Evolving with the patient: Optimising CAGT post-trial long-term follow-up

The tremendous growth in cell and gene therapy is no surprise to the pharma industry. In 2022 alone, 960 next-generation biotherapeutics were in development from Phase I through regulatory filing stages. However, the best methods to monitor for delayed adverse events or secondary malignancies associated with these innovative treatments are still evolving as the industry gains insights.

With more and more cell and gene therapies securing approval for use, clinical trial sponsors and researchers also have an opportunity to accumulate scientific knowledge and potentially modify clinical journeys based on CAGTs.

Based on product characteristics (e.g., use of genome-editing technology, potential for latency and reactivation associated with viral vectors, etc.), the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) have issued guidelines for the design and key data elements of required long-term follow-up (LTFU) studies for CAGT, which can last from five to 15 years. Longer study duration presents a spectrum of unique challenges to navigate while aiming to optimise this long-term data collection. It is beneficial for sponsors to explore approaches that can efficiently capture required safety data, while also planning for challenges that arise from an evolving patient journey, as well as the regulatory and technology changes that will happen during the many years of mandated follow-up.

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Unique design influencers

CAGT LTFU studies carry a multitude of clinical, data, and operational considerations that can add to the burdens placed on patients and sites for years. Because sponsors aim to collect long-term safety data and build on efficacy insights for these therapies, known factors to consider and plan for in study design include:

- Changes in patients' lives due to ageing, passing through life stages, relocating, changes in overall health status, etc., which can make it difficult to conduct follow-up over many years.
- A need for data collection that may exceed the data captured during patients' standard-of-care interactions.
- Patients may feel 'cured', making further participation seem unimportant. This can be true because some CAGT are meant to provide potential for cures, not treat symptoms alone, and patients may not want reminders of when they were ill.
- Sites of initial treatment may not be local or accessible to the patient over the long term, impairing the ability of the investigational site to conduct necessary follow-up.
- Added responsibility on providers and sponsors to detect adverse events rapidly, because many products will get marketing authorisation before completing the LTFU among patients with trial exposure.

LTFU innovation and optimisation

Most of the innovation in CAGT comes from small or midsize biotech companies. Stakes are higher for these sponsors, as they typically focus on a limited number of breakthrough assets, which can impact the company's livelihood. Biotech firms with a solid proof of concept or initial positive outcomes for their assets must be visionaries. In LTFU protocol design, they may already be thinking about how to broaden the therapeutic potential of their asset.

Early in planning for an asset, sponsors and clinical research organisation partners need to consider the impact of a number of clinical parameters on the LTFU programme, including the study population, whether they are adult or paediatric patients, underlying disease, and prognosis. These factors help determine:

- What data must be collected, where it is available and how best to obtain it.
- What the expected survival of patients may be, to understand the duration of follow-up.
- Whether patients will be transitioning to different life stages (passing ages of assent/consent) that involve varying healthcare systems or updated consent schema.
- If standard-of-care visits and the related standard-of-care data (e.g., electronic medical records or patient registries) can be leveraged.

Consideration of data sources

As more LTFU studies are conducted, CAGT LFU data is captured from a broader range of data sources. Traditional data collection methods via sites (e.g., regular observations in standard of care, specialist visits, and labs) are essential. However, now, sponsors are increasingly using direct-to-patient data collection methods (e.g., connected devices, wearables, and electronic diaries for symptom and progress tracking) and other secondary data sources, in order to reduce data collection burden on sites and patients and enrich primary site-based insights. There is hope that patient registries can also be useful for long-term safety and efficacy data collection, but existing databases may not always adequately support study requirements for certain data or have sufficiently robust research standards.

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By leveraging combinations of these data collection approaches, sponsors can tailor study methodologies to the needs of patients and the providers who oversee their long-term care. Decisions on what data to use rests upon consideration of data accessibility, quality, suitability, and potential for bias when evaluating source options.

Considering real-world clinical endpoints early in trial design planning can help sponsors determine how much they can rely on secondary or other existing data sources. The more we can move towards pragmatic real-world endpoints in the assessments of safety and efficacy for these LTFU programmes, the more options there will be for data sources. The adoption of data standards for these programmes would also assist the longer-term goal of moving towards lower burden surveillance efforts. As the industry accumulates knowledge on best practices and successful methods for long-term surveillance, there is the potential for collaboration between organisations to harmonise data from multiple sources to create richer and more accessible data.

Understanding patient journeys

Understanding how patients and caregivers move through the healthcare system during the span of a LTFU study and after a life-changing health experience is the most fundamental piece of the puzzle. During planning, to accommodate changes that patients may experience, sponsors and CROs need to ask:

- How is the patient travelling through the healthcare system?
- From what healthcare sources can we secure patient information?
- Where is the patient in age and life stage?
    - If initially a paediatric patient, but now a teenager, how do we approach the individual and caregiver? If the patient is now 65 years old or older, how will study design accommodate their needs and the caregiver's?
- Are patients expected to survive the full term of the LTFU commitment?
    - In some cases, life-threatening diseases may mean a patient's prognosis doesn't extend to the five or more years needed for LTFU.

To accommodate the natural evolution of patients' journeys, sponsors and CROs can develop a granular picture of what approach and useful solutions they should integrate into design to ensure patients' burdens are being addressed. LTFU studies often benefit from decentralised solutions, such as telehealth visits, remote data collection, home phlebotomy and nursing, and electronic clinical outcomes assessments because they reduce on-site follow-up, testing, and data collection. Additionally, scalable decentralised platforms that include mobile apps for text reminders, alerts, live chats, and ongoing communication can help to engage patients over long durations.

Data contextualization

Leveraging the breadth of existing real-world data allows sponsors to take an epidemiological lens to what is being seen through the LTFU study. This helps secure a stronger understanding of insights collected through the study as they relate to what is happening in the real world in terms of patient experiences, including adverse events. For example, it can be useful to leverage population-based data sources to contextualise secondary malignancies, thereby gaining a stronger understanding of the background rates for the malignancy, and in the assessment of relatedness to the gene therapy.

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Change is acceptable

Given the duration of LTFU studies, staying agile in approach and adapting as the programme evolves and there are increased advancements in tech-enabled solutions will be critical. When planning, it is beneficial to think of these studies using a segmented approach, where sponsors and CROs can plan several years at a time and then plan to revisit strategies and adjust as needed.

In traditional clinical trials, protocol amendments can be viewed as setbacks. In LTFU studies, when controlled, it can be considered good planning, with foresight about what may change. This shift in mindset can help socialise the necessary updates and adjustments to achieve fit-for-purpose models that enhance study strategy and ensure successful long-term data collection and safety monitoring. For some studies, the first few years of execution may include site-based approaches and the remaining years integrate decentralised solutions and real-world evidence to secure needed insights. Other studies may start with decentralised solutions and later transition to undefined future technologies.

One key factor sponsors need to build into a long-term programme is leveraging patient-generated data. Over time, the industry will have more research to gauge the reliability of this data. Access to this data will become more common, though not in every country. In the future, harmonisation and shared access to patient-generated data may help accelerate knowledge and market access, while decreasing patient burdens.

Additionally, there are industry discussions about the need for data harmonisation and standardised processes for mapping and understanding observational data found in medical records, including the Common Data Models Harmonization Fast Healthcare Interoperability Resources (FHIR) Implementation Guide. Led by the FDA and other countries' agencies, this guidance aims to create portability of medical information. Through these standards, patients can become the distributor of their own standard format healthcare information, making the sharing of that data, which is enabled by the patient, a common practice that would benefit this kind of long-term follow-up effort.

Accumulating scientific richness

Though relatively new in approach and design, data collection innovations in CAGT may accelerate the detection of positive outcomes and may decrease patient burdens over a longer duration. Using innovative methods to collect long-term outcomes can get us to scientific insights faster and help improve our understanding of these novel treatments.

The experience of previous and current LTFU studies and breadth of meaningful data insights accumulated will only add to the ability of sponsors and CROs to fine tune design and execution with innovation and heightened efficiency.

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