Fortrea

WHITE PAPER

Addressing the implications for long-term follow-up in discontinued gene therapy studies

Exploring collaborative solutions with sponsors, patient advocates, IRBs and regulators to minimize burden and maintain patient safety

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A long-term follow-up (LTFU) study is essential in assessing the extended safety and efficacy of a gene therapy that causes permanent or long-acting changes in the human body. But what happens when a drug development sponsor is suddenly unable to fulfill its LTFU commitment due to an uncontrollable circumstance, such as loss of funding or bankruptcy?

After managing a sponsor's unexpectedly terminated gene therapy study, our team at Fortrea recognized the lack of clarity for managing and reporting this event. This white paper shares guidance from key stakeholders in gene therapy and our proposed approaches for strengthening LTFU collaborations, spanning Institutional Review Boards (IRBs), Institutional Biosafety Committees (IBCs), regulators, sponsors, Clinical Research Organizations (CROs), clinical study participants and patient communities.

Case study: Unexpected study discontinuation inspires collaborative action

An emerging biotech organization selected Fortrea to support a rare disease gene therapy study, which included a five-year LTFU component. Recognizing that potential clinical study participants had concerns about participating, Fortrea worked with a patient advocacy group to select potential sites, help generate understanding and develop trust across the patient community.

Study recruitment and enrollment were progressing as planned and several enrolled participants were administered the gene therapy. The sponsor suddenly and prematurely terminated the entire study, which included the LTFU portion in the main study protocol, without sharing the rationale for study termination.

After the study site notified the IRB and the IRB agreed to study termination, Fortrea attempted to address patient safety concerning the lack of LTFU. They advised the sponsor to notify the U.S. Food and Drug Administration (FDA) and submit a protocol amendment containing:

- The long-term duration of follow-up
- Roles and responsibilities for follow-up
- Required visit assessments and visit frequency
- The proposed reporting loop for adverse events to the sponsor and the FDA
- A request for the FDA to review and provide feedback on the amended protocol

In the interim, Fortrea rapidly implemented measures to ensure short-term follow-up of the participants who were administered the gene therapy. However, the path to resuming the appropriate LTFU was cumbersome and slow, taking over six months to resolve.

To efficiently address and manage this potential risk in the future—while ensuring patient safety takes precedence—Fortrea is reimagining how to overcome the challenges of LTFU through a collaborative approach that incorporates the perspectives of sponsors, patient advocates, IRBs, CROs and regulators.

Understanding regulatory guidance and expectations

Global regulatory frameworks help sponsors tailor their LTFU approaches based on the type of therapy and patient demographics. The FDA's guidance document on LTFU after the administration of human gene therapy products provides detailed recommendations for LTFU protocols, including clinical considerations, goals and duration.[1]

With advancements in technology and safety insights, the FDA's approach to LTFU for gene therapy continues to evolve and has been shaped by several events over the past two decades.

Early guidelines (1994–2000s)

Historically, human gene transfer (HGT) research subject to the *NIH Guidelines for Research Involving Recombinant and Synthetic Nucleic Acid Molecules* needed study-level approval by a federal review body known as the Recombinant DNA Advisory Committee (RAC).[2] HGT protocols were reviewed by RAC with regard to biosafety and ethical considerations prior to release for site-level review by IRBs and IBCs representing individual clinical trial sites and institutions. Under these NIH guidelines, extensive reporting of enrollment and adverse events was mandated as specified in a section known as "Appendix M."

In 2000, after witnessing severe adverse events, such as leukemia in early retroviral vector trials (e.g., X-linked severe combined immunodeficiency [SCID] therapy), the FDA issued a "Gene Therapy Letter" requiring annual reports from sponsors on product safety and trial conduct.[3]

In 2006, draft guidance mandated a blanket 15-year follow-up for all gene therapies, including five years of annual exams and 10 years of annual questionnaires.[4,5] This one-size-fits-all approach aimed to mitigate risks from integrating vectors but faced criticism for inflexibility.

Shifting to a risk-based approach (2018–2020)

In 2018, the FDA introduced updated draft guidance (finalized in 2020) advocating a case-by-case, risk-based framework.[1] Key factors now include the vector type (e.g., integrating vs. non-integrating), biodistribution, disease population (e.g., life expectancy, comorbidities) and persistence of therapeutic effects.

The FDA's guidance, *Long Term Follow-Up After Administration of Human Gene Therapy Products,*[1] emphasizes the importance of monitoring clinical study participants in gene therapy trials for an extended period to understand and mitigate the risk of delayed adverse events—even when facing special circumstances:

"A sponsor may cease to operate or may decide to inactivate, transfer or withdraw an IND [Investigational New Drug Application] before completion of LTFU observations for all subjects exposed to the GT [gene therapy] 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 [Office of Tissues and Advanced Therapies] on the plans for completion of LTFU observation."

Duration recommendations were tailored to include 15 years for integrating vectors (gammaretroviral, lentiviral), transposons, genome-editing products and herpes vectors, with up to five years for adeno-associated viral (AAV) vectors. If data show reduced risk (e.g., declining vector persistence), the flexibility was offered to shorten follow-up.

In 2016 and 2019, two amendments were made to the *NIH Guidelines for Research Involving Recombinant and Synthetic Nucleic Acid Molecules*, eliminating the previous Appendix M and RAC review. As a result of these changes, the review of HGT research was devolved to review committees representing each institution. These amendments also created a more explicit delineation of separate responsibilities of IRBs and IBCs.

Recent developments (2020–2025)

The FDA has aligned with EU regulators on harmonized follow-up standards and core principles (e.g., risk-based follow-up duration), but regional nuances persist, as seen in EMA's 2019 guidelines.[6] This document emphasizes adaptability to patient-specific factors like comorbidities or prior treatments (e.g., chemotherapy preconditioning).[7, 8]

The emergence of genome-editing technologies like CRISPR-Cas9 and transposon systems has also prompted extended vigilance due to unexpected or potentially harmful risks.[1,7]

The regulatory evolution of gene therapies underscores the FDA's aim to balance safety and practicality, prioritize patient-specific risks and encourage innovation in monitoring strategies. Regulatory convergence will remain essential as gene therapies expand globally. The regulatory landscape will continue to evolve, and the space for LTFU will need to be closely monitored.

Examining the roles of the IBC and IRB

Oversight of gene therapy studies is a cooperative effort, with the IBC and IRB working together to provide appropriate oversight. IBC oversight of a gene therapy clinical trial may be terminated when dosing is complete, while IRB oversight is for the length of the study.

However, institutions have the option to maintain IBC oversight beyond the minimal dosing period.

In past years, the aspects of research reviewed by the IBC and the IRB had significant overlap. However, under current rules, the IBC and the IRB have a more distinct division of responsibilities.

- **IBCs** are primarily responsible for reviewing the safe handling of genetically modified drug products and focusing on exposure risks to study staff, the general public and those who may come into contact with clinical study participants.

  In many cases, IBCs remain a source of institutional expertise in molecular biology and genetic medicines, and IBC review teams can generally provide expert scientific and operational advice to IRB reviewers.
- **IRBs** are primarily responsible for reviewing ethical aspects such as risk, benefit and consent, focusing on the enrolled clinical study participants. Per the Office for Human Research Protections (OHRP) Code of Federal Regulations (CFR) 21 CFR 56.111/45 CFR 46.111, the IRB's review ensures that the criteria for approval—the regulatory requirements for research—are met and continue to be met to protect the rights and welfare of human research participants.[9] While best-case scenarios provide a smooth flow, less-than-best is common.

IBCs and IRBs roles in LTFU

Per NIH guidance, IBC review of a clinical trial at a site may end after enrollment is complete and the final dose of the gene therapy product at that site per the protocol has been administered. This means that IBCs are not formally required to approve LTFU protocols under NIH rules. Nevertheless, in light of the expertise noted above, IBC teams may make valuable contributions to institutional oversight of LTFU activities.

At the end of a gene therapy study, the IRB must take action on three key criteria for approval in certain situations.

1. Limiting risks

The first criterion to examine is in 21 CFR 56.111(a)(2)/45 CFR 46.111(a)(2), which states: "Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result." While heavily considered at the start of a study, this criterion must be maintained throughout the study.

Situation 1: The drug is not working

The IRB often encounters a standard situation where sufficient information has been collected to show that the drug is not working; this can occur during ongoing review or at a point in the research when data analysis has occurred. Learning what does not work is extremely valuable knowledge. At the same time, as soon as that knowledge is gained, the criteria for approval require a speedy and effective end to the trial. The goal is to limit the risks, given that the benefit of the research question has already been obtained.

For many interventional studies of a product treating a disease, cessation of the drug product would drastically curtail the risks. Simple close-out measures would occur, and people would exit the study to transition back to standard therapy. This situation requires that the residual effects of the drug are of limited duration. For standard drugs, 30 days is usually sufficient. However, for gene therapy products, a standard drug study is not the most accurate analogous situation to existing circumstances that the IRB encounters.

Situation 2: An implanted device is not effective

The IRB may face difficult situations in implanted device studies. In a standard implantable device study, data are collected during the active period to determine whether the device is effective. There may be a control arm, where the device is implanted but left off to be later turned on. This design is elegant in that the device is considered inert during its "off state." Similarly, if the device is shown not to work, then it can be turned off, and the residual risk is low if the implanted device is inert. This is an acceptable situation, considering there are potentially significant risks with the removal of implanted devices. With the benefit of the research question being answered, any further interventions do not meet the IRB criteria for approval. An explant may be further considered on a risk-benefit consideration that examines the level of inertness of the device, anxiety of the participant from having the device left in, MRI compatibility and compatibility with other devices that may need to occupy the same space or electrical signature.

While gene therapy studies are technically drug studies, they have many similarities with implanted devices. Many gene therapy products are designed to have an extended, perhaps lifelong duration of effect, with no "off state." In situations where substantial study changes are planned or required, early communication and collaboration with the IRB and IBC is critical for ensuring the regulatory and ethical aspects are addressed. Transparent communication also helps protect the trust of current and future participants in research to support their participation.

2. Monitoring the data collected

21 CFR 56.111(a)(6)/45 CFR 46.111(a)(6) states: "Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects."

This criterion importantly presumes adequate data are being collected and monitored. In the initial plan for the study, there may be very reasonable short-, medium- and long-term methods for data collection and monitoring, which the IRB approves to start the study.

Situation 1: The study question is answered; the gene therapy product does not work

Using the analogy described earlier with the implanted device, the IRB would know if the implanted device was inert and the potential level of monitoring. They would consider whether routine care could provide the skills and equipment necessary to monitor and maintain the safety of the implanted device and consider that the device could fail.

Similarly, the same level of detail is needed to evaluate gene therapy studies' need for long-term follow-up. FDA guidance for ongoing monitoring notes that monitoring can extend for years beyond dosing, depending on the product's nature.[1] In some cases, monitoring could be passive or active. For example, simple blood testing could be utilized whenever possible. However, if needed, more invasive testing may be required.

Whether using simple or complex testing, the IRB must consider if standard tests exist to monitor for activity if the gene product affects a clinical study participant's health. If a person's health starts to decline, could standard treatment determine whether the gene therapy product was at cause or exacerbating the disease? If standard care couldn't monitor adequately to ensure the safety of the participant, remanding to standard care would not be acceptable.

Situation 2: The sponsor cannot support LTFU

As shared earlier in the case study, a sponsor may face an unexpected situation and lose the ability to support LTFU. While research insurance may be required in some countries and can help resolve this situation, insurance may not cover all countries or situations. Regardless of insurance coverage, collaboration between IRB and IBC is especially important if the sponsor cannot support LTFU.

- **The IBC's role:** The IBC can apply its significant expertise in extrapolating previously unknown circumstances in gene therapy products and similar synthetic DNA products. The IBC can provide this invaluable knowledge to the IRB and may add to IRB deliberations to inform appropriate long-term monitoring and ensure the safety of clinical study participants. This close partnering of the IRB and the IBC mirrors how the IRB, the sponsor and the CRO would also partner.
- **The IRB's role:** The IRB can provide important insight into the clinical study participants' perspectives of how risk would remain reasonable, what appropriate measures are required to close out the study and the level of long-term follow-up needed. If unanticipated problems involving risks to the clinical study participants were encountered, the IRB would be responsible for reporting to the FDA. This evaluation would consider what resolutions could be needed in situations where the orderly close-out of a study cannot happen. The sponsor and FDA may then engage in appropriate measures to address the sponsor's responsibilities according to these circumstances.

3. Informed consent

The third criterion for the IRB to address pertains to 21 CFR 56.111(a)(6)/45 CFR 46.111(a)(4), which states that "informed consent will be sought and documented from each prospective subject or the subject's legally authorized representative in accordance with and to the extent required" by regulation.

For example, from the prior scenarios, IRB review is required to inform clinical study participants about the risks/benefits, monitoring and any changes. As the study progresses, the IRB determines what is presented and how. The IRB review relies on input from the IBC to ensure that the translation of scientific information to the likely non-scientific participant is accurate and complete throughout the life of the study.

It's important to note that informed consent is not a signature on a paper prior to the start of study participation but an ongoing process. Participants consenting prior to participation must understand the long-term risks, which include the risk of the aforementioned early study closure. Ensuring that these criteria are met represents a pillar of ethical research and requires sophisticated understanding and experience.

Assessing the impact of study discontinuation on patients and patient communities

As shared in the case study, Fortrea worked closely with a patient advocacy group (PAG)—before and during the rare disease gene therapy study—to generate understanding and develop trust across the patient community. The PAG also helped the study team select sites and educate participants on clinical trial participation. Given that there are no available treatment options for the disease and high unmet medical need persists, patients were eager to participate in the study.

However, when the study suddenly stopped, the patients and the broader community were caught off guard. Enrolled patients were understandably upset as there was no protocol-specified follow-up for those who were administered the gene therapy, and they experienced an overall lack of communication from the sponsor. The patients had also expected and planned for several study visits and assessments, which were detailed in their signed informed consent forms.

Using the sparse information they received from the sponsor, the PAG worked with patients and families to help minimize the impact, but the entire incident adversely affected patients' (and potential patients') emotional and mental well-being.

The patient community expressed concerns that the consequences of this experience could extend beyond the individual clinical program. Although these rare disease patients are generally interested in clinical trial participation and patient communities are eagerly pursuing the potential promise of these therapies, their enthusiasm could be easily eroded if a study is halted. All stakeholders must ensure that they can provide transparency, trust, agreed to follow-up and clear guidance in this situation.

Focusing on LTFU initiatives to meet the needs of patients, sites and sponsors

Since the FDA guidelines for LTFU[1] were published, Fortrea has been working on reducing patient, site and sponsor burden by developing thoughtful protocol design and new operating models. As part of this effort, Fortrea is also engaging with the FDA to discuss a platform study for collecting safety data on the long-term follow-up of global gene therapy studies.

At a high level, our team at Fortrea is focusing on three aims:

1 Making participation easy for patients

To maintain as many patients within the LTFU as long as possible, it is important to make it as easy as possible for patients to participate while maintaining their motivation. Early in the follow-up, we anticipate a high level of patient buy-in. At this stage, patients are usually keen to see their physician to assess how the treatment has worked and receive reassurance that there are no side effects. As the time from treatment lengthens, we observe that patients wish to move on from their treatment. Therefore, it is important that the study is designed to move to a more passive route of data collection over time.

Patient motivation starts with consent at the interventional phase, when patients must be made aware of the length of follow-up and the reasoning behind the LTFU length. Changes should come with a clear rationale. Our case study has demonstrated that without that clear rationale, patients' well-being is put at risk.

Additional resources for LTFU

Our recommendations for long-term follow-up protocols are detailed in the white paper:

"Designing an optimal long-term follow-up program for gene therapies and genetically modified cell therapies."

To reduce site and sponsor burden, long-term follow-up can be conducted under a separate protocol from the interventional study. At the point of consenting into these separate studies, there is a risk of losing patients. Planning early and keeping patients informed reduces this risk.

As the follow-up moves to the very long term, it is essential to continue to provide feedback and study updates to the patient throughout the life of the LTFU to ensure that they feel part of the study process and remain motivated.

2 **Increasing site motivation**

Maintaining site motivation over the long term can be a challenge, especially as the visit frequency drops and sites start to concentrate on newer interventional studies. Continued site-level communication should be maintained to ensure ongoing buy-in. Reducing the number of sites taking part in LTFU procedures can help with site motivation and allow more involvement in data sharing or publications, as appropriate. However, any site-level changes must be done carefully to reduce the chance of negatively impacting patients.

3 **Lowering sponsor burden**

Our experience shared in the case study highlights the importance of keeping the sponsor burden low. We must ensure continuity of care for patients who have taken part in gene therapy studies, and Fortrea is currently developing further solutions toward this aim.

The role of the CRO in LTFU

While the ultimate responsibility for LTFU resides with the sponsor, partnering closely with CROs, IRBs, health authorities and patients/patient advocates allows a more robust review of requirements, approaches and study design decisions.

CROs possess a unique perspective on the rapidly evolving landscape for human gene therapy products. Given the challenges and financial considerations of these long-term studies, sponsors may benefit from a CRO's support and partnership to meet the study's objectives and ensure that a study's status, expectations, roles, responsibilities and commitments are clear and communicated to all stakeholders.

CROs also play an important role in amplifying the voice of the patient and ensuring patient safety is at the forefront of all plans and decisions. In gene therapy studies, CROs often develop close relationships with patient advocacy groups and rely on their guidance to select appropriate sites, create well-accepted educational materials, identify potential patients and generate community understanding.

Today's patient-driven focus on addressing unmet medical needs with cell and gene therapies

The demand for CRO support of cell and gene therapy (CGT) programs is growing. In 2024, our team at Fortrea advanced 105 programs, up from 70 programs in 2023. Emerging biotech sponsors represented 60% of our clients and more than one-third of those were based in Asia.

Many of the innovative cell and gene therapy programs we have supported addressed diseases with poor or no treatment options. This activity is welcomed and often driven by patient communities, especially for rare diseases with no available treatment options.

Looking ahead to increase collaboration

Although challenging to operationalize, LTFU for gene therapy studies is critical to understanding the long-term safety of gene therapies and prioritizing patient safety. Generating gene therapy LTFU approaches for a study requires a collaborative approach to design meaningful endpoints that lead to robust data, address patients' needs and concerns, adhere to health authority guidelines and garner trust among all stakeholders.

At Fortrea, we see ourselves as a central partner to sponsors, patient advocates, IRBs and regulators. We are actively engaged in discussions to reimagine how to overcome the challenges of LTFU, better ensure continued safety oversight, support comprehensive safety reporting needs and help realize the full potential of gene therapies.

Please contact Fortrea to learn more about our patient-centric approach to navigating complex logistics, implementing practical solutions and optimizing the LTFU approach for your product:

https://www.fortrea.com/therapeutics/cell-and-gene-therapies

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