White Paper

Decisions in Cell and Gene Therapy Development

Implications across the development landscape.

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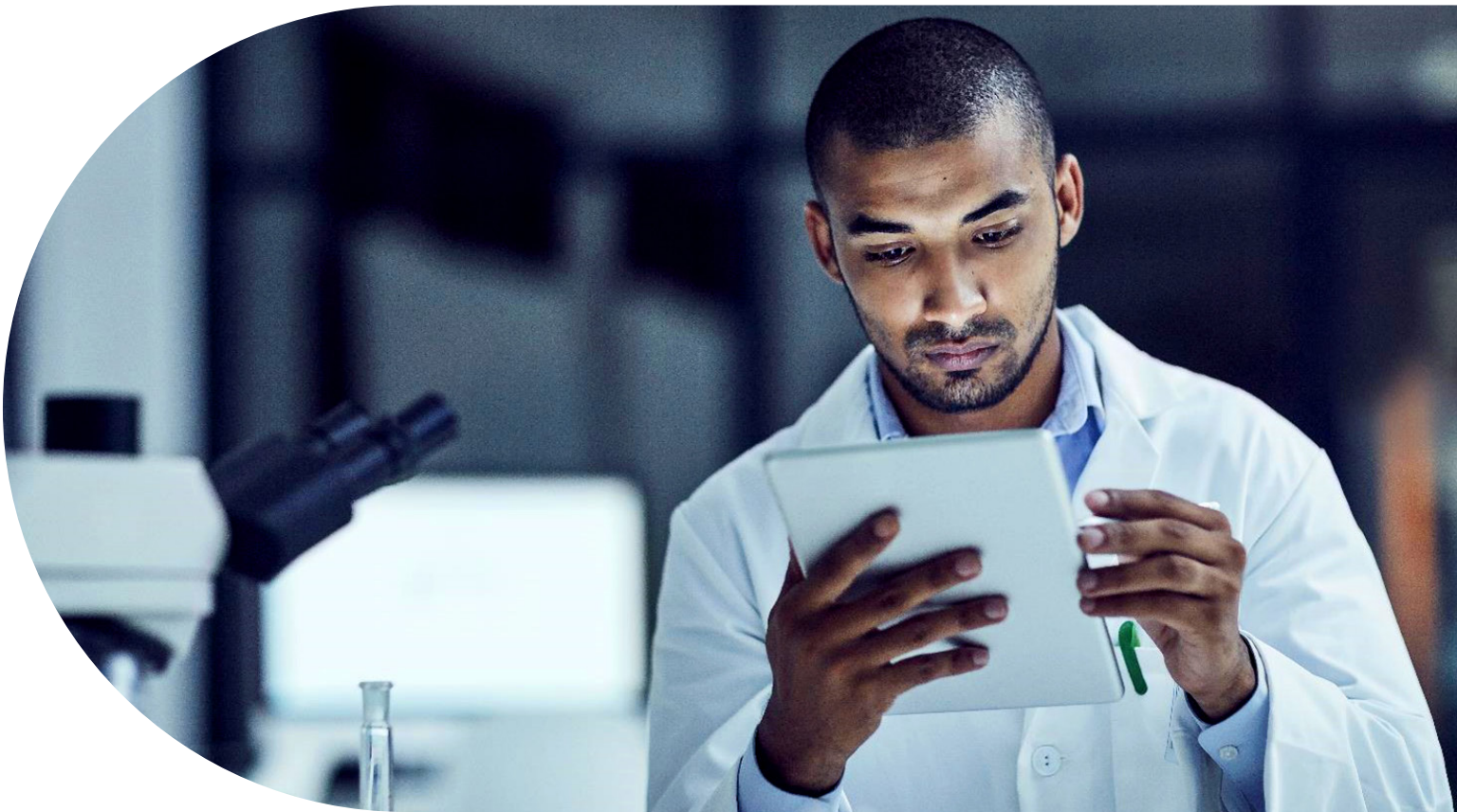
Introduction

Cell and gene therapies (CAGTs) hold promise for revolutionizing the treatment of many diseases that have previously been untreatable.

As of the third quarter of 2023, 3,866 cell, gene, and RNA therapies were in development, from preclinical through preregistration; 53% are gene therapies including gene-modified cell therapies, 25% are RNA therapies, and 22% are non-genetically modified cell therapies.[1] Eleven cell and gene therapies are approved for 16 indications in the US;[2] in 2024 alone, launches of up to 21 cell therapy and up to 31 gene therapy launches are anticipated.[3] The worldwide cell and gene therapy market is estimated at $22.7 billion in 2023, with a forecast compound annual growth rate (CAGR) of 28.7% in the period to 2030).[4]

Defining characteristics of clinical trials involving CAGTs include but are not limited to the involvement of rare patient populations, operationalization of complex protocols with high patient and site burden, unique site capabilities and requirements, management of expensive and often irreplaceable assets with multi-step processes and difficult logistics, and incorporation of mandated long-term monitoring to assess extended safety and durability. The successful development and commercialization of CAGTs relies on critical decisions made during the clinical development phases.

This white paper delves into the key decisions required in the development of cell and gene therapies and explores their profound impact on subsequent stages of the therapy's life cycle. From early decisions on indication prioritization, engagement with patients and patient advocacy groups, manufacturing and contract development and manufacturing organization (CDMO) selection, to long term follow up design, each decision bears consequences that ripple across regulatory approval, commercial viability, market access, and further iterations of therapy development. By mapping these decisions at the earliest possible point, stakeholders can navigate the complex landscape of cell and gene therapy development with enhanced precision and insight. Key decisions are needed in five main areas: clinical trial design, patient populations and recruitment, country and site selection, logistics and manufacturing, and long-term follow-up.



1. Clinical trial design

Clinical trials for CAGTs pose unique design challenges due to their novel nature and complex mechanisms. Available CAGT treatments are costly and the landscape is evolving quickly. Decisions taken at this stage are pivotal in establishing the candidate therapy's safety and efficacy characteristics, as well as its value proposition, laying the foundation for potential commercial success.

One of the primary challenges lies in selecting the right patient population. This choice can greatly impact the regulatory options for the therapy, with some rare disease therapies and other areas of high unmet need enabling potential fast tracking and a shorter time to market. Choosing a subgroup within a broader disease population may increase the chance of proving efficacy, but may add to the challenge of recruiting sufficient participants and restrict the label during commercialization approval.

CAGTs often target specific genetic mutations or cellular abnormalities; the stage of disease and patient sub-populations also need to be considered. Based on eligibility criteria, appropriate participant screening procedures will determine what is required from potential clinical sites, including access to appropriate facilities and understanding how candidate therapies would fit with the standard of care. Sites may need capabilities or access to genetic screening programs to confirm the presence of specific mutations, and be able to rapidly identify and refer patients to take advantage of the brief window for recruitment.

Studies typically involve small sample sizes, requiring innovative study designs, use of external comparators when available rather than placebo, and use of virtual tools to minimize burden. These studies are often complex, involving large numbers of visits and a high level of burden both to sites and to patients and their caregivers. Taking account of patient and caregiver perspectives is essential for streamlining study design and minimizing the burden of participation, for example by providing concierge services to handle participant logistics, which in turn supports recruitment and retention.

Trial design choices have multiple downstream effects. The study design (including endpoints) and population directly impact regulatory pathways, time to market, and the scope for later label expansions. Lack of streamlining can increase errors, negatively affecting data quality, while an excessive burden of participation can impact recruitment and retention, also reducing data quality. The choice of comparator can affect budgets and market competition, while inclusion/exclusion criteria can narrow the potential patient population, and necessitate additional referrals.

2. Patient populations and recruitment

Genetic screening or use of non-routine biomarkers for rare and genetic diseases can yield high screen failure rates and slow patient enrollment. Resulting delays may require additional investments and infrastructure, such as developing registries and pre-screening protocols, investing in biomarker data sets, and working with patient advocacy groups to support access to patients. The complexity of cell and gene therapies, typically associated with high patient burden, coupled with their risks and public perceptions of these therapies, can contribute to delays in recruitment, especially when challenging standard of care or in the presence of a highly competitive landscape.

Decisions to develop sustainable routes to patient identification can impact future commercialization and scale-up efforts. In addition to affecting regulatory decisions, the patient centricity of the protocol can impact patients' willingness to contribute to the further evidence generation that is essential to support pricing discussions and market access. The target population size also affects decisions on logistics, a complex and highly specialized topic.

3. Country and site selection

A key challenge in country selection is the need for a harmonized regulatory framework, especially for genetically modified therapies. In countries that meet

this requirement, sites need specific facilities and experienced staff to be able to run high-quality studies efficiently. This limits the number of sites suitable for the study and may affect patient burden and willingness to participate. Data-driven site identification and site networks can be helpful in identifying additional sites.

At an early stage, it is important to consider a strategy that considers the logistical implications of having manufacturing sites distant from clinical research sites. Furthermore, selection of their locations should also incorporate the possibility of targeting patients from diverse populations to support the democratization of research. As the candidate therapy advances through development, the countries and sites selected will be the launch pad into commercialization. Early investment in site start-up in areas with significant target patient populations can be an important market success factor.

4. Logistics and manufacturing

Significant logistical challenges and risks during the CAGT asset journey include tight pick-up windows, length of time from apheresis to administration in the case of autologous gene-modified cell therapy, cell viability during transit, and importation/exportation requirements. These are explored in detail in recent IQVIA white papers on cell and gene therapy logistics[5] and logistics management.[6]

Complex supply chains that involve multiple specialty vendors mean that sponsors should ensure that their manufacturing strategy is tightly aligned with the type of CAGT, target patient population, and site selection strategy. It is also essential to accommodate therapy-specific conditions, including requirements for scheduling and particular temperatures.

Sponsors should consider the logistical complexities of manufacturing, delivery, and the ability to scale up the production of their asset, thinking carefully about the needs of the specific therapy type and how to control variables in order to achieve consistent quality and speed. In addition, more targeted delivery and administration methods such as surgical delivery can create additional handoffs of the therapy/asset and require multi-disciplinary teams at sites. Sponsors should evaluate tradeoffs between multiple manufacturing locations and cross-continental shipping for global studies, and also incorporate possible implications for commercialization. Manufacturing time, location, and scalability are essential and complex considerations for sponsors.

Overall, manufacturing location and manufacturing timeline are dictated by three main factors: therapeutic area, site selection, and therapy type. Logistics and supply chain management strategies depend on type of therapy, manufacturing location, and number of patients. Sponsor strategy should take into account whether to tap into larger pharma in-house manufacturing or use a CDMO.

5. Long-term follow-up

Long-term follow-up (LTFU) studies to evaluate extended safety and durability of CAGTs have historically been seen as a post-launch requirement, including mandates from the U.S. Food and Drug Administration[7] and European Medicines Agency[8] to monitor adverse events for up to 15 years post-trial.[9] This is a costly and difficult process, requiring diligent efforts to stay in touch with study participants, which can be a particular challenge, especially with pediatric and adolescent/young adult (AYA) trial populations.

LTFU involves a trial design reflective of real-world conditions – a pragmatic study – with a defined balance between extended safety (primary) and durability/efficacy data. This may take the form of a single protocol with continuous main trial and LTFU, or involve a separate LTFU protocol that rolls over patients from the main trial. For sponsors with multiple assets in similar indications and/or therapeutic areas, there may be benefits to having a single, dedicated LTFU study with a centralized Principal Investigator to roll over patients from multiple trials. The PI designation is an important element, based on motivation, incentives, workload, and ability to

maintain follow-up. For example, rare disease physicians typically have useful experience establishing long-term relationships with patients and their families.

Another choice involves the best type of site to conduct the LTFU, including whether this should continue at the main trial sites, be carried out by a local physician using remote monitoring, or involve a hybrid alternative.

The patient burden and disease prognosis are key components in the design of the LTFU study, determining the depth and frequency of sampling and clinical assessments during the extended period of time. Specific solutions can be deployed to incentivize patients to remain with the trial over the long term, establishing 'light-touch' interactions – via telehealth, remote monitoring, connected devices or wearables – that minimize the patient burden while gathering vital data. This use of technology can make the commitment to continued contact easier to maintain for patient and caregivers.

A major consideration for sponsors is when is early enough to start thinking about LTFU. Starting this follow-up early in the clinical development process may bring long-term opportunities and benefits. This choice often depends on the state of maturity of the sponsor company. For example, emerging biotech firms may have a laser focus on developing their asset to the point where it can be a target for a strategic partnership and/or acquisition, wishing to minimize expenditure during this process. More established companies are likely to reap the rewards of an early start to LTFU, which can be achieved in a cost-effective way to minimize the physical and financial burden to the sponsor, for example by using some remote assessments to supplement in-person clinic visits.

Conclusion

Sponsor strategies for the five key areas discussed above – trial design, patient populations and recruitment, country and site selection, logistics and manufacturing, and LTFU – have important implications for clinical development. They also play a key role in post-approval options involving regulatory approval, scaling up production, commercialization, evidence generation, and label expansions. Against the backdrop of market growth and complexity, sponsors should consider working with a CAGT partner that offers holistic strategies and solutions to optimize the chance of clinical and commercial success.

About IQVIA

IQVIA is a leading global provider of advanced analytics, technology solutions, and clinical research services to the life sciences industry. IQVIA has a unique perspective across the landscape of CAGT. We work extensively with both biotech and large pharma manufacturers and draw upon our broad experiences to craft tailored solutions to help sponsors optimize and accelerate their clinical development.

Learn more about IQVIA's comprehensive approach to CAGT clinical development.

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