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

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Increasing numbers of patients are being exposed to gene therapies as investment in gene therapies continues to grow. By the end of 2023, 30 gene therapies were approved with a further 2,111 in development.[1] In addition to those patients in clinical trials, more and more patients are becoming eligible for approved treatment with these gene therapy products. The Alliance for Regenerative Medicine estimates that the first eight U.S. gene therapies for a rare genetic disease approved by the FDA have a combined eligible patient population of 18,000. In the EU, the estimate approaches 16,000 patients; the recent approval of gene therapy for sickle cell anemia looks likely to double that figure.[2]

As these therapies make permanent, long-acting changes to the human body, the hope is that they will make lifelong improvements to a patient's symptoms. However, the downside of these permanent changes is the increased risk of delayed adverse events (AEs), such as the possibility of causing a tumor or targeting the wrong cells. In response to this risk, regulatory authorities are demanding continued monitoring of patients in clinical trials as well as those treated with commercially available products. This monitoring is conducted via long-term follow-up studies.

Long-term follow-up (LTFU) is a significant commitment, both to study sponsors and to the patients who participate. As the number of patients that take part in gene therapy clinical trials increases, the industry has been looking for solutions that ease that commitment, while fulfilling requirements and maintaining patient safety.

Understanding regulatory requirements

To clarify expectations for LTFU in gene therapy, both the EMEA[3] and FDA[4] have provided guidance. Generalized points include:

Length of follow-up required: The guidelines give general recommendations around the length of follow-up required, which is based on several factors, such as the patient population, the vector persistence and the duration of transgene expression. However, sponsors should work closely with regulators to establish expectations, especially in response to the recent announcement from the FDA around T-cell malignancy following BCMA-directed or CD19-directed autologous CAR T-cell immunotherapies[5]. While traditional LTFU is expected to last between 5-15 years, in recent months, Fortrea has been speaking to sponsors who have been asked by regulators to plan for lifelong follow-up. This will only become logistically possible by almost entirely removing the patient burden associated with participation in that follow-up.

Minimum requirements of LTFU: A protocol should be established to maintain a case history for the patient for the duration of the LTFU period. Vector sequencing should be carried out for the duration of the vector persistence. The patient should be seen at a scheduled clinic visit for at least annually the first five years after administration, however, this may not need to be with an investigator if a method has been established to reliably collect this information from a different healthcare professional (HCP). If follow-up is expected to last longer than 5 years, the regulators support the use of more real-world data and the FDA expects that patients will be contacted at least once a year, but this may be in the form of a phone call or a survey rather than face-to-face.

Including LTFU in the interventional protocol versus creating a stand-alone protocol

The first critical decision in LTFU planning is determining whether it should be included in the interventional trial or planned for in a separate LTFU protocol. There are advantages and disadvantages to both designs.

Including LTFU in the interventional protocol can reduce some administrative burden, as this means that only one protocol is submitted to regulators and the IRB/IECs. Patients are expected to be informed and consented to LTFU from enrollment into the interventional trial; including LTFU in the interventional protocol facilitates this process.

A stand-alone protocol allows for the initial protocol to be closed once endpoints are met. These protocols can be lower burden and designed with low- or non-interventional designs, which have lower cost and regulatory requirements. It allows for the consolidation of several trials into one LTFU protocol and increased decentralization, reducing the burden for patients, sites and sponsors. However, if the length of the interventional trial is very short, regulators and/or IRBs/IECs can ask for the LTFU protocol to be submitted at the same time, reducing the advantages of a separate protocol and forcing decisions to be made about the requirements of LTFU with little clinical information. Logistically, sponsors need to be careful to ensure that the LTFU protocol is fully approved before any patient comes to the end of the interventional trial to avoid losing the patient or missing critical data. When the LTFU protocol is a stand-alone protocol, patients need to be consented again, leading to an increase in logistical burden and a point in time when losing patients becomes a possibility.

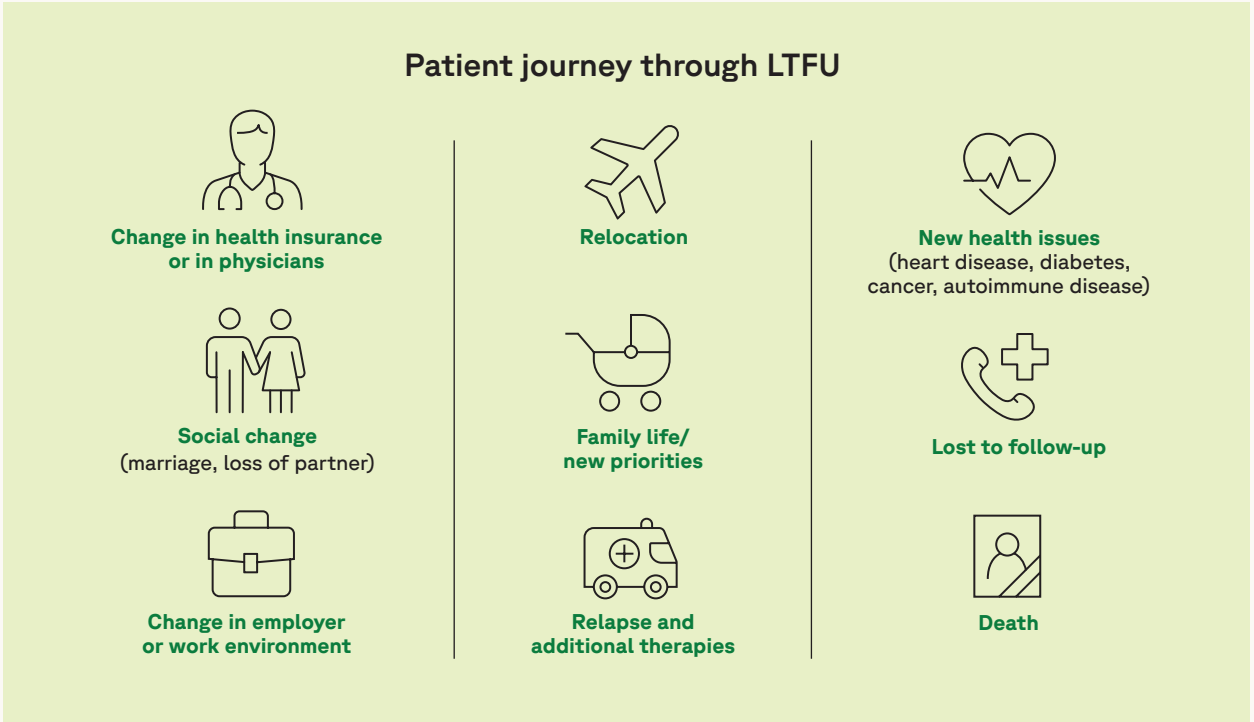
A hybrid approach can often represent the best LTFU solution. Starting with an integrated protocol involves the administrative burden of one protocol and fully consented patients while the treatment is administered and all sites are fully open. Once all patients are recruited to the study, sponsors have more information, such as: which sites recruited patients; the health and disease status of the patients; whether vector persistence will be a longer-term problem or not; and whether the sponsor will be conducting other gene therapy trials either with this candidate or with others. Supplied with this information, sponsors will have a better idea of what their longer-term follow-up will look like. At this point, they can amend the original protocol and/or establish a separate LTFU protocol, allowing them to consolidate sites/protocols and adapt expectations based on the data collected.

Sharing best practices in LTFU

Based on Fortrea's experience in LTFU studies in gene therapies, including genetically modified cell therapies, we have developed several best practices.

1. Keep patient burden low

While patients may be willing to travel long distances to receive potentially life-changing therapy this becomes more burdensome in the longer term. The therapy may have been highly effective, meaning patients are ready to move on with their life and leave the disease behind, Alternatively, patients may become very ill, and find it increasingly difficult to engage with trial participation. Over the very long-term, patients' lifestyles change, including patients treated as babies entering adolescence and those treated as children entering adulthood. Protocols need to be designed with these changes in mind, this not only increases patient retention but reduces site burden and sponsor cost.



In most cases, from around two years after treatment administration, visits can be reduced to once a year or bi-annually with every other visit performed remotely. Highly specialized tests for efficacy should be avoided or done at a reduced frequency. If there is a desire to continue to monitor efficacy as part of the LTFU, surrogate measures that can be measured remotely or are used as part of the standard of care should be identified.

2. Design a flexible protocol

The interventional period of a gene therapy study is intense by necessity for appropriate safety oversight and efficacy assessments. As this intensity diminishes over time, the frequency of visits is reduced, and follow-up can be transitioned to other HCPs, home health visits and/or remote follow-up. While guidelines use distinct time points to make these changes, the right time for each program and patient will be different.

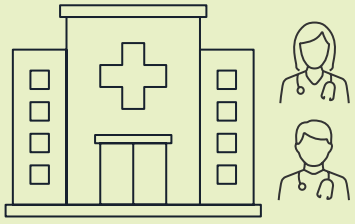
Including flexible elements in a protocol (within allowable boundaries) from the beginning can facilitate this transition, helping maintain patient retention and reduce protocol deviations. Examples include allowing for physical examinations and face-to-face assessments to be carried out by an HCP who is not an investigator or building in a lower-burden follow-up for patients who are too sick to travel to the site or are receiving palliative care.

3. Incorporate digital tools to facilitate hybrid solutions

The reduction of burden and flexibility of a protocol can be enhanced by the inclusion of digital elements. At Fortrea, we recommend using a patient app, which includes e-consent and can also include a telehealth platform, visit planners, motivational messages/milestones, direct AE reporting, study updates and communications. While the benefit of these tools becomes more evident as the follow-up becomes more remote, Fortrea recommends the inclusion of these in the interventional portion of the trial, as this allows patients to become familiar with them and allows troubleshooting while the investigator and patient are still meeting face to face. In indications with limited prior research, sponsors should consider whether integrating these tools during natural history studies might facilitate developing a patient-centered measure of efficacy that can be continued throughout LTFU.

LTFU: changing needs over time

Interventional/early follow-up phase



- Use traditional study design
- Facilitate on-site visits
- Understand burden to patients
- Work with small study populations

Early LTFU
(Home health, devices and sites)

- Reduce on-site visits/incorporate healthcare providers
- Reduce study fatigue
- Minimize patient dropout
- Enable LTFU with technology and services

Virtual model
(5+ years after administration)

- Incorporate real-world evidence
- Potentially use a central investigator
- Potentially collect samples as needed via home health

4. Continue to engage patients

As follow-up moves toward a more remote model, it can be easy for patients to become disengaged. Without feedback from the sponsor, patients can forget the importance of providing their information on an ongoing basis. It is important to periodically provide the patient community progress updates and remind them of the importance of their ongoing participation. However, too much information can become burdensome. Fortrea's Patient Recruitment and Engagement Team can help advise on how to achieve the correct balance.

Approaches for reducing LTFU burden

Methods of further reducing sponsor and site burden include:

Consolidating several LTFU studies into one central protocol with a "basket" study
As described above, optimizing an LTFU study potentially involves the use of digital tools, home health nurses and patient engagement materials. Some gene therapy protocols only enroll a small number of patients, and so the cost per patient of maintaining all these items over a longer period can be high. Where sponsors have a few gene therapy assets or protocols running, these studies can be consolidated into one, reducing the number of protocols (and so investigators) at larger sites and reducing administrative costs. This can be facilitated by a flexible protocol. For example, we have seen patients be reticent to change investigators where the protocol covers more than one indication, as they still would like to be seen by an expert in their indication. Allowing follow-ups to be conducted by an HCP means that they can still be seen by their preferred physician while taking part in the trial.

Using central site monitoring for all patients in a country
Fortrea has witnessed that sites and patients are keen to maintain contact for the first few years after administration. Sites value staying in contact with patients who are a "good news story" for their sites and seeing how their lives change. Patients are reassured by seeing the expert in the field and sharing their progress with the sites.

As time passes, sites become more interested in newer programs and patients' lives move on. At this point, and when the follow-up has become fully remote, sponsors should consider whether moving to a central site would be beneficial. This central site would maintain follow-ups for all patients in the country where they are based. Where there have previously been numerous sites following up on a handful of patients, this can further reduce site and sponsor burden.

Incorporating real-world data
Consider methods of accessing real-world data already available to reduce the burden on investigators and ensure a complete dataset. Possibilities include the use of tokenization to collect data from electronic medical records and leveraging available registries.

Incorporating risk assessment for the longer term

Any study that runs for years will have risks associated with its timescale. It is important to conduct regular risk reviews to put mitigation into place. Examples of risks inherent in a longer-term study include: the risk of patients becoming lost-to-follow-up; ensuring information isn't lost during inevitable staff transitions (at the sites, CRO and sponsor); maintaining site engagement; and establishing a robust change management process to deal with changes in vendors, regulations or technologies. Fortrea is experienced in running lengthy studies and has an established risk assessment methodology to address this.

Looking ahead to support sponsors

Several factors influence the right model of LTFU for a gene therapy asset. Sponsors must follow regulatory requirements and consider how to optimize their protocol design as they set up their trial. The use of digital tools and central site monitoring can help reduce patient and site burden, increase patient engagement and enable continued monitoring of patients in these important studies.

Fortrea's Rare Diseases, Advanced Therapies and Pediatrics Team (RAPT) works closely with sponsors to ensure that the right LTFU strategy is engaged for their gene therapy. **Learn more at:**

https://www.fortrea.com/scientific-expertise/by-therapeutic-or-specialty-areas/rare-diseases--advanced-therapies-and-pediatrics-team--rapt-.html

References

1. Gene, Cell, + RNA Therapy Landscape Report, Q4 2023. *Quarterly Data Report Citeline/ ASGCT.* https://www.asgct.org/global/documents/asgct-citeline-q4-2023-report.aspx Accessed 18 Apr. 2024
2. *Alliance for Regenerative Medicine.* Sector Snapshot. December 2023. Gene therapies poised to reach more patients. http://alliancerm.org/wp-content/uploads/2024/01/20231220_Sector-Snapshot-Outline-Fall-2023_V2.pdf Accessed 18 Apr. 2024
3. *European Medicines Agency.* Committee for Medicinal Products for Human Use (CHMP), Guideline on follow-up of patients administered with Gene Therapy Medicinal Products. 1 May 2010
4. *U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research.* Long Term Follow-Up After Administration of Human Gene Therapy Products, Guidance for Industry. January 2020. https://www.fda.gov/media/113768/download Accessed 18 Apr. 2024
5. *U.S. FDA.* FDA Investigating Serious Risk of T-cell Malignancy Following BCMA-Directed or CD19-Directed Autologous Chimeric Antigen Receptor (CAR) T cell Immunotherapies. November 28, 2023. https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/fda-investigating-serious-risk-t-cell-malignancy-following-bcma-directed-or-cd19-directed-autologous Accessed 18 Apr. 2024

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