Mitigating risk, protecting potential

Practical strategies that position cell and gene therapy development for success

With Heart™

The cell and gene therapy (CAGT) pipeline represents incredible promise for the patients who need these products, many of whom have rare conditions without approved treatments or others who have exhausted treatment options. In bringing these novel therapies to market, sponsors face new regulatory and manufacturing challenges, operational complexity, and obstacles to market access.

Parexel helps sponsors innovate in this growing but uncertain space, so our experienced colleagues have strategized approaches to the persistent and prevalent barriers that CAGT developers may encounter. In this guide, we share some of those strategies — actionable insights for protecting the potential of your product in every phase of development.

Prevalent challenges in cell and gene therapy clinical development

As part of a market study on the CAGT landscape, Parexel talked with professionals at more than 70 biopharma companies of all sizes across North America, Europe, and Asia in May and June 2022. Of the challenges developers face, we identified four that are among the most perennial and persistent.

1

Unclear regulatory pathways
CAGT regulatory frameworks vary by health authority — and in some regions, they do not yet exist. As a result, products can experience costly delays. An expert with regulatory experience can help sponsors navigate these nuanced, and sometimes unclear spaces.

2

Varying CMC requirements
Because the products themselves are often highly individualized, CAGTs require customized chemistry, manufacturing, and controls (CMC) processes. This makes manufacturing difficult to scale. To improve the likelihood of a product's approval, sponsors should plan for CMC activities as early and thoroughly as possible.

3

Complexity in clinical trial execution
Current research infrastructure cannot fully support CAGT studies, in which therapies are often complicated to administer and patient populations are generally small and difficult to identify. Now is the time for new approaches, including trials in the community that put the patient at the center of research.

4

Barriers to market uptake
Given the high cost of CAGTs, payers demand compelling data before they will accept a therapy's value. Every product needs a compelling value story that establishes its clinical and economic worth.

1 Strategizing your approach to regulatory pathways

Given their novel nature and the rapid expansion of their development, CAGTs present new challenges for regulators. In many regions, CAGT regulatory frameworks have yet to be created. Where approval pathways do exist, requirements are often unclear and vary by national health authority. As CAGT development evolves, regulatory guidance also changes. In an uncertain landscape, products can experience costly delays on the path to market approval.

The challenge: Many regulatory reviewers are still coming up to speed on CAGTs — products often developed for incredibly complex indications. It may not be immediately evident how general guidances should — or should not — be applied to these new and nuanced products.

The approach: When working with the FDA, an INTERACT meeting (previously known as a pre-IND meeting) can be incredibly beneficial — an opportunity for the sponsor to receive advice but also to familiarize the reviewer with the product's novel attributes. Additionally, sponsors should use an INTERACT meeting to discuss safety evaluations and determine what data the reviewer expects, as current FDA guidance can be vague.

Within the European regulatory framework, sponsors have many opportunities for early dialog with the EMA. These can include interactions with the SME office (which serves micro, small, and medium-sized enterprises), as well as sponsor requests for Advanced Therapy Medicinal Product (ATMP) classification, for certification, and for scientific advice. The Innovation Task Force (ITF) offers discussions beginning in the R&D stage regarding novel regulatory and technical challenges for specific products. These face-to-face meetings, similar to INTERACT meetings, are popular with developers of ATMPs and are well attended by members of the Committee for Advanced Therapies (CAT).

To maximize the value of time spent with FDA and EMA reviewers, the Parexel team leads sponsors in preparatory mock meetings, rehearsing multiple scenarios developed by our former regulators. Parexel's experienced consultants can also help craft arguments that will resonate with regulatory officials. Recently, the EMA's CAT informed a sponsor that the health authority would require two separate Marketing Authorization Applications (MAAs) for one cell therapy because it was intended for two indications. Parexel's team, including a former CAT member, provided insight into the CAT's position and advised on how to best present study data within that context. The CAT accepted the sponsor's Parexel-aided appeal, approving the submission of a single MAA.

In addition, Parexel's regulatory consultants can help distinguish between specific sections of health authority guidance documents that must be followed and sections that may not apply to a sponsor's particular situation. For example, general guidance could recommend analysis using a specific primary efficacy endpoint or timepoint. But that recommendation might not be optimal for capturing patient benefit or even feasible based on product characteristics or the target patient subpopulation.

The challenge: When sponsors develop a platform that could be applied to multiple indications, choice of indication is often based on potential commercial performance.

The approach: Sponsors need to determine the indication for which a product will best perform medically and scientifically. This indication may not align with the highest commercial potential, but it will give the product a better chance for regulatory approval. Even within a given indication, sponsors may want to target a specific subgroup of patients. If a product is expected to work equally well for multiple indications or patient populations, sponsors should then consider existing unmet needs, competition in the space, and potential regulatory challenges.

Consider that the 21st Century Cures Act contains provisions for the use of real world evidence (RWE) to support approval of a new indication for an already approved product, which could significantly reduce burden of expanding the label after the original Biologics License Application (BLA).

The challenge: Unless a biologic receives a Regenerative Medicine Advanced Therapy (RMAT) or Breakthrough Therapy (BT) designation, the FDA does not prioritize its review. The RMAT designation, however, is available to only approximately 60 percent of products because many major product classes, such as mRNA-based therapies, do not qualify as Regenerative Medicine Therapy (RMT). Lack of such designation can be a major hurdle in CAGT development.

The approach: In applying for RMAT designation, a sponsor can provide justification for its request — even if the product would not traditionally be considered an RMT. For example, the FDA's Office of Therapeutic Products (OTP) highly emphasizes on durability of effect as a criterion to characterize a given product class as an RMT. There can be advantages to non-durability of effect, however, in particular settings regarding safety, which may impart a more favorable benefit-risk profile compared with traditional RMTs.

Ultimately, regulatory reviewers want data that makes them confident about the biologic's effects — so regardless of a product's designation, sponsors should use the most stringent study design possible.

2 Making CMC a day-one priority

Since CAGTs are often highly individualized, their manufacture can be complex. Sponsors need to thoroughly strategize CMC development as early as possible to smooth the path to regulatory approval and, ultimately, to the patient. When CMC planning occurs too late or without a comprehensive approach, the entire development endeavor can suffer in a way that is both difficult and expensive to remedy.

The challenge: CAGTs require small-scale, patient-specific manufacturing. CMC regulatory requirements can vary by product because of novel manufacturing processes, which can also present unique scale-up and scale-out considerations.

The approach: Without defined, standardized expectations for CMC regulatory compliance, sponsors should capitalize on early clinical trial data, frontloading development, and characterization studies. Teams should define quality target product profile (QTPP) and critical quality attributes (CQAs) at the beginning of development and identify potential critical process parameters (CPPs) early, allowing sponsors to proactively manage inevitable manufacturing process changes. By embedding manufacturing considerations into the development program, sponsors can demonstrate process validation, manufacturing consistency, and Current Good Manufacturing Practice (cGMP) compliance much earlier in the product lifecycle.

Reproducible, systematic CMC methods allow teams to meet phase-based regulatory requirements and to scale up and scale out manufacturing — an undertaking that's particularly challenging for autologous products with stringent production standards. Early action is especially important for products with an expedited regulatory approval mechanism such as BT designation, which can compress development timeframes—particularly through organizational commitment by FDA to involve senior managers in interactions with the sponsor and the resulting intensive guidance on critical issues for licensure. Recently, the Office Director of OTP issued public comments that BT- and RMAT-designated programs will receive meeting priority.

To address demanding and varying CMC requirements, many sponsors engage a partner to create regulatory and scale-up strategies. Recently, the developer of an adeno-associated virus (AAV) vector-based gene therapy needed a larger U.S. manufacturing operation capable of supporting pivotal clinical trials and commercialization. But the sponsor lacked experience with the complex facility-related requirements established by the FDA's Center for Biologics Evaluation and Research (CBER). The sponsor also questioned whether the number of batches used in its comparability study would yield sufficient data to adequately demonstrate comparability.

After briefing the developer on CBER expectations, Parexel consultants authored a BLA dossier on the sponsor's behalf. The Parexel team also reviewed the protocol for manufacturing comparability batches, offering process improvements, suggestions for optimizing existing data, and strategies for comparing pre- and post-change processes in a manner that would be acceptable to regulators. As a result, the developer successfully transferred operations to a new facility where its therapy is being manufactured in the quantities required to support a global commercial launch.

The challenge: Sponsors lack clarity on CMC regulations for CAGTs. In addition, many CAGTs are developed by small biotech companies or academic institutions — teams that may have limited experience with interpreting regulatory guidance or preparing for health authority inspections.

The approach: In the absence of in-house regulatory specialists, sponsors can enlist outside experts to conduct CMC gap audits. Such audits — which can uncover problems related to data integrity, Good Clinical Practice (GCP), or cGMP — should be run early and regularly during process development, giving teams sufficient time to mitigate risks without upending manufacturing.

Common shortcomings identified during Parexel-led audits include:

- Incomplete understanding of manufacturing facility needs. CAGTs require aseptic processing. Because a typical open-floor manufacturing configuration creates cross-contamination risk, regulators will not favor this ballroom-style setup.
- Contracts that do not hold vendors to key standards or are unclear about data exchange. If outsourcing manufacturing and logistics, sponsors need agreements that require strict compliance with cGMP. Contracts should also allow the sponsor to audit vendors' facilities and call for changes to manufacturing if necessary.
- Lack of phase-appropriate regulatory compliance. Even in early development, sponsors should work with late-phase requirements in mind. For example, sponsors should develop potency-indicating assays as soon as possible and gather data alongside other quality-indicating product attributes, even if these are not yet part of the actual specification.

The challenge: Given their unique product characteristics, CAGTs must be distributed with strict adherence to time and temperature requirements. The process is intricate, requiring coordination among many stakeholders — and one misstep can compromise a patient's potentially life-saving therapy.

The approach: At Parexel, we strongly advocate embedding clinical trial supplies and logistics experts within the study team to maintain the chain of custody. For example, at Parexel a single manager owns a study's entire logistics process — investigational product supply, ancillary supplies, and lab services — and is responsible for linking each element of the supply chain.

This commitment to ownership was key to the successful delivery of a patient-specific allogeneic cell therapy — a product that needed to be infused within 48 hours of manufacture. While sites and patients were in the U.S., Asia, and the Middle East, the therapy was manufactured in Europe, so Qualified Person (QP) release and import processes had to be built into a tight and inflexible timeline. Additionally, each shipment had to be kept within a strict temperature range of 2 to 8 degrees Celsius.

To ensure complete coordination among multiple stakeholders, we tested our chain for vulnerabilities long before the therapy was distributed. In addition to considering cold-chain logistics and necessary biosafety licensures, we planned for a guaranteed chain of custody and chain of identity, with one Parexel logistics expert steering the product's entire journey from manufacturing facility to the patient. With 200 on-time, in-specification shipments, this is a reproducible delivery model for subsequent studies.

3 Addressing complexity in study execution

Thanks to scientific advances and resource investment, the CAGT pipeline continues to expand. Current research infrastructure, however, cannot support the increased clinical development. The use of exploratory endpoints is growing, and often-small patient populations are difficult to identify and recruit. Meanwhile, sites are understaffed and overwhelmed.

The challenge: Sponsors must choose investigators and sites carefully, matching expertise to the indication. But many experienced sites are overburdened, leaving sponsors with fewer options.

The approach: Now is the time to engage new sites and to mentor investigators within them. At Parexel, we are working to identify new clinics — particularly those outside of academic settings — that demonstrate potential for success. Emerging sites and investigators will require additional training and monitoring visits. But that investment will yield returns for patients and sponsors.

To streamline study startup, sponsors and CROs should grow their site networks. At Parexel, our Site Alliance Network includes more than 500 sites and 21,000 investigators. Our Site Alliance managers work directly with institution-level central research offices to efficiently match researchers to projects that align with their capabilities, capacity, and interests — including CAGTs. Currently, 28 Alliance member sites hold Foundation for the Accreditation of Cellular Therapy - Joint Accreditation Committee ISCT-Europe & EBMT (FACT-JACIE) accreditation. These standards promote quality medical and laboratory practice for conducting hematopoietic progenitor cell transplantation or immune effector cell therapy clinical services.

The challenge: CAGT studies have historically been conducted at large research institutions in major cities where all aspects of the clinical trial are handled within the same institution across multiple departments. Yet, many patients who will be served by these therapies live far from these cities and have complicated health conditions that make travel and lengthy or frequent visits difficult.

The approach: While it may be challenging to bring complex studies to patients, we have the tools and technology to make it happen. Even CAGT protocols can be conducted in community-based health settings, but this model requires investment, focusing on long-term gains rather than immediate payoffs.

To accommodate the increasing volume of CAGT development work and bring studies closer to patients, sponsors and CROs should consider multiple-party infrastructure models in which community research institutions partner with external FACT-accredited service providers for involved procedures such as leukapheresis, bone marrow transplants, and complex inpatient care.

Parexel is working to identify community practice research sites willing to develop CAGT capabilities by collaborating with regional hospitals and accredited blood banks. Lack of training is one barrier to community-based research, so we are also developing curriculums for local providers that cover the operational, logistical, and data collection complexities of CAGT trials. And we can connect sites with consulting and training resources for Institutional Biosafety Committee (IBC) readiness, staff role development, vendor coordination, and the eventual pursuit of FACT accreditation, which indicates that an institution has met rigorous standards in every aspect of stem cell therapy.

> Scientists tend to create the proposed protocols for patients based on statistical probabilities, powering of numbers, and desired primary and secondary outcomes. **Someone else needs to look at it from the patient experience perspective.**

HCP interview, Parexel CAR-T research

The challenge: Given their dispersed patient populations and strict inclusion and exclusion criteria, CAGT studies present significant challenges for recruitment.

The approach: While some factors that impede CAGT study enrollment are beyond a team's control, protocol designers have many opportunities to remove barriers to patient participation, making studies more accessible. Putting the patient at the center of research ultimately improves recruitment.

Recently, Parexel's Patient Engagement team interviewed patients, caregivers, and health care providers (HCPs) about their experiences with CAR-T cell-based gene therapy for cancer. From that research, we heard:

- People who enroll in CAGT studies have likely exhausted other care options. These patients, often very ill, are expected to undergo demanding protocols. But because many CAGTs are still young, study designs are not yet time-tested and may not fully consider the patient experience.
- Many CAGT regimens involve long inpatient stays for therapy administration and follow-up appointments, making study participation financially restrictive for some patients. Reimbursements and related support will be critical to success.
- Due to the nature of CAGT testing, preparation, and inpatient and follow-up requirements, every participant needs a personal support plan for the duration of the study.
- To fully support patients, a study must also support its site staff. Because of the complexities of the patients and procedures involved, site staff need comprehensive training, including:
  - Hands-on practice runs of cell collection (apheresis) and cell therapy product handling and administration where step-by-step systems, labeling/documentation, and procedural training are provided for patient scheduling
  - Chain of identity and chain of custody procedures
  - Receipt, storage, preparation and administration of manufactured cell therapy product
- Site staff also need a responsive study team when questions arise. Sponsors and CROs should provide around-the-clock call support for the clinical operations team, treatment site, apheresis center, manufacturer, and courier service. A medical monitor should also be available for verification of eligibility and patient safety monitoring on cell collection and product administration days.

Once teams understand the patient groups they seek to enroll, sponsors should develop target population archetypes. HCPs can use these tools to flag potential study candidates during chart review. If providers lack familiarity or comfort with CAGTs, a comprehensive archetype can foster confidence and help prevent miscommunication.

And for recruitment, we cannot overstate the value of partnering with patient advocacy groups. Their unique expertise makes study designs more successful. Advocacy groups are incredibly important when identifying and enrolling patients — but advocates want to contribute to all aspects of the study, not just recruitment. When possible, involve them from the start.

The challenge: Because CAGTs use incredibly complex workflows, sites need additional support.

The approach: Consider ways to redistribute logistical or non-technical responsibilities. For instance, Parexel often serves as a patient scheduler, coordinating imaging and biopsies with multiple departments within a medical facility and freeing the study coordinator to focus on other responsibilities. We have also learned that both sites and patients appreciate travel concierge services, which lessen site workloads and make it easier for patients with complex health needs to attend necessary visits. Finally, if you are working with a CRO, consider embedding one of their professionals at a site that could benefit from additional support.

The challenge: Because of the potential value they offer for future research, exploratory endpoints are expanding in CAGT development. But endpoints are also impeding progress at sites, which are already working above their capacity.

The approach: While exploratory endpoints advance science, they do so at significant cost to sites, which are swamped by multiplying workflows. There are also costs to patients, who must undergo additional procedures and monitoring. As sponsors and CROs, we need to gauge how many endpoints a study can realistically sustain and design with those limitations in mind. The key: Balancing future-focused exploration with the need for efficiency and expediency in the present.

> **Some patients just give up** because it is too much effort to travel and coordinate efforts.
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> HCP interview, Parexel CAR-T research

4 Making the case for your therapy's value

CAGTs carry extremely high development costs, and payers will necessarily weigh a therapy's benefits against its price. To give CAGTs the best possible advantage, create a compelling value story: an evidence-based case for the clinical and economic merits of a therapy.

The challenge: To manage risk, payers demand data that demonstrates long-term value. There is understanding and reducing the uncertainty associated with short-term and long-term comparative clinical and economic value that teams must mitigate earlier in the development process.

The approach: For successful commercialization, sponsors must minimize uncertainty for payers. This is done, in part, by demonstrating a therapy's lasting performance — but in the case of many CAGTs, natural history studies are rare and trial data is immature. To offset, sponsors need models to project long-term outcomes. Because the sensitivities of these models are only revealed as they are used, sponsors should develop and deploy them as early as possible. This early engagement helps payers' willingness to accept the modelled approach – as well as build the evidence needed to support submission. It also gives statisticians ample time to refine, ensuring each model's accuracy and credibility.

Capitalizing on early scientific advice

Because evidence requirements vary worldwide among payers and health technology assessment (HTA) agencies, CAGT sponsors face uncertainties in gaining market acceptance for their products. Real-world evidence tailored to an agency in the U.K., for example, may not sufficiently support payer coverage in Germany.

To mitigate uncertainty, sponsors can pursue early scientific advice (ESA). Through this fee-based consulting, stakeholders provide recommendations on how a data package can best demonstrate a product's value.

At Parexel, we recommend that sponsors first seek ESA in countries with established early HTA processes. Sponsors should also consider an HTA agency's record of results in their product's therapeutic area, as well as country-specific incidence rates of the condition treated by the product and the country's established standard of care.

Increasingly, HTA agencies are cooperating among countries, offering sponsors a streamlined process and consolidated feedback. One example is the Parallel Scientific Advice Program, established in 2019 between the U.K.'s National Institute for Health and Care Excellence (NICE) and the Canadian Agency for Drugs & Technologies in Health (CADTH).

Working with the Parallel Scientific Advice Program usually takes about 20 weeks — only two weeks longer than a single engagement with either organization. In addition, the process is likely to be more efficient than separate engagements as applicants submit just one dossier and attend one joint advice meeting.

CADTH and NICE also recently partnered with four additional HTA bodies in Australia, Scotland, and Wales to collaborate on shared priorities — one of which is joint clinical assessment. The agencies will also consider recognizing partner HTA work, which may help sponsors with more consistency across markets. Because all six agencies use cost-effectiveness methodology for decision-making, we see strong potential for cross-agency alignment on economic models, utility measures, and approaches for addressing uncertainty.

The challenge: While a cell or gene therapy may offer unique treatment benefits, payers will always compare it to the current standard of care for the indication it treats. The fact of a product's novelty will not, on its own, justify its cost to payers.

The approach: Sponsors are responsible for meeting multiple evidentiary needs — regulatory approval is not the same as payer acceptance, and evidence of a therapy's clinical efficacy will not necessarily establish its value proposition.

Sponsors should test a therapy's value proposition as early as possible. For this, we recommend one-on-one meetings with payer experts in relevant markets. By presenting these experts with multiple scenarios, including different endpoints and comparators, sponsors can determine which reimbursement levels will likely be acceptable under various circumstances. Sponsors should also interview and educate patients and clinicians, who can be advocates for new products, and health care providers, whose opinions of therapies could drive or derail their success.

The challenge: Current health technology assessments (HTAs) assume a pricing model for treating non-rare conditions. These are diseases for which long-term outcomes are better understood and for which treatment costs are known and often spread out over long periods of time. Curative therapies offer a particular challenge, as the benefit is prolonged, but the treatment period is short and therefore investment is expected upfront.

The approach: CAGTs require new risk-based pricing methods that accommodate uncertainty due to a lack of long-term data. Under such agreements, reimbursement rates are tied to therapy performance, with mechanisms such as payments made across time and rebates for treatment failures.

There are a range of innovative reimbursement schemes being explored across markets, which include:

- Financial risk sharing: tools include free stock, fixed per patient pricing, price-volume agreements, budget caps, and dose caps
- Performance-based: Tying reimbursement to how well the drug works in real-life clinical practice in terms of individual patient outcomes
- Dynamic pricing: Reimbursing a medicinal product at a temporary price that can change upon the generation and appraisal of subsequent data

Risk-based agreements are bespoke contracts, so sponsors should enlist market access experts to advise on terms and ensure that a contract addresses the payers' challenges. Before entering any risk-sharing agreement, a sponsor should model its terms and measure potential payoffs or shortfalls. For maximum value, conduct price modeling before phase 3 studies begin.

In developing CAGTs, sponsors face unparalleled challenges. But the work is worthy — and the right partner can guide you through the process.

At Parexel, we've earned a reputation for helping companies navigate complex product development. Parexel's Center of Excellence for Cell & Gene Therapy works *With Heart*™ to deliver innovative trial designs built on a deep understanding of the patient journey and more than 350 completed global projects. We combine an Early Advisory Service of medical, regulatory, genomics, and biostatistical specialists with an experienced multidisciplinary team and key technology platform partnerships to give you a faster, smarter route to proof of concept. We integrate regulatory expertise with clinical study execution, so you can better anticipate and tailor evidence requests from regulatory bodies. And our program and project managers combine CAGT and regulatory experience and make continuity and consistency in your team a priority.

Could a partnership like that put your product ahead?
We're always available for a conversation.

With Heart™

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