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA), have developed guidelines based on product characteristics regarding the design and key data elements of required long-term follow-up (LTFU) studies. The duration of required gene therapy LTFU studies can range from 5 to 15 years, depending on the nature of the gene therapy. LTFU studies for these therapies present unique challenges, and there are important considerations for different kinds of sponsors, including biotech and emerging biopharma.

Through a tailored, patient-centered approach that may include decentralized solutions, sponsors can successfully conduct LTFU studies of a gene therapy product.

There is tremendous momentum and growth in the field of gene therapy. However, because of the relatively early stage of the field, there is still pioneering work to be done on how best to monitor for delayed adverse events that may be associated with these treatments. To be conducted efficiently and cost-effectively, gene therapy LTFU requires innovative approaches.

In this overview, we will discuss the key clinical, data, and operational considerations for gene therapy LTFU. We will also highlight key considerations for biotech sponsors. As standard approaches to LTFU often increase burden on patients and sites over time, new patient-centered technologies and decentralized tools can be used to capture the required safety data while decreasing burden and offering flexibility to patients, their families, and healthcare providers.

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GENE THERAPY LTFU – WHAT IS IT AND WHEN IS IT NEEDED?

To determine whether a gene therapy LTFU is required, sponsors should first begin by asking themselves key questions, which are summarized in Figure 1. They should also consult with representatives from regulatory agencies.

There are two types of extended follow-up associated with gene therapy clinical development:

- **Gene Therapy Clinical Trial LTFU** occurs after the follow-up that is part of the clinical trial and can extend for up to a total duration of 15 years. The level of monitoring is generally less intensive than the follow-up within the clinical trial. Because of the duration of this type of LTFU, strategies to reduce patient and site burden need to be considered. It is reasonable to consider less intensive follow-up during the later years of this phase, especially if there is an accumulation of safety data.
- **Gene Therapy Post-Approval LTFU** occurs after patients receive approved treatment as part of clinical care and can also extend for up to 15 years post-therapy. Generally, this kind of follow-up requires lighter monitoring as the safety and efficacy of the therapy has been demonstrated in clinical trials and associated post-trial LTFU. Also, given that the expected sample sizes will be larger and ongoing monitoring of patients in clinical practice will be required, it is critical that data collection be as efficient and patient-centered as possible, leveraging standard of care visits and available sources of data such as EMR and existing registries.

Figure 1

Key Questions to Determine Need for Gene Therapy LTFU:

- Does the product use genome-editing technology?
- Are vector sequences integrated, or is human genome altered?
- Does product have potential for latency and reactivation?
- Were there specific issues discovered in preclinical studies to address?
- How long will the study have to run to detect possible adverse events?

Figure 2

CLINICAL CONSIDERATIONS IN DESIGNING GENE THERAPY LTFU

The goals of gene therapy LTFU will depend on the patient population, the investigational therapy, and the objectives of the sponsor. The key mandated goal of gene therapy LTFU is long-term safety surveillance. However, sponsors may also wish to assess the durability of the drug or the need to use other therapies in conjunction with the gene therapies.

Clinical parameters to take into consideration include who the study population is, what the underlying disease is and the associated prognosis, and whether it is an adult or pediatric population. These factors help determine:

- What data to collect?
- How long the duration of follow-up for each patient is likely to be?
- Whether standard of care visits and data can be leveraged?
- Whether patients will be going through different life stages that will involve needing to interface with various health care systems—potentially presenting challenges to data collection?

The nature of the investigational therapy is also important to consider. Some therapies, such as gene editing therapies or CAR-T, which utilize integrating lentiviruses, require a 15-year follow-up. Gene therapies that are delivered using an adeno-associated viral vector require shorter durations of follow-up, usually 5-10 years, because they are considered non-integrating and lower risk vectors. The duration of the follow-up will have an impact on the study design and the cost.

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DATA CONSIDERATIONS FOR GENE THERAPY LTFU

The data required for gene therapy LTFU typically comes from a constellation of sites and sources: regular observations in standard of care, specialist visits, and labs. In addition, data about events that take place in the course of patients' daily lives can be captured through wearables and daily diaries.

The early gene therapy LTFUs, in both clinical trial and approved product settings, took place via traditional site based data collection approaches. This enabled close to real-time safety event monitoring and reporting. However, as gene therapies are increasing in number, and real-world technology, data and regulations evolve, data collection is increasingly taking place via multiple channels. Site-based data collection is still required, especially for clinical trial patients, but where possible, many sponsors are exploring use of EMR extraction and direct-to-patient data collection methods to reduce the data collection burden on sites. In these cases, monitoring of adverse events in patients receiving approved product happens through pharmacovigilance processes.

Additionally, regulators, especially the European Medicines Agency, are asking sponsors to use existing registries for post-approval LTFU. Their aim is both to minimize burden on sites and to ensure data objectivity. While this approach does create some efficiencies, the data in some registries is not always fit for purpose and needs to be augmented with traditional site-based and direct-to-patient sources.

Sponsors are leveraging combinations of these data collection approaches, tailoring their study methodologies to the needs of patients and the providers who are overseeing their long-term care.

OPERATIONALIZING GENE THERAPY LTFU STUDIES

Because patients will need to be followed for extended periods during the gene therapy LTFU, it is important to consider ways to streamline data collection, lighten patient and site burden, and enhance retention through patient engagement. Gene therapy LTFU studies often benefit from decentralized solutions such as remote data collection, home phlebotomy, home nursing, electronic clinical outcomes assessments, and patient-reported outcomes.

The use of purpose-built, highly secure, scalable electronic study platforms that support telemedicine visits, data collection, and patient engagement is also a central strategy for gene therapy LTFU. Scalable decentralized platforms that include mobile apps that support text reminders, alerts, live chats, and ongoing communication can help to engage patients over long durations. Remote data collection of clinical and patient reported outcomes can also help to optimize retention by eliminating the need for onsite visits. In addition, it is a best practice to obtain consent for the gene therapy LTFU a few months before the end of the clinical trial, so patients are not lost after the completion of the initial study.

Another study design consideration is transitioning to centralized gene therapy LTFU investigators after the clinical trial or after a few years of the required LTFU. This approach is especially suitable if assessments are being done remotely and real-world data is being leveraged to capture clinical events. To ensure that patients feel comfortable with the centralized investigator model, it is critical to ensure a good communication between the clinical trial investigator, the centralized LTFU study investigator, and the patient. In addition, the centralized LTFU study investigator should be introduced a few months before the transition takes place, at which time consent can be obtained.

Finally, it is key for sponsors to consider the design of the required LTFU early in their clinical development plans, even before they launch their first-in-human study. If a sponsor has several therapies in the pipeline, then consideration for a master LTFU protocol and platform may offer efficiencies in terms of identifying sites and investigators. In addition, because there is a fixed infrastructure associated with gene therapy LTFU studies, the costs are driven primarily by the duration of the study, rather than the sample size. Therefore, master LTFU platforms that utilize the infrastructure for more patients across more studies may be more cost-effective.

CONSIDERATIONS FOR BIOTECH SPONSORS

Despite common regulations and standards across the industry, there are aspects of the LTFU phase that present distinct challenges unique to biotech and emerging biopharma companies. Biotech sponsors have higher stakes because they are often laser focused on a single breakthrough asset and, in the early days, do not have a portfolio for hedging their risks. In this space, livelihood of the company is often at stake, which requires a careful balance between the innovative, pure, scientific pursuit for the sake of the asset and progressing the asset through requisite development stages for the sake of the company.

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First, given that most biotech companies are focused on developing one or two therapies, it is difficult both financially and in terms of efficiency, to achieve economies of scale. With fewer assets being developed at a time, there is limited ability to consolidate multiple clinical trials into one long-term trial protocol. Biotech sponsors are often obligated to transition each single trial into its own LTFU trial, which increases costs due to the fixed infrastructure required, regardless of sample size, and offers few operational efficiencies to realize. In addition, development pathways for each asset can vary greatly based on the investigational treatment or established business objectives. In some cases, biotech companies may consider mergers or licensing arrangements, potentially changing the strategic direction of asset development and eventual LTFU design. The opportunities within the industry to self-develop or to partner in a future state can cause difficultly for planning LTFU at the very start of clinical development, therefore, agility and ability to pivot is essential.

The desire to accumulate a deep and extensive understanding of the asset is often part of the biotech company's mission, with sponsors dedicating significant amounts of time and resources to defining the mechanism of action and gaining full cellular insights, for example. While this almost pure focus on science and knowledge is important, it must be carefully balanced with the patient in mind. The priority focus on scientific pursuits can significantly increase patient and site burden, which can become unmanageable over extended periods and can undermine data quality and the success of a gene therapy LTFU study. Finding a balance between collecting the required safety information and additional data to further clinical development is important. Sponsors can often get insights to patient and site impact by leveraging patient advocacy networks and KOLs to help balance their science-heavy pursuits in a way that is effective and supportive for patients and sites.

Lastly, planning LTFU around long, unpredictable patient journeys can be difficult for sponsors due to the considerable duration of time required. To accommodate the change in a patient's overall health status, the potential for caregivers or family life changes, relocation needs, or changes in daily living can feel nearly impossible for biotech sponsors. However, technology based solutions that can allow the patient to participate from the comfort of home, such as decentralized trials to allow the patient to participate locally, and remote monitoring solutions that can permit monitors to readily review the data from a distance, can help to reduce the burden or accommodate the natural evolution of patient needs over the duration of the LTFU phase.

While biotech companies face distinct operational, tactical, patient-focused and even financial considerations during the LTFU phase, there are solutions that should be considered during early stages of asset planning that can help increase the probability of success for the asset, the patient, and the vitality of the biotech sponsor.

TAILORING SOLUTIONS

The requirements for each LTFU will be different depending on the clinical parameters, the countries being considered, and the goals of the sponsor. In supporting biotech companies to advance their gene therapy LTFU study plans, a key focus for IQVIA Biotech is considering patient centricity. We leverage a wide range of decentralized tools to execute gene therapy LTFU studies with the goal of optimizing patient safety

Finding ways to bring the gene therapy LTFU to the patient is essential to keeping patients engaged and actively involved.

Figure 3

THERAPEUTIC-SPECIFIC CONSIDERATIONS

IQVIA has supported 174 cell and gene therapy clinical trials since 2008, focused mainly on oncology, neurology, cardiovascular, and hematology indications.

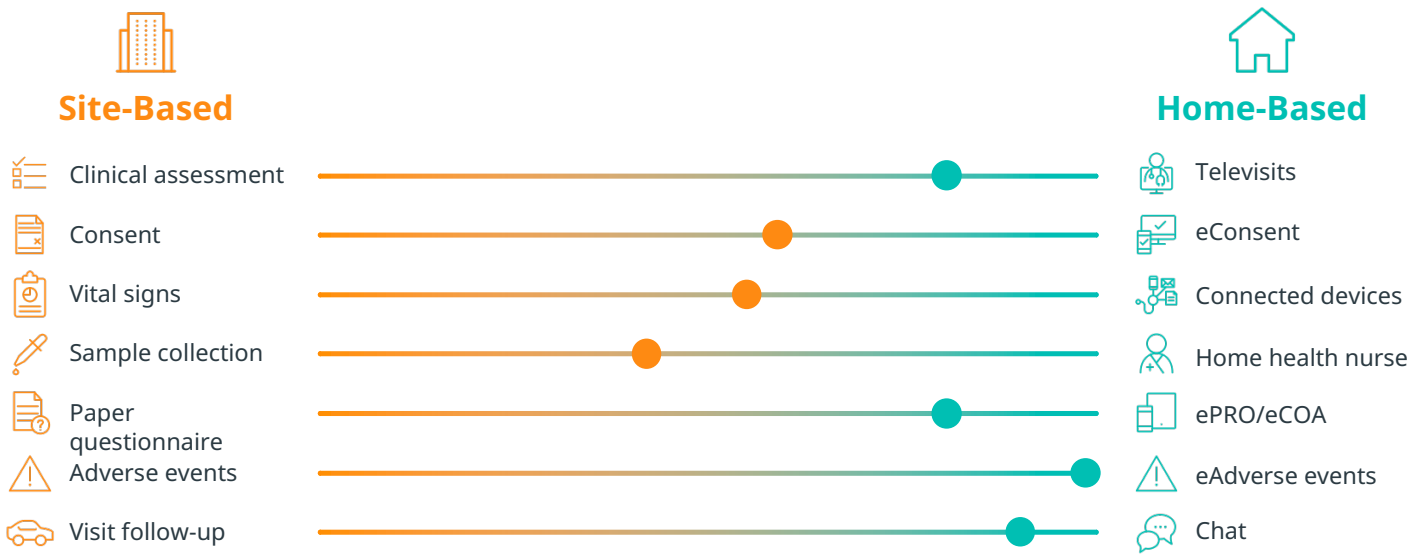
It is important to design LTFU studies with patient-centered solutions and considerations relevant to each specific therapeutic indication. Sponsors and site teams should consider the following implications for patients:

- Shorter life spans (prognosis may not extend beyond 5 years), specifically critical for oncology patients and those living with rare disease
- Some required onsite visits for specialized assessments (e.g., neuroimaging, CSF sampling, infusions, etc.)
- Potential need for caregiver support as patients age, mobility issues, or due to severity of disease
- Anticipating logistical adjustments as patients may relocate (e.g., pediatric patients who relocate for college)
- Addressing unanticipated events
- Specimen management

Enhance patient support

- Telemedicine
- Home health nursing and phlebotomy
- Digital engagement solutions
- Concierge services for travel to site
- 24/7 patient support
- Advocacy group partnership
- Information sharing through a patient portal and dedicated website

Figure 4 - Decentralized Approaches



while decreasing patient burden and increasing patient engagement and retention. We believe a patient-centered approach that enhances patient engagement will ultimately ensure more robust results.

DECENTRALIZED CLINICAL TRIAL SOLUTIONS

Finding ways to bring the gene therapy LTFU to the patient is essential to keeping patients engaged and actively involved while also reducing time, effort, and cost in the development process.

Incorporating elements of tech-enabled decentralized clinical trial (DCT) solutions into LTFU models can help sponsors and site teams better meet patient needs by reducing onsite follow-up, testing, and data collection. Strategies for transitioning standard onsite elements to a decentralized approach is summarized in Figure 3.

For gene therapy LTFU where the Principal Investigator manages treatment interventions and treatment risk is greater, decentralized trial elements such as use of televisits to connect with patient care teams and integration of home health services to reduce onsite visits can help patients better engage in trials and their healthcare while reducing logistical burdens. Additionally, IQVIA uses a purpose-built, highly secure, scalable DCT platform, which is also available as a mobile app, giving patients access to a concierge digital experience that includes text reminders, alerts, live chat, 24/7 support and a scheduling tool for study visits. At the same time, study teams facilitate the patient journey using telemedicine, mobile technologies, and connected devices. Through centralized monitoring, teams can collect and disseminate data in real time and make gene therapy LTFU study adjustments quickly to ensure patient safety standards and data quality remain high. During the COVID-19 pandemic, IQVIA's decentralized solutions have helped maintain clinical studies, including LTFU studies with engaged patients and site teams and continuous data monitoring despite site closures and regional shutdowns.

For many gene therapy LTFU studies, the patients' treatments are complex and will require some on site evaluations. In these cases, hybrid trials that combine decentralized elements with standard onsite assessments may be a more optimal solution. In addition, given that gene therapy LTFU can extend for up to 15 years, a study design that allows for flexibility to accommodate life events such as patients moving or changing physicians is key.

CONSULTATIVE EXPERTISE

With successful gene therapy LTFU design and execution, it is vital to consider the need for expert knowledge around a highly innovative area of medicine where there is constant scientific breakthrough and change. With decades of therapeutic and scientific experience in gene therapy, IQVIA Biotech offers biotech customers continuous, real-time knowledge of the space that can influence patient-centric gene therapy LTFU design and execution.

A systematic approach to gene therapy LTFU that incorporates clinical perspectives, regulatory requirements, data collection efficiencies, and flexibility and patient centricity is critical. At IQVIA Biotech, we encourage sponsors to take a programmatic approach and consider planning for both the gene therapy clinical trials and the LTFU at the same time to maximize efficiencies and accelerate clinical development.

Conclusion

The field of gene therapy is exciting and rapidly growing, requiring innovation in clinical study execution to keep up with the pace of scientific discoveries. Taking a comprehensive and holistic approach, and early on considering the unique requirements for the gene therapy LTFU – clinical issues, data needs, and key study objectives – will allow sponsors to plan a more efficient and cost-effective program and ultimately accelerate clinical development and achieve the goal of getting these important new therapies to patients faster.

About the authors

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As head of IQVIA's Cell and Gene Therapy Center of Excellence, Dr. Monica Shah works collaboratively with sponsors, the scientific community, and other stakeholders to develop and implement strategic approaches to cell and gene therapy clinical trials. She is a board-certified heart failure and transplant cardiologist and has more than 20 years' experience in developing, leading, and executing complex, multi-disciplinary research programs. Dr. Shah is also clinically active and attends on the Advanced Heart Failure Service at the University of Maryland, where she is Clinical Professor of Medicine.

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Elizabeth is Category Lead for regulatory and safety offerings in IQVIA's Real World Solutions division. She has over 20 years of experience in biotech and pharma, with a particular focus on the intersection of pharma and regulators, payers, and HTA bodies.

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As Vice President of Immuno-Oncology at IQVIA Biotech, Erin is responsible for leading the team's strategic direction to help sponsors focused on immuno-oncology trial programs meet their goals with high quality and delivery of innovative services and solutions and expertise.

As advancements in immuno-oncology continue to transform cancer care, Erin is able to successfully guide sponsors through a dynamic landscape with strong therapeutic expertise and more than 18 years of experience in global clinical research and drug development processes, including adoptive cellular trials.

Erin's educational background, including a bachelor's in Biology from the University of California, Berkeley and a master's degree in immunology from the University of Virginia, provides a solid foundation for her therapeutic expertise. She has also earned a Master of Business Administration in Finance and Accounting from Louisiana State University, Shreveport.

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