WHITE PAPER

Important Considerations to Optimize Long-term Follow-up Studies for Cell and Gene Therapies

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Cell and gene therapies (CGTs) have shown great potential in treating a wide range of diseases, including cancer, genetic syndromes, autoimmune diseases and neurological disorders. Gene therapy uses modified genetic material to correct a disease-causing gene defect or mutation, while cell therapy introduces functioning living cells to treat diseases. Both approaches offer long-term benefits for patients, although, as with any emerging medical technology, safety and efficacy must be thoroughly evaluated before widespread clinical use. As a result, CGTs almost always require long-term follow-up (LTFU) studies starting in Phase I clinical trials.

The number of CGTs is only increasing. According to the latest quarterly report (Q4 2023) from the American Society of Gene & Cell Therapy and Citeline, the gene, cell and RNA therapy pipeline from preclinical to pre-registration grew by 6%, and the total number of gene therapies and genetically modified cell therapies in development (including preclinical) is currently 2,111.[1]

This white paper highlights:

- The importance of LTFU studies in the continuous benefit-risk assessment of CGTs
- Considerations for the design of these studies, such as regulatory requirements, data collection, patient/site burden, retention and engagement

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What are LTFU Studies?

LTFU studies follow patients for long periods of time, typically several years, and allow researchers to monitor the long-term effects of the therapy, including potential side effects, durability of effect and long-term outcomes. These studies are critical for evaluating long-term safety by identifying delayed adverse events of CGTs over an extended period. For example, a gene therapy that successfully treats a patient's disease in the short term may have long-term side effects that are not immediately apparent. Similarly, a cell therapy that initially shows promise may not be effective in the long term. To help identify these risks as early as possible, LTFU studies for CGTs begin rolling patients in starting with the first in-human use and continue through commercial use. This use of LTFU studies allows researchers to refine therapies throughout development and improve patient outcomes.

These studies are usually undertaken as part of a regulatory mandate primarily to monitor adverse events. They can also be conducted voluntarily by CGT sponsors to evaluate a variety of research questions beyond safety, such as effectiveness, quality of life (QoL) and survival. LTFU studies usually include patients who were initially exposed to the therapy of interest as part of a clinical trial but can also include patients who were treated with the commercially available treatment in the post-marketing phase.

Importance of LTFU Studies for CGTs

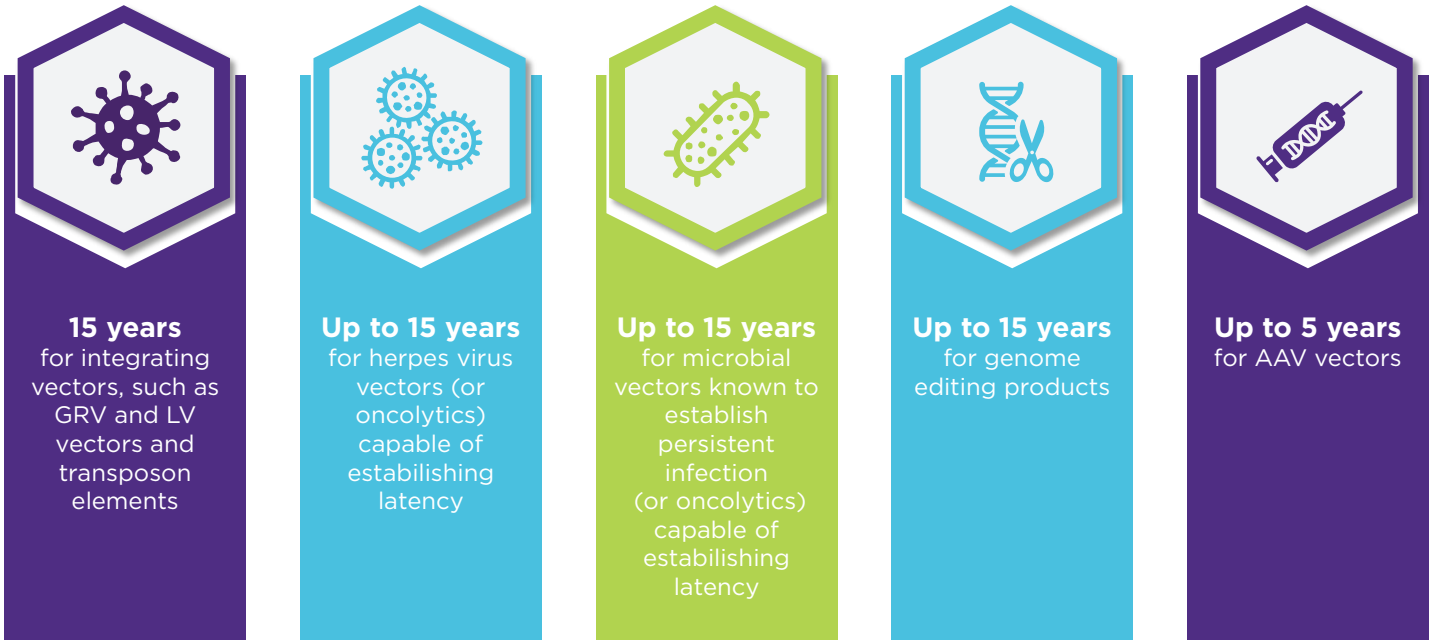
The U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) require LTFU studies for both cell and gene therapies in most cases, although the specifics of study protocols and durations vary depending on treatment and trial specifics.[2-4] Delayed risks in gene therapies, for example, could include malignancy, impaired gene function, a utoimmune-like reactions and resistant infections. while adverse events in cell therapies could manifest as secondary malignancies, autoimmune disorders and new persistent hematological disorders.[5] As mentioned above, efficacy, durability and long-term outcomes can also be monitored during LTFU studies to further enhance learnings from these therapies, both for current recipients and for future development and populations. By continued observation of these patients, researchers can better understand and mitigate future risks of adverse events and regulators can refine the assessment of these therapies' benefit-risk ratio.

This continuous evidence generation continues throughout all stages of development and after-market authorization to strengthen the evidence base for therapies, allow adjustments to move research forward or guide go/no-go decisions. Unlike traditional treatments, which may have different types of post-launch requirements, all CGTs have regulatory commitments requiring post-marketing long-term safety studies that continue to assess the benefit-risk of the therapy after launch. The design requirements for pre- and post-launch LTFU regulatory commitments are usually similar (e.g., follow-up duration and endpoints of interest) and can often be planned to merge the ongoing, pre-launch and post-marketing LTFUs.

Regulatory Requirements for LTFU Studies in CGT

The FDA's approach to LTFU studies is based on the level of risk of delayed adverse events. In case an LTFU is needed, the FDA advises sponsors to observe subjects for delayed adverse events for as long as 15 years for an investigational gene therapy product. The LTFU observation should include a minimum of five years of annual examinations, followed by ten years of annual queries of study subjects, either in person or by questionnaire. This continuous evidence generation continues throughout all stages of development and after-market authorization to strengthen the evidence base for therapies, allow adjustments to move research forward or guide go/no-go decisions. Unlike traditional treatments, which may have different types of post-launch requirements, all CGTs have regulatory commitments requiring post-marketing long-term safety studies that continue to assess the benefit-risk of the therapy after launch. The design requirements for pre- and post-launch LTFU regulatory commitments are usually similar (e.g., follow-up duration and endpoints of interest) and can often be planned to merge the ongoing, pre-launch and post-marketing LTFUs.

The FDA's Recommendations for the Duration of a Gene Therapy LTFU Protocol Based on Vector Type are as Follows:[6]



***GRV** = Gammaretroviral*
***LV** = Lentiviral*
***AAV** = Adeno-associated virus*

Source: Long Term Follow-up After Administration of Human Gene Therapy Products | FDA

EMA Guidelines

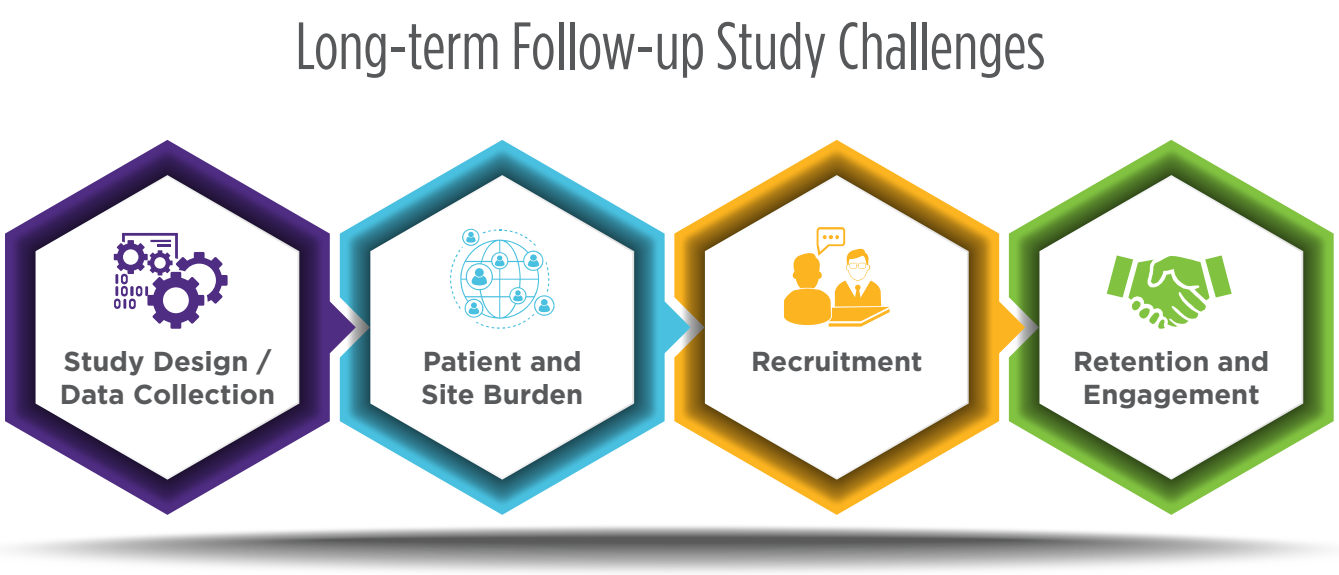
The EMA has made recommendations in response to the development of CGT products. Duration of follow-up is established on a case-by-case basis. However, for gene therapy medicinal products using integrating vectors or for those that have the potential for latency followed by reactivation, LTFU studies are usually expected to follow the patients up to 15 years.

The EMA has guidelines regarding the strategy and design of LTFU studies as well as details related to investigational product characteristics, patient-related factors and preclinical and clinical data that should be considered when assessing the need for LTFU for a CGT product.[7-8] EMA guidelines on post-marketing follow-up of efficacy and safety of advanced therapy medicinal products mention that post-marketing LTFUs are either post-authorization safety studies (PASS) or efficacy studies (PAES). The EMA's preference is that all patients receiving the therapies are followed, including those receiving the commercially available treatment post-launch. The EMA encourages designing the LTFU program "holistically, considering data generation in the post-authorization phase in addition to data obtained pre-authorization.[9]"

Regulatory considerations for LTFU studies for CGT products in different geographies are complex and vary quite a bit. Therefore, it is important to consider these studies when developing your overall regulatory strategy. The unique nature of having to begin these studies after first in-human use warrants clear delineation of development goals, and the evidence needed to achieve those goals before Phase I trials begin.

Scientific and Operational Challenges and Considerations

Knowing that the FDA and the EMA require LTFU studies as part of the approval process for CGTs, many scientific and operational factors need to be considered when planning the LTFU protocol. While some challenges are consistent with those found in other studies, there are several unique challenges in LTFU studies, especially given any CGTs are in rare diseases which have small, dispersed populations.



Data Collection and Burden

CGTs are often used to treat rare diseases or target small populations with specific treatment eligibility criteria. LTFUs are most often descriptive studies, however, the sample size is important for the level of precision of long-term efficacy and safety outcomes. LTFU studies try to enroll all patients treated within a clinical trial (and later on, treated as per routine clinical practice) to maximize the sample size and the quantity of information. Sample size needs to be optimized by maximizing consent and minimizing withdrawals and loss to follow-up.

Most importantly, patients should be kept at the forefront when developing such studies. Following up on patients for prolonged periods – sometimes up to 15 years or more — is often challenging for participants, so it is critical to reduce barriers and complexity to ensure patient engagement and data quality over a long period of time. The patient perspective must be taken into consideration as early as study design and protocol development, carefully defining the objectives and streamlining the data to be collected. For example, any patient-reported data, such as QoL, should be carefully evaluated, especially the feasibility of long-term data collection. If too many patient-reported outcomes (PROs) are included, the burden on patients becomes too heavy and threatens compliance. Discussion of "need-to-have" vs. "nice-to-have" data is particularly important for LTFU studies from both a clinician- and patient-reported perspective.

In general, every effort should be made to reduce the data collection burden, especially if data is already available elsewhere. There are a growing number of existing clinical registries (also called patient registries), particularly in the rare disease space, and their use should be explored for all CGT LTFU studies to complement observational LTFU data collection and reduce the overall burden to both patients and sites. Regulatory agencies, such as the EMA, encourage CGT sponsors to plan ahead and support or develop patient registries to be used as data sources for future studies, including LTFU. Assessing the existence and suitability of patient registries should be part of the feasibility assessment for any LTFU.

Study design must also account for data collection issues that may not appear in other shorter-term studies, such as how consent/assent and PRO updates may occur as a patient grows up, changes in technology, and the long-term burden on sites, patients, and caregivers due to the duration of the study.

Patient Recruitment

One major challenge of LTFU studies in CGT is convincing patients to participate for an extended time when they have already received their treatment. For therapies where patients continue to get treatment over time, they are already seeing clinicians regularly, so collecting additional data for the LTFU study is not usually an inconvenience. However, for many of these therapies, patients may only require one treatment for their entire life.

Why would patients agree to participate in a study where they may be required to make additional trips to a clinician or trial site? Or potentially go through uncomfortable or time-consuming testing?

While there are definite challenges in patient recruitment and retention for LTFU studies, there are major benefits to patients who have undergone CGT.

First, these studies provide patients with ongoing monitoring, which leads to potential improvements in their overall health and well-being.

Second, LTFU studies help identify potential issues early on, allowing patients to receive prompt treatment if needed.

Finally, participating in these studies contributes to the advancement of medical knowledge and helps improve outcomes for future patients, which is very compelling for patients who understand the struggle of not having adequate treatment for their illness.

Patients also receive additional support by connecting with patient advocacy groups (PAGs) in their disease community. Gaining support enables greater outreach to patients within the disease community. PAGs also help with communications, expectation setting and patient identification for a research study. They are a valuable source for patient input at the start of a study. Talking with advocacy groups to inform protocol design empowers patients to use their experience to help make changes that might make it easier for others to participate and identify outcomes that are important to patients that are not currently captured in the clinical outcomes of a study.

Even if patients understand these benefits and initially agree to participate, maintaining follow-up over an extended period can be affected due to patients moving, changing healthcare providers or becoming lost to follow-up. This makes it difficult to collect long-term data.

In rare diseases specifically, patients are very aware of how important their participation is in clinical research. However, patient numbers tend to be lower, and patients are more spread out, regionally. The LTFU design must consider the schedule of assessments and the ability to see a local physician or implement decentralized approaches to reduce burden and ensure patients are willing to participate long-term.

Patient Retention and Engagement

Patient retention is especially critical when one considers the operational challenge of cost and complexity. LTFU studies require significant resources to implement and maintain. Both patients and clinicians need to stay engaged throughout the duration of the study. When a study's duration lasts for 10-15 years, motivation can wane. Clinicians may also move or retire, affecting the study continuity. It is crucial to identify the most optimal approach to study design and proactively consider risks and ways to mitigate those risks over the course of the study, including motivation for patients and clinicians to participate.

To achieve success, studies should also appeal to caregivers by considering their specific needs when finalizing the study design. This includes the assessment schedule, timing and duration of assessments, length of survey completion, reimbursement, lost wages, emotional and mental strain, etc. It is important to apply these considerations when implementing strategies for patient recruitment and retention.

How to Avoid Study Fatigue and Keep Retention High

Study fatigue happens to patients, caregivers, clinicians and site staff over time and can affect adherence. There are several ways to combat fatigue.

Clinicians and Site Staff:

- Provide fair market value compensation for the level of study work required, accounting for inflation over time or even periodically re-evaluating studies with 10-15 years duration
- Implement an eConsent platform to help sites manage informed consent form version control and reconsent as patients age up
- Streamline the volume and frequency of data collected, along with the selection of an easy-to-use electronic data capture system
- Explore or plan for registry-based solutions to supplement data collection and reduce burden
- Offer patient recruitment services that reduce site burden while maintaining patient engagement (i.e., patient concierge and travel services, study-level materials for dissemination to patients, vendor-provided payments for travel/meal reimbursement or reimbursement or PRO completion)

Patients and Caregivers:

- Consider the schedule of events and length of assessments, aligning with the standard of care when possible
- Reimburse for time, travel, parking or meals
- Offer services that lighten patient and caregiver burden such as scheduling support, visit reminders, travel arrangements, telehealth and home health services
- Use appropriate language and culture-specific information to keep participants informed and engaged by reminding them why trial participation is so critical or offering study progress and disease updates
- Understand the patient's healthcare journey to highlight critical time points for creative and continued patient engagement. For example, a branded blanket for use during treatment or another token of appreciation can go a long way in letting the patient know they are cared for, helping them keep the study top of mind

Reducing Site and Patient Burden with Virtual and Hybrid Strategies

Using virtual/decentralized clinical trial approaches often reduce patient and site burden, helping to keep engagement and retention high by offering an alternative way for patients to maintain participation amid life changes, such as moving or changing providers.

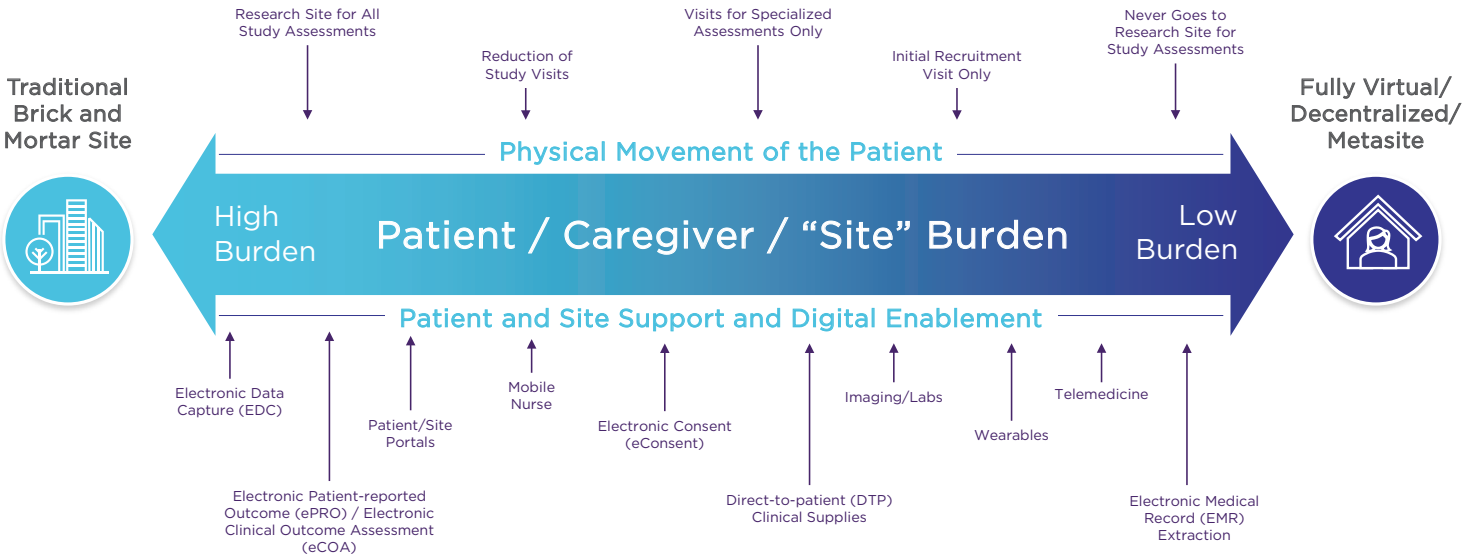
LTFUs can use a hybrid or fully virtual study design. In a hybrid study model, in-person visits are often reserved for specialized assessments where a clinical setting is needed, while most of the data collection activities can be done virtually by patients, caregivers or home health providers. The goal is to eliminate inconveniences that cause a patient to become non-compliant, or worse, drop out of a trial altogether. One example of flexibility is the use of telemedicine, where investigators can receive the information needed from participants through remote contact.

When a study is designed, the goal is always to simplify requirements for patients. Ongoing contact via telephone or questionnaires maintains the patient connection. Employing home health nurse visits and telemedicine, along with eConsent, electronic patient-reported outcomes (ePROs) and other digital tools bring the study to the patient while meeting the needs of timely endpoint collection.

The ultimate goal is to leverage decentralized technologies and retain better connectivity with participants while minimizing burden. When considering technology, it is critical to understand how that solution will evolve or adapt over the study duration. It is important to work with a vendor that has a plan to manage upgrades or provide support if study technology becomes obsolete.

This diagram shows alternative operational approaches to incorporate virtual elements to bring the LTFU study directly to the patient. Implementation of a virtual or hybrid study model reduces overall site and patient burden and increases participation and retention.

Digital and Decentralized Solutions Enable the Shift from Traditional to Virtual Study Implementation



Incorporating Flexibility to Increase Study Success

A lot can change in the 15 years of an LTFU study. A well-designed LTFU study should be built to adapt to changing patient age, patient needs or locations, regulation adjustments, clinical team turnover and technology.

Technological advancement in the clinical sector is a given. In the last 15 years, we have seen improved data collection capabilities, accessibility and traceability. In addition, there has been wider development of automated data capture and linking of different sources of real-world data (RWD), development of associated real-world evidence (RWE), and a rapid increase in artificial intelligence (AI) and machine learning.

Another valuable technological consideration includes the collection of electronic clinical outcomes assessment data. Phones, tablets or wearables enable the collection of remote bespoke data, reducing the number of office visits for a study participant and reducing patient and clinician burden. How the technology and the patient will evolve is an important consideration. The use of devices may not be suitable as the patient ages or the technology itself becomes obsolete.

Data collection and curation also need to be considered and addressed. Over time, electronic medical record systems could change, or new data collection technologies implemented. See "The Evolution of Technology Enablement in Long-term Follow-up Studies" for more information on technology and data collection in LTFU studies. The good news is that studies can be agile. The COVID-19 pandemic was the ultimate test in flexibility. Studies proved they could quickly shift to rely less on in-person data collection to avoid gaps in patient care and ensure research study continuity.

Examples of Successful LTFU Studies in CGT

Despite the challenges, many LTFU studies in CGT have been successful. For example, an LTFU study of patients with severe combined immunodeficiency treated with gene therapy showed sustained immune reconstitution and clinical benefit over several years.[10] Another study of patients with beta-thalassemia treated with gene therapy showed sustained production of hemoglobin and reduced transfusion requirements over several years.[11]

CASE STUDY: Success Implementing Global LTFU Model with Patient Services and Decentralized Technologies

The following LTFU case study highlights how patient-level focus and digital enablement helped drive engagement and minimize burden over the long term.

Scenario:

- Gene therapy LTFU with 5–15-year requirements

Challenges:

- Single treatment site required cross-border enrollment of 50 international patients across 20 countries
- Reduce patient burden for several years of safety surveillance and remote data collection
- Ensure retention of patients and long-term follow-up data collection informing the safety of the product and meeting regulatory requirements

Solutions:

- Established one primary site for LTFU and worked with patients in their home countries
- Implemented platform technology for remote collection of LTFU data
- Used multilingual technology to successfully engage patients, caregivers and multiple healthcare providers and provide remote collection of LTFU data
- Platform triggered email alerts to primary investigator and care team at the treatment center
- Deployed country-specific patient concierge personnel to assist patients with study, technology and travel logistics

Results:

- Successfully captured primary outcomes data
- Reduced excessive travel for participants
- Continued use of the technology platform to collect outcomes data while providing important safety data required by regulators
- Achieved 0% patient attrition to date

Future Directions in Advancing LTFU in CGT

As CGT continues to advance, LTFU studies will continue to play a critical role in evaluating the safety and efficacy of these therapies. Future directions for these studies may include the use of novel technologies, such as wearable devices and telemedicine, to improve patient monitoring and data collection, as well as the anticipation and development of patient registries to use as a source of data for LTFU. Additionally, advances in data analytics and AI may help researchers identify patterns and trends in LTFU data, allowing for more precise and targeted interventions.

These studies provide valuable data on the long-term benefits and risks of these therapies, allowing researchers to refine their treatments and improve patient outcomes. Continued research and investment in LTFU studies will be essential for advancing the field, managing the challenges of long-term data gathering and management, retaining patients in the face of study fatigue and enhancing results. Regulatory agencies require these studies to monitor patients over an extended time period for delayed adverse events, and patients who have undergone these therapies may benefit from participating.

Working with a partner that understands regulatory strategy, streamlined data collection, ways to reduce patient/caregiver/site burden, and increasing patient and clinician retention while maintaining flexibility and adaptability are essential for long-term study success.

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