Executive Summary

Toolkit for Supporting the Design, Conduct, and Reporting of Long-term Follow-up Studies for Gene Therapies

This Executive Summary is organized into three parts:

Purpose of the Toolkit and Intended Audience

Long-term follow-up (LTFU) studies of gene therapy (GT) recipients are essential for assessing the overall risk-benefit profile of these innovative pharmaceutical products. The results of LTFU studies have implications for clinical care, research, the regulatory evaluation of the benefits and risks of GTs, future investment into these products, as well as reimbursement policies for them. LTFU studies provide critical information to guide decision-making for patients, caregivers, sponsors, regulators, payers, and the broader medical community. However, scientific, operational, financial, and logistical challenges make the design and execution of LTFU studies difficult, posing a significant burden on both patients and sponsors.

In September 2024, the MRCT Center launched an LTFU Working Group, with the aim of developing guidance and associated tools for the ethical design and conduct of LTFU studies for GTs, including genetically modified cell therapies. Another goal was to envision how LTFU studies could be improved, potentially using new approaches.

The committee was comprised of patients, as well as representatives from patient advocacy organizations, industry sponsors, academic medical centers, clinical research organizations, and organizations responsible for human oversight protection. This enabled the project to benefit from diverse perspectives and complementary scientific, medical, regulatory, and ethical expertise.

On November 4, 2025, the MRCT Center released the Toolkit for Supporting the Design, Conduct, and Reporting of Long-Term Follow-Up Studies for Gene Therapies, v. 1 as a draft for public comment. The MRCT Center is now releasing the v. 2.0 of the Toolkit, which has been updated to include this Executive Summary and a new Patient Resource on LTFU. Building upon regulatory authorities' LTFU guidance, the Toolkit is comprehensive, providing background information, practical resources, and recommendations to support best practices for LTFU. The Toolkit also explores ideas for how LTFU studies could be improved in the future, raising questions that the field should discuss and address.

The Toolkit will likely be of greatest benefit to those who regulate, design, conduct, support, oversee, and/or interpret LTFU studies, including academic and industry researchers, clinicians, regulators, patient advocacy organizations, and research oversight professionals. The new version includes a Patient Resource specifically designed for patients and their supporters; however, the broader Toolkit may also be of interest to patients who wish to learn more about LTFU. The resources apply to LTFU studies of patients who received investigational gene therapies (GTs) as research participants or via preapproval nontrial access pathways, and to LTFU studies of patients who have received approved GTs.

Toolkit Structure and Navigation

The Toolkit enables easy navigation to various sections and subsections via multiple clickable, interactive toolbars. We anticipate that most Toolkit users will not read it cover-to-cover; rather, they will jump to the sections that address their specific questions or needs.

The heart of the Toolkit is comprised of three main components:

- **Guiding Principles for LTFU studies for GTs**: a high-level framework for the ethical design, conduct, and reporting of LTFU studies.
- **Considerations and Recommendations for the Design, Conduct, and Reporting of LTFU Studies for GT**s: the most detailed section of the Toolkit, providing facts about and guidance for LTFU studies across nine categories: Purpose and Limitations; Objectives and Endpoints; Anticipating Protocol, Technology, and Site Evolution; Enrollment and Informed Consent; Participant Retention and Withdrawal Criteria; Signal Detection/Safety Reporting; Data Sharing/ Results Dissemination; Operationalizing the LTFU Protocol; and Clarification of Responsibilities.
- **Looking Forward**: this resource offers bigger, perhaps bolder, questions about the scope of LTFU, data harmonization, and data sharing that the Working Group thought needed future consideration and deliberation.

The Toolkit also contains additional resources that provide background and/or helpful LTFU-related information:

- **Introduction and Background**, summarizes the need for and challenges with LTFU studies.
- **Types of LTFU studies**, discusses various LTFU study designs, such as integrated and standalone protocols, and the classification of studies as interventional or observational, which has regulatory implications, particularly for oversight and reporting.

- **Visual LTFU flowcharts** show different pathways for long-term follow-up in both research and clinical care settings.
- **Key Design Elements of LTFU Studies for FDA-approved GTs**, a resource that provides publicly available information about how GTs that have received FDA marketing authorization have satisfied LTFU requirements, in one easy-to-find place.
- **Regulatory Guidance Relating to LTFU of GTs**, with citations, hyperlinks, page annotations, and select quotes.
- **Patient Resource: Long-Term Follow-Up Studies After Gene Therapy**. This resource explains in plain language why long-term follow-up studies are important and the choices patients may have. It also provides a list of suggested questions that patients may want to ask to find out more about an LTFU study they are considering.
- **Compiled Glossary of Scientific LTFU-Related Terminology**, from a variety of respected scientific/regulatory/medical sources.
- **Easy-to-Understand (Accessible) LTFU-Related Definitions from the MRCT Center's Clinical Research Glossary**, which provides a complementary glossary to the more scientific and technical one.
- Appendices: **List of Acronyms** and **Abbreviations Used and References Cited**

Summary of Major Points

Although not exhaustive, key points from the Guiding Principles and Considerations and Recommendations sections are listed below:

Planning, Clarifying Responsibilities, and Operationalizing LTFU Studies

1. If LTFU studies are required for a specific GT research and development plan, planning for their design and execution is a necessary part of the overall strategy and should occur in its earliest stages.

2. Sponsors may encounter financial, operational, manufacturing or scientific and medical challenges. In some cases, sponsors may cease to operate or decide to inactivate, transfer or withdraw an IND. Sponsors should consider the impact of LTFU program termination on study participants and the broader patient community and make plans for and clarify how LTFU commitments will be fulfilled in such cases. The default plan should be communicated to participants during the informed consent process.

3. LTFU studies are a collaborative effort that requires coordination among different entities. Responsibilities as well as the rights of various entities should therefore be clearly established during the planning for LTFU and if the need arises, clarified as the study progresses.

4. Patients, their caregivers, and their communities should be engaged and consulted during the design and conduct of LTFU studies to ensure that the studies meet their needs and expectations. Early stakeholder engagement with patient groups, advocacy groups, advisory boards, and other relevant parties can also provide helpful input on operational factors and, importantly, how to anticipate and navigate potential obstacles.

5. Identification and mitigation of long-term health risks to individual patients should not be considered the responsibility of LTFU studies, which should be aimed at understanding and communicating safety risks at an aggregate level. Careful and ongoing monitoring should be standardly included in clinical care after a patient receives an investigational or approved GT.

Purpose, Scope, Objectives, Endpoints, and Anticipating Evolution

6. To maximize the scientific value, interpretability, and interoperability of LTFU studies, adverse event monitoring and reporting should be standardized and harmonized to the extent possible to facilitate meta-analysis across products and patient populations.

7. The specific goals of each LTFU study must be clear. Study design and conduct, including outcome selection, frequency of measurement, and methods to ensure data integrity and reliability, must be aligned with the stated goals.

8. Understanding the overall risk/benefit profile of GTs requires evaluation of both long-term risks and long-term effectiveness. Sponsors should ideally include assessments of efficacy in their LTFU protocols; some endpoints may be indicators of both safety and efficacy.

9. The need for LTFU data collection and monitoring should be balanced with the need for participant adherence and retention. The burdens of LTFU studies on participants and study sponsors should be justified by the knowledge to be gained about the benefits and risks of GTs and minimized to the extent possible.

10. In order to support the feasibility of LTFU studies and the sustainability of investment into the development of innovative GT products, the minimum data set that is sufficient to address LTFU study endpoints and meet the needs of key stakeholders (regulators, sponsors, patients, payers) should be collected.

11. The design and analysis of LTFU studies should anticipate the potential need to modify the LTFU protocol and/or Informed Consent documents as knowledge, data collection procedures, and participant journeys are likely to evolve over time. To minimize the need for amendments or changes, the LTFU protocol should allow for flexibility in the conduct of the study, to the extent possible.

Participant Enrollment, Informed Consent, Retention, and Withdrawal Criteria

12. Enrollment and recruitment methods, including inclusion and exclusion criteria, for LTFU studies should be scientifically justified and designed to minimize selection bias.

13. GT clinical trial participants should be informed about LTFU commitments, including the purpose of LTFU and associated procedures, before they receive GTs. Patients who receive approved GTs should be offered the opportunity to participate in LTFU, if appropriate, after they receive the GT.

14. Pediatric patients who are eligible for LTFU studies should be offered the opportunity to assent if they have the capacity to do so. They should confirm or withdraw consent to continue participation in an LTFU study when they reach the age of majority.

15. Informed consent documents should explicitly cover LTFU duration and cadence, remote/local follow-up options (tele-visits, home health, local labs), participant-selected contact modalities, data sharing (registry/EHR linkage), withdrawal and re-entry, and return of individual and aggregate results. The consent should also specify expected burden, including time, travel, technical expectations and requirements, out of pocket costs, and reimbursements.

16. Study teams should inform participants about their rights to withdraw from an LTFU study. However, they need to educate them that withdrawing from LTFU is not withdrawing from the GT intervention—only from the safety follow-up and/or data sharing involved with the study. Once someone receives a GT, modifications to a person's genes may persist. Withdrawal from the intervention is often not possible in a traditional sense.

17. As noted above, to support participant retention and completion of the study, sponsors should minimize burden as much as possible. LTFU study designers should carefully consider eliminating non-critical and explanatory endpoints and making study procedures as feasible and convenient as possible for patients.

18. For example, LTFU study planners should consider ways to decentralize the studies, minimize the number of visits and their durations, and include mobile health technologies. If in-person visits are necessary, sponsors should consider whether the number, duration, and intervals (spacing) of visits can be minimized or optimized to ease participant burden. Planners should also aim to maximize the use of local visits and laboratory assessments.

19. Retention mechanisms (e.g., reminders, visit cadence, flexibility, decentralized elements, and incentives) should be developed in collaboration with patient representatives. LTFU study sponsors should reimburse participants for out-of-pocket expenses and/or provide support with transportation, childcare, and eldercare. Reimbursement for time and burden should be considered.

Signal Detection / Safety Reporting

20. The design and analysis of LTFU studies should consider and/or anticipate the need for prompt identification of emerging or possible safety concerns.

21. In order to identify potential safety issues associated with GTs, researchers must promptly attend to and characterize adverse events as well as abnormalities in clinical tests, diagnostic tests, and laboratory results.

22. When safety events occur, findings need to be contextualized based on the aggregate results, disease context, expectations about potential intervention-related adverse events, and any specific details that emerge. Usually, the steps taken are determined on a case-by-case basis, but some advanced planning is helpful.

23. Sponsors should consider whether a specific mechanism, such as a Data Safety Monitoring Board (DSMB) or an Observational Study Monitoring Board (OSMB), should be employed to support the LTFU study's ability to promptly detect and assess safety signals. A DSMB or OSMB could potentially be established for a particular study or a class or category of GTs.

24. It is important to develop algorithms regarding study results and events—for when to retest, report to the FDA, or notify study participants, investigators, and the larger patient and medical communities. Safety signals, including patient-reported concerns, should have pre-specified triage procedures and escalation to safety oversight of the study.

Data Sharing / Dissemination of Results

25. LTFU participants should be provided with any actionable individual results obtained, including interim results. Actionable results have medical or personal decision-making utility (this may include more frequent screenings for cancer or other adverse events that may be identified during LTFU). Sponsors should prespecify which individual and aggregate results will be shared with participants, as well as how often and under what circumstances.

26. Detection of safety concerns in LTFU studies warrants timely communication to participants as well as the patient, scientific, medical, and regulatory communities. The design and analysis of LTFU studies should consider and/or anticipate a mechanism for prompt information sharing with regulators, site staff, LTFU study participants, and ethics committees.

27. Important changes to the risk and/or benefit profile of a GT may necessitate the timely provision of this information to LTFU study participants as well as patients beyond the LTFU study, e.g., updates to the informed consent documents/process for all studies with the same GT, or to the product label if the GT under study has been approved. Patients should be informed about changes to a GT's risk/benefit profile that might impact their decision-making.

28. Sponsors and researchers should make every effort to publicly and transparently share final, and interim as appropriate, aggregate results of LTFU studies.

29. Sponsors of LTFU studies should exceed regulatory and policy requirements for registration and results reporting required by ClinicalTrials.gov and other clinical trial databases. All LTFU studies should be registered, and results should be submitted in accordance with the expectations for interventional studies.

The Looking Forward section articulates unresolved questions about the optimization of LTFU that need further discussion, several of which are highlighted below as noteworthy examples:

1. What data are essential to derive the value of LTFU, helping to define long-term safety and efficacy of GTs, considering the burdens on patients, care partners, sponsors, investigators, and the direct and indirect consequences of the associated financial costs?

2. What incentives, if any, will drive efforts to harmonize LTFU data definitions and collection, optimize interoperability, and share data and results to maximize value?

3. What incentives, if any, will propel increased LTFU data transparency, information sharing and reporting of results?

4. Would a central repository/registry for LTFU data, enabling studies that include larger numbers of GT recipients, be useful? Who would manage such a repository?

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* Please note that this Executive Summary does not include reference citations; these can be found in the main Toolkit.

To cite this resource, please use the suggested citation for the main Toolkit:
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Thank you for your interest in the LTFU Toolkit. If you have any questions or suggestions, please reach out to the MRCT Center at mrct@bwh.harvard.edu using "LTFU Toolkit" in the subject line.
