MULTI-REGIONAL CLINICAL TRIALS

THE MRCT CENTER OF BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

Long-Term Follow-Up (LTFU) for Gene Therapies:

Toolkit Release Webinar

Carolyn Riley Chapman, PhD MS

Lead Investigator, Brigham and Women's Hospital

Member of the Faculty, Harvard Medical School

November 4, 2025

www.mrctcenter.org

The Multi-Regional Clinical Trials Center of BWH and Harvard

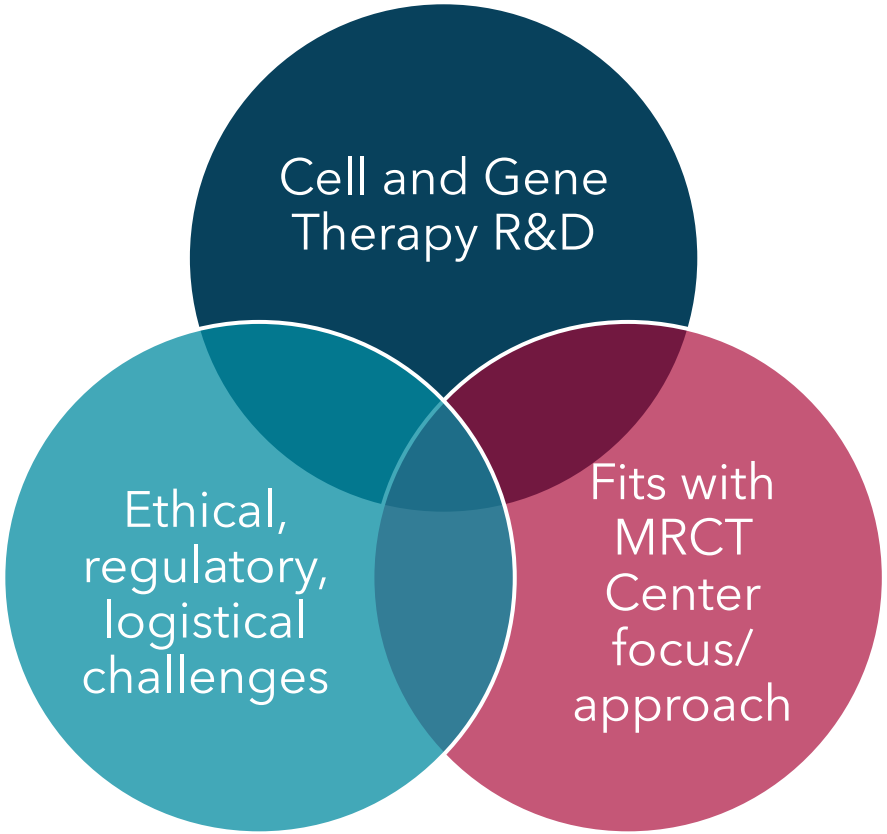
- The MRCT Center is an applied policy center focused on addressing the conduct, oversight, ethics and regulatory environment for clinical trials around the world.
- We engage diverse stakeholders to define emerging issues in global clinical trials and to create and implement ethical, actionable, and practical solutions.

Disclaimer

- The opinions contained are those of the authors and presenters and are not intended to represent the position of Brigham and Women's Hospital or Harvard University.
- The MRCT Center is supported by voluntary contributions from foundations, corporations, international organizations, academic institutions, and government entities (see www.MRCTCenter.org), as well as by grants.
- We are committed to autonomy in our work and to transparency in our relationships. The MRCT Center—and its directors—retain responsibility and final control of the content of any products, results, and deliverables.
- We have no personal conflicts of interest relevant to this discussion.
- We are recording this meeting and plan to make the recording publicly available on our website.

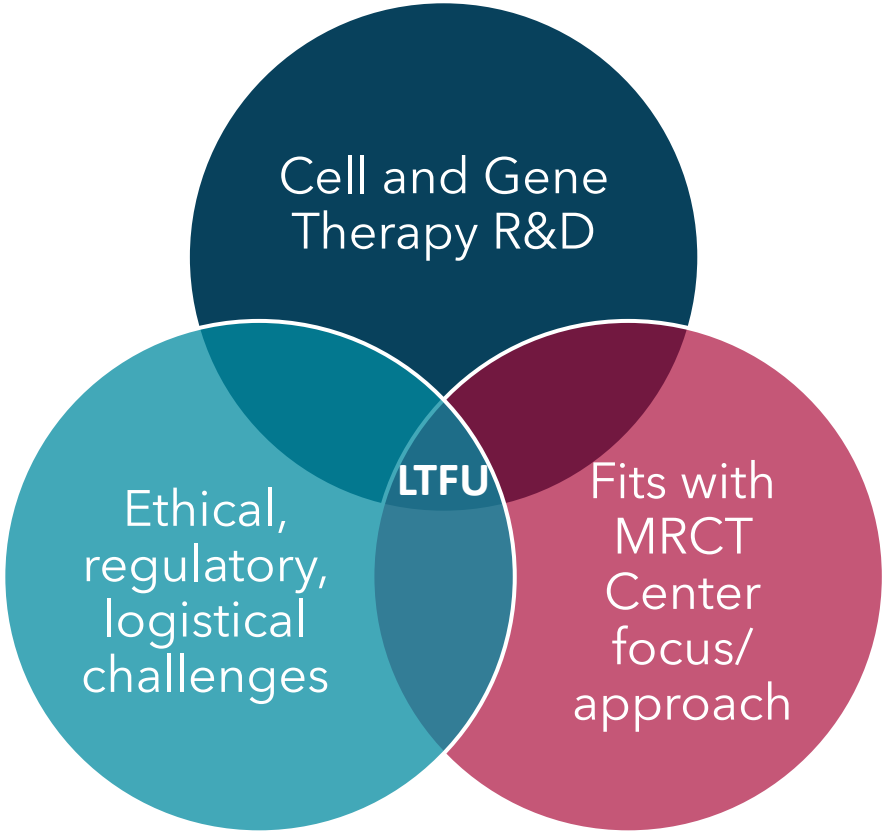
The Cell and Gene Therapies Project objectives are aligned with the MRCT Center's mission

- Identify and characterize ethical, regulatory, and logistical challenges arising in the context of global research and development of cell and gene therapies.
- Collaborate to co-develop actionable and practical mechanisms for addressing these challenges to support efficient, safe, and respectful clinical development of CGT products.



The Cell and Gene Therapies Project objectives are aligned with the MRCT Center's mission

- Identify and characterize ethical, regulatory, and logistical challenges arising in the context of global research and development of cell and gene therapies.
- Collaborate to co-develop actionable and practical mechanisms for addressing these challenges to support efficient, safe, and respectful clinical development of CGT products.



Initial focus for CGT project: Long-Term Follow-Up Studies for Gene Therapies

- Gene therapies (GTs) are a class of pharmaceutical products that modify a person's genes to treat disease.
- GTs are expected to yield permanent and beneficial health outcomes for patients with significant unmet medical needs, often with only one dose or administration, but they also have the potential for delayed detrimental side effects, such as the development of cancer, immunological reactions or infections.
- Given this possibility, there is a critical need to monitor the health of GT recipients over time.
- Regulatory agencies such as the FDA, the EMA, NMPA, and PMDA recommend LTFU studies of recipients of certain types of GTs.

LTFU studies are important and valuable to many stakeholders, for different reasons

Stakeholder Groups Table

Different stakeholder groups derive different value and benefit from LTFU studies.

STAKEHOLDER GROUP	Value of LTFU studies
LTFU participants	Enable prompt detection of health issues to direct appropriate and timely care. Ability to contribute to a better understanding of GT products to help future patients.
Patients who have disease targeted by GT	Provide information to guide decision-making about receipt of GT products.
Sponsors	Satisfy regulatory requirements. Provide up-to-date safety and effectiveness information about GTs in development or on the market. Generate information to guide future investment and development, including to broader patient populations.
Regulators	Help protect the public by ensuring the safety and effectiveness of GTs.
Medical community	Provide information to guide clinical care decision-making, including optimizing the frequency and type of health monitoring after receipt of specific GTs.
Society, public, broader patient communities	Increase knowledge about long-term benefit/risk profile of GT products, particularly on long-term safety.

However, LTFU studies are challenging and burdensome

The "unprecedented duration of engagement with patients and caregivers raises logistical challenges that will require innovation and collaboration across sponsors and regulators."

—Rhode et al, 2024

For Sponsors

- Significant length of time involved in following and monitoring participants
- Challenging and expensive to design, conduct, and operationalize

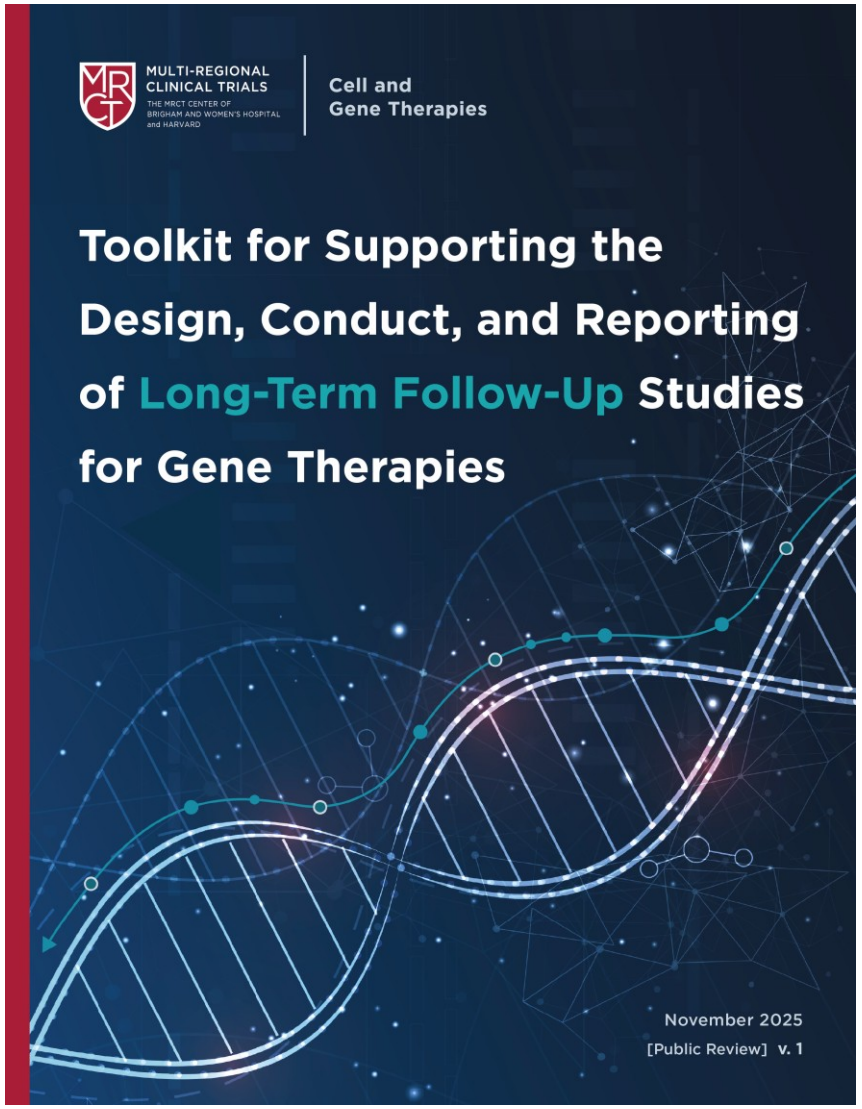
For Academic Investigators

- LTFU requires substantial resources; may need support.

For Patients

- LTFU participation can be burdensome in terms of time, expense, and opportunity costs.

LTFU Working Group launched September 2024→ Major milestone~ LTFU Toolkit Release November 4, 2025



Toolkit Release today!

https://mrctcenter.org/LTFUToolkit

Version 1, a Draft for public comment

Feedback: mrct@bwh.harvard.edu

LTFU Toolkit Table of Contents

- Introduction and Background
- Types of LTFU studies for GTs
- Flowcharts
- Guiding Principles
- Considerations and Recommendations for the Design, Conduct, and Reporting of LTFU Studies for GTs
- Looking Forward
- Key Design Elements of LTFU Studies for FDA-approved GTs
- Regulatory Guidance Relating to LTFU of GTs
- Compiled Glossary of Scientific LTFU-Related Terminology
- Easy-to-Understand (Accessible) LTFU-Related Definitions from the MRCT Center's Clinical Research Glossary
- Appendices
  - List of Acronyms and Abbreviations Used
  - References Cited

LTFU Toolkit Table of Contents

- Introduction and Background
- Types of LTFU studies for GTs
- Flowcharts
- Guiding Principles
- Considerations and Recommendations for the Design, Conduct, and Reporting of LTFU Studies for GTs
- Looking Forward
- Key Design Elements of LTFU Studies for FDA-approved GTs
- Regulatory Guidance Relating to LTFU of GTs
- Compiled Glossary of Scientific LTFU-Related Terminology
- Easy-to-Understand (Accessible) LTFU-Related Definitions from the MRCT Center's Clinical Research Glossary
- Appendices
  - List of Acronyms and Abbreviations Used
  - References Cited

LTFU Study Types Table

Different Types of LTFU Studies for GTs Table

CHARACTERISTIC, DESIGN, OR APPROACH	BRIEF EXPLANATION
Investigational or Approved GTs	Whether the LTFU protocol monitors recipients of investigational GTs (e.g., clinical trial participants) or recipients of GTs that have already received regulatory approval/market authorization (e.g., patients)
Integrated or Standalone Protocols	For post-clinical trial follow-up, whether the LTFU is incorporated into the main (or parent) trial or conducted according to a separate protocol
Observational/ Non-interventional or Interventional	Regulatory classification of studies/trials with implications for design, oversight, and reporting requirements
Registry Studies	LTFU studies that employ registries
Centralized or Decentralized	Whether the trial takes place at a centralized location such as an academic medical center or whether study activities are decentralized (e.g., monitoring is remote or at local sites).

MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER OF BRIGHAM AND WOMEN'S HOSP TAL and HARVARD

LTFU of Recipients of Investigational vs. Approved GTs

One factor that differentiates types of LTFU studies is whether they follow recipients of investigational GTs or approved GTs (or sometimes, both). As noted in the Introduction, LTFU studies involve extended assessments of GT research participants long past the active period of the main or parent clinical trial.[2] Patients who receive approved GTs may also participate in LTFU studies, as part of regulatory agency-required post-approval surveillance and pharmacovigilance, or as a best practice by the manufacturer. Note that post-approval, post-marketing and post-authorization have similar meanings and are considered interchangeable in this Toolkit.

It is important to consider that patients receiving approved GTs may have a more heterogeneous medical and clinical history than patients who participate in clinical trials of GT products, and it is therefore possible for outcomes to differ between post-trial and post-approval LTFU studies. Outcomes may differ for other reasons as well, including the quality of the GT product, the conditioning and care of the patient and any associated procedures they may receive, the prescriber, and the site where the patient receives their care.[8]

Although the purpose of post-approval and post-clinical trial LTFU is similar, another key difference is that clinical trial participants generally receive investigational GTs that are still under study and have not yet received full regulatory approval (at least, for that particular indication) and therefore are not a standard component of clinical care (at least not yet). Typically, the patients' physicians did not prescribe or administer, and may not be familiar with, the GT, unless they are also trial investigators. For LTFU of GT clinical trial participants, researchers may be able to

ToC
Introduction & Background
Types of LTFU
LTFU Flowcharts
Guiding Principles
Considerations & Recommendations
Looking Forward
Key Design Elements
Regulatory Guidance
Compiled Glossary
Accessible Definitions
Appendices

Integrated vs. Standalone LTFU Protocols

In the context of LTFU studies that follow recipients of investigational GTs, LTFU studies may be conducted as a component of the original, parent (interventional) GT clinical trial—this is termed an integrated protocol design. Alternatively, LTFU studies may be conducted as a separate protocol where eligibility is defined as patients who have received a GT either as part of a clinical trial or in a post-approval setting—this is considered a standalone protocol design. FDA guidance states that either design is acceptable.[2]

When considering whether to design a post-clinical trial LTFU study as an integrated or standalone protocol, it is important to consider the potential advantages and disadvantages of each approach (see the **Integrated and Standalone LTFU Table**, below, which is adapted from [45]).

A hybrid design may also be possible, meaning that an LTFU study can start as an integrated component of the parent trial, but be changed to a standalone protocol via amendment.[45] This may facilitate making updates to the LTFU plans as knowledge is gained through the parent trial.[45] However, as with a standalone LTFU protocol, there may be an administrative burden involved with writing a new protocol and submitting it to the Institutional Review Board (IRB)/Ethics Committee (EC) and regulatory agencies, as required.[45] Also, participants would need to rollover to a new study with a new consent process, and this may increase the risk of attrition of participants who do not elect to join the new LTFU study. We are not aware of any specific examples where an LTFU study was converted from an integrated to a standalone protocol.

MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER OF BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

ToC
Introduction & Background
Types of LTFU
LTFU Flowcharts
Guiding Principles
Considerations & Recommendations
Looking Forward
Key Design Elements
Regulatory Guidance
Compiled Glossary
Accessible Definitions
Appendices

LTFU Registry Studies

There can be confusion between the related terms, "registry" and "registry study." The EMA acknowledges that "regulators have sometimes requested marketing authorization holders (MAHs) to establish a registry, although the objective was to perform a post-authorisation safety study (PASS) to monitor the safety of a product. Some existing guidance seems also to use the terms 'registry' and 'study' interchangeably."[52] In short, and as used here, a registry is a data collection system, while registry studies employ the use of registries to investigate a hypothesis or research question.[52] Registry studies are sometimes referred to as registry-based studies.

REGISTRIES

According to the EMA, a patient registry is an "organized system that collects uniform data (clinical and other) to identify specified outcomes for a population defined by a particular disease, condition or exposure."[52] The FDA and ClinicalTrials.gov provide similar definitions, which are provided in the Compiled Glossary.

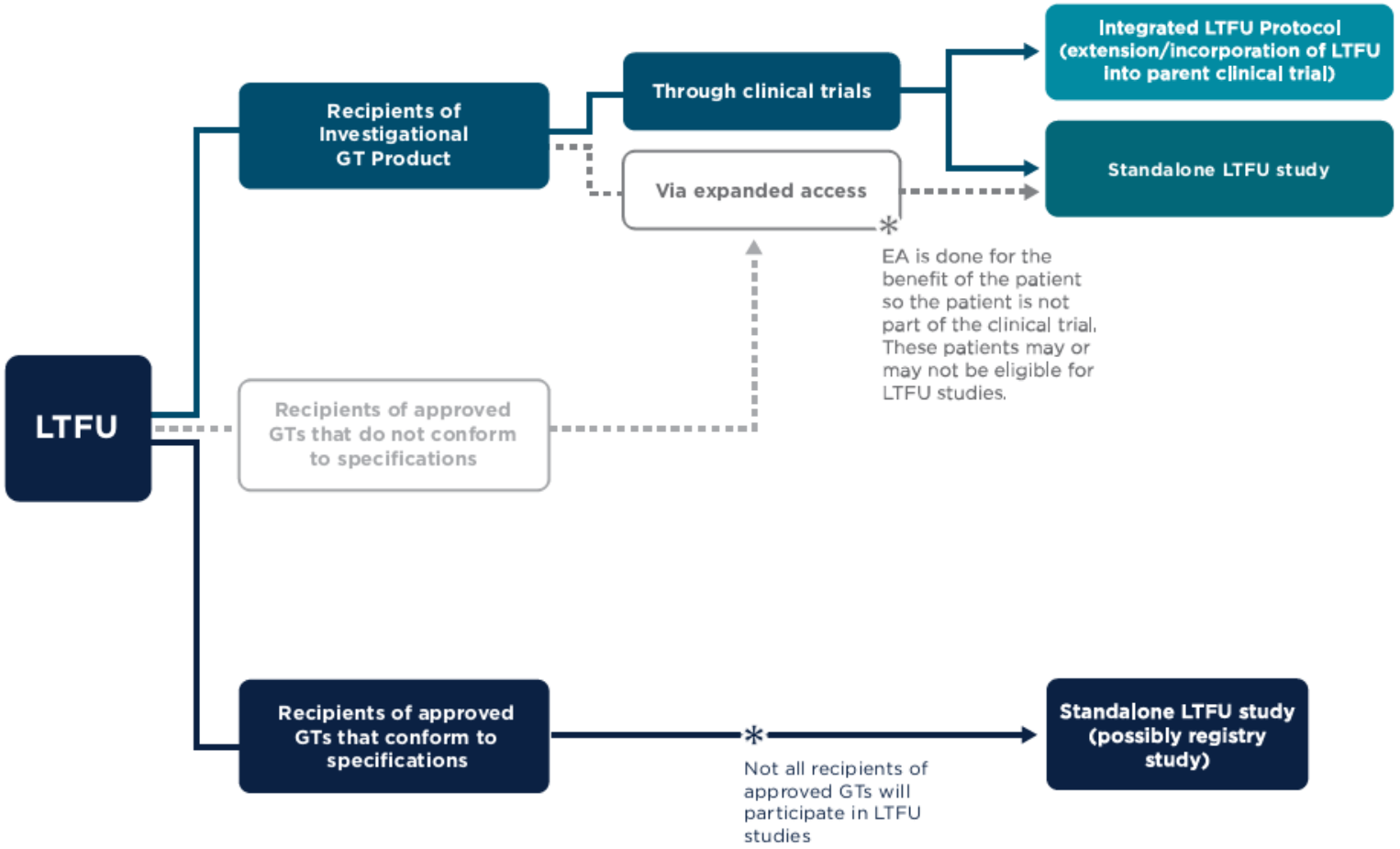
Registries can include patient-level clinical and laboratory data and can also be repositories for genetic data, histopathology specimens, imaging data, and patient-generated data (e.g., ePROs).[18] Registries offer advantages over other RWD sources because they allow the longitudinal collection of predefined data in a specific population.[18] Registries are valuable for detecting rare events and for LTFU, since they track people for much longer periods of time than most clinical trials; they also generally have lower operational costs and are less burdensome for registry participants.[56] In the context of LTFU, the relevant inclusion criteria for a registry could be treatment with a specific GT or set of GTs.

LTFU Toolkit Table of Contents

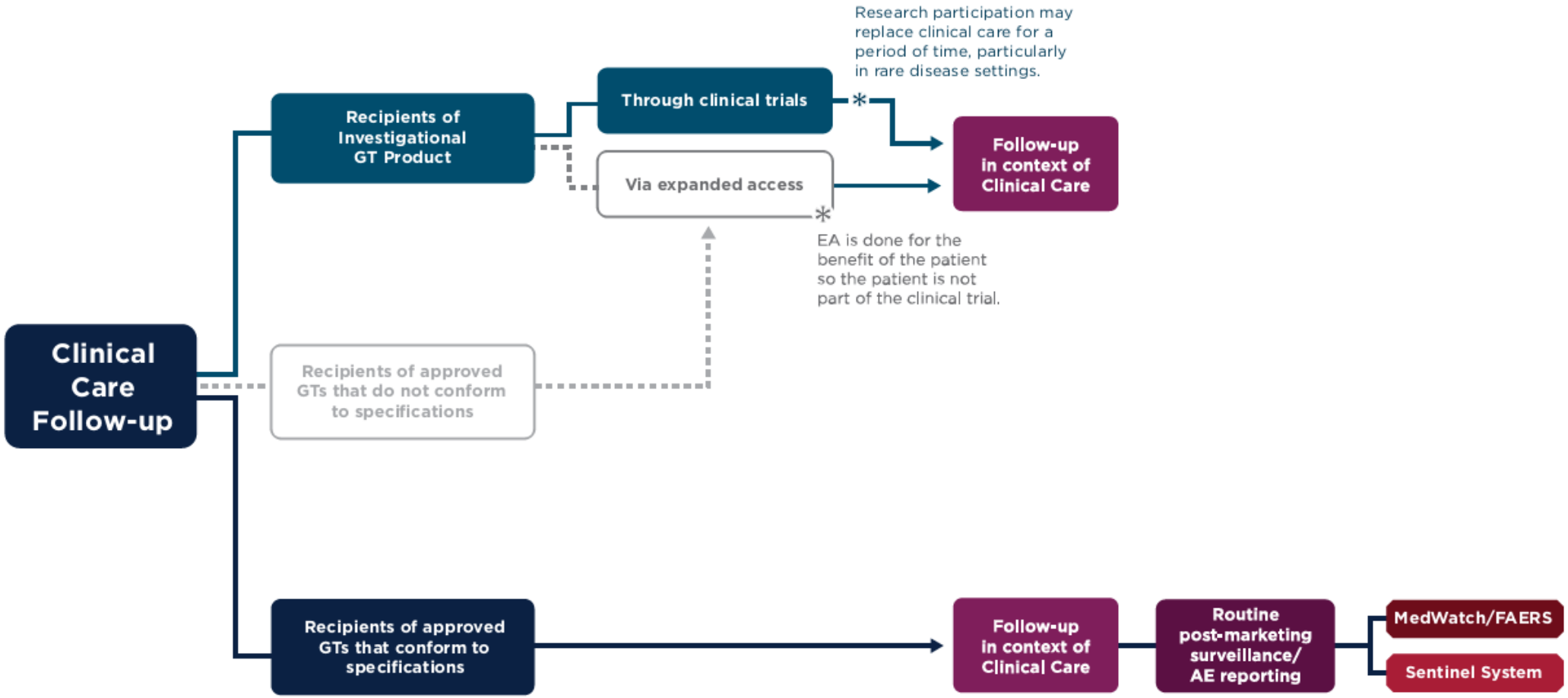
- Introduction and Background
- Types of LTFU studies for GTs
- Flowcharts
- Guiding Principles
- Considerations and Recommendations for the Design, Conduct, and Reporting of LTFU Studies for GTs
- Looking Forward
- Key Design Elements of LTFU Studies for FDA-approved GTs
- Regulatory Guidance Relating to LTFU of GTs
- Compiled Glossary of Scientific LTFU-Related Terminology
- Easy-to-Understand (Accessible) LTFU-Related Definitions from the MRCT Center's Clinical Research Glossary
- Appendices
  - List of Acronyms and Abbreviations Used
  - References Cited

Flowchart for LTFU
In the Context of Research

*Note that participation in LTFU is voluntary, and participants can also withdraw



Flowchart for Follow-Up In the Context of Clinical Care



LTFU Toolkit Table of Contents

- Introduction and Background
- Types of LTFU studies for GTs
- Flowcharts
- Guiding Principles
- Considerations and Recommendations for the Design, Conduct, and Reporting of LTFU Studies for GTs
- Looking Forward
- Key Design Elements of LTFU Studies for FDA-approved GTs
- Regulatory Guidance Relating to LTFU of GTs
- Compiled Glossary of Scientific LTFU-Related Terminology
- Easy-to-Understand (Accessible) LTFU-Related Definitions from the MRCT Center's Clinical Research Glossary
- Appendices
  - List of Acronyms and Abbreviations Used
  - References Cited

Guiding Principles for LTFU Studies for GTs

MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER OF BRIGHAM AND WOMEN'S HOSP TAL and HARVARD

Guiding Principles for LTFU Studies for GTs[1]

These guiding principles were developed to provide a high-level framework for the ethical design, conduct, and reporting of LTFU studies for GTs.

1. Although many gene therapies (GTs), including genetically modified cell therapies, have the potential for durable effectiveness, delayed detrimental health effects are possible. Therefore, LTFU studies are important for evaluating the overall benefit and risk profile for many GTs.
2. LTFU results support informed decision-making by various stakeholders, including participants, patients, care partners, potential and current research participants, physicians, researchers, sponsors, regulators, oversight committees, policymakers, funders, and insurers.
3. Information about long-term safety issues must be coupled with an understanding of long-term benefits to guide clinical decision-making about GTs.
4. LTFU studies are a collaborative effort requiring coordination between different individuals and entities. Depending on the LTFU study, regulators, academic medical centers, study sites, registries, clinical research organizations, patient groups, and sponsors may be involved.
5. 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.
6. 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.

[1] The Emanuel et al. clinical research ethics framework was helpful for drafting these principles.[66, 67]

MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER OF BRIGHAM AND WOMEN'S HOSP TAL and HARVARD

7. There are tradeoffs between expanding the scope of LTFU studies and minimizing study burdens on participants, sponsors, and others. 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.
8. Study sponsors, investigators, regulators, and others should consider, plan, and make provisions for LTFU studies early in the product development program when designing and conducting human clinical trials for GTs.
9. 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.
10. Enrollment and recruitment methods, including inclusion and exclusion criteria, for LTFU studies should be scientifically justified and designed to minimize selection bias.
11. GT clinical trial participants should be informed about LTFU commitments, including the purpose of LTFU and associated procedures, before they receive GTs.
12. Patients who receive approved GTs should be offered the opportunity to participate in LTFU, if appropriate, after they receive the GT.
13. Informed consent for LTFU study participation includes providing education about what is involved, opportunities for prospective participants to ask questions, and giving prospective participants time to absorb and understand the information.
14. Study teams should inform prospective 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. 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.

ToC | Introduction & Background | Types of LTFU | LTFU Flowcharts | Guiding Principles | Considerations & Recommendations | Looking Forward | Key Design Elements | Regulatory Guidance | Compiled Glossary | Accessible Definitions | Appendices

MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER OF BRIGHAM AND WOMEN'S HOSP TAL and HARVARD

15. Pediatric patients who are eligible for LTFU studies should be offered the opportunity to assent if not deemed locally inappropriate and 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.
16. Study teams should focus on education, reducing burdens, and creating positive participant journeys to encourage engagement and retention in LTFU.
17. The design and analysis of LTFU studies should consider and/or anticipate:
    a. the likelihood of complicated patient and participant journeys, including potential confounding issues, such as patients receiving different approved treatments and/or investigational products before or after receipt of the GT.
    b. the potential need to make changes to the LTFU protocol, as data collection procedures and participant journeys are likely to evolve over time.
    c. the potential inclusion and biobanking of participant samples, with appropriate consent for future use, to enable research on genotoxicity and other factors that will support the evaluation of LT safety.
    d. the need for prompt identification of emerging or possible safety concerns (e.g., incorporation of regular interim analysis by sponsor and/or a Data Safety Monitoring Board).
    e. a mechanism for prompt information sharing with regulators, site staff, LTFU study participants, and ethics committees.
    f. the potential need for Informed Consent documents to be updated during the study.
18. Sponsors and researchers should make every effort to publicly and transparently share final, and interim as appropriate, aggregate results.
19. 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).

ToC | Introduction & Background | Types of LTFU | LTFU Flowcharts | Guiding Principles | Considerations & Recommendations | Looking Forward | Key Design Elements | Regulatory Guidance | Compiled Glossary | Accessible Definitions | Appendices

LTFU Toolkit Table of Contents

- Introduction and Background
- Types of LTFU studies for GTs
- Flowcharts
- Guiding Principles
- Considerations and Recommendations for the Design, Conduct, and Reporting of LTFU Studies for GTs
- Looking Forward
- Key Design Elements of LTFU Studies for FDA-approved GTs
- Regulatory Guidance Relating to LTFU of GTs
- Compiled Glossary of Scientific LTFU-Related Terminology
- Easy-to-Understand (Accessible) LTFU-Related Definitions from the MRCT Center's Clinical Research Glossary
- Appendices
  - List of Acronyms and Abbreviations Used
  - References Cited

As a set, the subsections of this resource provide comprehensive recommendations intended to support best practices for the design, conduct, and reporting of LTFU studies for GTs. That said, these considerations and recommendations are not meant to be exhaustive nor prescriptive. An overarching recommendation is to seek consultation with the applicable regulatory authority or authorities on the appropriate design of LTFU for any particular GT.

The subsections are as follows:

II. Objectives and Endpoints

Although LTFU studies for GTs are generally not intended to be as comprehensive as the parent clinical trials, there is a desire to satisfy multi-stakeholder expectations for data collection. However, it is important to avoid overburdening participants, families, researchers, healthcare providers, and sponsors with excess data collection. At a minimum, LTFU protocols must fulfill regulatory expectations, including for post-authorization marketing commitments.

Regarding primary, secondary, and exploratory objectives of a LTFU study and corresponding endpoints, it can be challenging to determine what endpoints and outcomes to monitor, which data to collect (and how often), and for how long. Finding the right balance is important, not only to minimize the burden but also to limit participant attrition and support data collection, protocol compliance, and study completion. For this reason, our working group referred to this challenge—determining how much, how often,and which data endpoints to collect—as the "Goldilocks" issue. In other words, what is "just right" with respect to data collection?

CONSIDERATIONS AND RECOMMENDATIONS

C1 **The involvement of patients and care partners is critical for the ethical design and conduct of LTFU studies.** Their perspectives on which LTFU data should be collected, and how, may differ from those of sponsors or regulators. Patient and care partner perspectives are important throughout the course of the LTFU study, from design through reporting of results.

R1.1: Patients and/or patient advocacy organizations should be involved in the design of LTFU studies to ensure inclusion of primary and secondary endpoints that are most meaningful and relevant to patients, their families, and care partners.[61]

R1.2: Although FDA guidance notes that objective data/endpoints are better for regulatory purposes, as subjective data measurements can be challenging to standardize,[43] LTFU protocol designers should consider whether PRO should be included as endpoints, recognizing their value as well as their limitations.[68]

CONSIDERATIONS AND RECOMMENDATIONS

C1 **According to the FDA, all GT clinical trial participants are expected to roll into LTFU, and consent for follow-up should be incorporated into the parent trial.**[2] **FDA guidance on clinical trials involving a human gene editing product takes the same stance.**[7]

R1.1: When patients and/or their surrogates consider and consent to an interventional GT clinical trial, they should be informed about LTFU components, if applicable.

R1.2: The right of research participants to withdraw must be respected; therefore, GT trial participants should understand that enrollment in LTFU is important and an expectation, although not a requirement, and that they can withdraw from the study at any time.

R1.3: Study teams also need to educate patients that withdrawing from LTFU is not from the GT intervention itself, but only from the safety follow-up.

R1.4: Depending on the disease context, researchers should consider the need for assessing participant capacity at regular intervals. If appropriate, plans to allow smooth transfer of decision-making to a legally authorized representative (LAR) should be considered, in case a participant loses the capacity to make decisions for themselves.[42]

C2 **To fully understand the long-term benefit/risk profile of GT products through LTFU studies, patients must be offered the opportunity and be willing to participate and/or provide their data.** Exclusion of patients from eligibility for either post-trial or post-approval LTFU studies may introduce bias, preclude the collection of valuable data, and deny patients their opportunities for ongoing surveillance and the ability to contribute to furthering the science of GTs. Important associations or findings may be missed.

R2.1: Given that the purpose of LTFU is to understand the safety of GTs and to identify and mitigate risks for patients/participants, all GT clinical trial participants should be offered participation.

CONSIDERATIONS AND RECOMMENDATIONS

C1 **LTFU participant retention, which is important to ensure accurate study results, will have different challenges for different GTs.** Rates of participant retention may depend on treatment outcomes and the patients' needs for ongoing care.[61] If patients who experience significant benefit from the GT are particularly prone to withdraw from follow-up, this has the potential to negatively bias the results.[61]

R1.1: As noted previously, it is ideal to involve patients and patient advocacy groups in LTFU design, specifically asking for their input on feasibility and mechanisms for retention.[68]

R1.2: Researchers should consider the inclusion of patient-centered objectives in the study, which can enhance the overall study experience and promote engagement and retention.

- If participants feel that the LTFU study tracks outcomes that are important to them, they may be more interested and engaged with the study. On the other hand, if they feel that the study asks for irrelevant or unimportant information, the participants may feel less committed and lose interest.

R1.3: It is important to solicit the help of patient organizations to convey the importance of LTFU completion.[68]

C2 **The scope of the LTFU study, including the intensity of the follow-up procedures will impact participant retention.**[61]

R2.1: As noted above, 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 (e.g., regulators, sponsors, the patient community, and payers) should be that which is collected (expanded from recommendation in [68])

CONSIDERATIONS AND RECOMMENDATIONS

C1

Given the length of LTFU, knowledge and understanding of risks and benefits of the GT will grow over time, and technology, regulations, expectations, and participants' lives will change as the study progresses. With studies that span years, it is necessary to anticipate changes in investigators, staff, and HCPs.[61] In the context of post-approval LTFU (or any LTFU studies that rely on assessments done in the context of clinical care), the standard of care at the local and/or global level may evolve over time; some data elements may no longer need to be collected, while others may need to be added.[61] Also, for studies that use data from clinical practice, such as post-approval LTFU protocols, changes in the principal investigator can be frequent and are complex to navigate.[61]

R1.1: In order 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. This can also support retention and minimize protocol deviations. Protocols may incorporate flexible visit schedules or allow remote or in-person visits with local providers.[78] Another possibility is building in alternative or decreased, lower burden data collection for patients who are too sick to travel to appointments.[45]

R1.2: Given expected changes in personnel with long study timeframes, training and onboarding for new affiliates of the study should be anticipated and planned.

R1.3: Sponsors should plan and integrate ways to support and engage sites and investigators for studies that last several years, in order to maintain the commitment to LTFU.[61]

R1.4: Also, there is a need to support the coordination between sites and staff if the patient journey involves the transition of care from one site to another.[61]

R1.5: Sponsors should plan in advance how protocol changes will be communicated to all affected stakeholders, including participants.[68]

VII. Data Sharing and Dissemination of Results

Whether and how study data will be shared and how study results will be disseminated to both individual participants and the broader patient and medical community must be planned, and the responsibilities (e.g., sponsor, investigator, registry/database) for these activities should be clear. Sharing of LTFU data and study results is an ethical imperative from a reciprocity standpoint, in terms of honoring participant contributions, but also because aggregate findings may have relevance to the ongoing clinical care of GT recipients. Also, the scientific value of LTFU can only be maximized if LTFU data are shared to enable analysis of aggregated data and/or comparisons across studies, with advanced statistical analyses.

As LTFU data accumulates, patterns may emerge to allow researchers to generate new hypotheses and design targeted data collection efforts or identify cohorts for prospective research. There are open questions about whether and how more collective approaches might maximize the benefits of LTFU studies.[5] For example, collaborative sharing and public dissemination of LTFU data and results could maximize and hasten knowledge generation, promote standardization and best practices, minimize duplication of effort, and reduce siloed information that would be more valuable if combined.[90] In this way, collaborative approaches may also reduce burdens on sponsors, patients, and the healthcare system at large.[91] Coordinated efforts can be inherently challenging in the industry, but the importance of LTFU data for patients obligates us to find a pre-competitive, patient-centric pathway forward.

CONSIDERATIONS AND RECOMMENDATIONS

C1

Data sharing across studies, for a particular GT product and for GTs in the same or different classes, is important for the accurate and timely detection of safety signals.

R1.1: It would be worthwhile to develop a central repository/registry for LTFU data that could enable prospective and/or retrospective safety studies that include larger numbers of GT recipients, which may increase power for signal detection.

LTFU Toolkit Table of Contents

- Introduction and Background
- Types of LTFU studies for GTs
- Flowcharts
- Guiding Principles
- Considerations and Recommendations for the Design, Conduct, and Reporting of LTFU Studies for GTs
- Looking Forward
- Key Design Elements of LTFU Studies for FDA-approved GTs
- Regulatory Guidance Relating to LTFU of GTs
- Compiled Glossary of Scientific LTFU-Related Terminology
- Easy-to-Understand (Accessible) LTFU-Related Definitions from the MRCT Center's Clinical Research Glossary
- Appendices
  - List of Acronyms and Abbreviations Used
  - References Cited

Looking Forward… questions needing further consideration and deliberation

MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER OF BRIGHAM AND WOMEN'S HOSP TAL and HARVARD

Looking Forward

In this section, we offer questions about the scope of LTFU, data harmonization, and data sharing that the Working Group thought needed future consideration and deliberation. This list is not exhaustive. We welcome suggestions from and engagement with interested parties.

- 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?
- What data and/or outcomes are necessary to warrant consideration of shortening the length of LTFU studies for specific GTs or classes of GTs?
- As the length of time between a GT intervention and an adverse event increases, relatedness and causality become more difficult to assess. Can data collection be streamlined over time?
- In the absence of safety signals or concerns, should LTFU studies convert to observational LTFU, including only data that are collected, measured, and reported in the context of patient follow-up in clinical care?
- What incentives, if any, will drive efforts to harmonize LTFU data definitions and collection, optimize interoperability, and share data and results to maximize value?
- What incentives, if any, will propel increased LTFU data transparency, information sharing, and reporting of results?
- Would a central repository/registry for LTFU data, enabling studies that include larger numbers of GT recipients, be useful? Increased enrollment may increase the power for signal detection. Who should manage such a repository?
- Although both the FDA and EMA state that one of the main purposes of

MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER OF BRIGHAM AND WOMEN'S HOSP TAL and HARVARD

ToC
Introduction & Background
Types of LTFU
LTFU Flowcharts
Guiding Principles
Considerations & Recommendations
Looking Forward
Key Design Elements
Regulatory Guidance
Compiled Glossary
Accessible Definitions
Appendices

LTFU is to identify and mitigate health risks to participants, should careful health monitoring of GT recipients years post-GT receipt be considered the responsibility of sponsors of LTFU studies? When should this responsibility be shared or appropriately transferred to the context of clinical care? Do responsibilities need to be recalibrated and/or clarified?

- The long-term safety of many novel medical interventions is unknown, yet specific requirements for LTFU studies are rare; routine pharmacovigilance is considered adequate for identification of long-term adverse events. Given that we have accumulated more experience with GTs over the past decade, should long-term pharmacovigilance for GT products remain significantly different than other types of pharmaceutical products and medical interventions? Why or why not? What information or data would be sufficient to move LTFU of GTs to routine pharmacovigilance approaches?

Key questions from Looking Forward

Data harmonization

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

Central repository

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

Transparency

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

LTFU Toolkit Table of Contents

- Introduction and Background
- Types of LTFU studies for GTs
- Flowcharts
- Guiding Principles
- Considerations and Recommendations for the Design, Conduct, and Reporting of LTFU Studies for GTs
- Looking Forward
- Key Design Elements of LTFU Studies for FDA-approved GTs
- Regulatory Guidance Relating to LTFU of GTs
- Compiled Glossary of Scientific LTFU-Related Terminology
- Easy-to-Understand (Accessible) LTFU-Related Definitions from the MRCT Center's Clinical Research Glossary
- Appendices
  - List of Acronyms and Abbreviations Used
  - References Cited

Key LTFU Design Elements for 25 FDA-approved GTs

MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER OF BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

Table of LTFU Studies for FDA-Approved GTs

*Int=Integrated, SA=Standalone | Inv=Investigational, App=Approved | Inter=Interventional, Non-Int=Non-Interventional, Obs=Observational | RS=Registry Study (left blank if not a registry study)

Brand Name	Generic Name	Sponsor	In or ex vivo Delivery/ Description	LTFU Study Number	Title	Duration	*Int/SA | Inv/App | Inter/Non-In/Obs | RS	Population
Abecma	**Idecabtagene Vicleucel**	Bristol-Myers Squibb	Ex vivo/CAR-T (lentiviral vector)	NCT06698887	A Study to Evaluate the Long-Term Safety of Idecabtagene Vicleucel Treatment in Adults with Newly Diagnosed Multiple Myeloma in Korea	15 years	SA | Inv | Obs	Adult participants (18+) with newly diagnosed multiple myeloma (NDMM) who had a suboptimal response after autologous stem cell transplantation (ASCT) and who were treated with idecabtagene vicleucel in the KarMMa-9 (CA089-1043) Phase 3 clinical trial.
		Celgene	Ex vivo/CAR-T (lentiviral vector)	NCT03435796	Long-Term Follow-up Protocol for Participants Treated with Gene-Modified T Cells	15 years	SA | Inv | Inter	All pediatric and adult participants exposed to Gene-modified (GM) T-cell therapy participating in a previous Celgene sponsored or Celgene alliance partner sponsored study. Participants who received at least one infusion of GM T cells will be asked to enroll in this LTFU protocol upon either premature discontinuation from, or completion of the prior parent treatment protocol.
Adstiladrin	**Nadofaragene firadenovec**	Ferring Pharmaceuticals A/W	In vivo/ Non-replicating adenoviral-based; intravesical administration	NCT02773849	ADSTILADRIN (=INSTILADRIN) in Patients With High-Grade, Bacillus Calmette-Guerin (BCG) Unresponsive Non-Muscle Invasive Bladder Cancer (NMIBC)	Up to 60 months	Int | Inv | Inter	Patients With High-Grade, BCG Unresponsive Non-Muscle Invasive Bladder Cancer (NMIBC)

Thank you!!!

Long-Term Follow-Up Working Group Members

- Barbara E. Bierer, MD
- Emina Berbić, MPH
- Laurie Adami
- Barbara Isquith Arone, MS
- Alison Bateman-House, PhD, MPH, MA
- Patrick Cullinan, PhD,
- Colleen H. Dansereau, MSN, RN, CPN
- Elizabeth Donahue, BSc
- George Eastwood
- Abhi Gupta, MBA
- Melissa (Missy) Heidelberg, BS, MSBE
- Amritha Jaishankar, PhD
- Daniel Kavanagh, PhD, RAC
- Barbara A. Konkle, MD
- Erin Lee, RN, MSN
- Amy Moskop, MD, MS
- Denise E. Sabatino, PhD
- Tesha F. Samuels
- Jessica Scott, MD, JD
- Aimee C. Talleur, MD
- Pamela Tenaerts, MD, MBA
- Susan B. Watson, PhD
- Chris White
- Durhane Wong-Rieger, PhD

Others

- Mena Shaikh, MPH
- Lindsey T. Henriques, MFA
- Sarah White, MPH
- Tonia M. Sabo, MD, MBA
- MRCT Center's Cell and Gene Therapies project Strategic Advisory Committee members

TOOLKIT

https://mrctcenter.org/LTFUToolkit

Our panelists today

Barbara Isquith Arone, MS
IQVIA

Patrick (Paddy) Cullinan, PhD
Adverum Biotechnologies

Durhane Wong-Rieger, PhD
Canadian Organization for Rare Disorders