



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

Cell and  
Gene Therapies

# Toolkit for Supporting the Design, Conduct, and Reporting of **Long-Term Follow-Up** Studies for Gene Therapies

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[For Public Comment] v. 1

## Contributors

We greatly appreciate everyone who has supported and contributed to this project in various ways and from its earliest stages, including members of the MRCT Center's Cell and Gene Therapies project Strategic Advisory Committee.

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## Note

This Toolkit is being released as version 1, a draft for public comment.

## Description of Resources in this Toolkit

Building upon regulatory authorities' long-term follow-up (LTFU) guidance, this Toolkit is applicable to all gene therapies for which LTFU is recommended, including genetically modified cell therapies. The resources apply to LTFU studies of patients who received investigational gene therapies (GTs) as research participants or via expanded access, and to LTFU studies of patients who have received approved GTs.

We start out with an [Introduction and Background](#) providing information about gene therapies and the need for and challenges associated with LTFU. The next section describes different [Types of LTFU studies for GTs](#). We also include [Flowcharts](#) which provide visual representations of different approaches and paths to LTFU in the context of research (the main focus of this guidance) but also to follow-up that occurs in the context of clinical care, data from which can contribute to the assessment of long-term safety and effectiveness of GTs.

The heart of this Toolkit is made up of three sections. First, we present a set of [Guiding Principles for LTFU studies for GTs](#) as a high-level framework for the ethical design of LTFU studies. More detailed recommendations for best practice are provided in the [Considerations and Recommendations for the Design, Conduct, and Reporting of LTFU Studies for GTs](#) resource. In the [Looking Forward](#) section, we ask bigger—perhaps bolder—questions about LTFU commitments that need further consideration and deliberation.

The Toolkit also includes additional tools that provide important references and relevant information. The [Key Design Elements for LTFU Studies for FDA-approved GTs](#) resource presents publicly available facts about how GTs that have received marketing authorization have satisfied LTFU requirements—in one easy-to-find place. A list of [Regulatory Guidance Related to LTFU of GTs](#) is also provided. We also include a [Compiled Glossary of Scientific LTFU-Related Terminology](#) from a variety of respected scientific/regulatory/medical sources, and a second vocabulary resource, [Easy-to-understand LTFU-related definitions from the MRCT Center's Clinical Research Glossary](#).

There are also two appendices, [Acronyms and Abbreviations Used](#) and [References Cited](#).

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# Introduction and Background

## GENE THERAPIES

Gene therapies (GTs) are a class of pharmaceutical products that modify a person’s genes to treat disease.[1] As defined by the U.S. Food and Drug Administration (FDA), GTs, which include gene transfer vectors, genetically modified cell therapies (e.g., CAR T-cells), and genome editing products, “mediate their effects by transcription or translation of transferred genetic material or by specifically altering host (human) genetic sequences.”[2] GTs may replace a gene, inactivate a gene, or introduce a new or modified gene (DNA).[1, 3] GTs vary in terms of mechanism of action, delivery mechanism, and route of administration; most are intended to make permanent or long-lasting changes to human cells.

According to a report from the American Society of Gene and Cell Therapy (ASGCT) and Cyteline, as of June 2025, 36 GTs have received marketing authorization for clinical use globally, many of which target serious and/or life-threatening diseases and/or disorders that previously lacked effective treatments.[4] GTs are approved to treat cancer (e.g., melanoma, leukemia, lymphoma, and multiple myeloma), hematological disorders (e.g., hemophilia, thalassemia, and sickle cell disease), and genetic diseases (e.g., spinal muscular atrophy, early cerebral adrenoleukodystrophy, Duchenne muscular dystrophy, and recessive dystrophic epidermolysis bullosa). Hundreds more are in various stages of clinical development, from preclinical to registration, with oncology, rare diseases, and neurology the top therapeutic areas.[4]

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, harmful immunological (e.g., autoimmune-like) reactions, liver toxicities, or infections.[2, 5] Given this possibility, there is a critical need to monitor the health of GT recipients over time.[2]

## LONG-TERM FOLLOW-UP STUDIES FOR GENE THERAPIES

To understand the overall benefit-risk profile of GTs, regulatory agencies such as the FDA, the European Medicines Agency (EMA), China's National Medical Products Administration (NMPA), and the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan recommend long-term follow-up (LTFU) studies of recipients of certain types of GTs.[2, 6–15] See [Regulatory Guidance Relating to LTFU](#).

LTFU studies are recommended for GTs that have characteristics associated with long-term health risks, such as those with the potential for causing changes to the human genome (e.g, GTs with integrating vectors or gene editing products), including genetically-modified cell therapies such as CAR T-cell therapies, or those with the potential for latency and reactivation (e.g., those that use herpes simplex viral vectors, such as Imlygic).[2, 16, 17] This Toolkit is applicable for all gene therapies for which LTFU is recommended, including genetically modified cell therapies. Notably, most cell therapies do not involve genetic modification and, therefore, LTFU is only applicable to a subset of cell therapies.

The FDA states that LTFU studies involve extended assessments of recipients of investigational GTs, primarily for safety monitoring, past the active follow-up period of a parent clinical trial.[2] After product approval, patients who receive approved GTs may also participate in LTFU studies, as part of post-approval surveillance and pharmacovigilance required by regulatory agencies. Different types of LTFU studies, including follow-up of recipients after receiving investigational and approved GTs, are discussed further in the resource [Types of LTFU Studies for GTs](#).

Postapproval LTFU studies may be required, in part because the number of GT trial participants may be relatively small.[2, 18] Small patient populations limit the ability to detect and discern delayed health effects that are product-related, particularly rare ones, in the post-trial LTFU patient population. The FDA notes that postapproval efficacy considerations for cell and gene therapy products include treatment durability and safety considerations, including monitoring for long-term and unknown effects and mortality.[18] The EMA also has guidelines on post-authorization risk management, including follow-up studies on efficacy and safety, which can employ passive or active surveillance, observational studies, or clinical trials.[8]

## Gap in Knowledge about Long-term Safety of GTs

There are known cases of delayed adverse events believed to be causally related to GTs, substantiating the need for LTFU. Yet there is a gap in knowledge about the long-term safety of GTs for several reasons.[19, 20] First, GTs are still a relatively new therapeutic class, with the first U.S. approval in 2017.

Second, the approval of some GTs may be based on more limited evidence than for other types of pharmaceutical products. GTs are a relatively new class of therapeutics, generally target rare diseases with small overall patient populations, and may qualify for expedited regulatory pathways [19] in that they treat diseases with significant unmet medical need. Consequently, the aggregate number of treated patients is small.[21]

Third, adverse reactions may not develop until years after GT administration.[22] For example, hematological malignancy has been diagnosed from 14 months to 10 years after the administration of elivaldogene autotemcel (Skysona®), a hematopoietic stem cell (HSC)-based GT.[22] The association became apparent not only because of the high frequency of recipients developing hematological malignancies (15% of clinical trial participants),[22] but also because the predominant clones contained vector insertions in cancer-related genes.[23]

In addition, LTFU studies are often conducted on a product-specific basis. Although there are some registries that capture LTFU data for multiple GTs, such as the Center for International Blood & Marrow Transplant Research (CIBMTR) and the World Federation of Hemophilia (WFH) Gene Therapy registry, most LTFU studies focus on a specific GT or GTs from a specific organization's development pipeline. Information sharing across studies is not optimal; as rare delayed adverse reactions may not be identified in small LTFU studies, their association with a particular GT may remain unrecognized.[24–27] Since the early days of GT research and development, there have been repeated calls for collaboration and data sharing to better understand long-term effects.[24, 28–30]

## Value of LTFU Studies

Different stakeholder groups derive different value and benefit from LTFU studies (see **Stakeholder Groups Table**). For participants, the benefits of participating in LTFU include prompt detection and notification of adverse events or health issues to direct appropriate and timely care, as well as the knowledge that they are contributing to a better understanding of GT products to help future patients.

Benefits of LTFU studies to society—and to other patients—include the generation of information about the long-term benefit/risk profile of GT products, particularly on long-term safety. Patients, care partners, and their physicians want LTFU information to help their decision-making about research and treatment options. Companies need LTFU information to satisfy regulatory requirements and to guide future investment and development, including potential expansion to broader patient populations. Regulators want to understand the overall long-term safety and efficacy of GTs to fulfill their obligations and protect the public. Payers, insurers, and health technology assessors want LTFU data to be able to value GTs, set formularies, and determine appropriate reimbursement. Over time, LTFU studies will increase the knowledge about the long-term benefits and risks of different types of GTs, and the need for them may decrease.

## Stakeholder Groups Table

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

| STAKEHOLDER GROUP                                   | Value of LTFU studies                                                                                                                                                                                                                          |
|-----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>LTFU participants</b>                            | 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.                                                                        |
| <b>Patients who have disease targeted by GT</b>     | Provide information to guide decision-making about receipt of GT products.                                                                                                                                                                     |
| <b>Sponsors</b>                                     | 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. |
| <b>Regulators</b>                                   | Help protect the public by ensuring the safety and effectiveness of GTs.                                                                                                                                                                       |
| <b>Medical community</b>                            | Provide information to guide clinical care decision-making, including optimizing the frequency and type of health monitoring after receipt of specific GTs.                                                                                    |
| <b>Society, public, broader patient communities</b> | Increase knowledge about long-term benefit/risk profile of GT products, particularly on long-term safety.                                                                                                                                      |

## Recommended Duration of LTFU for Different Types of GTs

LTFU studies are recommended for GTs that have long-term health risks, such as those with the potential for causing changes to the human genome (e.g., GTs with integrating vectors or gene editing products), or those with the potential for latency and reactivation, the latter of which persist for the life span of targeted cells and could cause symptomatic viral infection.[2, 16] Depending on the characteristics of specific GTs and their risk of delayed adverse reactions, the regulatory agencies recommend different durations of LTFU (see **LTFU Duration Table**).[2, 16] LTFU studies may last 5 years, 15 years, or even longer after the administration of the GT. Guidance from the PMDA is not specific about the duration of LTFU but notes that it should be determined by characteristics of the GT and the target disease, and that the duration might need to be extended, depending on results.[13, 15, 31]

### LTFU Duration Table

LTFU duration recommendations by different regulatory authorities

| GT Type                                                             | Characteristics                                                     | FDA Recommended LTFU Duration[2]                                 | EMA Recommended LTFU Duration[16]                                                                                      | NMPA Recommended LTFU Duration[14]                                                |
|---------------------------------------------------------------------|---------------------------------------------------------------------|------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| <b>Gammaretroviral, lentiviral vectors, and transposon elements</b> | Integrate into the genome                                           | <b>15 years</b><br>(15 years for CAR T-cell therapy)[6]          | <b>Minimum 5 years</b> with potential for longer follow-up until no risk remains. (15 years for CAR T-cell therapy)[9] | <b>Minimum 15 years</b>                                                           |
| <b>Herpesvirus vectors (or oncolytics)</b>                          | Vectors capable of establishing latency                             | <b>Up to 15 years</b>                                            | <b>Minimum 5 years</b> with potential for longer follow-up until no risk remains                                       | <b>15 years</b> or until there is no longer risk of infection or reactivation     |
| <b>Microbial vectors</b>                                            | Vectors that are known to establish persistent infection            | <b>Up to 15 years</b>                                            | Risk-based approach, <b>minimum 5 years</b>                                                                            | <b>15 years</b> or until there is no longer risk of infection or reactivation     |
| <b>Adeno Associated Viral (AAV) vectors</b>                         | Generally present a lower risk of delayed adverse events            | <b>Up to 15 years</b>                                            | <b>Minimum 5 years</b> (categorized as “without integration, latency or reactivation potential”)                       | <b>5 years</b> or until there is no longer risk present                           |
| <b>Genome editing products</b>                                      | Capable of causing intended and/or unintended changes to the genome | <b>Up to 15 years</b>                                            | <b>Based on vector used for delivery</b>                                                                               | <b>15 years</b> or until there is no longer risk present                          |
| <b>Other vectors (e.g., plasmids, adenovirus)</b>                   | Generally present a lower risk of delayed adverse events            | <b>Duration based on product persistence and risk assessment</b> | <b>5 years</b>                                                                                                         | Products with low safety risks <b>do not require long-term clinical follow-up</b> |

The FDA and the EMA are aligned on characteristics of GTs with higher risk, but the EMA adds additional factors such as replication competence or incompetence of the vector, its biodistribution, and known interactions with concomitant treatments. [2,16] The EMA specifies that LTFU recommendations also depend on characteristics of the patient population, including the nature of the targeted disease and associated co-morbidities, as well as data from nonclinical and clinical studies, including research on similar products. [16]

Notably, a recent white paper co-authored by representatives of pharmaceutical companies and patient advocacy organizations, which is currently available as a pre-print but not yet peer-reviewed, calls for the 15-year requirement for CAR T-cell LTFU to be reduced to 5 years, based on an analysis of accumulated safety data.[32]

## Challenges Associated with LTFU

While regulatory guidance holds that long-term safety monitoring is important in the context of GTs, regulatory agencies, sponsors, and researchers acknowledge that LTFU studies are challenging and expensive to design, conduct, and operationalize. [32–38] One key distinction of LTFU from other types of clinical research is the length of time involved in following and monitoring participants.

The duration of LTFU studies poses challenges to both patients and sponsors. Participation in some GT clinical trials may require years of follow-up, which may involve regular or annual travel to central academic medical centers. Participating in LTFU can pose burdens on patients and their families in terms of time, expense, and opportunity costs. As lives and priorities often change over time, it can be difficult for some to remain in the study.[38–40]

The potential length of LTFU also means that sponsors—and in some cases, academic investigators—must resource research programs for unprecedented lengths of time. The duration of time from the initiation of Phase 1 trials to the completion of LTFU may span decades. Planning for LTFU may involve a substantial change in how sponsors typically resource research programs, requiring a mindset shift, careful planning, and sustained financial commitments. Academic investigators also need significant support to fulfill LTFU commitments. In October 2023, one FDA official

acknowledged that the agency “may need help to determine how to ensure 15 years of patient follow-up is completed despite physician retirements, company closures, and other issues that could impact the post-market commitments for gene therapies.”[36]

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

**—Rohde et al.[24]**

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Another challenge is striking the right balance between maximizing the value of LTFU studies for GT recipients and patient communities at large and minimizing burdens on participants, sponsors, and researchers. The benefits of more LTFU data collection, which would potentially increase knowledge generation and scientific value, may jeopardize patient and/or physician support, resulting in participant attrition in either post-trial or post-approval LTFU and threatening scientific validity.[5, 41] Further, the resources required for prospective, intensive LTFU studies can disincentivize the research and development of GT.

## Types of LTFU Studies for GTs

LTFU studies for GTs are conducted to better understand the long-term benefit/risk profile of this relatively new class of therapies. Although they share a common purpose, there are different types of LTFU studies for GTs. In this section, we explore various kinds of LTFU studies and terminology that is used to characterize different study designs (see [LTFU Study Types Table](#)).

For example, whether an LTFU protocol addresses one or more GT products is one example of differences in study design. LTFU protocols may focus on a single GT product, or they may be conducted as master or umbrella protocols, in which patients who have received different GT products are all followed up under the ‘umbrella’ of one master LTFU protocol.

Master or umbrella studies have the potential to increase efficiency, reduce burden, and harmonize data collection and reporting, facilitating meta-analysis. But there are tradeoffs; for example, the endpoints, whether for safety or efficacy or both, may not be as specific or customized to a particular product.[42] Below, we discuss other ways that LTFU studies can differ in their design or categorization.

Examples of different types of LTFU studies can be found in the [Key Design Elements for LTFU studies of FDA-approved GTs](#) resource.

## LTFU Study Types Table

### Different Types of LTFU Studies for GTs Table

| CHARACTERISTIC,<br>DESIGN, OR APPROACH                                                                                                                 | BRIEF EXPLANATION                                                                                                                                                                                                  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  <b>Investigational<br/>or Approved GTs</b>                           | 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) |
|  <b>Integrated or<br/>Standalone Protocols</b>                        | For post-clinical trial follow-up, whether the LTFU is incorporated into the main (or parent) trial or conducted according to a separate protocol                                                                  |
|  <b>Observational/<br/>Non-interventional<br/>or Interventional</b> | Regulatory classification of studies/trials with implications for design, oversight, and reporting requirements                                                                                                    |
|  <b>Registry Studies</b>                                            | LTFU studies that employ registries                                                                                                                                                                                |
|  <b>Centralized or<br/>Decentralized</b>                            | 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).                           |

## 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

extract specific safety outcomes data from the context of clinical care, but this is only possible if trial participants have access to the required follow-up after the parent trial ends in clinical care settings; consents, contractual agreements, and mechanisms for retrieving the follow-up data are in place; and health professionals are specifically educated on their responsibilities.

LTFU conducted in the post-approval setting can usually be designed to use data that is collected in the context of clinical care following receipt of the GT. The FDA defines Real World Data (RWD) as “data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.”[43] Real World Evidence (RWE) is defined as “the clinical evidence about the usage and the potential benefits or risks of a medical product derived from analysis of RWD.”[43] Registries can support the conduct of interventional or non-interventional studies for various purposes, including evaluation of a pharmaceutical product delivered “during routine medical practice.”[43] For this reason, registry studies are often used to support LTFU in the post-authorization setting. As discussed further below, **LTFU Registry Studies** leverage the use of a registry to investigate a hypothesis or research question.

For GTs that receive market authorization, there will likely be a period of overlap where LTFU studies of trial participants and LTFU studies of recipients of approved GTs (in the context of clinical care) are both active; however, these are usually conducted separately, under different protocols.

Although most LTFU studies are specific to one population or another (e.g., received an investigational or approved product), we have identified a number of LTFU studies that follow patients who received a particular GT as a participant in a clinical trial or as an approved therapy in the context of a Phase 4 trial or in clinical care (i.e., [NCT06971939](#) and [NCT04917874](#)). NCT numbers are unique identification codes assigned to clinical study records registered on ClinicalTrials.gov.[44]

## 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.

## Integrated and Standalone LTFU Table

Advantages and disadvantages of integrated and standalone LTFU protocol design in the context of post-clinical trial LTFU. *Adapted from [45].*

| LTFU Protocol Design | Advantages                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Disadvantages                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Integrated</b>    | <ul style="list-style-type: none"> <li>• Facilitates enrollment into LTFU component of the study</li> <li>• With one integrated protocol, participants build trust with research team over time which may support retention</li> <li>• May facilitate continued monitoring of safety and efficacy, if outcome measurements continue from parent trial [42]</li> <li>• May reduce administrative burden, with only one protocol</li> <li>• Only one ethics committee review may be required</li> <li>• Only one study consent process for participants</li> </ul> | <ul style="list-style-type: none"> <li>• Decisions about LTFU protocol must be made at time of initiation of parent interventional trial</li> <li>• Does not allow for umbrella approaches (i.e., conducting LTFU for several GTs under one protocol)</li> <li>• When an LTFU study is built into the original parent protocol, it may limit assessment of LTFU safety data to that study/population, and not to the overall product</li> <li>• Does not allow for closure of the trial documents (data collection, trial master file, etc) prior to applying for product approval</li> </ul> |

| LTFU Protocol Design                                                         | Advantages                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Disadvantages                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Standalone</b><br><br>Includes umbrella/<br>master protocol<br>approaches | <ul style="list-style-type: none"> <li>• Allows parent, interventional clinical trial to be closed once endpoints are met</li> <li>• May enable LTFU study to proceed under observational study classification,[42] which may have decreased regulatory and reporting requirements</li> <li>• May allow more time to develop LTFU protocol, with more clinical information in hand, although regulators and/or IRBs may request the LTFU protocol when approving parent trial</li> <li>• Allows for umbrella/master protocol approaches (i.e., conducting LTFU for several GTs or trials under one LTFU protocol)</li> </ul> | <ul style="list-style-type: none"> <li>• Need for development of two different protocols, informed consent forms and process, review, etc. [46]</li> <li>• LTFU protocol will need to be ready and fully approved before the first patient completes the parent interventional clinical trial, to avoid loss to follow-up or missing data</li> <li>• Patients need to consent for a separate study, which may have different study sites than the parent trial</li> <li>• Some GT trial participants may choose not to enroll in the LTFU, risking a higher chance of participant attrition and loss to follow up</li> <li>• Increased administrative burden with two protocols/studies</li> </ul> |

## Non-Interventional (Observational) vs. Interventional LTFU Studies

Whether a study qualifies as interventional or non-interventional (observational) matters for regulatory compliance, as well as the appropriate, adequate, and ethical protection of research participants. [47, 48] However, there can be significant confusion around this classification, which likely results from non-harmonized terminology, definitions, and guidance across organizations and regions (see the [Interventional and Non-Interventional/Observational Terminology Table](#)). The classification depends on the definitions of particular regulatory jurisdictions. The impacts of the classification, in turn, depend on applicable regulatory requirements and guidelines, which can also vary by country and region.[49] For this reason, it is important to understand early in planning how the design of LTFU studies will be classified in the countries in which they will be conducted.[49]

As interventional studies are usually considered higher risk, they typically receive more intense review from ethics committees and have more robust regulatory requirements. The informed consent process will typically be more rigorous in the context of interventional studies. Also, interventional studies involving drugs usually meet the FDA definition of a clinical investigation and may therefore be subject to approval from regulatory agencies in addition to local ethics committee review.[50]

Notably, study registration and reporting requirements may also differ for interventional and non-interventional studies. Various laws and policies (including the Final Rule for FDAAA 801 42 CFR Part 11, the NIH Policy on Dissemination of NIH-funded Clinical Trial Information, the World Health Organization (WHO) International Clinical Trials Registry Platform, and the International Committee of Medical Journal Editors (ICMJE)) require

registration and/or results submission to ClinicalTrials.gov for certain types of clinical trials.[51]

In the United States, whether LTFU studies are classified as interventional or non-interventional depends on a number of factors. Although many non-interventional studies involve the analysis of data that is collected in the context of routine medical practice in clinical care settings, some may include research protocol-specified activities or procedures, such as laboratory tests, imaging studies, or surveys.[50] FDA does not consider these types of studies to be clinical investigations under part 312; however, the FDA also notes: “If the [research] protocol-specified activities or procedures alter the patients’ treatment regimens or plans, the study becomes interventional and requires an IND, unless exempt, because the drug is no longer being used ‘in the course of medical practice.’ See 21 CFR 312.3(b).”[50] Although the FDA does not consider non-interventional studies to be clinical investigations, it emphasizes that protection of human subjects in these studies is still critical.[50]

In contrast, in Europe, non-interventional studies cannot include any research-specific diagnostic or monitoring procedures, whether or not they affect the patient-participant’s clinical treatment plan. Importantly, in the European Union, the definitions of noninterventional and interventional studies can vary across countries, as can standards of care.[49]

Some sources note that registry studies, which are discussed further below, are observational clinical studies.[47, 48] However, both FDA and EMA guidance clarify that registry studies may be interventional or observational/non-interventional (the FDA specifies that, in either event, sponsors should submit protocols and statistical analysis plans to the agency if sponsors or researchers plan to use the evidence for regulatory submissions).[43, 52]

In the context of LTFU studies that follow GT clinical trial participants, if the LTFU protocol is integrated into the main/parent clinical trial, the study as a whole would be considered interventional, in both the United States and Europe. If the LTFU study is run as a standalone protocol, it could be considered interventional or non-interventional/observational: the classification would depend on regulatory jurisdiction and whether the study includes research protocol-specified interventions. For example, a standalone LTFU study that includes research-specified diagnostic or monitoring tests would qualify as an interventional study in Europe. In the United States, the classification would depend on the nature of the research protocol-specified interventions and whether they have the potential to impact the participant's clinical treatment plan or delivery of care. [50]

While most LTFU studies in the post-approval setting are likely to be classified as observational (e.g., post-approval safety surveillance studies) in both Europe and the United States, this may not always be the case. In Europe, post-approval LTFU studies would be interventional if they involve any research-specified diagnostic or monitoring procedures. In the United States, the classification would again depend on whether the research-specified tests impact the clinical care or treatment plans of the participants.

It would be helpful if sponsors justify their classifications of LTFU studies as observational or interventional. They should clearly specify which assessments are performed for research purposes only, and which are considered part of routine monitoring that would occur in the context of usual clinical care. Further, they should note if the results of any research-specified activities have the potential to impact the participant's clinical care or treatment plan.

## Interventional (▼) and Non-interventional/Observational (●) Terminology Table

Different definitions of observational, non-interventional, and interventional studies from various sources.

| Term                             | Source                                            | Definition                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|----------------------------------|---------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ▼<br><b>Interventional Trial</b> | <a href="#">EU Clinical Trials Register</a>       | “An interventional trial sets up to discover or verify the effects of one or more investigational medicinal product(s) (IMP), to ascertain its (their) safety and/or efficacy. The assignment of the patient to a particular therapeutic strategy is decided in advance by a trial protocol. The way the IMP(s) are used, and the way the patients are selected for the trial and followed up are not as per current practice, and the data from the trial are systematically analysed.”[53] |
| ▼<br><b>Interventional Study</b> | <a href="#">U.S. Food and Drug Administration</a> | “...(also referred to as a clinical trial) is a study in which participants, either healthy volunteers or volunteers with the condition or disease being studied, are assigned to one or more interventions, according to a study protocol, to evaluate the effects of those interventions on subsequent health-related outcomes. One example...is a                                                                                                                                         |

| Term                                                 | Source                                                      | Definition                                                                                                                                                                                                                                                                                                                                                                                               |
|------------------------------------------------------|-------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>▼<br/>Interventional Study</b><br><br>(continued) |                                                             | traditional randomized controlled trial in which some participants are randomly assigned to receive a drug of interest (test article), whereas others receive an active comparator drug or placebo. Other examples...include randomized clinical trials with pragmatic elements (e.g., broad eligibility criteria, recruitment of participants in routine care settings) and single-arm trials.”[50]     |
| <b>▼<br/>Interventional Study (clinical trial)</b>   | <a href="https://clinicaltrials.gov">Clinicaltrials.gov</a> | “A type of clinical study in which participants are assigned to groups that receive one or more intervention/treatment (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study’s protocol. Participants may receive diagnostic, therapeutic, or other types of interventions.” [44] |

| Term                                            | Source                                                   | Definition                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-------------------------------------------------|----------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>●</p> <p><b>Non-Interventional Study</b></p> | <p><a href="#">U.S. Food and Drug Administration</a></p> | <p>“(also referred to as an observational study) is a type of study in which patients received the marketed drug of interest during routine medical practice and are not assigned to an intervention according to a protocol. Examples of non-interventional study designs include, but are not limited to, (1) observational cohort studies, in which patients are identified as belonging to a study group according to the drug or drugs received or not received during medical practice, and subsequent biomedical or health outcomes are identified and (2) case-control studies, in which patients are identified as belong to a study group based on having or not having a health-related biomedical or behavioral outcome, and antecedent treatments received are identified.” [50]</p> |

| Term                                            | Source                                                                  | Definition                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-------------------------------------------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>●</p> <p><b>Non-Interventional Trial</b></p> | <p><a href="#">Europe Article 2(c) of Directive 2001/20/EC [30]</a></p> | <p>“a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorization. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data.”[54]</p> |
| <p>●</p> <p><b>Observational Study</b></p>      | <p><a href="#">ClinicalTrials.gov</a></p>                               | <p>“Observational studies are research studies in which researchers simply collect information (called data) from participants or look at data that was already collected. The data may be about participants’ health, habits, or environments. In observational studies, researchers do not assign participants to get an intervention. If there is an intervention, participants were already using it as part of their regular health care or daily life.”[55]</p>                                                                                                                         |

| Term                                       | Source                                                             | Definition                                                                                                                                                                                                                                                                                                                                                                                         |
|--------------------------------------------|--------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>●</p> <p><b>Observational Study</b></p> | <p><a href="https://clinicaltrials.gov">ClinicalTrials.gov</a></p> | <p>“A type of clinical study in which participants are identified as belonging to study groups and are assessed for biomedical or health outcomes. Participants may receive diagnostic, therapeutic, or other types of interventions, but the investigator does not assign participants to a specific intervention/treatment.</p> <p>A patient registry is a type of observational study.”[44]</p> |

## 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.

Registries may or may not include case controls.

In addition to cost effectiveness, the advantages of using registries relate to operational efficiency, such as a standard infrastructure for data collection that often includes data that medical claims datasets or electronic health records may not collect, such as PROs, treatment adherence, and measures of disease severity.[43]

However, there are also limitations of using registries for regulatory decision-making; consultation with FDA and other regulators is important. Registries can be limited in terms of patient population or data collected; there may be limited information about comorbid conditions, for example. [43] In particular, the registry will need to collect relevant (e.g., unbiased, inclusive) and reliable (e.g., accurate, complete, and traceable) data.

FDA guidance on the use of registries to support regulatory decision-making for drug and biological products specifically notes that registry infrastructures can be leveraged to support interventional (clinical trials) and non-interventional (observational) studies; the guidance also states that participants in such studies may need to provide specific consent. [25]

In the context of LTFU, the CIBMTR supports a Gene Therapy Registry, which includes data on patients who have received CAR T-cell therapies [57]; the WFH also hosts a GTR.[25, 32, 57, 58] ACCELERATE, Foundation for Children and Adolescents with Cancer, established LTFU Working Group with a mission to create an international, open, harmonized, and sustainable data registry to collect long-term side effects of anti-cancer therapies, including CAR T-cell therapies, in children.[59, 60] However, the ACCELERATE website indicates the LTFU Working Group is “paused for now.”

## REGISTRY STUDIES

According to the EMA, registry studies (also known as registry-based studies) have a number of characteristics that distinguish them from patient registries (see [Registry vs. Registry Study Table](#) below):

“A registry study is an investigation set up to answer a research question that uses data collected in the registry, and which may be initiated, managed or financed by a pharmaceutical company, a regulatory authority or another organization.”[43]

In the context of post-approval LTFU, “considering which data sources are suitable to generate the RWE [real-world evidence] required by regulators is important. Discussion with regulators is encouraged. Among others, the FDA and EMA guidance concerning registry-based studies provides several aspects to consider when assessing whether RWD [real-world data] sources are fit for purpose.”[61]

Post-approval LTFU registry studies sometimes leverage the resources of existing registries that are already set up to collect the relevant data and to reduce site and patient burden (e.g., CIBMTR is often used as a data source for LTFU CAR-T registry studies).

The distinction between registry LTFU studies and non-registry LTFU studies is not always clear. Registry studies are usually thought of as being based on data that is collected in the context of clinical care, e.g., real-world data (RWD). However, as noted above, some registry studies can involve assessments that go beyond the standard of care and could be classified as interventional.

There are many examples of LTFU registry studies to address post-authorization regulatory requirements for gene therapies. Registry studies are denoted with “RS” in the [Key Design Elements for LTFU Studies for FDA-approved GTs](#).

A recent whitepaper notes that the employment of registries in the context of LTFU can still require significant resources, as specific data must be manually extracted from EHRs and transferred to the registries. [32] The authors suggest that, instead, regulatory agencies grant sponsors the choice of using a third-party database or new technologies such as artificial intelligence to create an automated exchange of EHR information to a central third-party database.[32]

### Registry vs. Registry Study Table

Notable characteristics and differences between registries and registry studies. The information in the table below is taken from two EMA references.[52, 62]

|                   | Patient Registry                                                                                                                                                              | Registry Study                                                                                                                                            |
|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Definition</b> | “Organised system that collects uniform data (clinical and other) to identify specified outcomes for a population defined by a particular disease, condition or exposure”[62] | “Investigation of a research question using the data collection infrastructure or patient population of one or more patient registries”[62]               |
| <b>Nature</b>     | “Data collection system” [52]                                                                                                                                                 | “Investigation of a research question or hypothesis”[52]                                                                                                  |
| <b>Timelines</b>  | May be long term and open-ended. Timelines driven by data collection schedules and data analysis anticipated by needs for establishing the registry.[52, 62]                  | Driven and defined by the study objective(s), the collection/extraction and analysis of relevant study data, and described in the study protocol.[52, 62] |

|                    | Patient Registry                                                                                                                                                                                                                                                                                                                         | Registry Study                                                                                                                                                         |
|--------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Patient Enrollment | Aim to enroll all patients with a particular disease or condition; generalizability of registry population should be documented. [62] "Exhaustive within the boundaries of the purpose of the registry (e.g., all patients diagnosed with a disease in a hospital, region or country.)" [52]                                             | "Defined by research objective and described in the study protocol- it may be a subset of the registry population." [52]                                               |
| Data Collection    | <p>"Wide range of data may be collected depending on the purpose of the registry" [52]</p> <p>"collection of additional data not routinely collected in the registry may be required; if such additional data includes subject monitoring outside...normal clinical practice, the legislation for clinical trials may apply..." [62]</p> | "Restricted to what is needed by the research question including data on potential confounders and effect modifiers- additional data collection may be required." [52] |
| Analysis Plan      | "Routine periodical data analysis; additional ad-hoc analyses" [52]                                                                                                                                                                                                                                                                      | "Statistical analysis plan separate from the study protocol." [52]                                                                                                     |

|                                                                | Patient Registry                                                                                                                                                                                                                             | Registry Study                                                                                                                                                        |
|----------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Collection and Reporting of Suspected Adverse Reactions</b> | “National requirements as regards the management of safety data apply. Any active data collection with involvement of a MAH must follow the regulatory framework for PASS.”[52]                                                              | “National requirements may apply. Regulatory requirements to MAHs differ between studies with primary or secondary data collection.”[52]                              |
| <b>Data Quality Control/Management</b>                         | “Applied routinely to all data and processes”[52]<br>Focus is on core set of data elements. Quality data management to be prospectively defined and documented and data systems should ensure data integrity, completeness and security.[62] | “Additional quality assurance may be needed”[52] “Study-specific data quality management to be prospectively defined and implemented with a risk-based approach.”[62] |

## Centralized or Decentralized

Centralized trials involve, as the name suggests, central locations, such as academic medical centers, where research data and information are collected.[63, 64]

According to the FDA, a decentralized clinical trial (DCT) includes decentralized elements where trial-related activities occur at locations other than traditional clinical trial sites.[18, 65]

Decentralized elements may include assessments that are performed remotely through electronic patient-reported outcome (ePRO) measures, via telehealth or in-home visits, or by local health care providers (HCPs), as appropriate.[63–65]

## Flowcharts of LTFU for Research and Post-GT Follow-Up in the Context of Clinical Care

In this section, we provide two flowcharts in order to provide visual representations of different types of patient follow-up after receipt of a GT. The main focus of this Toolkit is LTFU conducted for the purpose of research, which is mainly represented by the first chart. However, GT recipients will also be followed up for the purpose of clinical care, represented mainly by the second chart. The charts below represent these as separate charts, to clarify and simplify. As noted in different sections of this Toolkit, however, in reality, the lines between LTFU for the purpose of research and follow-up conducted for the purpose of clinical care can get blurry.

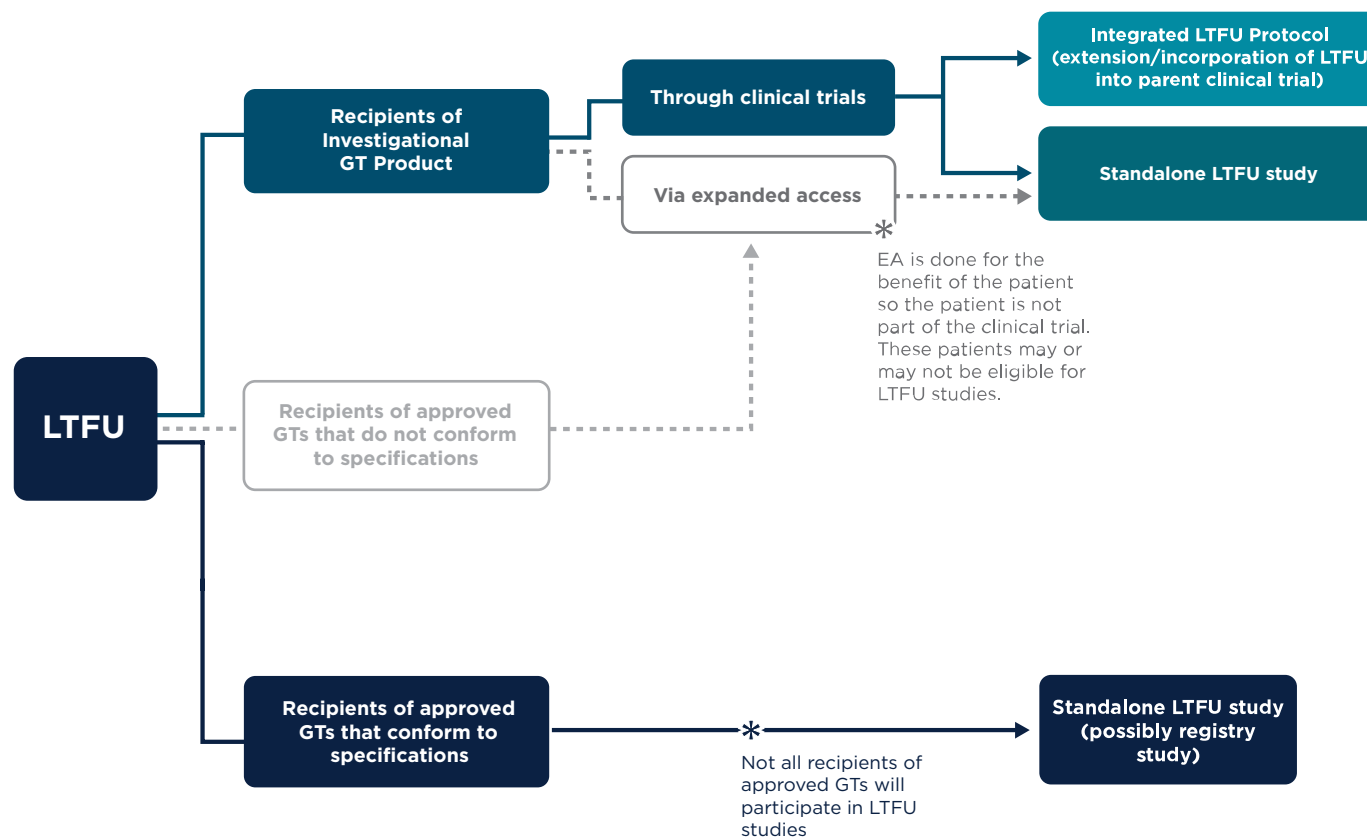
For example, LTFU for the purpose of research may leverage the use of RWD collected in clinical care settings; this is often true for postapproval LTFU studies but can also happen in LTFU studies that follow patients who received an investigational GT as clinical trial participants. As noted in FDA guidance, “Routine surveillance of licensed biological products includes adverse event (AE) reporting in accordance with 21 CFR 600.80 (reporting of expedited and non-expedited AEs as well as periodic safety reports).”[2]

Another way that LTFU for research and follow-up for clinical care intersect is that participants in LTFU studies will undergo monitoring that can facilitate the timely detection of health issues that can guide appropriate medical care for study participants.

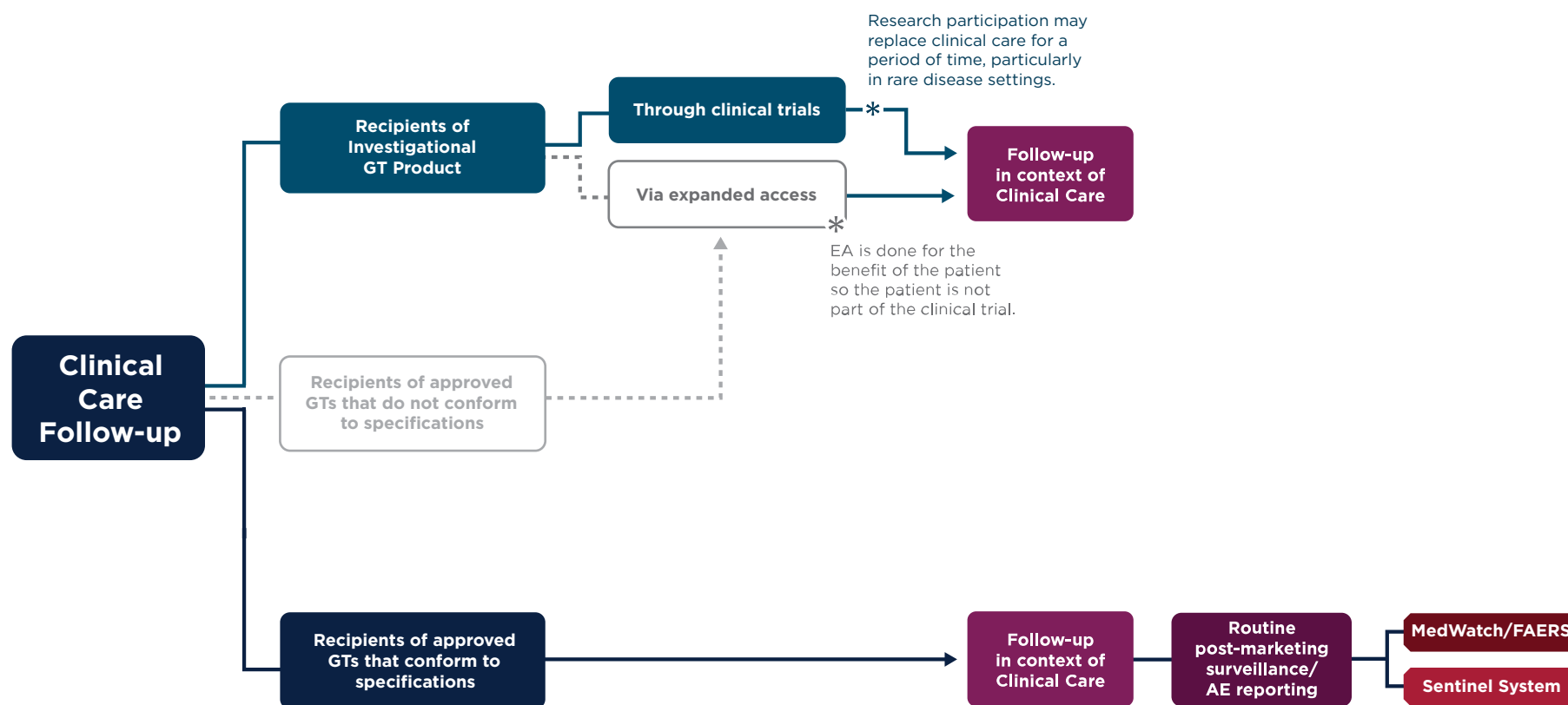
These flowcharts are also oversimplified in another way. Although most LTFU studies are specific to one population or another (e.g., received an investigational or approved product), it is possible for them to include both. We have identified a number of LTFU studies that follow patients who received a particular GT as a participant in a clinical trial or as an approved therapy in the context of a Phase 4 trial or in clinical care (i.e., [NCT06971939](#) and [NCT04917874](#)).

## 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



## Guiding Principles for LTFU Studies for GTs<sup>i</sup>

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.

<sup>i</sup> The Emanuel et al. clinical research ethics framework was helpful for drafting these principles.[66, 67]

- 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.

- 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).

# Considerations and Recommendations for the Design, Conduct, and Reporting of LTFU Studies for GTs<sup>ii</sup>

## Introduction

In this resource, we reflect on, respond to, and build upon health authorities' LTFU guidance and provide specific and detailed considerations and recommendations aimed at supporting the design, conduct, and reporting of LTFU studies. We do cite specific regulatory guidance documents here, but these references are meant as examples: a comprehensive analysis of international laws, regulations, or requirements related to LTFU is beyond the scope of this tool.

The resource applies to LTFU studies of patients who received investigational GTs as research participants or via expanded access, and to LTFU studies of patients who have received approved GTs. The aim is to strike the right balance between maximizing benefits—in the form of generalizable knowledge and direct benefits to participants—and minimizing burdens on participants, health care providers, and sponsors. Optimal design choices will depend on the characteristics of specific GT products, the potential for associated health risks and adverse reactions, and the particular patient population and disease context.

## Subsections

The Considerations and Recommendations section is divided into nine detailed subsections relating to different aspects of designing, conducting, reporting, and operationalizing LTFU studies.

In each subsection (I-IX), we enumerate a number of considerations ("C"); following each consideration, we list one or more Recommendations ("R"). Each subsection can generally be viewed as self-contained on a specific topic and can be read separately.

<sup>ii</sup> The Clinical Trials Transformation Initiative (CTTI) Quality by Design Project's Critical to Quality (CTQ) Factors Principles Document was a key resource in the early process of developing these considerations. [68]

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:**

|             |                                                              |
|-------------|--------------------------------------------------------------|
| <b>I</b>    | <b>Purpose and Limitations</b>                               |
| <b>II</b>   | <b>Objectives and Endpoints</b>                              |
| <b>III</b>  | <b>Anticipating Protocol, Technology, and Site Evolution</b> |
| <b>IV</b>   | <b>Enrollment and Informed Consent</b>                       |
| <b>V</b>    | <b>Participant Retention and Withdrawal Criteria</b>         |
| <b>VI</b>   | <b>Signal Detection and Safety Reporting</b>                 |
| <b>VII</b>  | <b>Data Sharing and Dissemination of Results</b>             |
| <b>VIII</b> | <b>Operationalizing the LTFU Protocol</b>                    |
| <b>IX</b>   | <b>Clarification of Responsibilities</b>                     |

## I. Purpose and Limitations

According to the FDA, the objective of LTFU studies is to identify and mitigate risks to GT recipients; LTFU studies should primarily be designed to detect delayed adverse events and to understand how long (and where) the GT product persists in the human body.[2] Sponsors may also include long-term efficacy outcomes in LTFU protocols to determine the durability of clinical benefit.[2] In recent draft guidance, the FDA notes that post-approval studies of cell and gene therapy products can be aimed at evaluating safety and efficacy outcomes.[18]

EMA guidance states that the purpose of LTFU is to detect adverse events and mitigate risks of any adverse reactions experienced by recipients of GT products. However, the EMA diverges from FDA guidance in that it explicitly states that an additional purpose of LTFU is to understand the long-term efficacy of GT products.[16] EMA guidelines also specify that lack of efficacy should be evaluated in LTFU for gene therapy medicinal products.[10]

The NMPA frames the main purpose of LTFU as safety and determination of the persistence of the GT product in the body, but states that it is also important to evaluate changes in efficacy over time to evaluate the overall benefit/risk profile of the product.[14]

The PMDA states that LTFU duration for GTs depends on product and disease characteristics. The guidance also notes that it is important to evaluate the sustainability of transgenes if the vector is anticipated to integrate into the genome, and that it may be important to obtain biosamples for investigation and analysis in the case of adverse events.[12]

Regulatory agencies also acknowledge limitations of LTFU for GTs. FDA guidance notes that LTFU observations may be less effective at determining the long-term risks of GT products if patients have characteristics that may confound the results, including short life expectancy, co-morbidities, or prior (or future) exposure to approved or investigational interventions, drugs, or biological products that incur risks of their own.[2]

According to the EMA, GT recipients with co-morbidities, life-limiting disease, or exposure to interventions with other risks may not be ideal candidates for LTFU studies due to the limited ability to determine whether the GT product is associated with delayed adverse reactions.[16] However, the EMA notes that “the clinical follow-up should be as long as possible and necessary.”[16]

Interestingly, the EMA seems to make a clear distinction between LTFU for the purposes of evaluating the long-term safety of GTs (research) and LTFU for the purpose of monitoring the health of individual GT recipients/patients (clinical care). In situations where LTFU for research purposes is less valuable, the EMA suggests that it could be forgone while follow-up in clinical care contexts continues.[16] The EMA stresses that health professionals conduct follow-up of patients after they receive a GT, including screening, monitoring, diagnosis, and treatment to detect complications, health issues, and concerns.[16]

The FDA’s communications are less clear in this regard: the line between LTFU conducted for research and for clinical care appears more blurred. In fact, in FDA guidance, the purpose of LTFU is explained at the individual patient level: “To understand and mitigate the risk of a delayed adverse event...”.[2] After reports of T-cell malignancies following BCMA- or CD19-directed autologous CAR T-cell therapies (ex vivo genetically modified cell therapy) and cases of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) after administration of a lentiviral autologous hematopoietic stem cell-based GT, the FDA recommended that recipients of these GTs should be monitored lifelong for new malignancies.[22, 69]

However, the FDA’s statements did not explicitly clarify who is responsible for the lifelong monitoring (i.e., after the required 15-year FU). A reasonable interpretation is that safety and health monitoring of patients who have completed LTFU studies would fall to their clinician(s). This is implied when the agency notes that detected malignancies “should be reported to FDA *and the manufacturer* [emphasis added] and instructions will be provided on collection of samples for further testing.” This interpretation is also supported by statements in an article by Verdun and Marks, both former FDA officials, in which they write, “It is important for clinicians caring for people who have received CAR T cells to report the occurrence of any new cancer. At this time, we recommend that patients and clinical trial participants who

receive treatment with [CAR T] products be monitored for new cancers throughout their lives, since—owing to the relatively recent widespread introduction of CAR-T products into clinical care—we don’t yet know how long after treatment people remain at risk for these adverse events.”[21]

## CONSIDERATIONS AND RECOMMENDATIONS

**C1**

**Sensitive and robust LTFU studies are important for detecting, assessing, and mitigating the long-term health risks associated with certain types of GTs (including genetically-modified cell therapies).** LTFU studies enable prompt identification of and communication about potential safety signals and adverse reactions to the patient and medical communities. This will enable specific safety monitoring, as part of clinical care or potentially a modified LTFU protocol, to be increased or improved. LTFU studies support decision-making in various ways across stakeholder groups (see [Stakeholder Groups Table](#)).

**R1.1:** If LTFU studies are required for a specific GT, planning for their design and execution is a necessary part of the overall strategy for the clinical development program and should occur in its earliest stages.

**R1.2:** Sponsors should commit to the long-term financial support and resources necessary to complete LTFU studies required by regulatory authorities and develop fallback plans in case the GT program is discontinued or business operations cease.[2, 18]

**R1.3:** To fully realize the value of LTFU studies and honor participant and patient contributions, timely, transparent communication of interim and aggregate results and data sharing are ethical and scientific obligations.

**C2**

**As currently framed in regulatory guidance, LTFU studies have two main purposes: to monitor the safety of GTs for knowledge generation and to mitigate risks to the patient community.**

**R2.1:** Although both the FDA and EMA state that one of the main purposes of LTFU is to identify and mitigate health risks to GT recipients/participants, careful ongoing health monitoring is (or should be) standardly included in clinical care after a patient completes a GT trial or receives an approved GT.

**R2.2:** 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.

**C3**

**The recommended duration of LTFU depends on the characteristics of specific GTs.**[2, 12, 16] FDA guidance suggests that, based on accumulated data and experience, sponsors may request shortening the duration of LTFU via an amendment justifying the change.[2] Both the PMDA and the EMA suggest that if signals emerge suggesting a need for longer follow-up, the sponsor should alter/extend the LTFU protocol.[12, 16]

**R3.1:** LTFU studies should only last as long as they provide value that justifies the burden on participants, patients, caregivers, and clinicians.[16]

**R3.2:** Should safety signals emerge and the need for LTFU be extended, ongoing LTFU commitments should be completed and extended, if possible. [12, 16]

**R3.3:** Once LTFU studies end, patient and medical communities should be encouraged to report related health issues that GT recipients experience to their care provider, regulatory agency, and manufacturer, consistent with recent communications from FDA.[21]

**C4**

**Some regulatory agencies (e.g., EMA, NMPA) state that efficacy assessments should be incorporated into LTFU, while others (e.g., FDA) position long-term efficacy assessment as optional.** Concerns about long-term safety may have more clinical significance than a decline in effectiveness over time, depending on the specific disease context and progression. EMA notes that decreasing efficacy could be a serious safety issue in the context of life-threatening diseases. FDA notes that post-approval studies can incorporate both efficacy and safety outcomes.[18]

**R4.1:** Because understanding the overall risk/benefit profile of a GT product requires evaluation of both long-term risk and long-term efficacy/effectiveness,[70] sponsors should ideally include assessments of efficacy in their LTFU protocols. Some endpoints and outcomes may be indicators of both safety and efficacy.

**C5**

**The persistence of the GT product may sometimes be used as a proxy for the durability of the therapeutic effect and/or the ongoing risk for adverse reactions; however, clinical effects and detection of the GT product may not always be in alignment.** It may be possible for the GT product to persist without the durability of the therapeutic effect, so long-term risks may remain even though beneficial effects do not. For example, a CAR-T product may persist in the body after the target tumor develops resistance to the therapy, known as tumor antigen escape (i.e., the tumor becomes capable of evading the immune response supplied by the CAR-T).[71] Alternatively, it may be possible for efficacy to be durable, even though GT persistence cannot be measured or detected. In systemic lupus erythematosus, CD-19 CAR-T may eliminate pathogenic B cells and then disappear, with enduring clinical benefit.[72]

**R5.1:** Sponsors should clarify and plan the purpose of measuring GT persistence and the appropriate next steps for different scenarios.

**C6**

**Determinations of causality can be challenging in LTFU studies.** Causality becomes increasingly difficult to determine as more time elapses between the administration of the GT product and an adverse event. Additionally, determination of causality is complicated when patients have complex medical histories and may have received other investigational products, approved treatments, and/or alternative/non-allopathic interventions with risks of their own, either before or after receipt of the GT of interest in a particular LTFU study. For example, chemotherapy increases the risk of secondary cancers, and many patients receive chemotherapy before or after receiving CAR T-cell therapy.

**R6.1:** Although characteristics of the patient population should be considered during the design of LTFU studies, as the EMA advises,[16] patients with complex medical histories should not be automatically excluded from LTFU as the data can be analyzed at the group and subgroup level. If there are adverse reactions associated with a GT, they will be easier to detect if more recipients are followed.

**R6.2:** LTFU data collection should include information about possible confounding factors, including relevant aspects of the participants' medical history.

**R6.3:** Although not usually included in LTFU studies, sponsors should consider using external control arms or comparator groups, such as natural history studies, chart reviews, and/or population-based matching, to help assess causality.[8, 61] Particularly in populations with high future health needs unrelated to the GT, the use of control groups becomes more important. The best control groups have comparable diagnoses and medical histories to the recipients of GT (i.e., the treatment group). These approaches are of particular utility in rare disease and oncology research.

## 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]

**C1**

**R1.3:** Patient, care partner, and patient advocate perspectives are also important for ensuring study feasibility, minimizing participant burden, and determining how results should be disseminated and returned.

**R1.4:** Engagement with the patient community should be planned and evaluated using resources and metrics for best practices. Examples such as the Patient Focused Medicines Development Patient Engagement Quality Guidance [73] and the Patients Active in Research and Dialogues for an Improved Generation of Medicines (PARADIGM) Patient Engagement Monitoring and Evaluation Framework [74, 75] are helpful.

**C2**

**Regulatory guidance provides high-level recommendations for what should be monitored in LTFU studies.** The FDA recommends the collection of data on new malignancies, new incidence or exacerbation of a pre-existing neurologic disorder, new incidence or exacerbation of a prior rheumatologic or other autoimmune disorder, new incidence of a hematologic disorder, and new incidence of potentially product-related infection.[2] The EMA recommends that LTFU studies collect data on mortality, the development of new and/or recurrent cancers, infection, and immunogenicity-related reactions, and that researchers also consider other safety endpoints of particular relevance to the target disease.[16]

**R2.1:** The design of LTFU protocols and selection of endpoints and outcomes should be focused and commensurate with clear scientific questions and the objectives of the study, based on an assessment of risk and need for monitoring, data interpretability, and weighed against the burdens on participants, sponsors, and others.[16, 68]

**R2.2:** The scientific questions and objectives of the study should be based on the mechanism of action of the GT and associated safety concerns, the target disease, characteristics of the patient population, and feedback from regulatory agencies.

**C2**

**R2.3:** As noted above, data on potential confounding factors, such as participation in clinical studies or exposures to other treatments with known risks, should be collected.[16]

**R2.4:** In order to support the evaluation of LT safety, the inclusion and biobanking of patient samples, with appropriate consent for future use, should be considered to enable research on genotoxicity and other factors.[61]

**C3**

**LTFU data collection requires significant resources and puts financial, operational, and social burdens on participants, care partners, sites, and sponsors that must be justified by the benefits to the participants and patients being followed and to society.** If study sites or investigators are burdened by broad data requests, it can increase the risk of misunderstanding and inconsistent reporting, which may threaten data integrity and validity and impact the final analysis.

**R3.1:** In order to support the feasibility of LTFU studies and support 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 that which is collected. (expanded from the recommendation in [68])

**R3.2:** LTFU study designers should carefully consider eliminating non-critical and exploratory endpoints in order to simplify data collection and reporting, and minimize the overall burden on investigators, sites, and patients. (see [68])

**C3**

**R3.3:** In order to reduce the financial and administrative burden associated with LTFU, sponsors should consider an umbrella/master protocol trial design to fulfill LTFU commitments and obligations. Rather than take a customized approach, a master protocol approach enables leveraging of a single protocol, informed consent form, electronic data capture system, operational team, and regulatory submission, which can increase efficiency and reduce costs and operational burden.[46]

- This approach may be more feasible for large pharmaceutical companies.
- Master protocol or umbrella approaches do have disadvantages, in that they may not capture endpoints that would be specific to a particular GT, including efficacy endpoints.

**C4**

**LTFU study design should seek to minimize burden on participants and care partners as much as possible.**

**R4.1:** Patient communities should be consulted to support feasibility and reduce burden.

**R4.2:** LTFU procedures, ePROs/diaries, and visit schedules should be usability tested with patient partners for readability, language/culture, and accessibility.

**R4.3:** The burdens placed on different participants can be evaluated using a tool (see [Burden Budget Tool/Table](#)).

**R4.4:** To reduce burden on participants and care partners, it is ideal to leverage, whenever possible, decentralized approaches and data collected during clinical care especially, but not exclusively, in the context of post-approval LTFU studies. An additional benefit is that incorporation of decentralized elements may help minimize loss-to-follow-up (see also section below).[18, 61]

**C4**

## Burden Budget Tool/Table

Burden budget tool that can support the estimation and minimization of participant burden, by encouraging consideration of burdens at the individual participant level. Not all participants will experience the same level of different types of burdens.

*Burden Budget Tool/Table kindly provided by the Canadian Organization of Rare Disorders.*

|               | Time | Travel | Out of Pocket Costs | Technological Steps | Invasiveness | Mitigation | Residual Risk |
|---------------|------|--------|---------------------|---------------------|--------------|------------|---------------|
| Participant A |      |        |                     |                     |              |            |               |
| Participant B |      |        |                     |                     |              |            |               |
| ...           |      |        |                     |                     |              |            |               |

**R4.5:** Possible LTFU data sources, such as secondary data from existing sources, the incorporation of primary data collection, or a combination, should be considered and undergo feasibility assessments to determine which are suitable to generate real-world evidence in terms of relevance and reliability.[18, 61]

**R4.6:** Sponsors should consider whether LTFU data collection can be conducted by the participants' HCPs and/or digitally retrieved from their EHRs. FDA guidance supports LTFU data collection by HCPs.[2] Medical records, including clinically indicated lab and test results, can be requested.

**R4.7:** The FDA recommends that sponsors develop templates for HCPs who are not investigators or subinvestigators to record and report LTFU observations.[2]

- The protocol should describe how HCPs will track and document effectiveness outcomes and/or adverse events.[18]

**C4**

**R4.8:** If follow-up needs to be in-person in the early stages of LTFU, consider whether data collection can be transitioned to HCPs or obtained via telehealth visits as the intensity and need for safety monitoring diminishes over time.[45]

**R4.9:** Consider how suitable local HCPs will be identified, educated, and supported in reporting LTFU outcomes, including adverse events.

- Procedures following reports of possible adverse reactions should specify the minimal information necessary, including that which enables product traceability.[8]
- The protocol should specify how care will be provided for adverse events that may require immediate care, follow-up care, and/or the steps to take for further research evaluation.[18]

**C5**

**Real-world evidence (RWE), obtained from the analysis of real-world data (RWD), can be used to evaluate efficacy and safety in postapproval settings.** [18] The FDA has released draft guidance for sponsors considering the use of RWD for certain purposes, including the assessment of clinical outcomes in GT-treated patients and background rates of outcomes of interest in patients without GT exposures.[18]

**R5.1:** As there are limitations and regulatory constraints on the use of RWD for RWE, sponsors should access RWD sources for reliability and validity in accordance with regulatory guidance.[18]

**C6**

**Some GT products may have direct ways to measure product persistence (e.g., cDNA or expressed protein), while other products rely on clinical outcome tests to infer product persistence (e.g., via blood tests or MRI).**

**R6.1:** The least invasive methods for determining GT persistence should be employed.

**C7**

**Comparison or aggregation of LTFU data across studies (either for the same GT or classes of GTs) may be scientifically valuable because it can increase power and enable hypothesis testing.**

**R7.1:** LTFU protocol designers should incorporate common data elements to promote standardized, consistent, and universal data collection and facilitate comparison across LTFU studies and/or allows datasets with similarities (e.g., type of GT) to be combined to maximize the value of LTFU efforts.[43, 68]

**R7.2:** LTFU protocol designers should carefully consider the use of MedDRA, a standardized medical terminology developed by International Council for Harmonisation of Technical Requirements for Human Use (ICH), which is used for safety monitoring of medical products and facilitates the sharing of regulatory information internationally.[76]

### III. Anticipating Protocol, Technology, and Site Evolution

Given the extended length of LTFU studies, there is a need to anticipate changes or amendments to the protocols over time. Flexibility can be built into the protocol, but sponsors must also anticipate and prepare for the need for resources (funding, staff, etc.), protocol changes, and amendments. For example, the standard of care at local or global levels may evolve over time, as knowledge grows, technology evolves, and new treatment options come to market. When designing a study that will last for longer than 10 years, it is important for sponsors to use systems that will be able to evolve alongside these changes.[77] There will also likely be staff changes at sponsor institutions, study sites, and care centers.

Another issue is that interim analysis of data from ongoing follow-up studies will provide more understanding about the risks/benefits of the GT. The data may suggest, for example, that the product is relatively safe and that there is a reduced need for LTFU, which may have protocol implications. Or the alternative may be true: safety concerns may arise that necessitate increased or more intensive long-term monitoring. Further, additional information and ideas for improving the protocol may be gained from a few years of experience, with more years of study still ahead.

## 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]

**C1**

**R1.6:** Sponsors should consider the use of a dedicated platform to sustain connection and support communication with participants over the course of the study.

**R1.7:** LTFU study designers may consider a modular design: breaking LTFU into time-confined (e.g., 5-year) intervals rather than the full anticipated duration, making it easier for participants to understand and agree to. Allowing participants opportunities to re-consent may increase participant retention and engagement, as it gives participants a realistic timeline with milestones to look forward to. This strategy also builds in planned opportunities to change the protocol; however, there will likely be more regulatory burden, as new protocols will need to undergo appropriate review.

**C2**

**Due to the extended duration of LTFU studies, the integrity and quality of the data collected in the LTFU study may change over time for non-scientific reasons. [79]**

**R2.1:** LTFU studies should incorporate periodic monitoring to ensure that the integrity and quality of the data collected are consistent over time.

## IV. Enrollment and Informed Consent

Although the assessment of comprehension and understanding of informed consent can be difficult in all types of clinical research, informed consent in the GT setting poses significant ethical challenges. In the context of serious or life-threatening diseases with high unmet medical needs, patients and their caregivers may be eager to gain access to an investigational GT by participating in a clinical trial. However, many GTs can only involve one administration and are associated with significant uncertainties about risks and benefits, including long-term safety, which drives the necessity of LTFU. With such high stakes involved with the choice of whether or not (and when) to receive a GT, LTFU may not be an important part of the decision. Additionally, patients and/or their care partners may feel compelled to agree to LTFU if it is incorporated into the consent process for the parent trial, even if they have concerns about the long-term commitment.

There are ethical arguments for linking the LTFU consent to the parent trial (as long-term monitoring is an important part of the research) and for doing it separately (as the decision whether or not to receive the investigational product will carry much more weight). Ethical challenges related to informed consent for LTFU are also further complicated by the fact that parent(s) or guardians provide consent on behalf of pediatric patients who receive GTs. If they have the capacity to do so, pediatric patients will need to undergo a new consent process when they reach the age of majority. They may choose not to continue long-term monitoring when they are offered the choice.[5] Another complication in the context of LTFU is that, as knowledge is acquired over time, new knowledge often necessitates updates to the consent due to changes in key information and/or the protocol. The informed consent process may need to be repeated regularly, and, in special circumstances, the communication of updates may need to be expedited.

## 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.

**C2**

**R2.2:** Patients who receive a non-conforming product or who do not meet eligibility criteria for a clinical trial but receive an investigational GT via single-patient IND or expanded access should also be included in LTFU as a special category that can be either analyzed separately or as part of the entire LTFU dataset.

**R2.3:** Similarly, if a participant receives an additional intervention (especially another GT or chemotherapy) after receipt of the LTFU-targeted GT, the default should be that they continue in the LTFU as a special category that can either be analyzed separately or as part of the entire LTFU dataset.

**R2.4:** It is unethical to prevent LTFU participants from receiving additional treatments in the future if they feel it is in their best interests. If a subset of patients goes on to additional future treatments, excluding them from LTFU might cause bias if this subset is particularly vulnerable to adverse events that are associated with the GT.

**R2.5:** Analysis of smaller sets of the population will have reduced statistical power compared to the main per-protocol cohort. It may be appropriate to limit data collection to critical endpoints only.

**R2.6:** When using registries to support the conduct of LTFU studies, sponsors should take steps to ensure that enrollment processes do not introduce bias, encouraging all eligible patients to participate.[18]

**C3**

**Some patients may be eligible for more than one LTFU protocol.**

**R3.1:** The fact that some participants and patients may be eligible for more than one LTFU protocol demonstrates a potentially increasing need for the creation of master/umbrella LTFU protocol(s) for GTs.

**C4**

**In the post-approval setting, the number of patients needed to participate in LTFU will depend on several factors, including the number of participants in the clinical trials, the rarity of the disease, and how much is already known.**

**R4.1:** Exclusion criteria for post-approval LTFU studies should be scientifically and/or ethically justified,[8] as results will be more reliable with higher enrollment numbers. A subset of the post-approval population would not be appropriate in rare disease settings.[8] The post-approval population will likely have heterogeneity (e.g., some patients may have had other conditions or interventions). Unjustified exclusion criteria may introduce bias and preclude the collection of important data on safety and effectiveness in relevant subpopulations.

**C5**

**Patient input is important to ensure that the informed consent documents and process are robust.**

**R5.1:** Patient representatives should review and potentially co-author plain-language informed consent, assent, and re-consent (e.g., at age of majority) documents.

**R5.2:** 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.

**C6**

**Community education and engagement are important for supporting LTFU enrollment.** Engagement is resourced with onboarding, training, accessibility support, and fair compensation.

**R6.1:** Sponsors should consider developing mechanisms to educate patients, communities, and health care providers about the importance of LTFU research and data collection.

**R6.2:** As noted above, sponsors should consider involving patient advocacy groups or networks to get feedback on the design of the LTFU study and generate interest in and support for the study.[68]

**R6.3:** Study participants should understand the importance and value of ongoing LTFU research and data collection and be recognized for their contributions.

**C7**

**For the results and conclusions to be accurate, the LTFU study population should be representative of the population as a whole.**

**R7.1:** The study should pre-define and monitor recruitment goals over time, including subpopulations or categories, as appropriate.

**C8**

**Over the course of an LTFU study, knowledge will grow and there may be a need to communicate changes in the GT's risk/benefit profile.[80]**

**R8.1:** Important changes to the risk and/or benefit profile of a GT may necessitate the timely provision of information to participants. In the context of LTFU for GTs, a participant or patient cannot generally withdraw from the intervention itself but only from the LTFU. However, depending on the nature of the new information, participants may have increased or decreased motivation to remain engaged with follow-up.

- To provide new information to participants, possible approaches include the use of an addendum to the original informed consent or oral disclosure. Both processes can be documented in the research records.[80]

## V. Participant Retention and Withdrawal Criteria

The right of study participants to withdraw is a key requirement for the ethical conduct of research.[66] Notably, after receiving a GT in a clinical trial, withdrawal from the ‘research’ is not possible in a traditional sense, as modifications to a person’s genes may persist. Similarly, patients who receive approved GTs cannot withdraw from the intervention, as would be typical for most pharmaceutical products.

When participants withdraw from LTFU, they are giving up opportunities for safety monitoring that may not be replicated in clinical care. This may increase the risk of delayed detection of health issues at the individual level and will decrease the chance that adverse reactions are identified at the aggregate level to alert the community. Rare adverse events that may be associated with the GT are difficult to identify and characterize; retention of all participants, therefore, is important.

However, retention is challenging for LTFU studies, not only because of their duration, but also because participation may involve long-distance travel to academic medical centers, invasive testing, significant out-of-pocket costs, and conflicts with other obligations.[39, 40] Participants who have regained health may prefer to opt out of elective—and inconvenient—medical appointments. They may also transition into different stages of life: going to college, moving to a different geographic location, getting a job, or retiring. Alternatively, participants who did not realize health improvements may find it challenging to adhere to LTFU commitments, depending on what is asked and the supports that are available. All of these complexities can impact the participants’ ability and desire to continue with the LTFU study.

Incomplete datasets pose challenges to the accurate evaluation of safety and can be problematic for regulatory submissions.[77] If a significant number of participants drop out, the data may not be representative or may be biased in a scientifically significant way, which may lead to incorrect interpretations and conclusions. Indeed, **“FDA recommends sponsors make every effort to prevent loss to follow-up to the extent feasible for completion of LTFU observations.”**[7]

## 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])

**C2**

**R2.2:** LTFU study designers should carefully consider eliminating non-critical and exploratory endpoints in order to simplify data collection and reporting, and minimize the overall burden on investigators, sites, and patients. (see [68])

**R2.3:** Sponsors should determine whether the planned study visits and procedures are likely to pose an impediment that may limit recruitment or negatively impact retention for the specific patient population involved; if so, changes to the protocol that are aligned with patient needs and long-term retention in the study should be considered. [68]

**C3**

**Sponsors should consider what measures and operational approaches to include in the LTFU study design to maximize the number of participants that complete the study, while also protecting and respecting their right to withdraw. [68]**

**R3.1:** Retention mechanisms (e.g., reminders, visit cadence, flexibility, decentralized elements, and incentives) should be developed with patient representatives.

**R3.2:** Sponsors should incorporate methods to monitor retention over time relative to key performance indicators, which are quantifiable, measurable targets that can be used to track and evaluate performance against goals.

**R3.3:** LTFU study designers should plan for anticipated transitions of the participant's journey/care (e.g., potential moves) and the implications for the participant, healthcare providers involved with LTFU, and the research team, with an aim to render continued participation in LTFU as feasible and convenient as possible.

**C3**

**R3.4:** It is best if the protocol offers participants the flexibility to choose to complete in-person visits at different study sites and/or via decentralized visits, including telehealth options.

**R3.5:** LTFU study sponsors should reimburse participants for out-of-pocket expenses, and/or support them with transportation, childcare, and eldercare. Reimbursement for time and burden should be considered.

- If reimbursement costs are prohibitive, then the financial burden on participants may be significant. There will be potential bias in who can remain in the study (i.e., wealthier participants), and protocol redesign should be considered.

**R3.6:** Sponsors should consider ways to mitigate issues that may arise if the participants' insurance coverage policies do not transfer across state lines, or if their insurance coverage changes due to employment or other change (e.g., loss of entitlements).

**R3.7:** The incorporation of ethically appropriate incentives, i.e., tokens of appreciation, payment for task completion, or the introduction of elements of 'gamification'[77] should be considered to keep participants engaged and active in continuing LTFU.

**C4**

**Bidirectional communication is ethically important and can help keep participants and patients engaged.** CIOMS ethical guidelines on human research note that in long-term studies, researchers should check in with participants to confirm their willingness to continue, “even if there are no changes in the design or objectives of the research.” [81]

**R4.1:** To support retention, participant and patient engagement, including bi-directional communication and information sharing, is critical.

**C4**

**R4.2:** Messages and reminders can be shared with participants via digital platforms, portals, texts, apps, and newsletters.[77]

- Communications can include updates about the participant's progress on the study, appreciation for the contributions the participant is making to science and community, and countdowns to the next check-in/visit.[77]
- Regular return of actionable and interpretable individual and/or aggregate LTFU results is a benefit to participants and may substantiate their engagement with the study.
  - Sharing aggregated PROs may help participants interpret their own experiences relative to the larger study population.

**R4.3** The FDA recommends that LTFU participants be provided with informational brochures and laminated wallet-sized cards with the investigator's contact information.[2]

**R4.4:** Sponsors should also encourage patients to share their perspectives, information, and data.

- FDA suggests that researchers consider providing participants with ways to record and share health-related events. Provision of this information on a digital platform could facilitate the accessibility and preservation of this information.

**“Various technologies and tools may support the patient's participation in LTFU data collection, from mobile phone apps to connected wearable devices or online platforms to inform, engage, and reward patients for their contributions. The use of such tools should be considered, ideally in collaboration with patients (or caregivers), throughout the study phases, from study design and enrollment to conduct and evidence dissemination.”**

**—de Haart et al.[61]**

**C5**

**There may be warning signs that participants are at risk of being ‘lost-to-follow-up’ (i.e., missed appointments).**

**R5.1:** The LTFU protocol should describe the outreach process in these situations, including clarifying if there are additional supports available to enable the participant’s continuation. It should also clarify who is responsible for these efforts.[43, 68]

- The plan should clarify specific ways that participants should be contacted (e.g., email, text, phone, mail, etc.) and describe whether the investigator(s) may seek to contact the participant via a designated third-party (e.g., doctor, family member).
- The benefits of LTFU participation, on both individual and aggregate levels, should be reviewed.

**R5.2:** With planning and specification in the protocol, sponsors may be able to offer participants a “step-down” approach as an alternative if they indicate they want to withdraw. The “step-down” approach should map out the different levels of data collection per therapeutic area/study. It should define a minimal data collection level (e.g., all-cause mortality data), as an alternative to complete loss to follow-up.

**R5.3:** The LTFU protocol should describe how the ‘step-down’ process works, if there is one. Options could include minimizing the frequency of data collection, eliminating certain procedures, collection of only AEs, EHR access, or survival tracking rather than complete withdrawal.

**R5.4:** Whether alternate data collection methods or ‘step-downs’ should be incorporated into the initial informed consent, allowing participants to opt in from the start of the study, should be considered. This may allow the acquisition of data from the EHR, if the data are already collected or if the participant is unable to be reached.

**C6**

**Despite best efforts to support retention, some participants will withdraw from LTFU.**

**R6.1:** The LTFU protocol (and Statistical Analysis Plan) should include what process will be followed if a participant discontinues participation or is unable to be reached. For example, there may be critical LTFU data that could still be collected through EHRs (with appropriate pre-consent)[68] or from public resources (e.g., U.S. National Death Index).[82]

**R6.2:** The LTFU protocol should also prespecify the analytic plan for data that are differentially obtained or missing.[68]

## VI. Signal Detection and Safety Reporting

Pharmacovigilance involves scientific activities aimed at detecting, assessing, understanding, and preventing drug-related adverse events or problems.[19] Signal detection is the process of searching for and identifying potential safety concerns with drugs or biologics and is a key part of pharmacovigilance. Notably, spontaneous reports are an example of passive surveillance (e.g., from medical professionals or patients) and are one of the key mechanisms for the identification of adverse drug reactions in the post-clinical trial period.[83]

Pharmacovigilance for GTs raises unique challenges for a variety of reasons. Because GTs often treat serious diseases with associated morbidities, it can be difficult to determine whether adverse events are associated with the GT or another factor, as discussed above.[19] Also, when GTs are administered only once, assessing the causality of adverse events by product dechallenge (seeing if the symptom goes away when the drug or product is stopped) and rechallenge (seeing if the symptom returns when the drug or product is reinitiated) is not possible.[19] Finally, because GTs often target rare diseases, there may be a limited number of participants in clinical trial datasets used to evaluate safety initially. As an example, onasemnogene abeparvovec (Zolgensma®), a GT used to treat spinal muscular atrophy type 1 in infants and young children, received approval based on data from 44 pediatric patients; concerns about thrombotic microangiopathy were only identified after analysis of post-approval data, which included over 500 patients.[19]

For GTs, therefore, the investigation of safety signals is challenging because the participant and patient populations are small and because confounding factors, including co-morbidities and complex treatment histories, complicate causality assessments.[19] Further, GT-treated diseases, particularly rare diseases, often do not have a well-documented natural history of the condition (or they may have a documented natural history that is out-of-date, due to the introduction of new therapies). In pediatric diseases that have significant mortality, data on natural history may not be available if patients do not survive past a certain age.

Unique challenges in the context of pharmacovigilance for GTs have led to the identification of specific approaches to mitigate risk, e.g., through the use of immunomodulators such as corticosteroids to prevent immune-mediated toxicities[19] and to the development of various international guidance documents on this issue, particularly on LTFU (see section on [Regulatory Guidance](#)).

## CONSIDERATIONS AND RECOMMENDATIONS

### C1

**Although LTFU studies are typically not blinded or randomized, they are conducted to evaluate the safety of GTs, a new therapeutic class with known long-term risks, typically involve vulnerable populations, and are usually conducted at multiple sites.** These characteristics can be used to justify the establishment of a Data Safety Monitoring Board (DSMB, also termed a Data Monitoring Committee, DMC) for a study.[84]

**R1.1:** Sponsors should consider whether a specific mechanism, such as a 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.

- According to the U.S. National Center for Advancing Translational Sciences, a DSMB “monitors the safety of study participants and the effectiveness of the study investigational therapy during a clinical trial.” [85]

**C1**

- A DSMB reviews data at regular intervals to evaluate participant safety, study conduct and progress, and the effectiveness of the investigational therapy.[85]
- According to the U.S. NIH National Heart, Lung, and Blood Institute, the principal role of an OSMB is to regularly monitor the data from an observational study, review and assess the performance of its operations. [86] The OSMB also makes recommendations with respect to:
  - Performance of individual centers (including possible recommendations on actions to be taken regarding any center that performs unsatisfactorily)
  - Issues related to participant safety, confidentiality, and informed consent, including notification of and referral for abnormal findings
  - Adequacy of study progress in terms of recruitment, quality control, data analysis and publications
  - Issues pertaining to participant burden
  - Impact of proposed ancillary studies and sub-studies on participant burden and overall achievement of the main study goals
  - Overall scientific directions of the study [86]

**C2**

**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.[40]**

This includes determining appropriate next steps for patient care, such as increased patient monitoring to mitigate health risks,[19] and assessment of whether the outcomes or results could potentially be related to the GT.

**R2.1:** 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.

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**C2**

**R2.2:** If LTFU is being conducted in a decentralized manner (i.e., at local clinical care settings and/or via EHR linkage), care providers will also need to be involved in facilitating appropriate next steps. This should also be considered in advanced planning.

**C3**

**The “Guidelines for Preparing Core Clinical-Safety Information on Drugs,” Second Edition Report of CIOMS Working Groups III and IV (1999), includes a process for establishing which adverse events should be considered adverse drug reactions associated with a particular pharmaceutical product and reported as safety information in the Development Core Safety Information (DCSI) in the Investigator’s Brochure.** These guidelines explicitly note that it is not possible to be specific about the exact criteria for adverse drug reaction determinations, but that relevant factors (it provides a list of 39 “Threshold Criteria,”) should be considered; see [CIOMS Threshold Criteria Table](#) below.[87] For serious events, the strength of association is particularly important.[87]

**R3.1:** In order to assess the association and/or causality of potential related adverse events that are identified during the course of LTFU, follow-up procedures should be conducted.[2] These activities may include the collection of samples for follow-up analysis, which may involve biopsy or autopsy, if the patient has died.[2]

**R3.2:** The analysis of samples may require participation of investigators outside of the clinical team with expertise in pathology, immunology, and state-of-the-art DNA analysis methods. Consulting with experts prior to sample collection can ensure that the most informative samples are collected using appropriate methods.

- Specific tests may include blood tests, cytogenetic and histological analysis, PCR, HLA typing, or deep sequencing, which involves using next-generation technologies to sequence a specific region in the genome multiple times to ensure accuracy and sensitivity.[2]

**C3**

- For **example**, to determine whether secondary malignancies were caused by CAR T GTs, polymerase chain reaction and genomic next-generation sequencing tests were performed to determine if the CAR transgene was detectable in a malignant clone.[88]
- In another **example**, tumor and non-tumor tissue from patients who developed solid tumors after AAV GT were analyzed to determine whether AAV was involved in the malignancy, which included pathology and next-generation DNA sequencing studies.

**R3.3:** Assessment of association or causality may need to involve the analysis of population data (e.g., rate of events) to determine if adverse events could be related to the GT.

- When three cases of thrombotic microangiopathy were detected within one year of onasemnogene abeparvovec (Zolgensma®) administration were identified in a post-approval database of 500 treated patients, causality was suspected because yearly incidence rates of TMA are estimated at 1-3 cases per million in the general population.[19]

**R3.4:** For LTFU for GTs, adverse events that may be specifically related to receipt of the GT should be distinguished from those that may be caused by other procedures the participant or patient may have received (e.g., conditioning, chemotherapy).

**C4**

**With regards to safety reporting, sponsors must satisfy regulatory requirements in applicable jurisdictions.**

**R4.1:** According to the FDA, as the LTFU study proceeds, study sponsors must follow applicable IND safety reporting requirements in 21 CFR 312.32. [2] This involves reporting potential serious risks (related to the investigational product) to the agency and all participating investigators, no later than 15 calendar days after the sponsor determines the information qualifies for reporting, as described in 21 CFR 312(c)(1).

**C4**

**R4.2:** FDA guidance recommendations also include submission of annual reports summarizing all IND safety reports submitted during the past year (information for the LTFU Observation Annual report and a sample template are provided as appendices in FDA guidance).[2]

**R4.3:** The EMA's main LTFU guidance refers to the European Union's rules for routine pharmacovigilance and states that Annual Safety Reports and Periodic Safety Update Reports are required for investigational and marketed GT products, respectively.[16]

**R4.4:** The NMPA also states that safety reporting must proceed in accordance with "relevant regulatory requirements" and includes periodic update reports that summarize adverse events.[14]

**C5**

**Detection of safety concerns in LTFU studies warrants timely communication to participants as well as the patient, scientific, medical, and regulatory communities.[89]**

**R5.1:** Sponsors should consider how important information will be communicated to study participants.[68]

**R5.2:** 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.

- Safety signals may trigger additional investigation and/or data analysis, protocol amendments, communications to study participants, and/or referral to clinical care, as appropriate.

**R5.3:** The protocol should specify triggers for updating the informed consent as well as information in the Investigator's Brochure (IB), e.g., Relevant Information Summaries (RIS). For significant findings, this process should be expedited by both study sponsors, study sites, and IRBs/ECs.

**R5.4:** There is a need to determine the right balance between transparency and avoiding patient and/or community distress. Sponsors and investigators may face difficult decisions about when to report findings of uncertain significance to patients (e.g., related to insertion site analysis). The findings may have unknown significance, or the test results could also involve inconsistent findings if different tests lead to alternate conclusions. Premature reporting risks unnecessary alarm, while delay in reporting risks the perception of withholding information.

### CIOMS Threshold Criteria Table.

CIOMS Threshold Criteria [for determining when adverse events should be added to a product's core safety information]. *This table of CIOMS Threshold Criteria was developed by CIOMS [87] and is recreated below. Threshold criteria are ranked in terms of importance (via survey of CIOMS committee/working group members).*

- Evidence from individual cases
- ◆ Evidence from Clinical Trials/Studies
- \* Other factors
- Supportive evidence from both the prior sources,
- ^ Previous Knowledge of the Adverse Event or the Drug/Class, including the metabolites

|                                                                                                                                               |   |
|-----------------------------------------------------------------------------------------------------------------------------------------------|---|
| 1. Positive rechallenge [when drug is reintroduced, symptom reappears]                                                                        | ■ |
| 2. There is a positive outcome in a study specifically designed to investigate the association between the drug and the adverse drug reaction | ◆ |
| 3. There are statistically significant differences                                                                                            | ◆ |
| 4. It is a recognized consequence of overdosage with the drug                                                                                 | ^ |
| 5. There is pharmacokinetic evidence (for interactions)                                                                                       | ^ |
| 6. Corroborative evidence from different methods of investigation (e.g., clinical trials, animal models)                                      | ◆ |
| 7. There is a relative increase in frequency in treated group over placebo                                                                    | ◆ |
| 8. There is a known mechanism                                                                                                                 | ^ |
| 9. Recognized class effect of the drug                                                                                                        | ^ |
| 10. Definitive cases                                                                                                                          | ■ |
| 11. Consistency between cases in the pattern of presenting symptoms                                                                           | ● |
| 12. Similar findings in animal models                                                                                                         | ^ |
| 13. Consistency of time to onset between cases reported                                                                                       | ● |
| 14. Closeness of the drug's characteristics with those of other drugs known to cause the ADR, e.g., being in the same therapeutic class       | ^ |
| 15. Similar adverse reactions are already recognized for the drug                                                                             | ^ |

**C5**

- Evidence from individual cases
- ◆ Evidence from Clinical Trials/Studies
- \* Other factors
- Supportive evidence from both the prior sources,
- ^ Previous Knowledge of the Adverse Event or the Drug/Class, including the metabolites

|                                                                                                        |   |
|--------------------------------------------------------------------------------------------------------|---|
| 16. Evidence from clinical trials rather than from spontaneous cases                                   | ◆ |
| 17. The time to onset is plausible in the cases                                                        | ■ |
| 18. Positive de-challenges [symptoms disappear when drug is removed]                                   | ■ |
| 19. An identifiable subgroup at particular risk                                                        | ● |
| 20. High frequency of reports                                                                          | ● |
| 21. Biological plausibility                                                                            | ^ |
| 22. The adverse experience when it occurs in normal clinical practice is usually drug-related          | ^ |
| 23. There is evidence from observational post-marketing surveillance studied                           | ◆ |
| 24. Lack of confounding factors in the reported spontaneous cases                                      | ■ |
| 25. The amount and duration of exposure is appropriate in the patients                                 | ■ |
| 26. There is a consistent trend in studies, even though not statistically significant                  | ◆ |
| 27. The studies identifying the Adverse Drug Reaction (ADR) are well developed/designed                | ◆ |
| 28. The drug is known to affect the same body system as the Adverse Drug Event (ADE) in some other way | ^ |
| 29. Corroboration of the accuracy of the spontaneous case histories                                    | ■ |
| 30. Individual cases considered probably due to the drug by the person reporting them                  | * |
| 31. A low background incidence of the event                                                            | ^ |
| 32. Cases are clear-cut i.e., easily evaluated                                                         | ■ |
| 33. The data are objective rather than subjective                                                      | * |
| 34. The lack of obvious alternative explanations                                                       | ■ |
| 35. Co-medication unlikely to play a role                                                              | ■ |
| 36. It is reported to occur in (healthy) children                                                      | ■ |
| 37. Cases were reported outside any period of turbulence surrounding the drug                          | * |
| 38. The reporters are of high status (credibility)                                                     | * |
| 39. Although there is no other corroborative evidence, there is no contrary evidence                   | ◆ |

There was one additional criterion on the Threshold Criteria chart in CIOMS Guidelines that was not ranked in the Appendix: Positive specific laboratory or in vitro test<sup>87</sup>.

## 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.

**C2**

**At the present time, combining or linking LTFU data sources may result in operational burdens secondary to the lack of interoperability and the high costs of doing so.[61]** While it is important for sponsors and researchers to carefully consider the optimal fit-for-purpose design and conduct of each LTFU study, it would be scientifically valuable to compare LTFU outcomes in particular diseases or across diseases. It would also be helpful to be able to compare within and across GT types, classes, or categories.

**R2.1:** To maximize the scientific value, interpretability, and interoperability of LTFU studies, LTFU endpoints and data collection should be harmonized and standardized to the extent possible, to facilitate meta-analysis across products and patient populations.

**C3**

**The COMET Initiative, or Core Outcome Measures in Effectiveness Trials Initiative, aims to standardize outcome measures in clinical trials, which makes it easier to compare and synthesize research results across studies, including those that measure long-term outcomes.** In addition to standardizing outcomes across studies for particular diseases, the COMET Initiative also prioritizes patient and community engagement to ensure that the selection of outcomes is patient-centered, rather than researcher/clinician-defined.[92, 93]

**R3.1:** Given the heterogeneity of diseases and types of GTs, it may be difficult to develop core outcome measures for LTFU across all GTs, but the goal of improving standardization should not be lost. Using approaches such as those recommended by the COMET Initiative,[92, 93] standardization of LTFU core outcomes by the type of GT (gene editing vs cell therapy), target tissue, and/or disease-specific measures should be considered.

**C4**

**Master protocol/umbrella trial designs can reduce burdens on sponsors and enable data sharing and interoperability.**

While master protocol trial designs may be feasible for larger companies, they are less accessible to small biotechs and academic investigators.[79]

**R4.1:** GT research and development stakeholders should collaborate to facilitate the use of master protocol trial designs for LTFU.

**C5**

**Timely and transparent reporting and publication of interim and final LTFU study results maximize the scientific value of these important studies and increase generalizable knowledge about methodologies and results,**

**including awareness about potential safety concerns.** Publication of LTFU studies also enables researchers and communities to learn from the successes and challenges of prior efforts.

**R5.1:** Sponsors and researchers should make every effort to share final and interim, as appropriate, aggregate LTFU results publicly and transparently.

**R5.2:** Sponsors should make every effort to publish and report the results from LTFU studies to the highest standards and in a timely manner.

**C6**

**Patient communities will be interested in the study results and have the right to be informed.**

**R6.1:** Plain language summaries of the results should be co-designed with patient representatives, returned to participants, and made publicly available.

**R6.2:** Plain language summaries of patient-driven protocol changes and lessons for future LTFU should be considered.

**R6.3:** The development of lay summaries should follow best practice (see, e.g., the [Good Lay Summary Practice](#) guidance).[94]

**C7**

**Unless LTFU studies are classified as interventional, they are not required to register on or submit results to ClinicalTrials.gov.[51]**

**R7.1:** Sponsors of LTFU studies should exceed regulatory and policy requirements for registration and results reporting required by ClinicalTrials.gov and other clinical trial databases (e.g., [EU Clinical Trials Register](#)). All LTFU studies should be registered, and results should be submitted in accordance with the expectations for interventional studies.

**C8**

**Actionable results have medical or personal decision-making utility, which may include more frequent screenings for cancer or other potential adverse events that may be identified during LTFU.**

**R8.1:** Pre-specify which individual and aggregate results will be shared with participants, as well as how often and under what circumstances.

**R8.2:** In alignment with their choices and autonomy, LTFU participants should be offered the opportunity to receive any actionable and interpretable individual results obtained, including incidental findings or interim results. This includes results that may not be directly actionable but may have personal utility to participants.

## VIII. Operationalizing the LTFU Protocol

Translation of a written protocol to conduct of a study entails planning, ongoing monitoring, and the allocation of resources to enable the goals to be achieved. Salient considerations include: **1)** assigning roles and responsibilities, at the individual, group, and organizational level, **2)** developing clear, bidirectional and systematic lines of communication between sponsors and investigators, and between investigators and participants, **3)** ensuring compliance with all relevant ethical, legal, and regulatory requirements, which may change over time, and **4)** planning periodic review of the protocol, progress, and results to allow revision and adjustments if necessary, and timely planning for next steps.

After these fundamental decisions about authority, roles, responsibilities, and communication are decided, the relevant personnel can delineate the day-to-day operational details of the LTFU study, such as clarifying when and how data will be collected throughout the LTFU study, and who is responsible, when, and with what resources.

## CONSIDERATIONS AND RECOMMENDATIONS

### C1

#### **Operationalizing LTFU protocols is complex and requires significant planning.**

**R1.1:** Early stakeholder engagement with patient groups, advocacy groups, advisory boards, and other relevant parties can provide helpful input on operational factors and, importantly, how to anticipate and navigate potential obstacles.

**R1.2:** Before engaging these stakeholders, determine if these entities will function in advisory capacities or if they will have active roles to play in the LTFU study (e.g., administrators or investigators at an established registry). Also, it is important to determine and specify, in the case of a conflict, who has final decision-making authority, and for which decisions.

### C2

#### **LTFU studies can involve in-person visits at centralized research sites, if necessary.**

**R2.1:** In selecting sites, it is important to assess the feasibility of successful completion of the study at possible locations, if in-person visits are required.[68] Determination of the location and number of LTFU sites should take patient perspectives and experiences into consideration.

**R2.2:** If in-person visits are necessary, consider whether the number, duration, and intervals (spacing) of visits can be minimized or optimized to ease participant burden. For example, consider whether testing (or testing and imaging) could be combined into one visit rather than multiple.

**C3**

**LTFU studies can involve decentralized elements.** Decentralized elements include the use of digital prompts (SMS/email), registry/EHR linkages, telehealth visits, ePRO, other mobile health technologies approaches (e-diaries, questionnaires, remote monitors), or web or mobile applications. DCT platforms may offer sponsors scalability, flexibility, and adaptability for data collection that spans years or decades.[77, 95]

**R3.1:** LTFU study planners should consider ways to decentralize the studies, minimize the number of visits and their durations, and include mobile health technologies.

- Maximizing decentralized elements (such as permitting local laboratory testing) is important for supporting participant retention, as sponsors can experience issues with participant attrition, particularly if travel is required to complete LTFU assessments.

**R3.2:** Researchers should aim to maximize the use of local visits and laboratory assessments rather than requiring travel to central sites and the use of central laboratories.

**C4**

**Participants in LTFU studies may be assessed by investigators, members of the research study team, or healthcare professionals, or they may enter their own data using decentralized technologies.**

**R4.1:** It is important to clearly define study endpoints and describe how they should be measured, collected, and reported to ensure consistency across sites.[68]

**R4.2:** Patients can be asked to report new or worsening symptoms, functional impact, insurance issues, access barriers, or other issues that impact their lives.

**R4.3:** Strategies should be implemented to educate and support participants in self-reporting health issues or concerns.[2] This includes planning and clarifying how they will be informed if there are significant protocol changes.



**R4.4:** Reporting instruments and ePROs should be reviewed with patient representatives to ensure accessibility.

## IX. Clarification of Responsibilities

Communication and coordination of LTFU can be complicated. LTFU studies are a collaborative effort requiring coordination between different entities. Depending on the LTFU study, regulators, academic medical centers, study sites, investigators and their research teams, registries, clinical research organizations, patient groups, HCPs, and sponsors may be involved. Responsibilities as well as the rights of the various entities should therefore be clearly established during the planning for LTFU and if the need arises, clarified as the study progresses.

### CONSIDERATIONS AND RECOMMENDATIONS



**While the involvement of patients and their representatives (including care partners, where appropriate) in the design of LTFU is critical, it is also important to define and clarify their role, and appropriately acknowledge their contributions.**

**R1.1:** Consider how patient representatives are (or will be) trained for their roles. Resources exist that are designed to empower and equip individuals to participate meaningfully as partners in patient-centered research (e.g., the European Patients' Academy for Innovative Medicines (EUPATI) Patient Partner Training, the Canadian Institutes of Health Research (CIHR) Strategy for Patient-Oriented Research (SPOR) resources, others).[96, 97]

**R1.2:** Consider whether patient representatives should hold voting seats on the Protocol Steering Committee and/or on a standing LTFU Advisory Board.

**R1.3:** Consider whether patient partners should be co-investigators and/or co-authors, as appropriate. Collaborators who meet the International Committee of Medical Journal Editors' (ICMJE) authorship criteria should be included as co-authors.[98]

**C2**

**Clinicians may also be involved in collecting data in clinical care settings, which is used in LTFU studies.** After LTFU studies have been completed, clinicians may also be asked to report new potential adverse events (e.g., malignancies) that are detected in patients who have received GTs to regulatory agencies and manufacturers.

**R2.1:** The LTFU protocol should clarify the responsibilities of local health care providers if safety issues arise, related to the assessment of any potential association with the GT and appropriate care of and next steps for the patient/participant.

**C3**

**Sponsors of GT clinical trials may encounter financial, operational, manufacturing, or scientific and medical challenges.** It is possible for approved GTs to be withdrawn from the market, either voluntarily or based on regulatory advisement.

**R3.1:** LTFU protocols should clarify how LTFU commitments will be fulfilled in such cases, and the default plan should be communicated to participants during the informed consent process.

**R3.2:** Study planning should include clarification of entities that have the right to share and publish study results (and with whom, including regulators, trial participants, investigators, clinicians, and the public), and which entities have the responsibility to do so. This may involve specification in contractual agreements.

**C4**

**In the event that a sponsor of a GT ceases to operate or decides to inactivate, transfer, or withdraw an IND, they must consult with regulatory authorities in order to address LTFU obligations.**

**R4.1:** Sponsors should consider the impact of program termination on study participants and the broader patient community and make appropriate plans to fulfill LTFU commitments.[99]

**C4**

**R4.2:** The FDA recommends reaching out to the Office of Tissues and Advanced Therapies (OTAT) with plans for the completion of LTFU.[2] OTAT has been reorganized as the Office of Therapeutic Products (OTP).

**R4.3:** The EMA notes that even if Market Authorization Holders cease to exist, measures should be taken to ensure post-approval safety follow-up of patients. Suggestions include how to inform treating physicians about important monitoring in the context of clinical care.

**C5**

**Sponsors of GT clinical trials should ensure that data on the manufacturing, transport, and delivery of the investigational product are traceable in accordance with regulations.[16]** The EMA notes that in case of bankruptcy or liquidation of a sponsor holding a GT marketing authorization that is not transferred to another entity, traceability data for the product must be transferred to the EMA.[16]The holders of market-authorized products must also establish traceability and maintain records for 30 years after the expiration date of the product, or longer as required by the terms of the marketing authorization.[16]

**R5.1:** The hospital or practice where GT products are administered should establish and maintain a system for patient and product traceability.[16] (notes EMA guidance in preparation)

## 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

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 Design Elements of LTFU Studies for FDA-Approved GTs

Although some information about LTFU studies is publicly available, it is not centralized and can be difficult to find. Below, we provide a table of key design elements of LTFU studies for GTs that have received FDA approval. This central list of LTFU studies will be useful to many stakeholders, for several reasons. This information will help designers of new LTFU studies or seekers of information on interim or final results of LTFU studies of particular GTs. Patients and care partners may be curious about where and how to find information about LTFU studies of specific GTs or classes of GTs. They may be considering whether or not to receive a GT, or they may have already received one in a research or clinical care setting.

While we may expand this list over time, starting with FDA-approved GTs was a reasonable first step. We presume that sponsors of these studies have adhered to FDA requirements as well as recommendations from interactions with FDA officials. The list includes examples of integrated and standalone LTFU protocols (Int vs. SA below), those that are conducted to follow GT clinical trial participants and those that are conducted post-approval (Inv vs. App below), including registry studies (designated “RS”). If you know of a LTFU study for an FDA-approved GT that is not on this list and would like it to be included in updates or revisions, please contact the MRCT Center.

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

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| <b>Aucatzyl</b> | <b>Obecabtagene autoleucl</b> | Autolus | Ex vivo/CAR-T (replication-incompetent lentiviral vector) | <a href="#">NCT04404660</a> | A Study of CD19 Targeted CAR T Cell Therapy in Adult Patients with Relapsed or Refractory B Cell Acute Lymphoblastic Leukaemia (ALL) (aka the FELIX Phase 1b/II study) | N/A      | Int (implied, but not described)   Inv   Inter<br><br>(CT.gov record does not include LTFU protocol description but mentions that patients will be enrolled into LTFU<br><br>Reached out to company, they shared slide from presentation at EHA 2025 Congress, June 12-15, 2025, Milan Italy: "Can CAR T-cell therapy be a definitive treatment for adult R/R B-ALL with-out trans-plant? Long-term findings and predictors of sustained remission for obecabtagene autoleucl", Jae H. Park (MSKCC), et al.<br><br>This presentation references NCT04404660) | Adult patients with relapsed or refractory B cell acute lymphoblastic leukemia (ALL) |
|                 |                               |         |                                                           | <a href="#">NCT03628612</a> | AUTO1-LT1                                                                                                                                                              | 15 years | SA   Int   Obs                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Patients must have received an AUTO CAR T cell therapy on a clinical treatment study |

|                 |                                      |         |                                                           |                             |                                                                                                                                                                  |                       |                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| <b>Aucatzyl</b> | <b>Obecabtagene autoleucel</b>       | Autolus | Ex vivo/CAR-T (replication-incompetent lentiviral vector) | N/A                         | AUTO1-LT2                                                                                                                                                        | 15 years              | SA   App   Obs    | In addition to routine and enhanced pharmacovigilance, the postmarketing safety monitoring of AUCATZYL will include a 15-year long term follow-up (LTFU) observational safety study (AUTO1-LT2), as a postmarketing requirement (PMR) under 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA), to assess the serious risk of secondary malignancies following administration of AUCATZYL.<br><br>This study will enroll 500 adult patients with relapsed or refractory B cell precursor ALL. [100] |
| <b>Beqvez</b>   | <b>Fidanacogene Elaparvovec-dzkt</b> | Pfizer  | In vivo/GT (AAV); single infusion                         | <a href="#">NCT05568719</a> | Safety and Effectiveness of Giroctocogene Fitelparvovec or Fidanacogene Elaparvovec in Patients With Hemophilia A or B Respectively                              | 10 years              | SA   Inv   Inter  | Only participants who received investigational giroctocogene fitelparvovec or fidanacogene eleparvovec and were enrolled in a Pfizer-sponsored study (C0371002, C0371003, C0371005, C3731001, C3731003) are eligible.                                                                                                                                                                                                                                                                                      |
|                 |                                      |         |                                                           | <a href="#">NCT03861273</a> | A Study to Evaluate the Efficacy and Safety of Factor IX Gene Therapy With PF-06838435 in Adult Males With Moderately Severe to Severe Hemophilia B (BENEGENE-2) | Maximum up to 6 years | Int   Inv   Inter | Adult male participants with moderately severe to severe hemophilia B (participants that have a Factor IX circulating activity of 2% or less)                                                                                                                                                                                                                                                                                                                                                              |
|                 |                                      |         |                                                           | <a href="#">NCT03307980</a> | Long-term Safety and Efficacy Study and Dose-Escalation Substudy of PF 06838435 in Individuals With Hemophilia B                                                 | Up to 6 years         | SA   Inv   Inter  | Participants with Hemophilia B who were previously treated in the C0371005 (formerly SPK-9001-101) study                                                                                                                                                                                                                                                                                                                                                                                                   |

|                 |                                 |                             |                                   |                             |                                                                                                                                                |          |                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| <b>Breyanzi</b> | <b>Lisocabtagene Maraleucel</b> | Juno (Bristol-Myers Squibb) | Ex vivo/CAR-T (lentiviral vector) | <a href="#">NCT06788652</a> | A Study of Patients With Relapsed/Refractory Mantle Cell Lymphoma Treated With Lisocabtagene Maraleucel in the Post-Marketing Setting          | 15 years | SA   App   Obs   RS | Participants must have been treated in the postmarketing setting with at least 1 infusion of lisocabtagene maraleucel (Lisocel) used for the treatment of Mantle Cell Lymphoma (MCL) according to the FDA-approved indication and dose range (ie, per the US Prescribing Information) and with a product meeting the specifications for commercial release approved in the USA. The study population will include adults diagnosed with Relapsed/Refractory Mantle Cell Lymphoma (MCL) who are registered within the Center for International Blood and Marrow Transplant Research (CIBMTR) registry and have been treated with lisocabtagene maraleucel.                                       |
|                 |                                 |                             |                                   | <a href="#">NCT06794268</a> | A Study to Patients With Relapsed/Refractory Follicular Lymphoma Treated With Lisocel (Lisocabtagene Maraleucel) in the Post Marketing Setting | 15 years | SA   App   Obs   RS | Participants must have been treated in the post-marketing setting with at least 1 infusion of lisocabtagene maraleucel (lisocel) used for the treatment of relapsed/refractory (R/R) follicular lymphoma (FL), including FL Grade 1, Grade 2 and Grade 3a, within the FDA-approved indication and dosage per the United States Prescribing Information (USPI) and product specifications approved for commercial release in the USA. This study population will include adults with relapsed/refractory follicular lymphoma that are being treated with lisocabtagene maraleucel and are registered within the Center for International Blood and Marrow Transplant Research (CIBMTR) registry. |

|                 |                                  |                             |                                                           |                             |                                                                                                                                                                           |          |                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| <b>Breyanzi</b> | <b>Lisocabtagene Maraleucel</b>  | Juno (Bristol-Myers Squibb) | Ex vivo/CAR-T (lentiviral vector)                         | <a href="#">NCT06788639</a> | A Study of Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma Treated With Lisocabtagene Maraleucel in the Post-Marketing Setting | 15 years | SA   App   Obs   RS | Participants must have been treated in the post-marketing setting with ≥1 infusion of lisocabtagene maraleucel used for the treatment of relapsed/ refractory (R/R) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) within the approved indication and dosage per the United States Prescribing Information (USPI) and product specifications approved for commercial release in the USA. The study population will include adults with relapsed/refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) that are being treated with lisocabtagene maraleucel and are registered within the Center for International Blood and Marrow Transplant Research (CIBMTR) registry. |
| <b>Carvykti</b> | <b>Ciltacabtagene Autoleucel</b> | Janssen (Johnson & Johnson) | Ex vivo/CAR-T (replication-incompetent lentiviral vector) | <a href="#">NCT05201781</a> | A Long-term Study for Participants Previously Treated With Ciltacabtagene Autoleucel                                                                                      | 15 years | SA   Inv   Inter    | Adults administered with ciltacabtagene autoleucel (ciltacel)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                 |                                  |                             |                                                           | <a href="#">EUPAS49370</a>  | A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel                                              | 15 years | Int   App   Non-int | Adult patients with multiple myeloma. This study aims to document the short- and long-term safety of adult patients with multiple myeloma receiving ciltacabtagene autoleucel in the post-authorization setting per the health authority-approved product information in the respective country/region.                                                                                                                                                                                                                                                                                                                                                                                                                       |

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| <b>Casgevy</b>  | <b>Exagamglogene Autotemcel)</b>         | Vertex Pharmaceuticals Incorporated | Ex vivo/GT (autologous hematopoietic stem cells genetically modified via CRISPR editing at BCL11A enhancer region) | <a href="#">NCT04208529</a>      | A Long-term Follow-up Study in Participants Who Received CTX001                                                                                                              | Up to 15 years | SA   Inv   Inter        | Pediatric and adult participants who received CTX001 in parent studies 111 (NCT03655678) 141 (NCT05356195) or 161 (NCT05477563) (trans-fusion-dependent $\beta$ -thalassemia [TDT] studies) or Study 121 (NCT03745287) or 151 (NCT05329649), 161(NCT05477563),171 (NCT05951205) (severe sickle cell disease [SCD] studies) |
|                 |                                          |                                     |                                                                                                                    | <a href="#">EU-PAS1000000504</a> | Long-term registry-based study of patients with transfusion-dependent $\beta$ -thalassemia (TDT) or sickle cell disease (SCD) treated with exagamglogene autotemcel (exacel) | Up to 15 years | SA   App   Non-int   RS | Patients with TDT or SCD treated in participating transplant centers reporting data to EBMT or CIBMTR Registry and receiving Casgevy or allogeneic-HSCT.                                                                                                                                                                   |
| <b>Elevidys</b> | <b>Delandistrogene moxeparvovec-rokl</b> | Sarepta Therapeutics                | In vivo/GT (AAV based, delivers transgene to produce micro-dystrophin)                                             | <a href="#">NCT05967351</a>      | A Long-term Follow-up Study of Participants Who Received Delandistrogene Moxeparvovec (SRP-9001) in a Previous Clinical Study (EX-PEDITION)                                  | Up to 5 years  | SA   Inv   Inter        | Participants who received delandistrogene moxeparvovec in a previous clinical study                                                                                                                                                                                                                                        |
|                 |                                          |                                     |                                                                                                                    | <a href="#">NCT03375164</a>      | A Gene Transfer Therapy Study to Evaluate the Safety of Delandistrogene Moxeparvovec (SRP-9001) in Participants With Duchenne Muscular Dystrophy (DMD)                       | Up to 5 years  | Int   Inv   Inter       | Male children with DMD                                                                                                                                                                                                                                                                                                     |

|                 |                                              |                              |                                                                                                                                                              |                             |                                                                                                                                                        |                   |                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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| <b>Encelto</b>  | <b>Revakinagene<br/>Tarorecel-lwey</b>       | Neurotech<br>Pharmaceuticals | Ex vivo/GT<br>(genetically<br>modified allogeneic<br>retinal pigment<br>epithelial (RPE)<br>cells, which<br>produce ciliary<br>neurotrophic<br>factor (CNTF) | <a href="#">NCT06971939</a> | Phase 4 Study: Long-<br>term Safety and Efficacy<br>of NT-501 in MacTel<br>Type 2, Including Sham<br>Procedure Participants                            | 5 years           | Both   Both (prior<br>participants in<br>clinical trials-<br>but those who<br>received sham<br>can receive<br>intervention in<br>this Phase 4<br>study)   Inter | Male or female adult participants<br>who previously completed an<br>NT-501 MacTel clinical study and<br>who meet other characteristics<br>(placed into different arms)                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Hemgenix</b> | <b>Etranacoene<br/>Dezapavovec-<br/>drlb</b> | CSL Behring                  | In vivo/<br>GT (AAV6-<br>based using<br>liver specific<br>promoter)                                                                                          | <a href="#">NCT05962398</a> | Long-term Follow-up<br>Study of Male Adults<br>With Hemophilia B<br>Previously Treated<br>With Etranacogene<br>Dezaparvovec (CSL222)<br>(IX-TEND 3003) | Up to 10<br>years | SA   Inv   Obs                                                                                                                                                  | Adult male participants<br>with hemophilia B who were<br>previously treated with<br>CSL222 in study CSL222_2001<br>(NCT03489291) or CSL222_3001<br>(NCT03569891)                                                                                                                                                                                                                                                                                                                                                                        |
|                 |                                              |                              |                                                                                                                                                              | <a href="#">NCT06008938</a> | An Observational Cohort<br>Study to Characterize the<br>Effectiveness and Safety<br>of HEMGENIX® in Patients<br>With Hemophilia B (IX-<br>TEND 4001)   | Up to 15<br>years | SA   App   Obs  <br>RS                                                                                                                                          | Patients with hemophilia B<br>who have been treated with<br>HEMGENIX and are enrolled<br>in either the sponsor's study<br>or the ATHN Transcends study<br>NCT04398628 (Hemophilia<br>Cohort, Gene Therapy Outcomes<br>Arm), and patients who receive<br>routine prophylaxis treatment<br>with FIX replacement therapy<br>that are en-rolled in the ATHN<br>Transcends study (Hemophilia<br>Cohort, Natural History Arm), or<br>a similar registry. All patients will<br>provide signed informed con-sent<br>required for participation. |
|                 |                                              |                              |                                                                                                                                                              | <a href="#">NCT03569891</a> | HOPE-B: Trial of AMT-061<br>in Severe or Moderately<br>Severe Hemophilia B<br>Patients                                                                 | 5 years           | Int   Inv   Inter                                                                                                                                               | Adult (≥18 years) male subjects<br>with severe or moderately severe<br>Hemophilia B and have been<br>treated with factor IX protein                                                                                                                                                                                                                                                                                                                                                                                                     |

|                |                                    |                        |                                                                                    |                             |                                                                                                                                                                                                                               |                                                          |                         |                                                                                                                                                                                                                                                                 |
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| <b>Imlygic</b> | <b>Talimogene Laherparepvec</b>    | Amgen                  | Genetically modified oncolytic viral therapy                                       | <a href="#">EUPAS43115</a>  | A Registry Study to Evaluate the Survival and Long-Term Safety of Subjects Who Previously Received Talimogene Laherparepvec in Amgen or BioVEX-Sponsored Clinical Trials                                                      | -11 years                                                | SA   Inv   Non-int   RS | Subjects must have received at least one dose of talimogene laherparepvec on an Amgen or BioVEX-sponsored clinical trial for any tumor type and must have discontinued treatment and participation, including long-term follow-up (if applicable) in that trial |
| <b>Keblidi</b> | <b>Eladocagene Exuparvovec-neq</b> | PTC Therapeutics, Inc. | In vivo (Recombinant adeno-associated virus serotype 2 (rAAV2)-based gene therapy) | <a href="#">NCT04903288</a> | A Study of Smart-Flow Magnetic Resonance (MR) Compatible Ventricular Cannula for Administering Eladocagene Exuparvovec to Pediatric Participants                                                                              | 5 years                                                  | Int   Inv   Inter       | Pediatric participants with aromatic L-amino acid decarboxylase (AADC) deficiency                                                                                                                                                                               |
|                |                                    |                        |                                                                                    | <a href="#">EUPAS105422</a> | A Two-Part, International, Real-World, Observational Registry of Participants Diagnosed with Aromatic L-Amino Acid Decarboxylase Deficiency (AADC-d) With or Without Treatment With Eladocagene Exuparvovec (PTC-AADC-MA-406) | 10 years minimum                                         | SA   App   Non-int      | Participants with AADC-d                                                                                                                                                                                                                                        |
| <b>Kymriah</b> | <b>Tisagenlecleucel</b>            | Novartis               | Ex vivo/CAR-T (replication-deficient lentiviral vector)                            | <a href="#">NCT02445222</a> | CAR-T Long Term Follow Up (LTFU) Study (PAVO)                                                                                                                                                                                 | Up to 15 years                                           | SA   Inv   Inter        | Patients are enrolled following completion or early discontinuation from a Novartis sponsored or supported study of CAR T-Cell treatment                                                                                                                        |
|                |                                    |                        |                                                                                    | <a href="#">EUPAS32497</a>  | Registry study to assess the long-term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel                                                                                                        | Cohort 1: 5-year enrollment; Cohort 2: 3-year enrollment | SA   App   Non-int   RS | In cohort 1: 2,500 patients with either r/r pediatric/young adult B-cell ALL (at least 1,000 patients) or with r/r large B-cell lymphoma (at least 1,500 patients); In cohort 2: 300 patients with r/r follicular lymphoma.                                     |

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| <b>Kymriah</b>  | <b>Tisagenlecleucel</b>           | Novartis             | Ex vivo/CAR-T (replication-deficient lentiviral vector)                                                                                                         | <a href="#">NCT02445248</a> | Study of Efficacy and Safety of CTL019 in Adult DLBCL Patients (JULIET)                                     | 15 years              | Int   Inv   Inter   | Long-term clinical out-comes of tisagenlecleucel in patients with relapsed or refractory aggressive B-cell lymphomas (JULIET): a multicentre, open-label, single-arm, phase 2 study |
|                 |                                   |                      |                                                                                                                                                                 | <a href="#">NCT06785818</a> | Long-term Follow up Local Registry Study of Kymriah in South Korea                                          | Up to 15 years        | SA   App   Obs      | Patients with B-Lymphocyte Malignancies Treated with Tisagenlecleucel in South Korea                                                                                                |
| <b>Lenmeldy</b> | <b>Atidarsagene Autotemcel</b>    | Orchard Therapeutics | Ex vivo/GT (autologous hematopoietic stem cells genetically modified with lentiviral vector expressing ARSA gene, which produces ARSA enzyme, deficient in MLD) | <a href="#">NCT04283227</a> | OTL-200 in Patients With Late Juvenile Metachromatic Leukodystrophy (MLD)                                   | 8 years               | Int   Inv   Inter   | Late Juvenile MLD patients                                                                                                                                                          |
|                 |                                   |                      |                                                                                                                                                                 | <a href="#">NCT01560182</a> | Gene Therapy for Metachromatic Leukodystrophy (MLD)                                                         | Not clear from record | Int   Inv   Inter   | Patients affected by Metachromatic Leukodystrophy (MLD)                                                                                                                             |
|                 |                                   |                      |                                                                                                                                                                 | <a href="#">NCT03392987</a> | A Safety and Efficacy Study of Cryopreserved OTL-200 for Treatment of Metachromatic Leukodystrophy (MLD)    | Up to 5 years         | Int   Inv   Inter   | Pediatric subjects with pre-symptomatic Early Onset MLD (Late Infantile (LI) to Early Juvenile (EJ) MLD) and early symptomatic EJ MLD                                               |
|                 |                                   |                      |                                                                                                                                                                 | <a href="#">EUPAS48374</a>  | Long-term efficacy and safety follow-up of MLD patients treated with atidarsagene autotemcel (LongTERM-MLD) | Not available         | SA   App   Non-Int  | MLD patients treated with atidarsagene autotemcel (LongTERM-MLD)                                                                                                                    |
| <b>Luxturna</b> | <b>Voretigene Neparvovec-rzyl</b> | Spark Therapeutics   | In vivo/GT (AAV2 vector to provide WT RPE65 gene)                                                                                                               | <a href="#">NCT03602820</a> | Long-term Follow-up Study in Subjects Who Received Voretigene Neparvovecrzyl (AAV2-hRPE65v2)                | 15 years              | SA   Inv   Obs      | Individuals who received the subretinal administration of AAV2-hRPE65v2 (voretigene neparvovecrzyl) in the Phase 1 or Phase 3 clinical trials                                       |
|                 |                                   |                      |                                                                                                                                                                 | <a href="#">NCT03597399</a> | A Patient Registry Study for Patients Treated With Voretigene Neparvovec in US                              | Up to 5 years         | SA   App   Obs   RS | Individuals who received voretigene neparvovec-rzyl in at least one eye.                                                                                                            |

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| <b>Lyfgenia</b>   | <b>Lovotibeglogene autotemcel</b>      | bluebird Bio, Inc. | Ex vivo/genetically modified autologous hematopoietic stem cells using lentiviral vector to deliver modified betaglobin gene | <a href="#">NCT04628585</a> | Long-term Follow-up of Subjects with Sickle Cell Disease Treated with Ex Vivo Gene Therapy                                                                                     | 15 years                                                                          | SA   Inv   Obs      | Subjects with sickle cell disease treated with ex vivo gene therapy product in bluebird bio-sponsored clinical studies                                                                                     |
| <b>Rocktavian</b> | <b>Valoctocogene Roxaparvovec-rvox</b> | BioMarin           | In vivo/ GT (AAV5-based liver specific promoter delivers a B-domain deleted human factor VIII)                               | <a href="#">NCT05768386</a> | A Long-Term Follow-Up Study in Severe Hemophilia A Subjects Who Received BMN 270 in a Prior BioMarin Clinical Trial (270-401) (GENEr8-LTE)                                     | 15 years from dosing (5 years in parent trial, 10 additional years in this study) | SA   Inv   Obs      | Subjects must have completed their primary treatment study in which they were dosed BMN 270. Subjects may enroll in 270-401 even if they have restarted FVIII prophylaxis or other hemophilia A treatment. |
|                   |                                        |                    |                                                                                                                              | <a href="#">EUPAS49071</a>  | ENER8-COAS: A Non-Interventional, Multi-National, Longitudinal Study of Patients Treated with ROCTAVIAN™ (valoctocogene roxaparvovec) (GENEr8-COAS Observational Cohort Study) | N/A                                                                               | SA   App   Non-int  | Patients diagnosed with HA and treated with ROCTAVIAN™ (valoctocogene roxaparvovec                                                                                                                         |
| <b>Skysona</b>    | <b>Elivaldogene autotemcel</b>         | bluebird bio, Inc. | Ex vivo/GT (Lentiviral vector delivers functional ABCD1 into autologous hematopoietic stem cells)                            | <a href="#">NCT02698579</a> | Long-term Follow-up of Participants With Cerebral Adrenoleukodystrophy Who Were Treated With Lenti-D Drug Product                                                              | 15 years                                                                          | SA   Inv   Obs      | Participants with cerebral adrenoleukodystrophy (CALD) who have received Lenti-D Drug Product in a parent clinical study will be expected to participate in this long-term follow-up study.                |
|                   |                                        |                    |                                                                                                                              | <a href="#">NCT06224413</a> | A Study of Participants With Cerebral Adrenoleukodystrophy (CALD) Treated With Elivaldogene Autotemcel (Stargazer)                                                             | 15 years                                                                          | SA   App   Obs   RS | Participants with CALD treated with eli-cel in the post marketing setting at a center in the US that participates in the Registry Study.                                                                   |

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| <b>Tecartus</b> | <b>Brexucabtagene autoleucel</b> | Kite Pharma, Inc. (Gilead) | Ex vivo/CAR-T (retroviral vector)                                                                             | <a href="#">NCT05041309</a> | Long-term Follow-up Study for Participants of Kite-Sponsored Interventional Studies Treated With Gene-Modified Cells                                                                                                                      | Up to 15 years | SA   Inv   Obs                                                                                  | The participants who received an infusion of gene-modified cells and have not died, withdrawn consent, been withdrawn by the investigator, or been lost to follow-up at the time of transition from the completed parent study. |
|                 |                                  |                            |                                                                                                               | <a href="#">EUPAS45813</a>  | Long-term, Non-interventional Study of Recipients of Tecartus for Treatment of Adult Patients With Relapsed or Refractory (R/R) Mantle Cell Lymphoma (MCL) or Adult Patients With R/R B-Cell Precursor Acute Lymphoblastic Leukemia (ALL) | Not available  | SA   App   Non-int                                                                              | Adult Patients With Relapsed or Refractory (R/R) Mantle Cell Lymphoma (MCL) or Adult Patients With R/R B-Cell Precursor Acute Lymphoblastic Leukemia (ALL)                                                                      |
| <b>Tecelra</b>  | <b>Afamitresgene Autoleucel</b>  | Adaptimmune LLC            | Ex vivo/ GT (MAGE-A4)-directed genetically modified autologous T cell immunotherapy (T cell receptor therapy) | <a href="#">NCT04044768</a> | Spearhead 1 Study in Subjects With Advanced Synovial Sarcoma or Myxoid/Round Cell Liposarcoma                                                                                                                                             | 15 years       | Int   Inv   Inter                                                                               | Subjects With Advanced Synovial Sarcoma or Myxoid/Round Cell Liposarcoma                                                                                                                                                        |
| <b>Vyjuvek</b>  | <b>Beremagene Geperpavec</b>     | Krystal Biotech            | In vivo/ Herpes simplex virus 1-based GT delivers COL7A1                                                      | <a href="#">NCT04917874</a> | A Long-term Treatment With B-VEC for Dystrophic Epidermolysis Bullosa                                                                                                                                                                     | 2 years        | SA   Both (for Phase 3 participants and for those who did not participate in the study)   Inter | Participants aged 2 months and older, who have been diagnosed with Dystrophic Epidermolysis Bullosa (DEB)                                                                                                                       |
| <b>Yescarta</b> | <b>Axicabtagene ciloleucel</b>   | Kite Pharma, Inc. (Gilead) | Ex vivo/CAR T (replication-deficient retroviral vector)                                                       | <a href="#">NCT05041309</a> | Long-term Follow-up Study for Participants of Kite-Sponsored Interventional Studies Treated With Gene-Modified Cells                                                                                                                      | Up to 15 years | SA   Inv   Obs                                                                                  | The participants who received an infusion of gene-modified cells and have not died, withdrawn consent, been withdrawn by the investigator, or been lost to follow-up at the time of transition from the completed parent study. |

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| <b>Yescarta</b>  | <b>Axicabtagene<br/>ciloleucel</b>            | Kite Pharma,<br>Inc. (Gilead)   | Ex vivo/CAR<br>T (replication-<br>deficient<br>retroviral vector)           | <a href="#">EUPAS32539</a>                          | Long-term, Non-<br>interventional Study of<br>Recipients of Yescarta®<br>for Treatment of Relapsed<br>or Refractory Diffuse<br>Large B-Cell Lymphoma,<br>Primary Mediastinal Large<br>B-Cell Lymphoma, and<br>Follicular Lymphoma | 20 years          | SA   App  <br>Non-int | Patients treated with YESCARTA<br>(pooled and by indication)                                                                                                                                                                                                                                                                                        |
| <b>Zevaskyn</b>  | <b>Prademagene<br/>Zamikeracel</b>            | Abeona<br>Therapeutics,<br>Inc. | Ex vivo/<br>autologous cell<br>sheet-based GT                               | <a href="#">NCT05708677</a>                         | A Long-Term Extension<br>Study for Participants<br>Previously Treated With<br>EB-101 for the Treatment<br>of RDEB                                                                                                                 | 5 years           | SA   Inv   Obs        | Patient with previous EB-101<br>treatment                                                                                                                                                                                                                                                                                                           |
| <b>Zolgensma</b> | <b>Onasemnogene<br/>abeparvovec-<br/>xioi</b> | Novartis                        | In vivo/GT<br>(AAV9 vector<br>delivers SMN1<br>via intravenous<br>infusion) | <a href="#">NCT06019637</a>                         | A Long-term Safety<br>Study in Brazilian Patients<br>With a Diagnosis of<br>Spinal Muscular Atrophy<br>Treated With Zolgensma<br>(ARISER)                                                                                         | Up to 15<br>years | SA   App   Obs        | The study population will consist<br>of approximately 50 Brazilian<br>pediatric patients with SMA who<br>were treated with Onasemnogene<br>Abeparvovec (Zolgensma®) in the<br>commercial setting, the closed<br>MAP, or the phase IV OFELIA<br>trial. Patients will be recruit-ed in<br>up to 3 centers in Brazil, over one<br>year of recruitment. |
|                  |                                               |                                 |                                                                             | <a href="#">NCT04174157</a><br>(also<br>EUPAS41853) | Registry of Patients With<br>a Diagnosis of Spinal<br>Muscular Atrophy (SMA)                                                                                                                                                      | 15 years          | SA   App   Obs   RS   | The study will enroll at least<br>500 patients with a genetically<br>confirmed diagnosis of SMA. The<br>registry will attempt to enroll all<br>patients treated with OAV-101 in<br>the registry until the end of 2026.                                                                                                                              |
|                  |                                               |                                 |                                                                             | <a href="#">NCT05335876</a>                         | Long-term Follow-up<br>of Patients With Spinal<br>Muscular Atrophy Treated<br>With OAV101 in Clinical<br>Trials (SPECTRUM)                                                                                                        | Up to 5<br>years  | SA   Inv   Inter      | Patients with Spinal Muscular<br>Atrophy and participated in an<br>OAV101 clinical trial                                                                                                                                                                                                                                                            |

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| <b>Zolgensma</b> | <b>Onasemnogene<br/>abeparvovec-<br/>xioi</b> | Novartis              | In vivo/GT<br>(AAV9 vec-tor<br>delivers SMN1<br>via intravenous<br>infusion)                                                                                 | <a href="#">NCT03421977</a> | Long-Term Follow-up<br>Study for Patients From<br>AVXS-101-CL-101 (START)                                                                 | Up to 15<br>years | SA   Inv   Obs         | Patients in the AVXS-101-CL-101<br>gene re-placement therapy clinical<br>trial for SMA Type 1 delivering<br>onasemnogene abeparvovec-xioi<br>will roll over from the previous<br>study into the AVXS-101-LT-001<br>study for continuous safety<br>monitoring for up to 15 years.                                                                    |
|                  |                                               |                       |                                                                                                                                                              | <a href="#">NCT04042025</a> | Long-term Follow-<br>up Study of Patients<br>Receiving Onasemnogene<br>Abeparvovec-xioi                                                   | Up to 15<br>years | SA   Inv   Inter       | Participants in clinical trials<br>for spinal muscular atrophy<br>(SMA) who were treated with<br>onasemnogene abeparvovec-xioi                                                                                                                                                                                                                      |
|                  |                                               |                       |                                                                                                                                                              | <a href="#">NCT06019637</a> | A Long-term Safety<br>Study in Brazilian Patients<br>With a Diagnosis of<br>Spinal Muscular Atrophy<br>Treated With Zolgensma<br>(ARISER) | Up to 15<br>years | SA   App   Obs         | The study population will consist<br>of approximately 50 Brazilian<br>pediatric patients with SMA who<br>were treated with Onasemnogene<br>Abeparvovec (Zolgensma®) in the<br>commercial setting, the closed<br>MAP, or the phase IV OFELIA trial.<br>Patients will be recruit-ed in up to<br>3 centers in Brazil, over one year<br>of recruitment. |
| <b>Zynteglo</b>  | <b>Betibeglogene<br/>autotemcel</b>           | bluebird bio,<br>Inc. | Ex vivo/GT<br>(autologous<br>hematopoietic<br>stem cells<br>genetically<br>modified with<br>lentiviral vector<br>gene therapy<br>functional beta-<br>globin) | <a href="#">NCT02633943</a> | Long-term Follow-<br>up of Subjects With<br>Transfusion-Dependent<br>β-Thalassemia (TDT)<br>Treated With Ex Vivo<br>Gene Therapy          | 15 years          | SA   Inv   Obs         | Subjects with transfusion-<br>dependent β-thalassemia who<br>have been treated with ex vivo<br>gene therapy product in bluebird<br>bio-sponsored clinical studies                                                                                                                                                                                   |
|                  |                                               |                       |                                                                                                                                                              | <a href="#">NCT06271512</a> | A Study of Participants<br>with B-Thalassemia<br>Treated with<br>Betibeglogene<br>Autotemcel                                              | 15 years          | SA   App   Obs  <br>RS | Participants with β-thalassemia<br>treated with beticel in the post<br>marketing setting at a center<br>in the Unit-ed States (US) that<br>participates in the Registry                                                                                                                                                                             |

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| <b>Zynteglo</b> | <b>Betibeglogene autotemcel</b> | bluebird bio, Inc. | Ex vivo/GT (autologous hematopoietic stem cells genetically modified with lentiviral vector gene therapy functional beta-globin) | <a href="#">EUPAS36487</a> | REG-501: A Registry of Patients with $\beta$ -Thalassemia Treated with Betibeglogene Autotemcel                                                                                                                                         | 15 years      | SA   App   Non-int   RS | Patients with $\beta$ -thalassemia treated in Germany with Be-tibeglogene Autotemcel             |
|                 |                                 |                    |                                                                                                                                  | <a href="#">EUPAS41950</a> | A Non-Interventional Registry Study of Patients with $\beta$ -thalassemia to Characterise and Contextualise the Safety and Effectiveness of Betibeglogene Autotemcel (canceled due to decision not to commercialize Zynteglo in the EU) | Not available | SA   App   Non-int   RS | Patients with $\beta$ -thalassaemia treated with betibeglogene autotemcel or allo-HCST in Europe |

## Regulatory Guidance Relating to LTFU of GTs

In this section, we provide a list and characteristics of LTFU-related regulatory guidance from different international regulatory authorities. We have included an exemplar quote or quotes from each document.

| Country or Region | Regulatory Agency or Organization                         | Related Guidance                                                                                                                                                                                    | Publication Year           | Relevant Pages  | Links to English Translation                                                                                                                                                                                                                                                                      | Select Quotes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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| <b>China</b>      | Center for Drug Evaluation, NMPA                          | Guidelines for Long-Term Follow-Up for Clinical Research of Gene Therapy Products aka Technical Guidelines for Long-Term Follow-up Clinical Research of Gene Therapy Products (NMPA-No50-2021) [14] | Effective December 1, 2021 | Entire Document | <a href="https://clinregs.niaid.nih.gov/sites/default/files/documents/china/NMPA-No50-2021_Google-Translation.pdf">https://clinregs.niaid.nih.gov/sites/default/files/documents/china/NMPA-No50-2021_Google-Translation.pdf</a>                                                                   | "The main purpose of long-term follow-up of gene therapy products is to collect the late adverse reactions, and understand the persistence of gene therapy products in the body, so as to identify and reduce long-term risks for patients receiving gene therapy products... Considering the long-term effects of gene therapy products, observe changes in efficacy over time. The situation is also one of the purposes of long-term follow-up, which helps to evaluate the benefits and risks of the product."                                                                                                                                                                                                                                                                                                                              |
| <b>Europe</b>     | EMA Committee for Medicinal Products for Human Use (CHMP) | Guideline on Follow-up of Patients Administered with Gene Therapy Medicinal Products [16]                                                                                                           | October 22, 2009           | Entire Document | <a href="https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-follow-patients-administered-gene-therapy-medicinal-products_en.pdf">https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-follow-patients-administered-gene-therapy-medicinal-products_en.pdf</a> | "Healthcare professionals conduct the clinical follow-up of individual patients in a clinical setting. It includes prevention, screening, monitoring, diagnosis and treatment of diseases, injuries, complications, adverse reactions and medical errors. To collect the appropriate data for detection of delayed adverse reactions, the clinical follow-up protocol needs to have very clear objectives, be hypothesis driven, and be based on appropriate risk assessment (consistent with the risk management plans as these need to be in place at the point of licensing). Careful consideration should be given to the feasibility of long-term monitoring, the value it adds, and imposition on patients and clinicians. Therefore, the clinical follow-up period should only be extended as long as feasible and clinically relevant." |

| Country or Region | Regulatory Agency or Organization                         | Related Guidance                                                                                                        | Publication Year  | Relevant Pages     | Links to English Translation                                                                                                                                                                                                                                                                                                                                                                        | Select Quotes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| Europe            | EMA Committee for Medicinal Products for Human Use (CHMP) | Guideline on Safety and Efficacy Follow-up Risk Management of Advanced Therapy Medicinal Products [8]                   | November 20, 2008 | p. 4, 9, 10, 15-19 | <a href="https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-safety-and-efficacy-follow-risk-management-advanced-therapy-medicinal-products_en.pdf">https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-safety-and-efficacy-follow-risk-management-advanced-therapy-medicinal-products_en.pdf</a>                                                               | <p>“Based on the epidemiology of the target population (disease), anticipated frequency of risks and chosen endpoints for safety or efficacy follow-up, sample size may incorporate all exposed patients or a defined subset. When a subset of exposed patients is used, scientific justification should be provided. A subset is normally not acceptable for orphan drugs. Sample size calculations should consider the high potential for drop-outs over the years of follow-up. It may be appropriate to request scientific advice for this purpose from the EMEA.”</p> <p>“Safety and efficacy studies should use usual clinical practice for follow-up whenever possible to limit additional procedures and interventions. This should enable wider use of observational designs for studies in post-authorisation where suitable for generating or testing a particular hypothesis.”</p> |
|                   | EMA Committee for Advanced Therapies (CAT)                | Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells [9] | November 12, 2020 | p. 27              | <a href="https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-non-clinical-and-clinical-aspects-medicinal-products-containing-genetically-modified-cells-revision-1_en.pdf">https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-non-clinical-and-clinical-aspects-medicinal-products-containing-genetically-modified-cells-revision-1_en.pdf</a> | <p>“The clinical follow-up of patients enrolled in clinical trials with genetically modified cells should be ensured according to the principles laid down in the Guideline on follow-up of patients administered with gene therapy medicinal products (EMA/CHMP/GTWP/60436/2007) to detect early or delayed adverse reactions, a change in the efficacy profile, or additional unexplored risks with genetically modified cell products...According to the current knowledge, a 15 year follow up is recommended.”</p>                                                                                                                                                                                                                                                                                                                                                                        |
|                   | EMA Committee for Advanced Therapies (CAT)                | Guideline on the quality, non-clinical, and clinical aspects of gene therapy medicinal products [10]                    | March 22, 2018    | p. 39-40           | <a href="https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-non-clinical-and-clinical-aspects-gene-therapy-medicinal-products_en.pdf">https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-non-clinical-and-clinical-aspects-gene-therapy-medicinal-products_en.pdf</a>                                                                         | <p>“Lack of efficacy should be specifically followed in the long term follow-up of patients treated with GTMPs. Lack of efficacy can be due to various reasons, which are studied during the clinical development e.g. insufficient expression of the transgene, pre-existing immunity against the transgene product. In addition, the effect of the therapy may also decline over time e.g. due to a decline of transgene expression from the vector or a reduction of the number of vector-harboring cells.”</p>                                                                                                                                                                                                                                                                                                                                                                             |

| Country or Region | Regulatory Agency or Organization          | Related Guidance                                                                                                                             | Publication Year                                      | Relevant Pages | Links to English Translation                                                                                                                                                                                                                                                                                                                                                | Select Quotes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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| Europe            | European Commission                        | Guidelines on Good Clinical Practice specific to Advanced Therapy Medicinal Products, 7140 final [101]                                       | October 10, 2019                                      | p. 3, 12–15    | <a href="https://health.ec.europa.eu/document/download/2d8842cb-e785-488f-bfd0-bf8f2dablefe_en">https://health.ec.europa.eu/document/download/2d8842cb-e785-488f-bfd0-bf8f2dablefe_en</a>                                                                                                                                                                                   | “When long-term follow-up is foreseen in the Protocol, monitoring of subjects treated should be en-sured also in cases of early termination of the clinical trials. The sponsor should also ensure that there is a process in place for follow-up of the subjects treated with the product in cases where the product development is discontinued or the (former) sponsor ceases to exist, for instance, by providing appropriate information to the healthcare establishments involved in the clinical trial. If the product development is transferred to another entity, responsibility for the follow-up obligations of treated patients should be transferred to the new owner.” |
|                   | EMA Committee for Advanced Therapies (CAT) | Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials [11] | January 20, 2025                                      | p. 55          | <a href="https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-non-clinical-clinical-investigational-advanced-therapy-medicinal-products-clinical-trials_en.pdf">https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-non-clinical-clinical-investigational-advanced-therapy-medicinal-products-clinical-trials_en.pdf</a> | “The long-term efficacy and safety monitoring should be appropriately designed (e.g., sampling plan, sample treatment, analytical methods, endpoints) in order to maximize information output especially when invasive methods are used... Product persistence is assessed by determining the presence of cells, vector, virus, nucleic acids, proteins and other products in biological fluids and tissues... Patients can be followed up in a clinical trial or enrolled in a registry.”                                                                                                                                                                                            |
| Japan             | PMDA                                       | Ensuring the Quality and Safety of Gene Therapy Products, PSEHB/MDED Notification No. 0709-2 [12]                                            | July 9, 2019, Provisional Translation as of July 2020 | p. 34–35       | <a href="https://www.pmda.go.jp/files/000235607.pdf">https://www.pmda.go.jp/files/000235607.pdf</a>                                                                                                                                                                                                                                                                         | “If the vector is integrated into a chromosome, the observation to evaluate the sustainability of the transgene and, if feasible, the clonality of the genetically modified cells should be done at least once a year. It should be taken into account that the observation duration might have to be prolonged depending on the results of the follow-up. Preservation of the final product containing the vectors or genetically modified cells during the period until the end of follow-up should be considered to allow for investigation of the cause of adverse events.”                                                                                                       |

| Country or Region | Regulatory Agency or Organization | Related Guidance                                                                                                      | Publication Year                                            | Relevant Pages  | Links to English Translation                                                                                                                                                                                                                                                                    | Select Quotes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| Japan             | PMDA                              | Ensuring the Quality and Safety of Gene Therapy Products using genome-editing technology, PMDA Science Board [13]     | 2020                                                        | p. 2, 5, 10–13  | <a href="https://www.pmda.go.jp/files/000237636.pdf">https://www.pmda.go.jp/files/000237636.pdf</a>                                                                                                                                                                                             | “Since genome editing technologies are intended to modify target genes, genome editing requires long-term follow-up of patients for having similar risk to current gene therapy products using achromosomally integrated vector. Genome editing, which is utilized to deletes or inserts genes at specific sites, could be safer than current gene therapies involving random gene insertions unless no safety concern associated with off-target effect exists. However, genome editing using homologous recombination-possibly increases in mutation risk of DNA-repair genes such as p53 and is associated with the risk of chromosomal translocation. To identify adverse events related to these risks, the period of follow-up should be set in according to each risk.” |
|                   |                                   | Technical Guidance for Quality, Nonclinical Safety Studies and Clinical Studies of Regenerative Medical Products [15] | June 27, 2016 (Provisional translation as of February 2025) | p. 18–19        | <a href="https://www.pmda.go.jp/files/000273883.pdf">https://www.pmda.go.jp/files/000273883.pdf</a>                                                                                                                                                                                             | “The period of safety monitoring and the procedure for collection of information must be defined according to the characteristics of each product. When it is not known how long it takes for the product to be eliminated from the body, safety information must be collected for at least for a year. The necessity of follow-up for a period exceeding a year has to be examined based on the characteristics of each product.”                                                                                                                                                                                                                                                                                                                                             |
| United States     | FDA                               | Long Term Follow-Up After Administration of Human Gene Therapy Products, Guidance for Industry [2]                    | January 2020                                                | Entire Document | <a href="https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Long-Term-Follow-Up-After-Admin-Human-GT-Products_Jan_2020.pdf">https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Long-Term-Follow-Up-After-Admin-Human-GT-Products_Jan_2020.pdf</a> | “A sponsor may cease to operate or may decide to inactivate, transfer or withdraw an IND before completion of LTFU observations for all subjects exposed to the GT product under its IND. Under such circumstances, prior to inactivating, transferring or withdrawing an IND, or ceasing to operate, we recommend that a sponsor consult with OTAT on the plans for completion of LTFU observation.”                                                                                                                                                                                                                                                                                                                                                                          |

| Country or Region | Regulatory Agency or Organization | Related Guidance                                                                                                 | Publication Year | Relevant Pages | Links to English Translation                                                                      | Select Quotes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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| United States     | FDA                               | Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products, Guidance for Industry [6] | January 2024     | p. 3–4,7,32–33 | <a href="https://www.fda.gov/media/156896/download">https://www.fda.gov/media/156896/download</a> | “We recommend the clinical protocol describe the plans to determine the duration or persistence of the administered CAR T cells in trial subjects. The specimens for such a determination may include blood, body fluids, and tissues. If an invasive procedure is used to procure the specimen, a separate informed consent is recommended to inform the trial subjects of the risks of the procedure. Analytical methods for assessing CAR T cell persistence should be described in detail. Such methods could include tests for the presence of CAR T cells, or vector, and for the activity of the CAR T cells, including gene expression or changes in biomarkers. If death occurs during the trial, planning for postmortem studies to assess the cause of death, including CAR T cell persistence, toxicity, and activity, should be considered.” |
|                   |                                   | Human Gene Therapy Products Incorporating Human Genome Editing, Guidance for Industry [7]                        | January 2024     | p. 14          | <a href="https://www.fda.gov/media/156894/download">https://www.fda.gov/media/156894/download</a> | “Prior to enrolling subjects in a clinical study evaluating a human GE product, they should be asked to provide voluntary, informed consent to long term follow-up (LTFU). As discussed, the long-term safety and therapeutic effects of intended on-target editing, as well as off-target editing and unintended editing at the on target loci may be unknown at the time of GE product administration. Therefore, we recommend that sponsors conduct LTFU for up to 15 years after product administration...”                                                                                                                                                                                                                                                                                                                                           |

## Compiled Glossary of Scientific LTFU-Related Terminology

We have created a glossary of scientific LTFU-Related terminology, compiled from various respected sources. Please note that definitions are taken directly from the cited sources. They are either direct quotes or closely paraphrased. Bracketed text [ ] represents our clarifications or additions.

| Term                               | Definition                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Source                                                                                                                           |
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| <b>Active Surveillance</b>         | Active surveillance, in contrast to passive surveillance, seeks to ascertain completely the number of adverse events via a continuous pre-organized process. An example of active surveillance is the follow-up of patients treated with a particular drug through a risk management program. ... In general, it is more feasible to get comprehensive data on individual adverse events through an active surveillance than through a passive reporting system.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | <a href="#">EMA Guideline on Safety and Efficacy Follow-up- Risk Management of Advanced Therapy Medicinal Products</a> [8]       |
| <b>Adverse Drug Reaction (ADR)</b> | <p>In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.</p> <p>The phrase “responses to a medicinal products [sic]” means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.</p> <p>Regarding marketed medicinal products, a well-accepted definition of an adverse drug reaction in the post-marketing setting is found in WHO Technical Report 498 [1972] and reads as follows: A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.</p> <p>The old term “side effect” has been used in various ways in the past, usually to describe negative (unfavorable) effects, but also positive (favorable) effects. It is recommended that this term no longer be used and particularly should not be regarded as synonymous with adverse event or adverse reaction.</p> | <a href="#">ICH Topic E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Step 5</a> [102]   |
| <b>Adverse Event</b>               | <p>Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.</p> <p>An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | <a href="#">ICH Topic E 2 A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Step 5</a> [102] |

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| <b>Adverse Event</b>                                     | An occurrence that has a negative impact on the health or well-being of a patient in a clinical trial during or within a certain length of time after the study.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <a href="#">FDA Patient-Friendly Language for Cancer Clinical Trials</a> [103]                                                                         |
| <b>Adverse Event of Special Interest (AESI)</b>          | An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or programme [sic], for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted.                                                                                                                                                                                                                                  | <a href="#">ICH Harmonised Tripartite Guideline: Development Safety Update Report</a> (notes the definition is based on CIOMS VI) [104]                |
| <b>Biologics License Application (BLA)</b>               | The Biologics License Application (BLA) is a request for per-mission to introduce, or deliver for introduction, a biologic product into interstate commerce (21 CFR 601.2). The BLA is regulated under 21 CFR 600 – 680. A BLA is submitted by any legal person or entity who is engaged in manufacture or an applicant for a license who takes responsibility for compliance with product and establishment standards. Form 356h specifies the requirements for a BLA. This includes: Applicant information; Product/Manufacturing information; Pre-clinical studies; Clinical studies; [and] Labeling.                                                                                                                                            | <a href="#">FDA: Biologics License Applications (BLA) Process (CBER)</a> [105]                                                                         |
| <b>Chimeric Antigen Receptor T Cell Therapy (CAR-T)</b>  | A type of treatment in which a patient's T cells (a type of immune system cell) are changed in the laboratory so they will attack cancer cells. T cells are taken from a patient's blood. Then the gene for a special receptor that binds to a certain protein on the patient's cancer cells is added to the T cells in the laboratory. The special receptor is called a chimeric antigen receptor (CAR). Large numbers of the CAR T cells are grown in the laboratory and given to the patient by infusion. CAR T-cell therapy is used to treat certain blood cancers, and it is being studied in the treatment of other types of cancer. Also called chimeric antigen receptor T-cell therapy.                                                    | <a href="#">NIH: National Cancer Institute Dictionary of Cancer Terms</a> [106]                                                                        |
| <b>Clinical Follow-Up (EMA term)</b>                     | A follow-up of individual patients conducted by healthcare professionals. It includes prevention, screening, monitoring, diagnosis and treatment of diseases, injuries, complications, adverse reactions and medical errors.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | <a href="#">EMA Guideline on Safety and Efficacy Follow-Up – Risk Management of Advanced Therapy Medicinal Products</a> [8]                            |
| <b>Conforming Product (Conformance to specification)</b> | A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance, drug product, or materials at other stages of its manufacture should conform to be considered acceptable for its intended use. Conformance to specifications means that the drug substance and drug product, when tested according to the listed analytical procedures, will meet the acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval. | <a href="#">FDA: Guidance for Industry: Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products</a> [107] |

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| <b>Delayed Adverse Event</b>                      | Often, GT products are designed to achieve therapeutic effect through permanent or long-acting changes in the human body. As a result of long term exposure to an investigational GT product, study subjects may be at increased risk of undesirable and unpredictable outcomes that may present as delayed adverse event(s). To understand and mitigate the risk of a delayed adverse event, subjects in gene therapy trials may be monitored for an extended period of time, which is commonly referred to as the “long term follow-up” (LTFU) period (of a clinical study). | <a href="#">FDA: Long Term Follow-Up After Administration of Human Gene Therapy Products</a> [2]                            |
| <b>Durability</b>                                 | Durability of a drug or a drug combination may be defined as its ability to postpone or delay progression of disease, in a safe and well tolerated manner.                                                                                                                                                                                                                                                                                                                                                                                                                     | Kalra et al.: <a href="#">Defining Disease Progression and Drug Durability in Type 2 Diabetes Mellitus</a> [108]            |
| <b>Efficacy Follow-Up</b>                         | Any systematic collection and collation of data that is designed in a way that enables learning about the efficacy or effectiveness of a medicinal product. It may include passive or active surveillance, observational studies, or clinical trials.                                                                                                                                                                                                                                                                                                                          | <a href="#">EMA Guideline on Safety and Efficacy Follow-Up – Risk Management of Advanced Therapy Medicinal Products</a> [8] |
| <b>Electronic Case Report Form (eCRF)</b>         | An auditable electronic record of information that generally is reported to the sponsor on each trial subject, according to a clinical investigation protocol. The eCRF enables clinical investigation data to be systematically captured, reviewed, managed, stored, analyzed, and reported.                                                                                                                                                                                                                                                                                  | <a href="#">FDA Guidance Document: Electronic Source Data in Clinical Investigations</a> [109]                              |
| <b>Endpoint</b>                                   | In clinical trials, an outcome that can be measured objectively to assess whether a treatment worked.                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | <a href="#">FDA Patient-Friendly Language for Cancer Clinical Trials</a> [103]                                              |
|                                                   | In clinical trials, an event or outcome that can be measured objectively to determine whether the intervention being studied is beneficial. The endpoints of a clinical trial are usually included in the study objectives. Some examples of endpoints are survival, improvements in quality of life, relief of symptoms, and disappearance of the tumor.                                                                                                                                                                                                                      | <a href="#">NIH: National Cancer Institute Dictionary of Cancer Terms</a> [110]                                             |
| <b>Expanded Access</b>                            | A way to provide an investigational therapy to a patient who is not eligible to receive that therapy in a clinical trial, but who has a serious or life-threatening illness for which other treatments are not available. Expanded access allows patients to receive promising but not yet fully studied or approved cancer therapies when no other treatment option exists. Also called compassionate use.                                                                                                                                                                    | <a href="#">NIH: National Cancer Institute Dictionary of Cancer Terms</a> [111]                                             |
| <b>FDA Adverse Event Reporting System (FAERS)</b> | The FAERS database contains adverse event reports, medication error reports and product quality complaints resulting in adverse events that were submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products.                                                                                                                                                                                                                                                                        | <a href="#">FDA's Adverse Event Reporting System (FAERS)</a> [112]                                                          |

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| <b>Gene Therapy (GT)</b>                 | <p>Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use.</p> <p>Gene therapy is a technique that modifies a person's genes to treat or cure disease. Gene therapies can work by several mechanisms:</p> <ul style="list-style-type: none"> <li>• Replacing a disease-causing gene with a healthy copy of the gene</li> <li>• Inactivating a disease-causing gene that is not functioning properly</li> <li>• Introducing a new or modified gene into the body to help treat a disease.</li> </ul>                 | <a href="#">FDA: What is gene therapy? [1]</a>                                                                                   |
| <b>Gene Therapy Medicinal Product</b>    | <p>A biological medicinal product which has the following characteristics:</p> <p>(a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence.</p> <p>(b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.</p> <p>Gene therapy medicinal products shall not include vaccines against infectious diseases.</p> | <a href="#">Central Committee on Research Involving Human Subjects - Gene Therapy Medicinal Products [113]</a>                   |
|                                          | <p>Gene therapy medicines are one type of "ATMPs" advanced therapy medicinal products (EMA). Gene therapy medicines contain genes that lead to a therapeutic, prophylactic, or diagnostic effect. They work by inserting 'recombinant' genes into the body, usually to treat a variety of diseases, including genetic disorders, cancer or long-term diseases. A recombinant gene is a stretch of DNA that is created in the laboratory, bringing together DNA from different sources.</p>                                                                                                                       | <a href="#">EMA: Advanced therapy medicinal products: Overview [114]</a>                                                         |
| <b>Gene Transfer</b>                     | The transfer of genetic material into a cell                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <a href="#">FDA: Long Term Follow-Up After Administration of Human Gene Therapy Products [2]</a>                                 |
| <b>Genetically Modified Cell Therapy</b> | <p>In genetically modified cell therapy or gene-modified cell therapy, cells are removed from the body. A working gene is added or genetic information is modified in the cells and then these modified cells are put back into the body.</p> <p>[The genetically modified cells given to a patient may be derived from the patient themselves (e.g., autologous) or derived from another person (e.g. allogeneic). Also, in some cases, gene editing technologies, such as CRISPR, may be used to make changes to the DNA in cells before they are delivered back into humans]</p>                              | <a href="#">American Society of Gene &amp; Cell Therapy. "What are the Different Gene Therapy Approaches?" Infographic [115]</a> |
| <b>Genotoxicity</b>                      | When a substance is capable of damaging the DNA in cells. [e.g., toxicity to the genome]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | <a href="#">European Food Safety Authority [116]</a>                                                                             |

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| <b>Human Gene Editing Technology</b>   | Type of gene therapy product. The goals of gene editing are to disrupt harmful genes or to repair mutated genes.                                                                                                                                                                                                                                                                                                                                                                                                      | <a href="#">FDA: What is gene therapy?</a> [1]                                                                                                      |
| <b>Human Genome Editing</b>            | Genome editing is a method for making specific changes to the DNA of a cell or organism. It can be used to add, remove or alter DNA in the genome. Human genome editing technologies can be used on somatic cells (non-heritable), germline cells (not for reproduction) and germline cells (for reproduction).<br><br>NHGRI uses the term “genome editing” to describe techniques used to modify DNA in the genome. Other groups also use the term “gene editing.” In general, these terms are used interchangeably. | <a href="#">WHO: Human genome editing</a> [117] and <a href="#">NIH What are the Ethical Concerns of Genome Editing?</a> [118]                      |
| <b>Informed Consent</b>                | Informed means you are made aware of and understand possible risks and benefits of a treatment [e.g., investigational product], and consent means you have then given permission to proceed with the treatment. It is important to understand that informed consent is a process that begins with the recruitment and screening of a potential participant, the signing of the consent document and continues throughout the individual's involvement in the research or clinical trial and after it concludes.       | <a href="#">American Society of Gene &amp; Cell Therapy: Informed Consent</a> [119]                                                                 |
|                                        | While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an in-formed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.                                                                                                                                                                                                               | <a href="#">The Belmont Report</a> [120]                                                                                                            |
| <b>Insertional Mutagenesis</b>         | Mutagenesis where the mutation is caused by the introduction of foreign DNA sequences into a gene or extragenic sequence. This may occur spontaneously in vivo or be experimentally induced in vivo or in vitro. Proviral DNA insertions into or adjacent to a cellular proto-oncogene can interrupt genetic translation of the coding sequences or interfere with recognition of regulatory elements and cause unregulated expression of the proto-oncogene resulting in tumor formation.                            | <a href="#">National Library of Medicine National Center for Biotechnology Information</a> [121]                                                    |
| <b>Integration (of DNA)</b>            | The process whereby exogenous DNA sequences become incorporated into a genome.                                                                                                                                                                                                                                                                                                                                                                                                                                        | <a href="#">FDA Guidance Document: Long Term Follow-up After Administration of Human Gene Therapy Products</a> [2]                                  |
| <b>Integration Site Analysis (ISA)</b> | Allows for the precise localization of [exogenous gene] insertions in the genome and provides a tool for the longitudinal assessment of clonality in engrafting cell populations after gene modification and transplantation. Can also be used for assessment of integration events of GT vectors that do not frequently integrate (eg. AAV). The methods used for this analysis are evolving but include next generation sequencing approaches.                                                                      | <a href="#">Radtke, Stefan, and Hans-Peter Kiem. “The evolution of viral integration site analysis.” Blood vol. 135,15 (2020): 1192-1193.</a> [122] |
| <b>Investigational New Drug</b>        | A substance that has been tested in the laboratory and has been approved by the U.S. Food and Drug Administration (FDA) for testing in people. Clinical trials test how well investigational new drugs work and whether they are safe to use. An investigational new drug may be approved by the FDA for use in one disease or condition but still be considered investigational in other diseases or conditions. Also called experimental drug, IND, investigational agent, and investigational drug.                | <a href="#">National Cancer Institute Dictionary of Cancer Terms</a> [123]                                                                          |

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| <b>Investigational New Drug Application (IND)</b> | An Investigational New Drug Application (IND) is a request from a clinical study sponsor to obtain authorization from the Food and Drug Administration (FDA) to administer an investigational drug or biological product to humans. Clinical studies are often conducted to collect safety and effectiveness information in support of marketing applications for biologic and drug products. Unless exempted, the sponsor for a clinical study must obtain authorization from FDA for conducting the study by <a href="#">submitting an IND Application</a> . Such authorization must be secured prior to interstate shipment and administration of any new drug or biological product that is not the subject of an approved New Drug Application or Biologics Product License Application | <a href="#">FDA: Investigational New Drug Applications (INDs) for CBER-Regulated Products</a> [124]                                                           |
| <b>Investigational Study (Clinical Trial)</b>     | A type of clinical study in which participants are assigned to groups that receive one or more intervention/treatment (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study's protocol. Participants may receive diagnostic, therapeutic, or other types of interventions.                                                                                                                                                                                                                                                                                                                                                                                            | <a href="#">ClinicalTrials.gov Glossary Terms</a> [44]                                                                                                        |
| <b>Latency (of a viral infection)</b>             | A period of time during which a virus is present in the host without producing overt clinical symptoms.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | <a href="#">FDA Guidance Document: Long Term Follow-up After Administration of Human Gene Therapy Products</a> [2]                                            |
| <b>Long-Term Follow-Up</b>                        | To understand and mitigate the risk of a delayed adverse event, subjects in gene therapy trials may be monitored for an extended period of time, which is commonly referred to as the “long term follow-up” (LTFU) period (of a clinical study). LTFU observations are extended assessments that continue some of the scheduled observations of a clinical trial past the active follow-up period, and are an integral portion of the study of some investigational GT products. LTFU observations are important to monitor long term safety of GT products. For GT products that present long term risks to subjects, LTFU/surveillance plan(s) should also be put in place post-licensure for monitoring of delayed adverse events.                                                        | <a href="#">FDA Guidance Document: Long Term Follow-up After Administration of Human Gene Therapy Products</a> [2]                                            |
| <b>MedWatch</b>                                   | FDA program for reporting serious reactions, product quality problems, therapeutic inequivalence/failure, and product use errors with human medical products, including drugs, biologic products, medical devices, dietary supplements, infant formula, and cosmetics.<br><br>MedWatch receives reports from the public and when appropriate, publishes safety alerts for FDA-regulated products.                                                                                                                                                                                                                                                                                                                                                                                            | <a href="#">Reporting Serious Problems to FDA</a> [125]<br><br><a href="#">MedWatch: The FDA Safety Information and Adverse Event Reporting Program</a> [126] |
| <b>NCT Number</b>                                 | Unique identification codes assigned to clinical study records registered on ClinicalTrials.gov. Also called the ClinicalTrials.gov identifier.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <a href="#">ClinicalTrials.gov Glossary Terms</a> [44]                                                                                                        |
| <b>Nonconforming Product</b>                      | Nonconformity means the nonfulfillment of a specified requirement.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | CFR Title 21 / Chapter 1 / Subchapter H/ Part 820.3 Definitions [127]                                                                                         |
|                                                   | When a product fails to meet specified requirements, standards, or expectations set by design, regulations, or customer needs. By not adhering to the established criteria or quality standards, the final product is considered deficient or defective.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <a href="#">ComplianceQuest: What is Product Non Conformance?</a> [128]                                                                                       |

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| <b>Off-Target Effects</b>                             | <p>In the context of gene editing, off-target effects refer to unintended edits to the genome [in the wrong place]</p> <p>In the context of gene therapy, off-target effects could refer to “when tissues or cells other than the intended target may be affected after administration of a gene therapy.”</p>                                                                                                                                                                                                                                                                                        | <p><a href="#">NIH What are the Ethical Concerns of Genome Editing?</a> [118]</p> <p><a href="#">ASGCT glossary</a> [129]</p>                                                                        |
| <b>On-Target Effects</b>                              | In the context of gene editing, on-target effects refer to edits to the genome in the intended place.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <a href="#">Lackner et al Nucleic Acids Research 2023</a> [130]                                                                                                                                      |
| <b>Passive Surveillance</b>                           | A surveillance conducted by a method that relies on the collection of unsolicited initial safety information. The motivation of persons providing the information is not specifically encouraged by the passive surveillance. Examples of a passive surveillance include spontaneous reporting scheme, literature monitoring, and Internet searches.                                                                                                                                                                                                                                                  | <a href="#">EMA Guideline on Safety and Efficacy Follow-Up – Risk Management of Advanced Therapy Medicinal Products</a> [8]                                                                          |
| <b>Patient-Derived Cellular Gene Therapy Products</b> | Cells are removed from the patient, genetically modified (often using a viral vector) and then returned to the patient.                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | <a href="#">FDA: What is gene therapy?</a> [1]                                                                                                                                                       |
| <b>Patient Journey Mapping</b>                        | Visualization tools that can facilitate the diagrammatical representation of stakeholder groups by interest or function for comparative visual analysis. Therefore, journey maps can illustrate intersections and relationships between organizations and consumers using products or services.                                                                                                                                                                                                                                                                                                       | <a href="#">Joseph, Amanda L et al. “Exploring Patient Journey Mapping and the Learning Health System: Scoping Review.” JMIR human factors vol. 10 e43966. 27 Feb. 2023. doi:10.2196/43966</a> [131] |
| <b>Patient Monitoring</b>                             | Patient Monitoring refers to the regular observation and assessment of a patient's health status, typically using medical devices or technology, to track vital signs, symptoms, and treatment progress.                                                                                                                                                                                                                                                                                                                                                                                              | <a href="#">Patient Better: What is Patient monitoring?</a> [132]                                                                                                                                    |
| <b>Patient Reported Outcome (PRO)</b>                 | Information about a patient's health that comes directly from the patient. Examples of patient-reported outcomes include a patient's description of their symptoms, their satisfaction with care, and how a disease or treatment affects their physical, mental, emotional, spiritual, and social well-being. In clinical trials, patient-reported outcomes may provide information about the side effects of the new treatment being studied. The use of patient-reported outcomes may help plan the best treatment and improve quality of care.                                                     | <a href="#">National Cancer Institute (NCI) Dictionary of Cancer Terms</a> [133]                                                                                                                     |
| <b>Persistence</b>                                    | <p>“With respect to transferred or altered genetic material, the continued presence of transferred or modified genetic sequences in the host after acute exposure to a gene therapy agent, whether due to integration of the genetic sequence into the host genome, deletion, insertion, or otherwise modified following genome editing, or to latent infection with the viral vector bearing the genetic sequence.”</p> <p>[May also relate to persistence of the genetic sequence in an episomal or non-integrated form.]</p> <p>[Note that viral vectors are usually replication incompetent.]</p> | <a href="#">FDA Guidance Document: Long Term Follow-up After Administration of Human Gene Therapy Products</a> [2]                                                                                   |

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| <b>Pharmacovigilance</b>                   | The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine related problem.                                                                                                                                                                                                                                                                                                                                                                          | <a href="#">WHO: Regulation and Prequalification</a> [134]                                                         |
| <b>Plasmid DNA</b>                         | Circular DNA molecules that can be genetically engineered to carry therapeutic genes into human cells.                                                                                                                                                                                                                                                                                                                                                                                                                                    | <a href="#">FDA: What is gene therapy?</a> [1]                                                                     |
|                                            | An extrachromosomal, self-replicating piece of DNA. Plasmids are usually circular and transferable between cells, and they sometimes carry genes that provide accessory functions, including drug resistance and virulence.                                                                                                                                                                                                                                                                                                               | <a href="#">NEJM Illustrated Glossary</a> [135]                                                                    |
| <b>Polymerase Chain Reaction (PCR)</b>     | Sometimes called "molecular photocopying," the polymerase chain reaction (PCR) is a fast and inexpensive technique used to "amplify" or copy small segments of DNA. Because significant amounts of a sample of DNA are necessary for molecular and genetic analyses, studies of isolated pieces of DNA are nearly impossible without PCR amplification.                                                                                                                                                                                   | <a href="#">NIH: Polymerase Chain Reaction (PCR) Fact Sheet</a> [136]                                              |
| <b>Post-Marketing Study Commitments</b>    | Studies required of or agreed to by a sponsor that are conducted after FDA has approved a product for marketing. FDA uses post-marketing study commitments to gather additional information about a product's safety, efficacy, or optimal use. Agreements with sponsors to conduct post-marketing studies can be reached either before or after FDA has granted approval to a sponsor to market a product.                                                                                                                               | <a href="#">FDA: Postmarketing Clinical Trials</a> [137]                                                           |
| <b>Post-Marketing Surveillance</b>         | Because all possible side effects of a drug can't be anticipated based on pre-approval studies involving only several hundred to several thousand patients, FDA maintains a system of post-marketing surveillance and risk assessment programs to identify adverse events that did not appear during the drug approval process. FDA monitors adverse events such as adverse reactions and poisonings. The Agency uses this information to update drug labeling, and, on rare occasions, to reevaluate the approval or marketing decision. | <a href="#">FDA: Post-Marketing Surveillance Programs</a> [138]                                                    |
| <b>Primary Endpoint</b>                    | The main result that is measured at the end of a study to see if a given treatment worked (e.g., the number of deaths or the difference in survival between the treatment group and the control group). What the primary endpoint will be is decided before the study begins.                                                                                                                                                                                                                                                             | <a href="#">NIH: National Cancer Institute Dictionary of Cancer Terms</a> [139]                                    |
| <b>Protocol Extension (LTFU)</b>           | An LTFU observation conducted an extension of the main protocol study, and may begin immediately after the first subject completes their last visit in the main study and enrolls in the LTFU study.                                                                                                                                                                                                                                                                                                                                      | <a href="#">FDA Guidance Document: Long Term Follow-up After Administration of Human Gene Therapy Products</a> [2] |
| <b>Reactivation (of a viral infection)</b> | The re-emergence of a symptomatic or asymptomatic viral infection following a period of latency.                                                                                                                                                                                                                                                                                                                                                                                                                                          | <a href="#">FDA Guidance Document: Long Term Follow-up After Administration of Human Gene Therapy Products</a> [2] |

|                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                 |
|-------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Registry</b>                                       | An organized system that collects clinical and other data in a standardized format for a population defined by a particular disease, condition, or drug exposure. Establishing registries involves enrolling a predefined population and collecting pre-specified health-related data for each patient in that population (patient-level data). Data about this population can be entered directly into the registry (e.g., clinician- or patient-reported) and can also include data from other sources that characterize registry participants.                                                                                           | <a href="#">FDA Guidance: Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products</a> [43] |
|                                                       | Organised system that collects uniform data (clinical and other) to identify specified outcomes for a population defined by a particular disease, condition or exposure.                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <a href="#">EMA Guideline on registry-based studies</a> [62]                                                                                    |
| <b>Registry Study (a form of LTFU study)</b>          | Investigation of a research question using the data collection infrastructure or patient population of one or more patient registries                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | <a href="#">EMA Guideline on registry-based studies</a> [62]                                                                                    |
| <b>Regulatory Agency</b>                              | A regulatory agency is a common name for an <a href="#">agency</a> that has been delegated authority by Congress to is-sue <a href="#">rules</a> or <a href="#">regulations</a> , to issue licenses, to establish rates, or to undertake a combination of these actions.                                                                                                                                                                                                                                                                                                                                                                    | <a href="#">The Regulatory Group Glossary</a> [140]                                                                                             |
| <b>Replication Competent Lentivirus (RCL)</b>         | Virus particles capable of infecting cells and replicating to produce additional infectious particles.<br><br>The existence of RCL in stable cell lines generated by lentiviral vector transduction is a safety concern. Lentiviral vectors have been engineered to significantly reduce the likelihood of RCL production.                                                                                                                                                                                                                                                                                                                  | <a href="#">Imanix Life Sciences: What is replication competent lentivirus (RCL)?</a> [141]                                                     |
| <b>Replication Competent Virus (RCV)</b>              | The presence of virus that is able to replicate [i.e., produce new virus]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <a href="#">Imanix Life Sciences: What is RCV Testing?</a> [142]                                                                                |
| <b>Risk Evaluation and Mitigation Strategy (REMS)</b> | A drug safety program that the FDA can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.<br><br>REMS are designed to reinforce medication use behaviors and actions that support the safe use of that medication.<br><br>While all medications have labeling that informs health care stakeholders about medication risks, only a few medications require a REMS.<br><br>REMS focus on preventing, monitoring and/or managing a specific serious risk by informing, educating and/or reinforcing actions to reduce the frequency and/or severity of the event. | <a href="#">FDA: Risk Evaluation and Mitigation Strategies   REMS</a> [143]                                                                     |
| <b>Safety Follow-Up (EMA term)</b>                    | Any systematic collection and collation of data that is designed in a way that enables learning about the safety of a medicinal product. It may include passive or active surveillance, observational studies, or clinical trials.                                                                                                                                                                                                                                                                                                                                                                                                          | <a href="#">EMA Guideline on Safety and Efficacy Follow-Up – Risk Management of Advanced Therapy Medicinal Products</a> [8]                     |

|                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                 |
|-----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Secondary Endpoint</b>         | In clinical trials, an additional result beyond the primary endpoint measured at the end of the study.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <a href="#">NIH: National Cancer Institute Dictionary of Cancer Terms [144]</a>                                                                                                                                                                                                                                 |
| <b>Secondary Endpoint</b>         | May extend understanding of an effect related to the primary endpoint or provide evidence of a distinct clinical benefit.<br><br>Should be included in the prospective statistical analysis plan if they provide evidence of additional effects of the drug.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <a href="#">FDA Guidance: Multiple Endpoints in Clinical Trials Guidance for Industry [145]</a>                                                                                                                                                                                                                 |
| <b>Sentinel Initiative</b>        | The FDA leads the Sentinel Initiative. FDA created the Sentinel Initiative to meet a mandate by Congress in the FDA Amendments Act of 2007. Through the Sentinel Initiative, FDA aims to develop new ways to assess the safety of approved medical products including drugs, vaccines, and medical devices.<br><br>The Sentinel System helps to answer the FDA's questions on approved medical products. It does this by creating computer programs that analyze electronic healthcare data. These computer programs use statistical methods to study relationships and patterns in medical billing information and electronic health records.                                                                                                                                            | <a href="#">About the Food and Drug Administration (FDA) Sentinel Initiative [146]</a>                                                                                                                                                                                                                          |
| <b>Serious Adverse Event</b>      | An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life- threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. | <a href="#">FDA: Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies [147]</a><br><br>(Also see <a href="#">ICH Harmonised Tripartite Guideline, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A (1994) [148]</a> )        |
| <b>Standalone Protocol (LTFU)</b> | An LTFU observation conducted under a protocol (LTFU protocol) that is separate from the main [parent] study protocol.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Definition is a combination of information provided in <a href="#">Designing and optimal long-term follow-up program for gene therapies and genetically modified cell therapies [45]</a> and <a href="#">Long Term Follow-Up After Administration of Human Gene Therapy Products: Guidance for Industry [2]</a> |
| <b>Traceability</b>               | The ability to trace each individual unit of an ATMP [Advanced Therapy Medicinal Product] from the donor and/or source material to the patient and vice versa.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | <a href="#">EMA Guideline on Safety and Efficacy Follow-Up - Risk Management of Advanced Therapy Medicinal Products [149]</a>                                                                                                                                                                                   |
| <b>Transgene</b>                  | A gene that is transferred from an organism of one species to an organism of another species by genetic engineering.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | <a href="#">Collins Dictionary [150]</a>                                                                                                                                                                                                                                                                        |
| <b>Transgene Expression</b>       | The process by which an exogenous (originating from outside the organism) gene is transcribed and translated into a protein in a host organism.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | <a href="#">Collins Dictionary [151]</a>                                                                                                                                                                                                                                                                        |

|                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                          |
|------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Treatment-Emergent Adverse Event (TEAE)</b> | A category of adverse events that can particularly occur with cancer or autoimmune condition treatments during a clinical trial is the treatment emergent adverse event. This is an often unexpected adverse (negative) outcome or event that arises during the course of treatment that did not appear to exist beforehand or appears to be worsening a pre-existing condition or problem. Whereas adverse events may or may not be related to a treatment, a TEAE is distinguished by its appearing specifically while treatment is ongoing or very soon there-after, often with an infusion therapy or a treatment that re-quires multiple visits over time. | <a href="#">Association of Health Care Journalists</a> [152]                                                                                             |
| <b>Tumorigenicity</b>                          | Producing or tending to produce tumors.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | <a href="#">Merriam-Webster Dictionary</a> [153]                                                                                                         |
| <b>Unexpected Adverse Drug Reaction</b>        | An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product).                                                                                                                                                                                                                                                                                                                                                                                                                                                             | <a href="#">ICH Harmonised Tripartite Guideline, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A (1994)</a> [148] |
| <b>Viral Vector</b>                            | Viruses have a natural ability to deliver genetic material into cells, and therefore some gene therapy products are derived from viruses and employ viral vectors for delivery. Once viruses have been modified so they cannot cause infectious disease, these modified viruses can be used as vectors (vehicles) to carry therapeutic genes into human cells.                                                                                                                                                                                                                                                                                                  | <a href="#">FDA: What is gene therapy?</a> [1]                                                                                                           |

# Easy-to-Understand (Accessible) LTFU-Related Definitions from the MRCT Center's Clinical Research Glossary<sup>4</sup>

|                                              |                                                              |                                             |
|----------------------------------------------|--------------------------------------------------------------|---------------------------------------------|
| <a href="#">Adverse event</a>                | <a href="#">Evaluate</a>                                     | <a href="#">Pharmacovigilance</a>           |
| <a href="#">Adverse reaction</a>             | <a href="#">Exploratory Research</a>                         | <a href="#">Placebo</a>                     |
| <a href="#">Analyze</a>                      | <a href="#">Generalizability (use generalizable)</a>         | <a href="#">Post-Market Surveillance</a>    |
| <a href="#">Assent</a>                       | <a href="#">Hypothesis</a>                                   | <a href="#">Primary Endpoint</a>            |
| <a href="#">Assessment</a>                   | <a href="#">Immune Response (use immunological reaction)</a> | <a href="#">Prospective Study</a>           |
| <a href="#">Benefits of a research study</a> | <a href="#">Inclusion Criteria</a>                           | <a href="#">Purpose</a>                     |
| <a href="#">Bias (research)</a>              | <a href="#">Informed Consent</a>                             | <a href="#">Questionnaire</a>               |
| <a href="#">Conduct</a>                      | <a href="#">Investigational Product</a>                      | <a href="#">Registry (study)</a>            |
| <a href="#">Confounding</a>                  | <a href="#">Investigator</a>                                 | <a href="#">Retrospective Study</a>         |
| <a href="#">Data</a>                         | <a href="#">Longitudinal Study</a>                           | <a href="#">Sample Size</a>                 |
| <a href="#">DMC/DSMB</a>                     | <a href="#">Monitor</a>                                      | <a href="#">Secondary Endpoint</a>          |
| <a href="#">Database (research)</a>          | <a href="#">Objective</a>                                    | <a href="#">Serious Adverse Event (SAE)</a> |
| <a href="#">Discontinue (participant)</a>    | <a href="#">Outcome Measure</a>                              | <a href="#">Side Effect</a>                 |
| <a href="#">Efficacy</a>                     | <a href="#">Participate (related term: participants)</a>     | <a href="#">Study Feasibility</a>           |
| <a href="#">Effectiveness</a>                | <a href="#">Patient Reported Outcomes (PROs)</a>             | <a href="#">Study Participant</a>           |
| <a href="#">Eligibility Criteria</a>         |                                                              | <a href="#">Withdraw</a>                    |
| <a href="#">Endpoint</a>                     |                                                              |                                             |

<sup>4</sup> MRCT Center's Clinical Research Glossary is available at <https://mrctcenter.org/glossary/>.

## APPENDICES

### List of Acronyms and Abbreviations Used

|               |                                                                   |
|---------------|-------------------------------------------------------------------|
| <b>AAV</b>    | Adeno-Associated Virus/Viral                                      |
| <b>ADE</b>    | Adverse Drug Event                                                |
| <b>ADR</b>    | Adverse Drug Reaction                                             |
| <b>AE</b>     | Adverse Event                                                     |
| <b>ALL</b>    | Acute Lymphoblastic Leukemia                                      |
| <b>AML</b>    | Acute Myeloid Leukemia                                            |
| <b>ASGCT</b>  | American Society of Gene and Cell Therapy                         |
| <b>CAR T</b>  | Chimeric Antigen Receptor T-cell therapy                          |
| <b>CHMP</b>   | Committee for Medicinal Products for Human Use                    |
| <b>CIBMTR</b> | The Center for International Blood and Marrow Transplant Research |
| <b>CIHR</b>   | Canadian Institutes for Health Research                           |
| <b>CIOMS</b>  | Council for International Organizations of Medical Sciences       |
| <b>COMET</b>  | Core Outcome Measures in Effectiveness Trials Initiative          |
| <b>CTQ</b>    | Critical to Quality                                               |
| <b>DCT</b>    | Decentralized Clinical Trial                                      |
| <b>DCSI</b>   | Development Core Safety Information                               |
| <b>DNA</b>    | Deoxyribonucleic Acid                                             |
| <b>DSMB</b>   | Data Safety Monitoring Board                                      |
| <b>EC</b>     | Ethics Committee                                                  |
| <b>EHR</b>    | Electronic Health Record                                          |
| <b>EMA</b>    | European Medicines Agency                                         |
| <b>ePRO</b>   | Electronic Patient Reported Outcome                               |

|               |                                                                                                     |                                  |
|---------------|-----------------------------------------------------------------------------------------------------|----------------------------------|
| <b>EU</b>     | European Union                                                                                      | Introduction & Background        |
| <b>EUPATI</b> | European Patients' Academy on Therapeutic Innovation                                                |                                  |
| <b>FAERS</b>  | FDA Adverse Event Reporting System                                                                  | Types of LTFU                    |
| <b>FDA</b>    | Food and Drug Administration of the United States                                                   |                                  |
| <b>GT</b>     | Gene Therapy                                                                                        | LTFU Flowcharts                  |
| <b>GTR</b>    | Gene Therapy Registry                                                                               |                                  |
| <b>HCP</b>    | Health Care Provider (or Professional)                                                              | Guiding Principles               |
| <b>HLA</b>    | Human Leukocyte Antigen                                                                             |                                  |
| <b>HSC</b>    | Hematopoietic Stem Cell                                                                             | Considerations & Recommendations |
| <b>IB</b>     | Investigator's Brochure                                                                             |                                  |
| <b>ICH</b>    | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use | Looking Forward                  |
| <b>ICMJE</b>  | International Committee of Medical Journal Editors                                                  |                                  |
| <b>IMP</b>    | Investigational Medical Product                                                                     | Key Design Elements              |
| <b>IND</b>    | Investigational New Drug (application)                                                              |                                  |
| <b>IRB</b>    | Institutional Review Board                                                                          | Regulatory Guidance              |
| <b>LAR</b>    | Legally Authorized Representative                                                                   |                                  |
| <b>LTFU</b>   | Long-Term Follow-Up                                                                                 | Compiled Glossary                |
| <b>MAH</b>    | Marketing Authorization Holder                                                                      | Accessible Definitions           |
| <b>MDS</b>    | Myelodysplastic Syndrome                                                                            |                                  |
| <b>MRI</b>    | Magnetic Resonance Imaging                                                                          |                                  |
| <b>NCT</b>    | National Clinical Trial number                                                                      |                                  |
| <b>NMPA</b>   | National Medical Products Administration of China                                                   |                                  |
| <b>OOP</b>    | Out-of-Pocket (referring to expenses)                                                               |                                  |
| <b>OSMB</b>   | Observational Study Monitoring Board                                                                |                                  |
| <b>OTAT</b>   | Office of Tissues and Advanced Therapies (FDA)                                                      |                                  |
| <b>OTP</b>    | Office of Therapeutic Products                                                                      |                                  |

|             |                                                     |
|-------------|-----------------------------------------------------|
| <b>PASS</b> | Post-Authorization Safety Study                     |
| <b>PCR</b>  | Polymerase Chain Reaction                           |
| <b>PEQG</b> | Patient Engagement Quality Guidance                 |
| <b>PFMD</b> | Patient Focused Medicines Development               |
| <b>PMDA</b> | Pharmaceuticals and Medical Devices Agency of Japan |
| <b>PROs</b> | Patient Reported Outcomes                           |
| <b>RIS</b>  | Relevant Information Summaries                      |
| <b>RS</b>   | Registry Study                                      |
| <b>RWD</b>  | Real-World Data                                     |
| <b>RWE</b>  | Real-World Evidence                                 |
| <b>SMS</b>  | Short Message Service (text messaging)              |
| <b>SPOR</b> | Strategy for Patient-Oriented Research              |
| <b>WFH</b>  | World Federation of Hemophilia                      |
| <b>WHO</b>  | World Health Organization                           |

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Note: During production stages, we noticed that three references have two different numbers. #8 is the same as #149. #12 is the same as #31. #21 is the same as #88.