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New Medicines, Novel Insights: Accelerating Development of Cell and Gene Therapies

An Executive Summary

JUNE 2023

In this report

Bringing cell and gene therapies to market faster

Cell and gene therapies (CAGTs) offer extraordinary hope to patients with advanced cancers and genetic diseases; enthusiasm has never been higher. With recent approvals in a variety of different gene therapies and cell therapies, we are progressing towards a new day for patients. CAGT may be the new face of medicine in the future, and we owe it to our patients to stay invested in this critical area.

But CAGT poses unprecedented challenges for sponsors. Pipelines are constraining and constricting due to financial pressures. Making choices about which assets will go forward and how to develop them will be fundamental to success.

At Parexel, we believe partnership within the broader CAGT ecosystem will create advantages now and in the years ahead. We are developing innovative protocols and working closely with our sponsors toward that end. In this report, Parexel experts share insights that can help bring these complex treatments to market faster and more efficiently.

Patients face their own challenges – beginning even before enrolling in a CAGT trial.

To gain a deeper understanding of the patient journey before, during, and after CAR T-cell therapy for hematological malignancy, Parexel gathered insights and feedback from patients, caregivers, and healthcare professionals. Our research methodology encompassed literature review, qualitative interviews with these stakeholders, and quantitative patient surveys.

We learned that patients often face hurdles in meeting clinical criteria or running out of time while healthy enough to enroll. Trial locations are often inconvenient. Since CAGTs are still novel treatments, they are unfamiliar to many healthcare providers, who do not always provide referrals to eligible patients. Even after a referral, patients can have trouble meeting trial participation requirements and provisioning the required financial and personal support. These are just a few of the obstacles sponsors could recognize when initiating a CAGT project.

Once patients embark on the trial, their experience is as important as the treatment itself. Patients face a range of challenges that can impact overall success. Understanding their lived experiences on their journey to CAGT therapy is essential. Patients in these studies have often exhausted other care options, and by the time they are enrolled in the trial, they may be drained and fatigued. Many treatment regimens involve long in-patient or local stays, including follow-ups, causing a financial burden for some patients. While every patient's diagnostic and treatment journey is unique, the testing, preparation, in-patient, and follow-up requirements for CAGT patients are intensive.

A thorough understanding of the dynamics of the patient's journey to anticipate and prepare to provide support is critical to seamless execution.

Sponsors, sites, and healthcare providers must work with patients and families to craft personal support plans. Site staff members play an essential role. Because of the complexities of the patients and procedures, the site staff must be able to clearly explain what to expect and make sure the patient and family grasp the implications. Finally, post-trial support is imperative. Survivors of the therapy often need help adjusting to being "cured." They might have been a full-time patient for years and now are in remission. This is the new day they have hoped for, but life will be very different.

Regulatory agencies worldwide are facing a sharp increase in new CAGT applications. A robust regulatory strategy can help mitigate the risk of delays.

The volume of CAGT applications to regulators increasingly makes it difficult for sponsors to receive timely regulatory advice. In a crowded field, sponsors need a savvy local and global regulatory strategy to avoid pitfalls and mitigate bottlenecks that can result in clinical holds or other delays and setbacks. At Parexel, we advise clients to be more self-reliant and use data to inform their development and defend their decisions. Here are three specific recommendations:

1. Be prepared. Often, CAGT companies wait for the regulators' advice to make sure their assays and specifications for evaluating a drug substance and product are adequate. But developers can do more internal preparatory work, building a data-driven argument for the choice of stage-appropriate parameters for the product. Studying precedents from already-approved products can help.

The scientific rationale for chemistry, manufacturing, and controls (CMC) decision-making becomes especially critical if you propose something novel to the agency. If there are no existing data or agency opinions, you may need to provide more evidence than they need to support their analytical methods and process steps. Regulators want proof that the manufacturing process yields a product with consistent, measurable quality characteristics.

Gather external opinions on the quality of your science and rationale, not just from regulatory consultants but from objective scientific experts. Challenge your CMC roadmap and provide a solid justification for each step of the validation or manufacturing process before presenting it to regulators.

2. Scrutinize your clinical development plan. Parexel advises our biopharma customers to think critically about whether the patient needs they are addressing would be better met by demonstrating the durability of the effect since, with many CAGTs, there will be no re-treatment. Just because a product represents a scientific or technological breakthrough does not mean it delivers long-term results. The goal is to make life longer and better lived; it's not to achieve short-term clinical outcomes. Consider making conservative stage-gate decisions in the context of a complete understanding of how the therapeutic landscape might change. Clinical development could require more time and money than anticipated unless a product demonstrates unprecedented and reasonable durable efficacy.

3. Think like a regulator, then make prudent tradeoffs. Many emerging companies must make critical development decisions with limited resources. Some understandably seek to do the minimum required at each step to preserve resources. But when regulators do not have the bandwidth to provide frequent and timely advice, companies need to ensure that short-term decisions do not create long-term gaps or problems. What appears to be an economical option may result in costly rework.

One way to manage risk is to assume a regulator's mindset. Have a solid working knowledge of all the relevant guidelines before meeting with regulators. Anticipate the questions they will ask and identify the data you need to answer them. This iterative process guides how you build your data package. Regulators are scientists. To convince them that you have made the right choices, you must show them how you made vital decisions step by step and offer hypotheses that are understandable and supported by evidence.

Clinical trials for CAGTs have soared since 2016, with more than 2,500 currently in progress, according to the Federal Drug Administration (FDA).[1]

The number of clinical trials for CAGTs has exploded in recent years. However, investigative sites qualified to conduct these trials, most at top-tier academic research centers, are limited. The infrastructure is overloaded, and site fatigue is the result.[2]

Moving CAGT trials to the community and regional centers could have a broad impact – addressing site fatigue, potentially increasing patient diversity, and widening access to new treatments. Making this happen, however, will require collaboration and capital investment by key stakeholders.

To begin with, less-experienced sites need introductory-level education and training materials. Producing easily accessible resources would require seasoned players to share their knowledge and experience.

New operating models may be required. For example, medical-practice investigators could work with accredited blood banks for leukapheresis, or partner with hospitals to handle the serious adverse events associated with administering CAR T-cell therapies. But will hospital research sites already conducting CAGT trials be willing to provide in-patient care services to medical-practice research sites in their community? And will accredited treatment centers (ACTs) of commercial cell therapies be willing to practice in-patient care for research participants? These and other tough questions need answers if community-based sites are to make progress in CAGT research.

Here are three critical actions for stakeholders:

Sponsors: Streamline protocols and move beyond comfort zones. The scope of some clinical trial protocols is crippling workflow and productivity at sites. Studies replete with exploratory endpoints, assessments, and genetic testing are straining resources.[3] At Parexel, we see institutional disease and resourcing review groups increasingly rejecting overly resource-intensive trials. While some of these elements are required, others can be reassessed. Streamlining CAGT protocols is the most effective way to lessen site burden.

And although we understand potential risk aversion, we advise our clients to consider community sites and quantify the risks and tradeoffs. Sponsors that invest in site development before initiating a trial require vision, discipline, resources, and capital. But companies can begin with small steps. What about reimbursing sites to attend workshops to learn the standards and capabilities required for certification? What about approaching ATCs to encourage them to support in-patient services for research patients from medical practice sites?

Sites: Examine resourcing and begin addressing gaps. When we talk with community-based practices that want to participate in CAGT trials, the biggest hurdle is the in-patient care requirement and procedural complexities of cell collection. Frequently, these sites must conduct a thorough gap assessment and then explore the options available to outsource the services they will need.

Sites can leverage their existing sponsor and CRO relationships to request formal assessments of their CAGT readiness using standard pre-qualification checklists. Evaluations should include detailed reports identifying which operational aspects require further development.

CROs: Support sites, build relationships, and achieve cost efficiencies. At Parexel, we are actively building relationships with community-based research centers to serve sponsors and clinical trial participants more effectively. We are working to identify non-academic research institutions already conducting CAGT trials and profiling their capabilities. With that knowledge, we can provide targeted support and advocate for them with sponsors during the site selection process. And we facilitate advisory groups for direct communications between sponsors and community sites to foster a transparent dialogue.

Designed to deliver a lifelong cure, CAGTs do not fit existing frameworks for valuing, pricing, and reimbursing pharmaceuticals. Three trends could impact patient access and market success.

CAGTs enter a healthcare marketplace that runs on annual budgets. In short, CAGTs do not fit existing frameworks for valuing, pricing, and reimbursing pharmaceuticals. For payers, the presumed one-time, front-loaded cost of CAGTs has almost no precedent. However, new payment models are emerging, and we have identified three trends that could impact patient access and market success.

1. Expanded use of surrogate endpoints. Because CAGTs often have long-term effects that may not be measurable in the short term, surrogate endpoints via accelerated approvals (A.A.) could be critical for expediting patient access. For example, a gene therapy that corrects a genetic defect might not show immediate results but could prevent or delay disease onset or provide a long-term cure. As developers and the medical–scientific

community identify more novel surrogate endpoints and biomarkers, the science is at risk of outpacing the regulatory and reimbursement infrastructure.

It's possible that, while the regulators work to address that issue, payers will choose to wait out the uncertainty. They could argue that, without a complete scientific and clinical understanding, they cannot reimburse Accelerated Approval products based on "experimental" surrogate endpoints. To do so, payers could require a larger body of real-world evidence (RWE) to substantiate the long-term value to patients and the healthcare system.

Sponsors can manage that risk proactively. We advise our clients to strengthen their scientific and clinical validation of novel endpoints by collecting patient report outcome (PRO) data and quantifying a range of medical and economic cost offsets in their evidence dossier.

2. The emergence of dynamic health technology assessments. In Europe, health technology assessment (HTA) agencies determine market access. The magnitude and durability of clinical benefits inform reimbursement negotiations. For CAGTs, it could take years to demonstrate that a debilitating or high-morbidity condition has been prevented or stabilized. HTA bodies can't calculate the value and systemic impacts without long-term outcomes data, and issue decisions based on the evidence available at the time of evaluation.

But fresh thinking and healthy debate are surfacing. For example, what if HTA decisions were not fixed by dynamic documents that evolve as real-world data accumulate? Developers could submit evidence from long-term follow-up or registry studies, and payers could adjust the risk-benefit profile accordingly.

If regulators approve more CAGTS using surrogate endpoints, an evolving assessment may capture value more quickly and accurately, increasing patient access. Some HTA agencies are already taking a semi-dynamic approach – notably the UK.'s Cancer Drugs Fund, which provides temporary reimbursement for innovative cancer drugs initially declined by the National Institute for Health and Care Excellence (NICE).

From 2025 forward, an EU-wide joint clinical assessment (JCA) will form the basis of CAGT reimbursement decisions.[4] Post-approval RWE collected in each country might be a mechanism to support EU-side reimbursement decisions. Dynamic HTA evaluations could track a product's performance over time, documenting outcomes such as slower disease progression and fewer adverse events. Developers should expect U.S. arbiters of cost-effectiveness to follow Europe's lead.

We advise our clients to develop a plan for post-marketing data collection that balances patient interests, emerging science, and prudent use of healthcare expenditures.

3. Increased investigation of CAGTs in non-orphan conditions. If CAGT technology proves effective for treating widespread, chronic diseases such as angina, diabetes, or frontotemporal dementia, far more patients will have access to life-changing therapies. While demonstrating long-term value may support pricing that rewards R&D investment and risk, the cost of paying for CAGTs to treat large prevalent populations will put considerable pressure on health systems and payers.

Sponsors must be strategic to avoid developing drugs that are too expensive relative to the standard of care (SOC). CAGTs may reach new populations, but not all of these populations will be equally valuable or "worthy" in the eyes of economists and payers. For instance, the younger the patient, the higher the lifetime value. When we advise rare-disease companies that seek to diversify into chronic conditions, we caution them that regulators and payers will demand a demonstration of efficacy, long-term safety, and cost-effectiveness against the SOC. CAGTs will not be exempt from this requirement even if they deliver breakthrough science and patient benefits. So far, CAGTs have addressed conditions that lack a SOC or where the SOC is expensive and inadequate, such as hemophilia. The calculus is dramatically different for prevalent chronic conditions with existing cost-effective therapies.

The competition will increase as CAGTs expand to non-orphan conditions. According to Parexel data, all novel CAGTs and supplemental indications approved by FDA between 2017 and 2022 were orphan-designated. If two or more therapies are entering a market within six months of each other, will payers be incentivized to wait and compare them before deciding on coverage? Will they slow down evaluations in response? In that scenario, we would have a marketplace rather than a monopoly. Further, safe delivery technologies and gene-editing platforms such as CRISPR may enable second and third-generation products to achieve durable outcomes at a lower cost.

We advise our clients to engage with patients, regulators, and payers from the earliest stages of development to ensure patient access by demonstrating better outcomes and to drive market uptake by delivering value to healthcare systems.

Partnership across the ecosystem holds the greatest potential.

Parexel is committed to doing everything humanly possible to accelerate the development of advanced therapies. In our latest report, New Medicines, Novel Insights: Accelerating Development of Cell and Gene Therapies, we identify numerous examples of the potential for partnership within the ecosystem. Stakeholders must come together with a shared mission: to bring healing treatment to patients quicker and more effectively.

Read the full report insights.parexel.com/cell-and-gene-therapy-report-home/

1 Brennan, Z. (2023) Thousands of gene and cell therapies are inundating FDA reviewers as the agency tries to keep up, endpts.com. Endpoints News. Available at: https://endpts.com/thousands-of-gene-and-cell-therapies-are-inundating-fda-reviewers-as-the-agency-tries-to-keep-up/ (Accessed: April 4, 2023).

2 Rotenstein, L.S. et al. (2023) "The association of work overload with Burnout and intent to leave the job across the healthcare workforce during COVID-19," Journal of General Internal Medicine [Preprint]. Available at: https://doi.org/10.1007/s11606-023-08153-z.

3 "Rising Protocol Design Complexity Is Driving Rapid Growth in Clinical Trial Data Volume," (2021) https://csdd.tufts.edu/ [Preprint]. Tufts Center for the Study of Drug Development. Available at: https://f.hubspotusercontent10.net/hubfs/9468915/TuftsCSDD_June2021/pdf/

4 Regulation (EU) 2021/2282 on health technology assessment (2021) eur-lex.europa.eu. Directorate-General for Health and Food Safety, European Parliament. Available at: https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A32021R2282 (Accessed: April 18, 2023). ng+Protocol+Design+Complexity+is+Driving+Rapid+Growth+in+Clinical+Trial+Data+Volume++++++++++%20(1).pdf (Accessed: April 11, 2023).

5 https://insights.parexel.com/cell-and-gene-therapy-regulatory-strategies/p1/p/4

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