Evolutions in Oncology Cell Therapy

Clinical Research Trends, Strategies, Insights, and Opportunities

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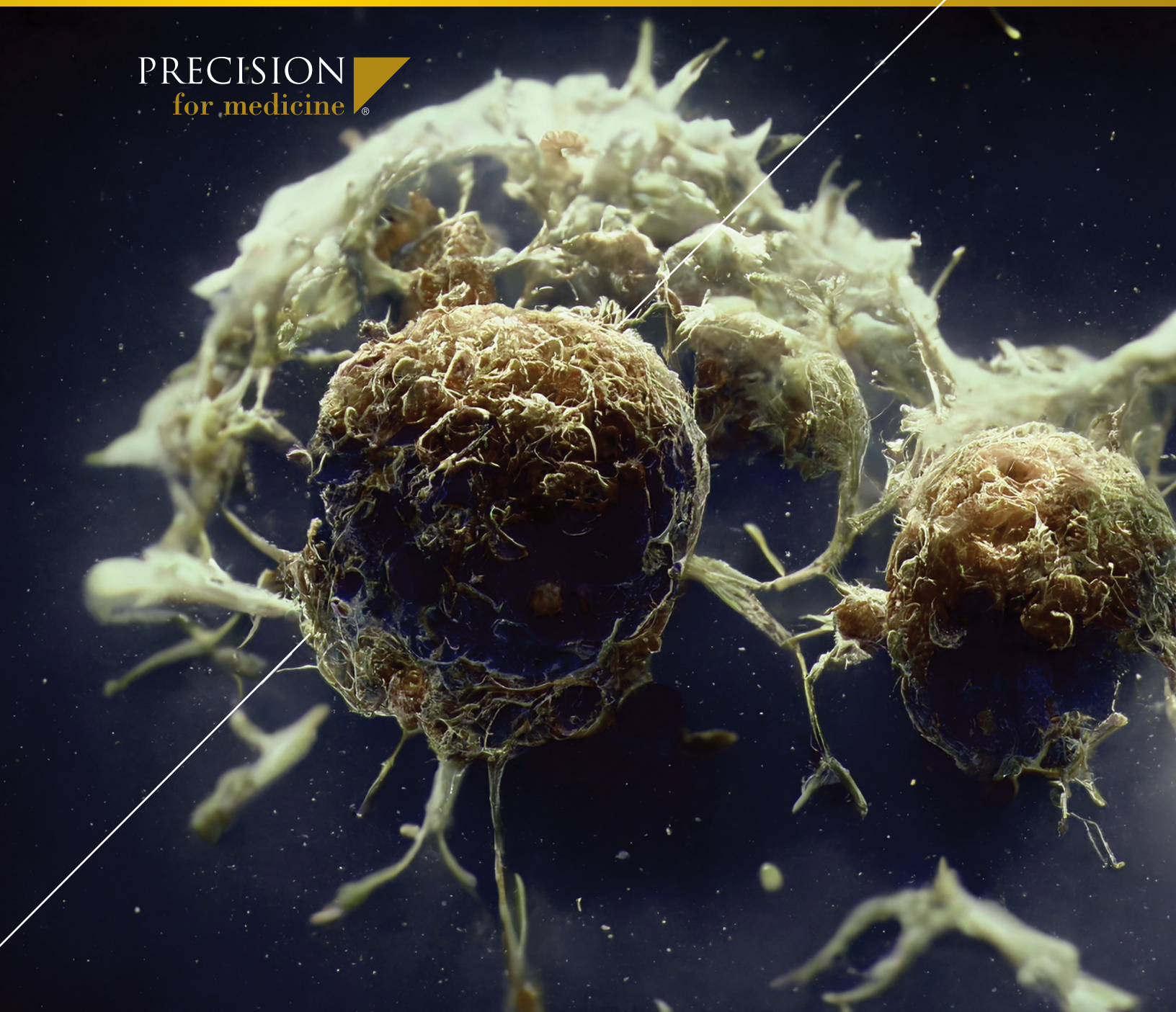
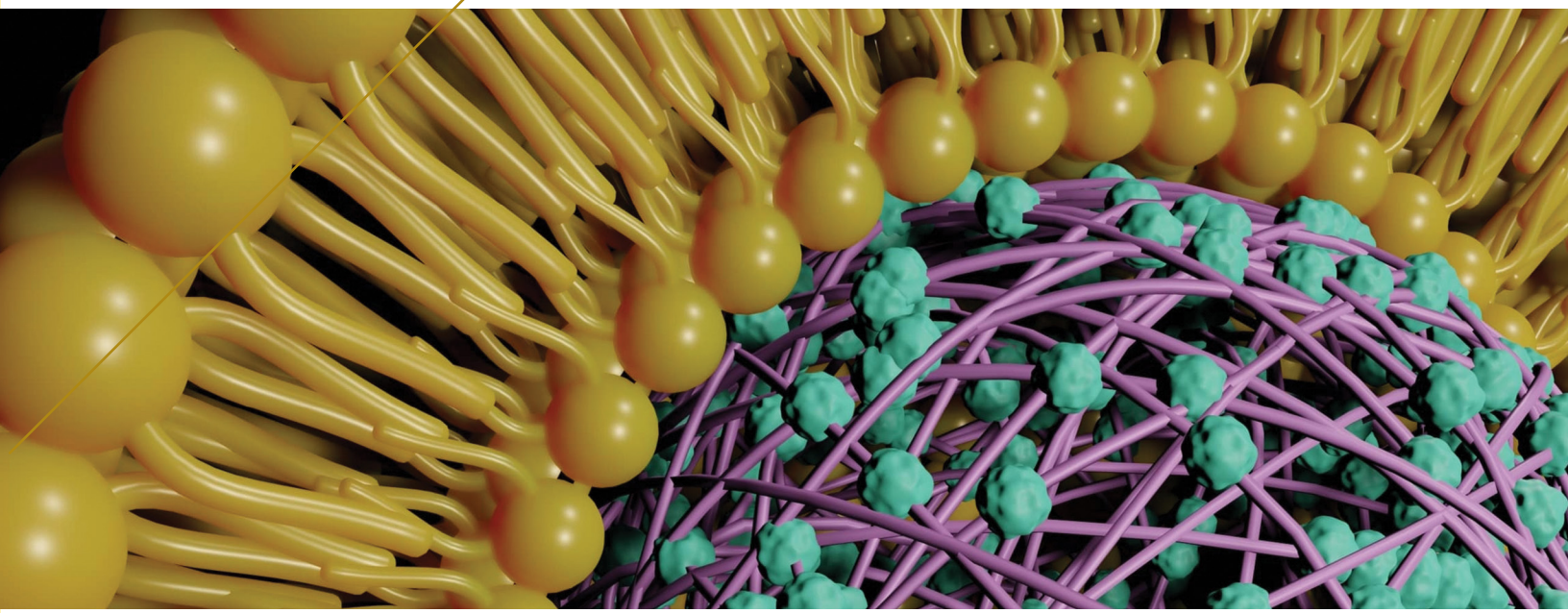


What's Inside



Addressing Challenges and Unmet Needs in Complex Cell Therapy Studies

The cell therapy field is expanding and evolving beyond the early success of chimeric antigen receptor (CAR) T-cell therapies in hematologic malignancies. While the pipeline continues to grow, the field also faces challenges. These include complex and evolving manufacturing processes, effective targeting of solid tumors, rigorous regulatory expectations, shortages of qualified staff and laboratories, and obstacles to large-scale commercialization and market access. Running safe and efficient oncology cell therapy clinical trials is vital to testing new hypotheses and constructs in patients and taking those observations back to the bench to fuel iterative development.

Precision for Medicine is an oncology-focused global precision medicine contract research organization (CRO) with expertise in all phases of cell and gene therapy development and market access. Driven by our purpose of helping companies improve the speed, cost, and success rate of developing and bringing life-changing therapies to patients, we mobilize our cell and gene therapy expertise through Precision ADVANCE, a collective of interconnected product and clinical development services and teams focused on solving the clinical, regulatory, manufacturing, and commercial complexities of successfully bringing new therapies to market. In this Ebook, informed by our real-world experience across 50+ research and clinical development projects, we explore the cell therapy landscape from three perspectives:

- **Environment** – A brief overview of current trends in cell therapy development
- **Execution** – A discussion of key nuances to planning and executing a cell therapy clinical trial, from therapeutic product/clinical development, regulatory, and manufacturing considerations to site selection, lab partner selection, logistics, and data monitoring
- **Evolution** – A look at how leveraging prior experience and knowledge streamlines the generation of new insights that propel cell therapy clinical trial execution forward

Environment of Oncology Cell Therapy Trials

Current Pillars of Oncology Treatment

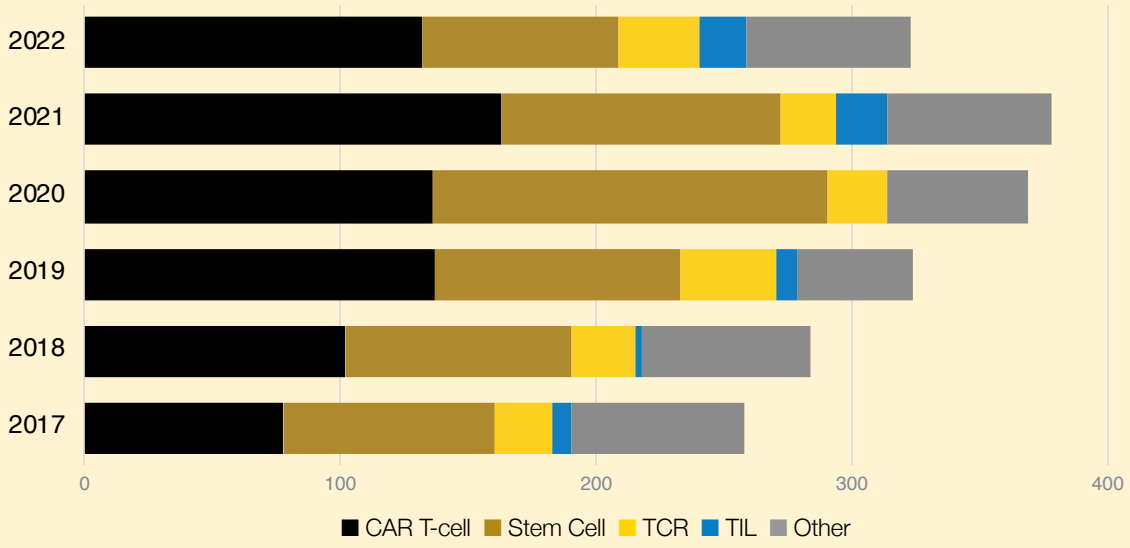
Oncology treatment can be categorized into five pillars—surgery, radiotherapy, cytotoxic chemotherapy, molecularly targeted therapy, and immunotherapy. Surgery remains a foundational treatment, and approximately 50% of cancer patients today receive different forms of radiotherapy to debulk or eliminate tumors. Cytotoxic chemotherapy was introduced following World War II, when a derivative of mustard gas was used to treat patients with lymphoma. Shortly thereafter, Sidney Farber used a folic acid–related compound to drive remissions in children with acute lymphocytic leukemia (ALL). Advances in our understanding of oncogenic drivers led to the development of molecularly targeted therapies, which, as a group, are associated with greater efficacy and fewer side effects than cytotoxic chemotherapy.

With roots dating back more than 100 years to William Coley's use of heat-killed bacteria to stimulate the immune system, immunotherapy is now coming of age. The immuno-oncology field has progressed from checkpoint inhibitors to bispecific T-cell and natural killer–cell (NK-cell) engagers, oncolytic viruses, cancer vaccines, and different types of genetically modified cell therapies. Since 2017 six different CAR T-cell therapies have been approved by the FDA and EMA for hematologic malignancies. Although cell therapies are becoming an increasingly important part of the oncology landscape, they are still used primarily in patients with advanced cancers who have exhausted other treatment options.

Growth in the Cell Therapy Field

While CAR T-cell therapies have seen success in regulatory reviews, the cell therapy field in general—across all therapeutic areas—is broader and includes stem cell–based, T-cell receptor (TCR)–based, tumor-infiltrating lymphocyte, macrophage, and NK-cell therapies. The field has exhibited consistent growth since 2017, with a notable increase in stem cell therapy trials in 2020 (see Figure 1). The prevalence of TCR-based therapies has remained stable throughout the years, likely because of the increased challenges of human leukocyte antigen (HLA) matching and antigen expression in tumors. NK-cell therapies currently make up 7% of all cell therapies under investigation, but this class is expected to grow as its low toxicity and potential for innate and direct cancer killing are leveraged and challenges such as durability of cells and duration of response are studied in greater detail.

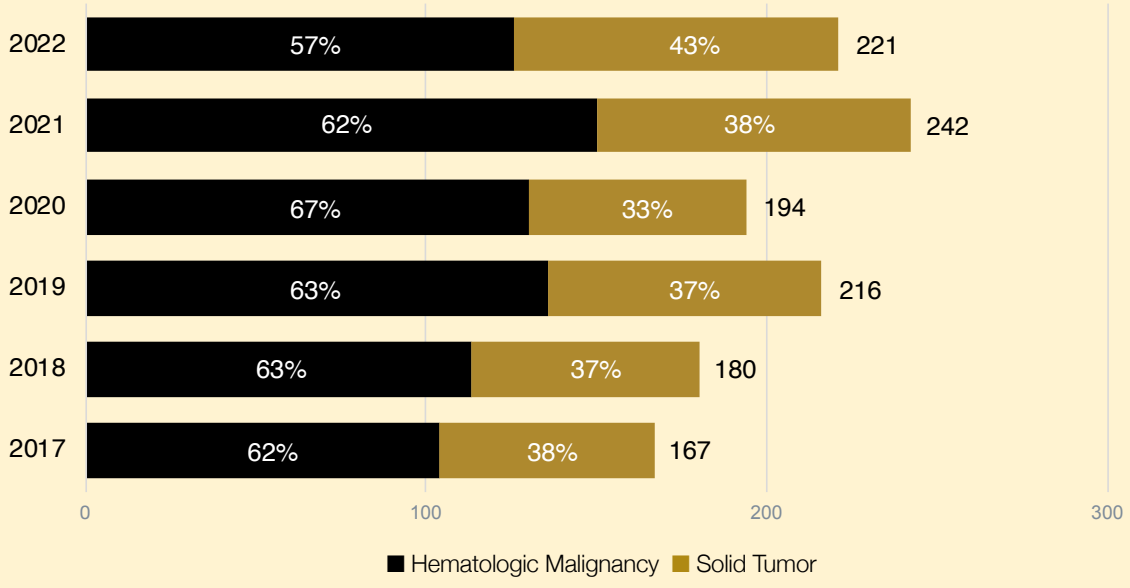
Figure 1. **Industry-sponsored cell therapy trials by type across all therapeutic areas[1]**



TIL = tumor-infiltrating lymphocyte.

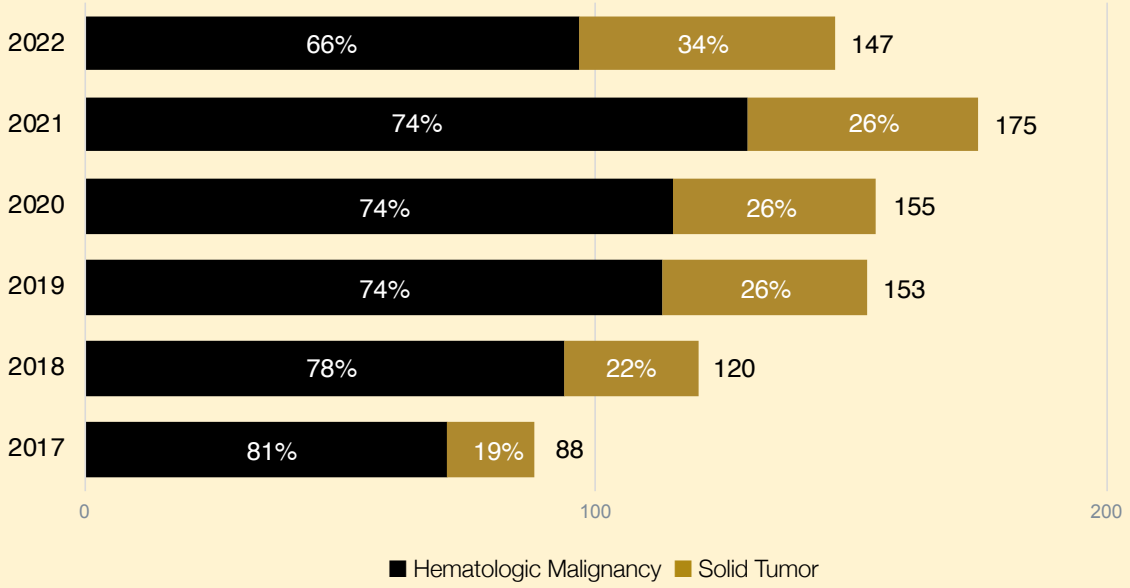
In the 5 years from 2017 to 2021, the distribution of cell therapy trials in oncology has been fairly consistent, with approximately two-thirds of studies targeting hematologic malignancies and one-third investigating solid tumors. In 2022 there appeared to be a small shift in distribution as of August, with a greater focus on solid tumors than seen previously (see Figure 2).

Figure 2. **Number of cell therapy trials in oncology[1]**



This change in distribution is even more pronounced when looking specifically at CAR T-cell therapy clinical trials, in which there has been a steady increase in the proportion of studies focused on solid tumors, from 19% in 2017 to 34% as of August 2022 (see Figure 3). This shift is consistent with our experience and indicative of the maturing of the CAR T-cell field and the progress being made in addressing the key challenges of these cell therapies in solid tumors: namely, antigen identification, an immunosuppressive tumor microenvironment (TME), and trafficking to tumors.

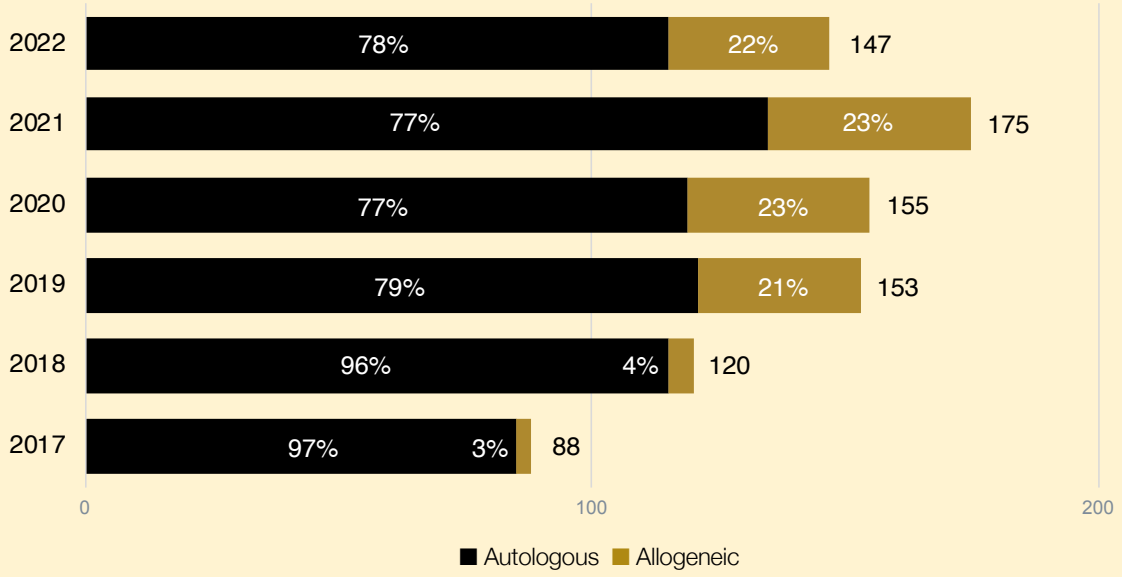
Figure 3. **Number of CAR T-cell therapy trials in oncology[1]**



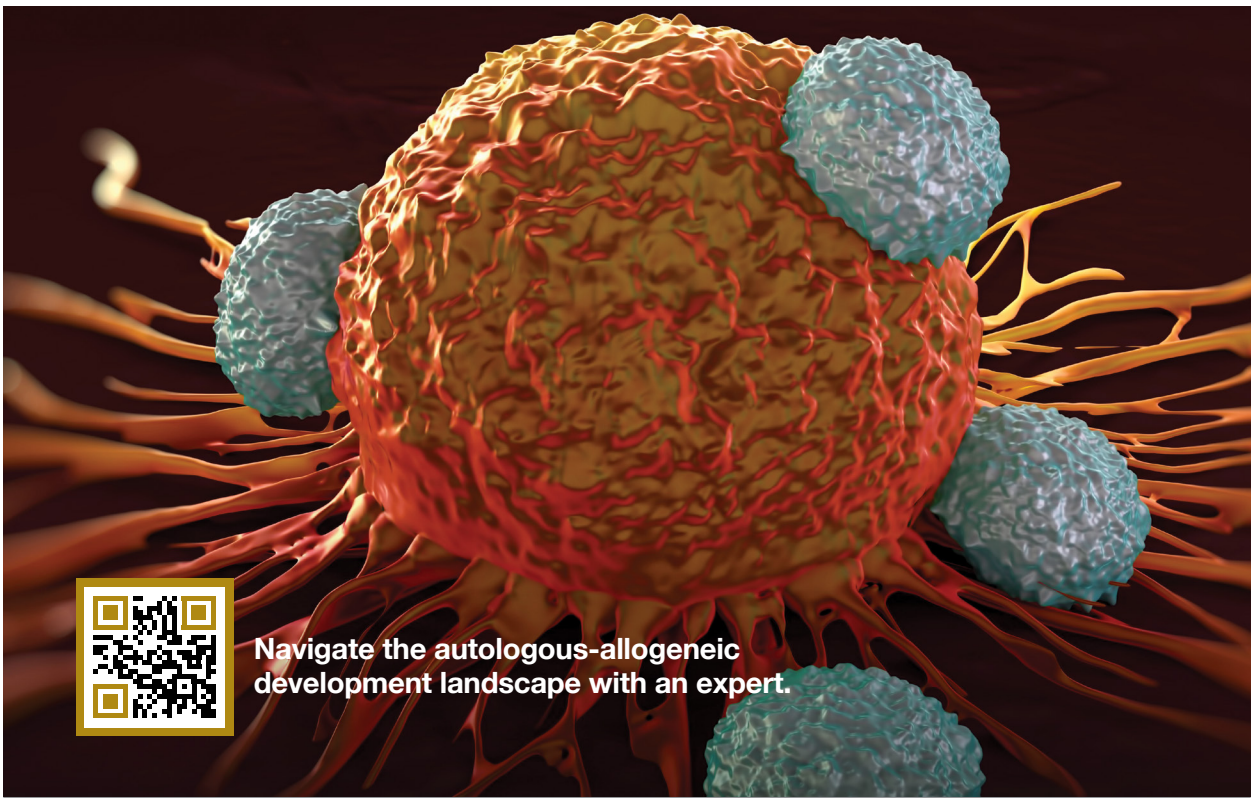
Autologous vs Allogeneic CAR T-Cell Therapy in Oncology

The challenges with autologous CAR T-cell therapies continue to fuel interest in allogeneic therapies. While the approval of Kymriah in August 2017 provided evidence that CAR T-cell therapies work, it also highlighted the difficulties of vein-to-vein turnaround time (TAT), manufacturing scale, and price associated with autologous approaches. Consequently, since then, there has been a dramatic increase and then plateau in the percentage of allogeneic CAR T-cell–focused clinical trials (see Figure 4).

Figure 4. **Autologous vs allogeneic CAR T-cell therapies[1]**



As of August 2022, 22% of all industry-sponsored CAR T-cell trials are studying allogeneic therapies. The plateau may be due, in part, to challenges related to the host versus graft (HvG) effect, which appears to reduce both CAR T-cell durability and duration of response (DoR). Still, the autologous vs allogeneic question will continue to unfold as vein-to-vein TAT and cost of goods decrease for autologous therapies and durability and efficacy increase for allogeneic cell therapy approaches.



A Closer Look at Cellular Products

Key considerations for cellular therapies include donor eligibility/viral safety requirements for allogeneic cell therapies, product heterogeneity/variability, complex manufacturing, and both graft versus host (GvH) and HvG.

- **Donor eligibility.** The requirements for donor screening and testing are laid out in US regulations under 21 Code of Federal Regulations (CFR) part 1271, subpart C. In the EU, the requirements are delineated in Directive 2004/23/EC—which is also relevant to the manufacturing of products derived from human tissues and cells—and covered by other Directives: 98/463/EC and 2002/98/EC. Additional testing for other communicable disease agents may be needed, depending on the significant incidence and/or prevalence of these agents.

- **Viral safety requirements.** Changes in viral testing guidelines have made the safety requirements for allogeneic cell-based products more rigorous such that donor cells must be screened and tested. The final cell product must also be tested for additional human-specific viruses. This level of stringency is also linked to the fact that allogeneic cellular products cannot undergo the usual viral clearance steps that other noncellular biological products are often subjected to during the downstream steps of the manufacturing process.

- **Product heterogeneity/variability.** Cellular products can be affected by both intrinsic and extrinsic factors, including donor variability and manufacturing process changes—an example being changes in starting materials such as the viral vector used to modify the cells *ex vivo*—changes/discontinuation of critical materials and/or equipment used in the process, or manufacturing facility changes. These factors lead to potential differences in the composition, phenotype, and function of cellular products. The heterogeneity of cellular products is particularly important in the context of cell therapy development, as it can impact both the safety and efficacy of the product, adversely affecting long-term effectiveness and clinical success. Hence a good understanding and thorough characterization of these products are critical to conducting comparability studies and correlating product-specific characteristics with clinical outcomes.

- **Complex manufacturing.** The manufacturing of cell-based products is time consuming, and challenges including scalability and supply chain management can hinder timely launch and access. Efforts are underway to address these challenges, with the development of new technologies and processes, such as closed-system manufacturing and automation. These advancements aim to increase the efficiency and reproducibility of the manufacturing process, while also reducing the risk of contamination and other issues that can impact the safety and efficacy of the final product.

- **Management of GvH and HvG phenomena.** Avoiding these two detrimental and potentially toxic conditions is essential to the success of allogeneic cell therapies. GvH can be addressed by transient or constitutive inactivation of TCR expression in CAR T cells. Addressing HvG is less straightforward and likely requires both engineering strategies in cellular product design and a preconditioning regimen for lymphodepletion prior to cell transfer.

Execution of Oncology Cell Therapy Trials

Unlike small molecules, which have a chemically defined formulation that is fully characterizable, cell therapies are extraordinarily complex. Their complexity lies not just in composition but also in how these therapies are designed and how such clinical trials are executed. Effective study execution requires a nuanced approach to anticipating obstacles and building solutions that increase both efficiency and the probability of success.

Challenges of Developing Cell Therapies

There remain key limitations that must be addressed on the path to bringing new cell therapies to the clinic, including[2]

1. **Antigen selection**, which is critical to therapeutic cell targeting and specificity
2. **Antigen loss or escape**, one of the mechanisms of resistance in hematologic malignancies. One strategy for addressing this limitation is developing cell therapies that target multiple antigens
3. **On-target/off-tumor toxicity**, in which the tumor-associated antigen (TAA) targeted by the CAR T cell is also expressed by healthy tissues. Strategies in development include affinity-tuned CAR T cells, dual-signal CAR T cells that take advantage of loss of heterozygosity (LOH) in tumor cells, and logic-gated constructs
4. **Trafficking and tumor infiltration**, which are essential for efficacy in solid tumors
5. **Toxicity**, including cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS), which may be modulated by decreasing binding domain affinity or developing alternative targeting domains outside of single-chain fragment variables (scFvs)

6. **Cell phenotype**, which impacts both persistence and maintenance of the desired phenotype

7. **Suppressive TME**, which affects cell therapy persistence and durability. Engineering strategies such as armored CAR T cells that secrete cytokines or express cytokine receptors to modulate the milieu of the TME show promise in improving efficacy[3]

8. **Setting for administration**, which involves understanding risk factors for major toxicities, predicting time to CRS, and assessing the availability of caregiver support

Given all the variables and approaches that researchers, clinicians, and developers/sponsors can explore in the clinic, there is a keen demand for high-quality, efficient, well-run clinical trials that enable teams to move rapidly from bench to bedside in an iterative development cycle.

Planning for Success in Oncology Cell Therapy Trials

Key considerations and potential challenges in virtually every cell therapy clinical trial include

- Biosafety requirements
- Manufacturing
- Site selection
- Lab partner selection
- Logistics management and communication
- Data monitoring

Recognizing these challenges and preparing for known obstacles are critical to identifying and implementing solutions that increase the speed and efficiency of trial execution. Robust training, to include not only the sponsor, sites, and vendors but also patients, families, and caregivers, is also an essential element for success.

Biosafety requirements

Cell therapy studies are subject to additional review by Institutional Biosafety Committees in the US or adherence to genetically modified organism (GMO) directives in the EU, which vary by member state.

Site selection

Site selection involves finding accredited sites that have the infrastructure and capabilities to handle cell material and potential treatment-related toxicities. Because of their complexity, cell therapy studies must be conducted by certified sites with experience in managing complex trials. Site selection is therefore a critical activity, which must take into consideration several factors:

- Experience with complex, early-phase clinical trials, not just at the institutional level but at the site and the staff level
- Accreditation for cell collection and administration
- Experience in collection, storage, and shipment of time-sensitive biological samples
- Established interdepartmental networking and collaboration with the facilities involved in the chain of custody, which may include the Phase I unit, apheresis unit, inpatient facility, labs, and biobank
- Adequate number of resources trained on cell therapy requirements and both chain of custody and chain of identity processes
- Existence of well-defined institutional protocols for managing treatment-related adverse events, including safety assessments for early-phase studies and site-specific standard operating procedures for diagnosing and treating toxicities commonly observed in cell therapy trials such as cytokine release syndrome, neutropenic infections, and ICANS
- Ability to recruit patients as per agreed-upon projections and to activate referral processes when needed, which is especially important for biomarker population-based trials

Patient Enrollment: A Critical Factor in Site Feasibility

The pace and overall success of patient enrollment may be impacted by inclusion criteria, selection biomarkers, and the existence of competing trials. Evaluation of potential sites must include assessment of the site's ability to recruit an adequate number of patients. Enrollment projections are usually requested from sites during the feasibility assessment to better evaluate their contribution to meet the study goals and objectives within agreed-upon timelines. The need to work within certain time constraints impacts the possibility of completing the study phases in a timely manner.

For this reason, the following actions are crucial:

During site selection and study startup

- Clarify the site's experience with and exposure to the patient population of interest
- If a selection biomarker is used, ask whether the site routinely screens for that biomarker
- Put site-specific processes in place to monitor the patient journey from the identification to the treatment

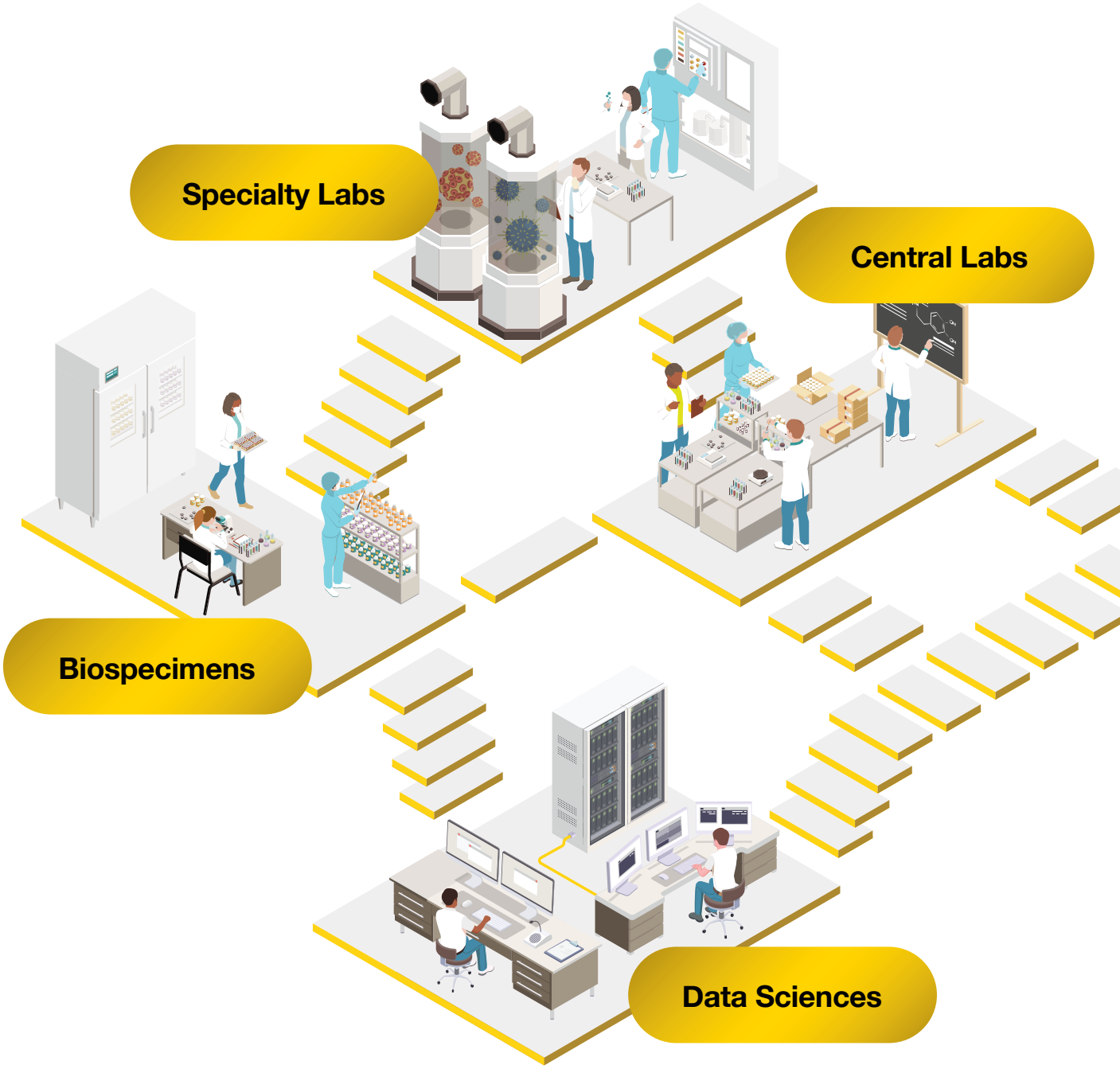
During enrollment and study execution

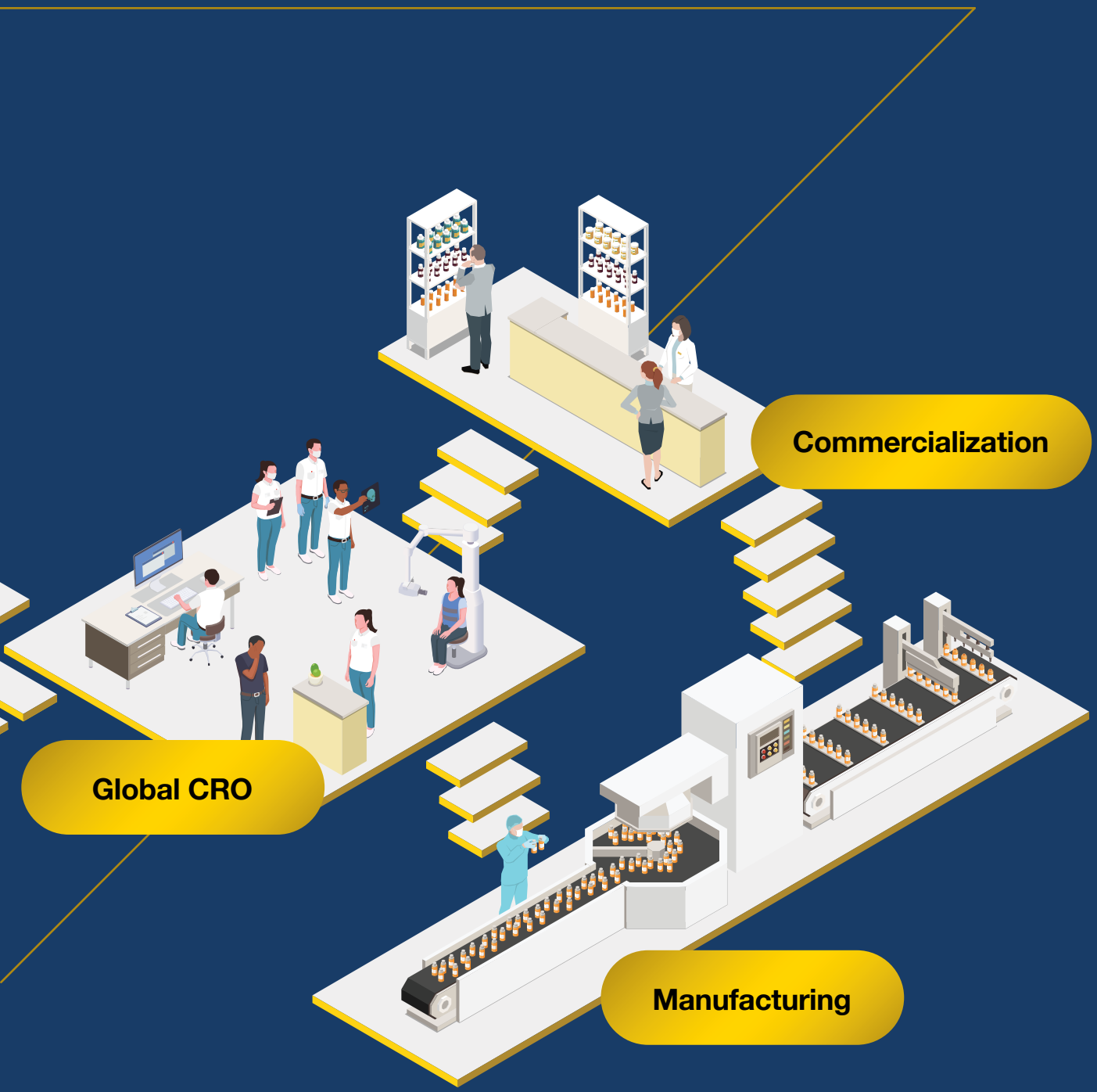
- Track every step of the process, from sample collection for biomarker testing and delivery to central labs
- Monitor turnaround times from sample collection to results
- Monitor turnaround times to provide tumor samples for immunohistochemistry (IHC) analysis
- Monitor recruitment projections on a rolling basis and have open conversations with the sites on their challenges, competing trials and, if needed, improvement strategies
- Reassess recruitment rates for the patient population to be prescreened on a rolling basis

Create patient- and caregiver-centric recruitment strategies that drive value.

A Transformational Infrastructure to Accelerate the Development of Complex Therapies

Precision experts support your work across the development life cycle with global reach, integrated capabilities, and deep oncology expertise.




Commercialization
Global CRO
Manufacturing

Lab partner selection

Selecting a lab partner involves identifying and partnering with an organization that has both deep and broad experience in executing a trial in this space with the concomitant assays required for both safety and early efficacy assessments.

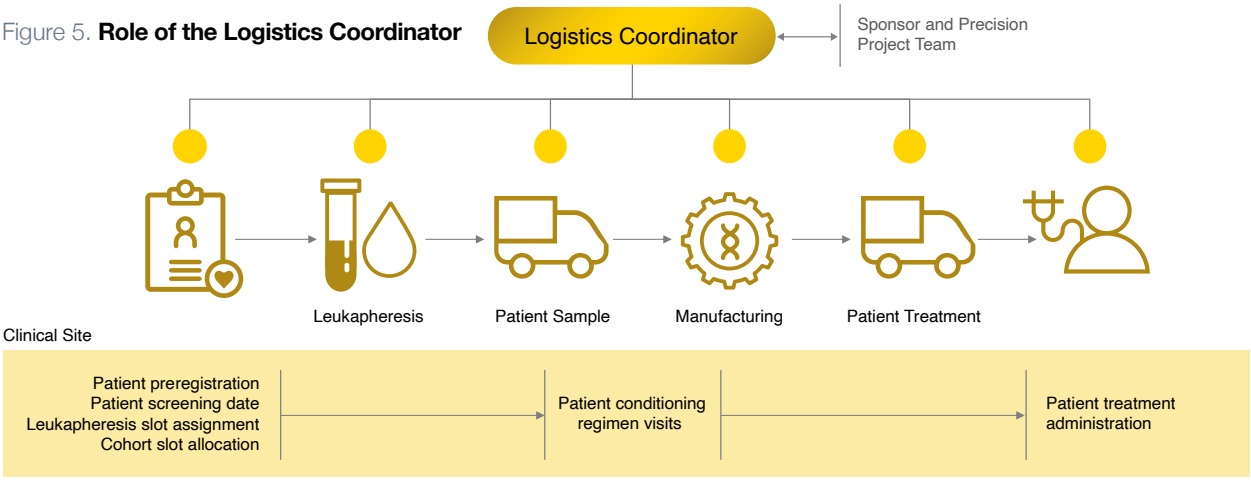
Logistics management and communication

The complex logistics involved in cell therapy clinical trials require careful management and constant, consistent communication across not just stakeholders, sites, and study teams but also all vendors who are handling biospecimens, including couriers, manufacturers, and specialty labs. Borrowed from the fields of distribution and operations management to improve efficiency, a new position, the Logistics Coordinator, has entered the trial management business. The Logistics Coordinator plays a crucial role, especially in cell therapy studies, where oversight, documentation, and tracking of sample collection and delivery and cellular product transport, storage, and handling are key to manufacturing and patient treatment.

The Logistics Coordinator position is central to all cell therapy trial interactions (see Figure 5).

- The sites that collect biological material at predefined timepoints
- The contract manufacturing organization (CMO) that produces the investigational product derived from patients' cells
- The central labs that analyze various biological materials, such as blood, urine, saliva, bone marrow, or cerebrospinal fluid
- The CRO team involved in the study, including the Clinical Research Associates (CRAs), Clinical Trial Manager (CTM), and Data Manager
- The sponsor, who in some cases is accountable for the management of slot allocation

Figure 5. **Role of the Logistics Coordinator**



Manufacturing

The manufacturing process for cell therapy products must be consistent, reproducible, and scalable, yielding a product of adequate quality and safety with sufficient doses to support ongoing clinical studies and, eventually, future long-term commercial viability. The manufacturing process must also be transferable to other manufacturing facilities, ensuring consistency across sites and enabling the product to be manufactured in different geographic regions without compromising its overall quality, safety, and efficacy attributes.

Data monitoring

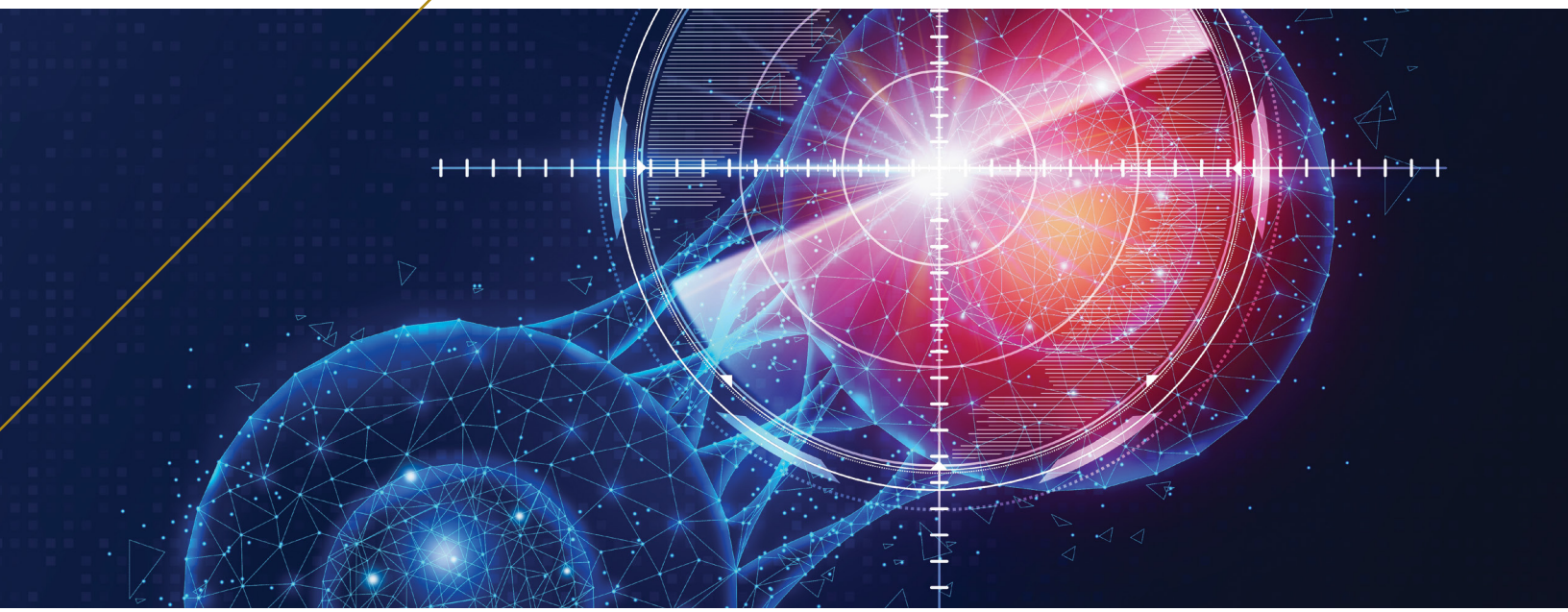
Cell therapy trials generate a high volume of diverse data in various formats, which must be supported by a robust data monitoring plan. Data entry expectations should be clearly documented and distributed at the outset of the study, and the type and frequency of monitoring should be designed to maximize both patient safety and data quality.

A Single Point of Contact for Advanced Therapy Medicinal Product Manufacturing in Cell Therapy Trials

The new role of Logistics Coordinator is custom-built for managing the unique process essential to the manufacture of the cell therapy product under evaluation in a clinical trial. The process starts with collecting patient or donor cells to generate the cellular starting material required for product manufacture and experimental analyses. Flawless coordination is crucial because any mishandling of samples can yield costly errors that may jeopardize product development and even the trial itself. The Logistics Coordinator's close oversight of the chain of custody ensures Good Manufacturing Practice (GMP) compliance at every step of the process, including constant monitoring of storage conditions and tracking of shipments.

The presence of a Logistics Coordinator means there is one professional charged with overseeing the complex process of advanced therapy medicinal product (ATMP) manufacturing, someone who resolves issues as they arise and interacts with all stakeholders as needed. Exceptional communications and interpersonal skills, combined with a proactive approach to problem-solving, keen attention to detail, and the ability to oversee and track multiple processes, allow the Logistics Coordinator to serve as the central point of contact for study sites, the CMO, central and specialty labs, and the sponsor, ensuring streamlined communication with all parties.

Stakeholder	Logistics Coordinator Responsibilities
Clinical Sites	• Field questions pertaining to cell and biological sample collection, storage, and shipment • Work with CRAs to address any issues • Provide slot dates, guidance on timing for patient identification and recruitment, and updates on manufacturing (especially if multiple releases are required) • Distribute documents to facilitate administration of the investigational product (IP) to the patient • Assist with kit resupply and guidance on proper use of kits
CMO	• Provides updates on patient identification and recruitment, timing of apheresis, shipment of samples, and other site-level activities • May handle certificates of analysis and documents when the IP is ready for administration
Central and Specialty Labs	• Inform on-site activation, kit requests, patient recruitment, cell collection, sample shipment, and other site-level activities
Sponsor	• Provides process updates • Assists in informing the sites about slot allocation



Evolution of Cell Therapy Trial Execution

Getting a Head Start on Manufacturing

Cell therapies are uniquely complex compared to other therapies, so planning for commercial-scale manufacturing up front, even before initiating clinical trials, can impact the overall efficiency of the development program. A solution for scaling up from the lab to a GMP facility is needed long before a product has achieved regulatory approval, with the goal of delivering life-saving therapies to patients in a cost-effective manner. Whether it is exploring strategies for reducing vein-to-vein TAT or deciding whether to manufacture in house or outsource, careful consideration of the potential hurdles to study enrollment and eventual commercialization in the earliest stages of clinical development is essential. A study using data from the JULIET clinical trial found that reducing treatment wait times by 2 months would increase the number of eligible patients receiving CAR T-cell therapy by nearly 11% and would generate a 3.3% increase in survival gains per treated patient.[4]

Industrializing Cell and Gene Therapy

At Precision for Medicine, we have vast experience in designing and building GMP-compliant cell and gene therapy facilities, ranging from 5000 sq ft to over 500,000 sq ft, using cutting-edge modular, emerging bioreactor, and single-use technologies. Our manufacturing playbook—which has been tried and tested by the leading cell and gene therapy organizations—has led to the development of the largest and most mature ATMP manufacturing footprint in the world.

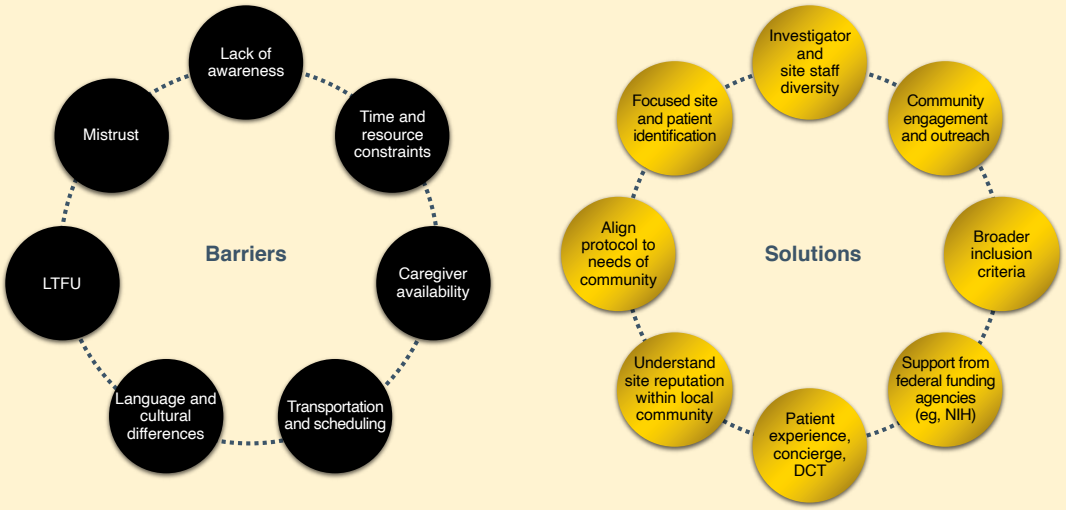
Leverage our expertise in cell and gene therapy manufacturing.

Planning for Racial and Ethnic Diversity

Now that many of the obstacles for executing cell therapy clinical trials are known and can be proactively addressed before study startup, it is time for sponsors, CROs, and vendors to focus on another critical aspect of clinical trial execution—increasing racial and ethnic diversity so that study populations reflect real-world disease demographics.

Many researchers, sponsors, and CROs are working to better understand the factors that contribute to demographically biased clinical trials and are developing solutions to overcome those barriers. A recent study found that Black patients were consistently underrepresented in pivotal clinical trials that led to FDA approval of CAR T-cell therapies, regardless of indication. The most pronounced disparity was found in the phase 2 trial of *idecabtagene vicleucel* for relapsed or refractory multiple myeloma, which included only 8 Black patients among 140 study participants, even though disease prevalence is greater among Black patients.[5]

Figure 6. **Barriers to—and potential solutions for—racial and ethnic diversity in clinical trials**



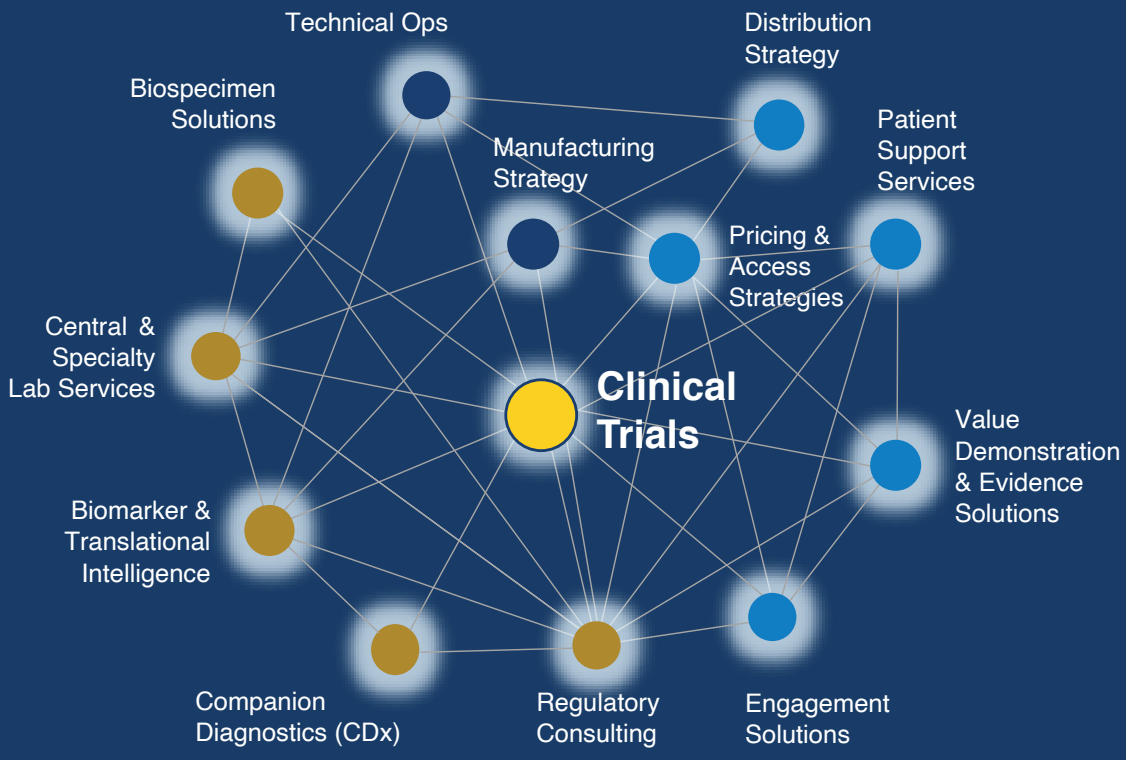
LTFU = long-term follow-up.
DCT = decentralized clinical trials.

Both the FDA and the American Society of Clinical Oncology (ASCO) are emphasizing the importance of advancing and achieving health equity in clinical trials as both an ethical and a scientific imperative. Each organization stresses that clinical trial populations should more accurately represent the population of patients with cancer, that clinical trials should routinely be offered as a treatment option, and that all patients should have equitable access to clinical trials.

The FDA has issued a draft guidance, *Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials*, to help sponsors plan for diversity.[6] ASCO's Equity, Diversity, and Inclusion (EDI) Action Plan also highlights the need for an oncology workforce that matches the diversity of the general population.[7]

At Precision for Medicine, we are exploring innovative, data-driven approaches to identifying experienced sites and investigators that can help increase clinical trial awareness and access among underrepresented patient populations. By incorporating claims data and social determinants of health (SDOH) into a validated process, we can help researchers and sponsors plan for racial and ethnic diversity. Once we have qualified those sites and investigators, we can build site-specific patient lists within our proprietary EHR Connect™ technology to help identify patients who meet specific clinical and demographic criteria (see Figure 6).

Navigate the Complex Ecosystem of Cell Therapy Development With Collective Intelligence

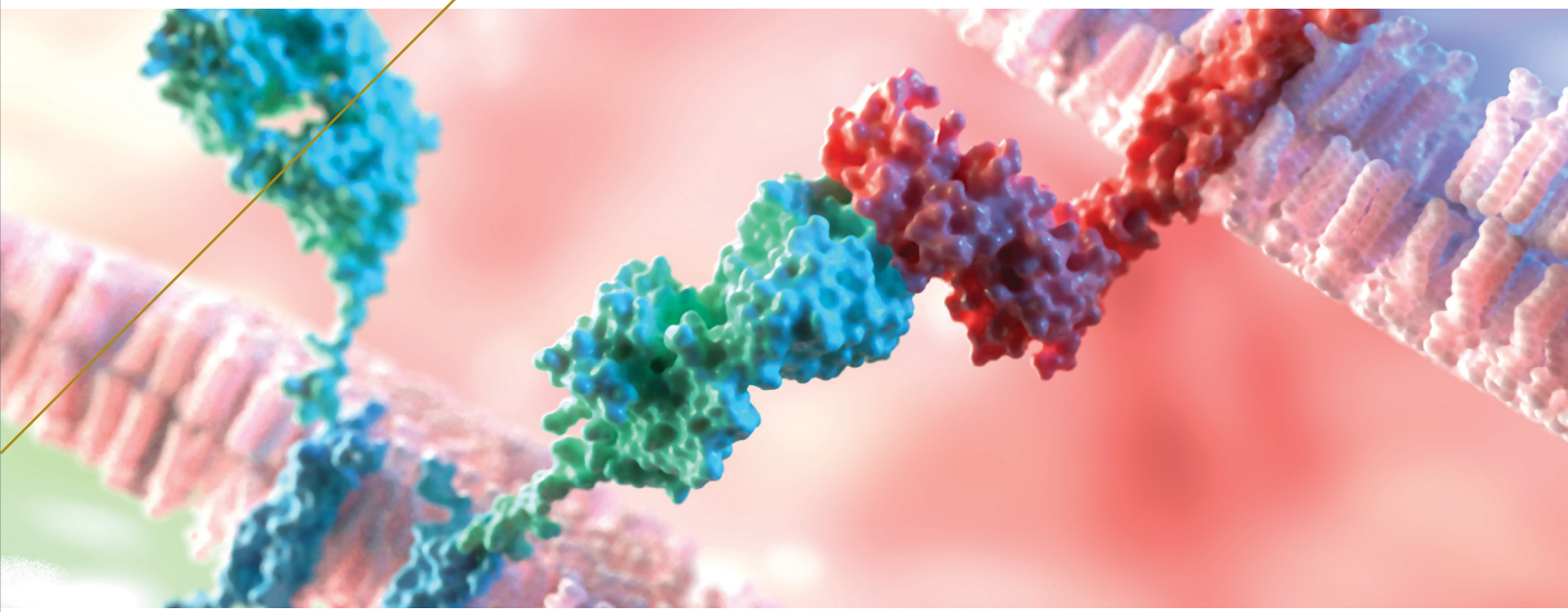


The combination of product-specific factors, clinical trial requirements, and access-related considerations creates a complex ecosystem that demands careful coordination among a variety of disciplines and stakeholders. To run a high-quality, efficient cell therapy trial, it is critical to break down silos and bring together all these disciplines and subject matter experts. At Precision for Medicine, we have created Precision ADVANCE cell and gene therapy collective, a collection of interconnected services and complementary teams uniquely focused on addressing the clinical, regulatory, manufacturing, and commercial challenges associated with successfully bringing cell therapies to market.

PRECISION ADVANCE the cell & gene therapy collective™

Moving a cell therapy from preclinical investigation to commercialization requires a comprehensive, integrated approach. The Precision ADVANCE cell and gene therapy collective brings together Precision for Medicine's unique expertise and capabilities across the continuum of early development, biological manufacturing, and commercialization.

Explore



Conclusion

Cell-based immuno-oncology therapies are an active area of clinical development, representing over 1200 active oncology cell therapy clinical trials.[8] The field is broadening beyond CAR T-cell therapies for hematologic malignancies, with increasing emphasis on other cell types, solid tumors, and even non-oncology indications.

Given the complexity inherent to both their design and the clinical trials necessary for evaluating their safety and efficacy, cell therapies require the collective intelligence of cross-functional, multidisciplinary teams for successful development, approval, and commercialization. Researchers, clinicians, sponsors, and CROs must leverage prior knowledge and utilize innovation to run high-quality, efficient studies that address unmet needs, including the need for diversity and equity in oncology clinical trials.

Talk to an Expert

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