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Designing Resilient Long-Term Follow-Up Studies: Save Costs, Reduce Burden, and Enable Better Research

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Background

Long-term follow-up (LTFU) studies represent a critical component of clinical research, particularly with interventions like cell and gene therapies (CGT) that induce long-lasting physiologic changes.[1] In these situations, delayed adverse effects may not manifest during the relatively short duration of most pivotal trials, requiring a comprehensive assessment of both safety and efficacy over extended observation periods.[2]

From an epidemiologic perspective, LTFU studies enable the examination of outcomes across the lifespan of drug development, supporting the identification of rare or cumulative risks and the durability of treatment effects that cannot be adequately assessed in shorter-duration studies.[1,3]

The U.S. Food and Drug Administration (FDA) and other regulatory agencies outline clear requirements for LTFU of therapies that pose a risk of delayed side effects. For example, the FDA's 2020 guidance on gene therapies mandates LTFU for products utilizing genome editing or integration, or those that have the potential for long-lasting expression, latency, or reactivation. Depending on the specific risks, follow-up can be required for up to 15 years. Sponsors are also expected to update their risk evaluations over time and adjust protocols as new information becomes available.[1]

Despite regulatory requirements and epidemiological importance, LTFU studies encounter substantial logistical and methodological challenges, including retaining participants over extended periods, adapting as data collection methods evolve, integrating follow-up data with initial trial datasets, and managing attrition bias, which can compromise the validity of long-term findings.[3,4]

This whitepaper examines the limitations and challenges of traditional approaches to conducting LTFU studies and presents an alternative, technology-enabled approach that leverages AI and scientific rigor to reduce patient burden and ensure the long-term safety and efficacy of medical interventions.

Challenges with Traditional LTFU Studies

Patient Engagement & Retention

LTFU studies vary in duration and may require participants to attend regular site visits for more than a decade after the initial intervention. While a portion of this follow-up time is accrued during the initial pivotal trial, the majority occurs as part of the LTFU protocol after completion of the trial.[1] During the trial, participants may have traveled long distances to receive these specialized, often curative therapies. As time elapses since the treatment, the burden of returning to the site — especially when no personal benefit is gained — is more pronounced and may be more than they can realistically bear. As a result, many patients will drop out of the study; high loss to follow-up rates challenge data collection and limit the insights researchers can draw.[3] According to the Emily Whitehead Foundation, a nonprofit dedicated to the fight against childhood cancer and CAR T research, 38% of patients who still attend follow-up visits 12 months after treatment do not expect to continue for all 15 years.[5] For every patient who is lost to follow-up, the opportunity to assess long-term safety and effectiveness of the treatment is diminished.[1-4]

Site Operations

Clinical research sites face cascading challenges when managing prolonged follow-up protocols. The conventional site-based model for LTFU data collection imposes an unsustainable operational framework. Sites must maintain dedicated research personnel, infrastructure, and administrative systems across multiple years, creating a sustained drain on resources that fundamentally conflicts with their operational priorities.[6] Sites may face the challenge of managing multiple simultaneous LTFU protocols, each requiring distinct data collection schedules, specialized training requirements, and regulatory compliance procedures, with over 60% of sites using more than 20 applications daily to manage study requirements.[7]

In 2024, sites considered the complexity of clinical trials to be their primary challenge, surpassing previous concerns about staffing and retention.[6] Staffing is still a challenge, however, with turnover rates for clinical research coordinators reaching 35-61%.[7]

Additionally, LTFU protocols can be difficult for sites to comply with because they no longer have direct patient oversight. Participants return to their routine healthcare providers after the trial concludes, and the trial sites must then proactively retrieve medical information from external healthcare providers to complete case report forms for the LTFU study. This process exacerbates the already existing challenges:

Data accessibility:

External providers may be uncooperative, lack complete records, or face operational constraints (e.g., staffing shortages or archived records).

Logistical complexity:

Retrieving information requires consent coordination, multiple contact attempts (e.g. phone, mail, electronic), and navigating disparate health record systems.

Cost & inefficiency:

Manual data extraction from external sources is resource-intensive and may not be cost-effective, especially for hospitalizations or rare events.

Evolving Research Needs

Given the extended duration of current LTFU requirements, protocol amendments during the course of a study are almost unavoidable. The life sciences sector therefore needs research methodologies that are inherently flexible and adaptable, enabling protocol modifications as new evidence emerges or as regulatory expectations evolve. At present, regulatory frameworks governing long-term research remain underdeveloped and are expected to undergo significant evolution in the coming years. Advances in technology and patient and regulatory expectations over the past decade underscore the likelihood that protocols and operational processes established at study initiation may become outdated, failing to reflect emerging best practices over time.[8]

Adapting a multi-site study to meet evolving regulatory and evidence generation needs is cumbersome and time-consuming. Ultimately, compliance with LTFU regulatory requirements necessitates the capacity to generate robust, longitudinal evidence. However, without innovative approaches to patient retention and engagement, the quality and completeness of long-term data — and thus the interpretability of study outcomes — are at risk of progressive deterioration.

Characteristics of a Novel Technology-Enabled Approach

A modern technology-enabled approach to LTFU studies integrates scientific rigor with AI and patient-centric operational models to address the unique challenges of extended monitoring periods. Overseen by an experienced principal investigator, tech-enabled studies leverage a remote-first model for patient engagement, reducing participation burden and dependencies on sites. These models increase study efficiencies and access more complete routine patient data by expanding their data retrieval to all sites of care, while ensuring high-quality data capture.[9]

Scientific & Regulatory

- **Regulatory-Aligned Safety Monitoring:** Designed to meet FDA requirements for tracking delayed adverse events (e.g., secondary primary malignancies) and therapy durability over 15-year periods, particularly for integrating vectors (lentiviral, CRISPR-Cas9) and adeno-associated viruses (AAV).[1]
- **Risk-Adaptive Protocols:** Incorporate real-time data (e.g., product persistence, transgene expression) to dynamically adjust monitoring intensity and duration, reducing unnecessary patient burden while maintaining scientific validity.[1]
- **Longitudinal Data Completeness & Integrity:** Ensures continuous capture of biomarker data and clinical endpoints via advanced AI retrieval and abstraction and integrated digital platforms to support robust safety/efficacy analyses.[9,10] This can be supplemented with HCP coordination and laboratory testing when relevant.

Operational

- **Tech-Enabled Patient Engagement:** Combines remote interactions with optional in-person healthcare provider visits when necessary, accommodating patient mobility and life changes over extended periods.
- **Decentralized Site Infrastructure:** Leverages local healthcare providers and mobile technology for data collection, reducing travel dependence.
- **Seamless Protocol Transition:** Integrated workflows bridge interventional trials to LTFU phases, preventing patient attrition during study handoffs.
- **Retrieval & Abstraction:** Using AI and a human-in-the-loop approach, structured and unstructured data is rapidly retrieved, and relevant data is abstracted.[10]

Patient-Centricity

- **Personalized Retention:** Tailored communication (e.g., adaptive reminders, educational content) and flexible participation options address barriers like distance and awareness gaps, countering attrition rates.
- **Reduced Patient Burden:** Digital tools minimize logistical and financial hurdles, making long-term participation more feasible and improving accessibility for diverse populations across socioeconomic strata.

Efficiency & Scalability

- **Cost Optimization:** Lowers operational expenses by ~30–50% by eliminating the need to maintain clinical sites over the duration of the follow-up, participant travel expenses, manual data retrieval and entry.
- **Unified Data Ecosystems:** Cloud-based platforms enable real-time protocol adherence monitoring and sponsor access to consolidated datasets, enhancing trial oversight.

Enabling a Better Future for Longitudinal Research

Persistent challenges with patient retention, site operations, and evolving research and regulatory needs will only increase as our needs for evidence continue to increase and evolve. As regulators increasingly require robust, multi-year evidence to verify the long-term safety and durability of novel therapeutics, the limitations of traditional approaches will only become more pronounced.

Modern, technology-enabled approaches to LTFU directly address these barriers by combining scientific rigor with operational flexibility and designs that work for patients in the real world. Platforms that minimize patient burden and maintain engagement over extended periods are essential for capturing the high-quality longitudinal data required.

Adopting this next-generation framework safeguards the completeness and integrity of long-term evidence while equipping sponsors to navigate an increasingly complex and changing landscape. Integrated, real-time monitoring within a unified trial ecosystem improves study efficiency and sponsor oversight. By transforming how LTFU studies are designed and executed, life sciences can deliver on the promise of safe, effective therapies.

Explore how PicnicHealth delivers their technology-enabled approach to drive efficient, effective long-term follow-up studies

References

1. U.S. Food and Drug Administration. 2020. Long Term Follow-Up After Administration of Human Gene Therapy Products. January. https://www.fda.gov/media/113768/download.
2. Llewellyn-Bennett, Rebecca, Danielle Edwards, Nia Roberts, Atticus H. Hainsworth, Richard Bulbulia, Louise Bowman, et al. 2018. "Post-trial Follow-up Methodology in Large Randomised Controlled Trials: A Systematic Review." Trials 19 (1): 298. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5975470/.
3. Hill, Karl G., Danielle Woodward, Tiffany Woelfel, J. David Hawkins, and Sara Green et al. 2016. "Planning for Long-Term Follow-Up: Strategies Learned from Longitudinal Studies." Prevention Science 17 (7): 806–818. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5337427/.
4. Song, Jae W., and Keywan M. Chung. 2010. "Observational Studies: Cohort and Case-Control Studies." Plastic and Reconstructive Surgery 126 (6): 2234–2242. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2998589/.
5. Myers, Nancy Bradish, Taryn Serman, Betsy Foss-Campbell, and George Eastwood. 2024. Amplifying the Voice of CAR T-Cell Therapy Patients and Caregivers: Survey Results to Better Understand Patient Experiences with Long-Term Follow-Up Studies. Catalyst Healthcare Consulting and Emily Whitehead Foundation. https://emilywhiteheadfoundation.org/wp1/.
6. WCG Clinical. 2024. 2024 Clinical Research Site Challenges Report. October. https://www.wcgclinical.com/wp-content/uploads/2024/10/WCG_2024_Clinical_Research_Site_Challenges_Report.pdf.
7. Society for Clinical Research Sites. 2024. Open Letter on Workforce Challenges at Research Sites. https://myscrs.org/workforce-challenges-letter/.
8. de Haart, Karin, Keiko Asao, Quazi Ataher, Jamie Geier, Jodie Hillen, Kui Huang, Peter Mol, et al. 2025. "Long-Term Follow-Up after Authorization of Gene Therapy: Leveraging Real-World Data." Drug Discovery Today 30: 104337. https://doi.org/10.1016/j.drudis.2025.104337.
9. PicnicHealth. 2025. The Modern Approach to Observational Research. https://research.picnichealth.com/publication-download/the-modern-approach-to-observational-research.
10. Porter, Robert, Adam Diehl, Benjamin Pastel, J. Henry Hinnefeld, Lawson Nerenberg, Pye Maung, Sebastien Kerbrat, et al. 2024. "LLMD: A Large Language Model for Interpreting Longitudinal Medical Records." arXiv preprint arXiv:2410.12860. https://arxiv.org/abs/2410.12860.

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