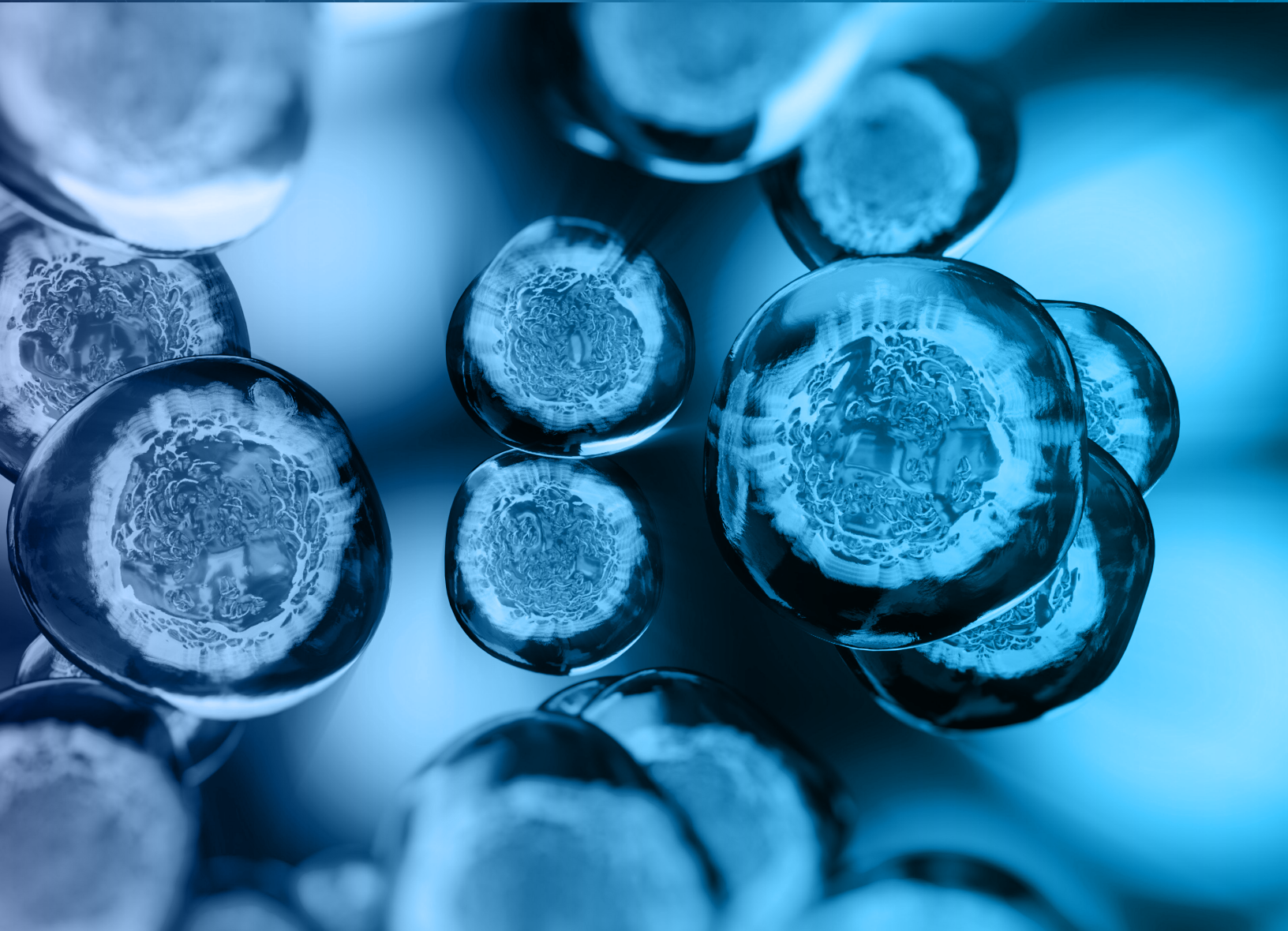


WHITEPAPER

Cell Therapy: How to Avoid Clinical Trial Pitfalls and Bring Products to Market Quickly



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The cell therapy industry is growing rapidly. With the number of clinical trials soaring and investments setting the stage for still more R&D, the industry is striving to improve the lives of millions of people with unmet medical needs. However, there are barriers to the realization of that vision. To succeed, the cell therapy industry will need to avoid the common pitfalls in clinical development created by its growing pains.

Cell Therapy Market Growth

From 2017 to 2019, the number of cell therapies in clinical development rose by 29%.^{1,2} The increase reflects 70% growth in phase 3 cell therapy trials, as well as more than 20% growth in the number of phase 1 and 2 studies. Cell-based immuno-oncology was a key growth driver, but other applications contributed. Going forward, the industry is set to pursue opportunities across therapeutic areas.³⁻⁵

North America, which is home to 543 gene, cell and tissue-based therapeutic developers, has been a key driver of the growth.¹ However, the region is far from the only significant contributor. Asia-Pacific, with 295 companies, and Europe, with 209 companies, are important geographies and collectively account for almost half of the 1,085 developers worldwide.

Most companies in the space are small and lack internal resources that are critical to the success of cell therapies. Fifty percent of members of the Alliance for Regenerative Medicine, a cell therapy trade group, have fewer than 50 employees. A further 17% have 50 to 99 employees.¹

The FDA expects the surge in advanced therapy R&D to lead to 10 to 20 cell and gene therapy approvals a year by 2025.⁶ Across the Atlantic, the European Medicines Agency is



braced for a similar level of cell therapy activity, having seen the number of annual advanced therapy classifications jump 102% from 2018 to 2020.⁷

Investment activity suggests there is more to come. The broader regenerative medicine and advanced therapy sector raised \$19.9 billion in 2020, up 100% over the previous year. The record funding sets the stage for even more clinical trial activity in the future. Investors committed the funding in the belief cell therapies are a fast-growing, multibillion-dollar opportunity. Allied Medical Research forecasts a 25.6% compound annual growth rate that will create a \$48 billion market by 2027.⁸

Challenges in the Clinical Development of Cell Therapies

The forecasted value of the industry reflects the potential of the modality to transform the lives of patients with major unmet medical needs. However, the industry faces a range of barriers to the successful execution of the clinical trials needed to translate therapeutic potential into life-changing cell therapies with regulatory approval.

1) Capacity and Experience of Clinical Resources

Clinical resource capacity is a major challenge. The pool of investigators with the interest, training and capacity to take on cell therapy trials is far smaller than the pool for traditional modalities. With the number of cell therapy studies growing quickly, competition for investigators has intensified.

The bottleneck is exacerbated by the limited number of sites with accredited cell therapy capacity and infrastructure. Accreditations such as compliance with the FACT-JACIE Standards show sites are equipped to take on certain studies. Growth in cell therapy clinical trials has outpaced the rise in accreditations. While sponsors can work with unaccredited sites, they must invest time to ensure the centers are qualified and suitable for their studies.

2) Reaching Clinical Trial Participants

Investigators and sites face their own challenges. Notably, there is intense competition for patients in certain therapeutic



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areas, such as multiple myeloma. Annual filings to run multiple myeloma trials in 2020 were up 36% over the 2015 level, despite disruption caused by the pandemic.⁹ The increase means cell therapy studies are competing with a growing number of clinical trials of antibody-drug conjugates, bispecific antibodies and other modalities for patients with multiple myeloma. The multiple myeloma situation is echoed in other competitive therapeutic areas.

The ability for patients to choose from clinical trials involving a range of modalities puts cell therapies at a disadvantage. While cell therapies have the potential to be powerful, highly efficacious treatments, they also impose more burdens on patients than other modalities. The week-long inpatient observation, lymphodepletion and leukapheresis involved in autologous cell therapy trials require significant commitment from patients and can make recruitment challenging.

The recruitment challenges are magnified by the fact many cell therapies target highly specific patient subgroups to limit functional heterogeneity, which can impact the success of the trial.

3) Capacity and Standardization of Manufacturing

Access to cell therapy manufacturing has emerged as a key bottleneck as the cell therapy pipeline has expanded quickly. BioPlan Associates, a biopharma market information service provider, estimates cell and gene therapy manufacturing capacity needs to increase by five times to meet demand.¹⁰ There is a push to bring new facilities online but for now there are simply not enough manufacturing organizations with the level of experience and capacity to support the pipeline.

The situation is complicated by regulatory requirements. Globally, there is a lack of consistency in what is required by regulatory authorities. The divergent regulatory requirements and the fast pace at which the sector is growing and changing have created a shortage of people who understand what is needed. For small biotechs, it can be hard to access the expertise that is essential to the successful navigation of the regulatory landscape.



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4) Managing Complex Logistics

Sponsors are struggling to access the appropriate level of support from depots, manufacturers and logistics vendors, again because of the rapid growth in the clinical pipeline. The logistics of cell therapy clinical trials are complex, making it unlikely a single vendor can manage everything. For example, companies that provide logistics services are not usually experienced with or able to manage clinical operations, resulting in the need for a vendor or point person who will manage communication between the logistics vendor and the clinical sites and ensure impacts of logistical delays are handled appropriately and in line with the trial protocol at the clinical site. Similarly, a manufacturer may not have experience with the site expectations or needs for cell therapy packaging and a point person with experience in both arenas is crucial. Sponsors can tie everything together themselves but often lack the internal resources, bandwidth and experience to do so.

“Oftentimes, cell therapy companies that are starting out don’t have the knowledge or understanding of what’s needed from a regulatory standpoint, as far as cell tracking. Specifically, there are regulatory requirements that are unique to tracking cellular based products, unlike tablets or capsules. It is really important to consider how you will track cells and have appropriate documentation very early. If you don’t do it right, it will cost time and money later on,” said Jeff Vassallo, Director, Clinical Operations at Medpace.

The situation is driving soaring demand for CROs that have visibility into all the aspects of cell therapy logistics and thereby making it hard for sponsors to access the support of experienced service providers. When sponsors do find vendors, it is important to establish communication pathways and an overall process that facilitate study execution. A lack of consistency across the logistics for cell therapies is challenging to accommodate, for both vendors and sites.

5) Early Development of Regulatory Strategy

Often, sponsors hold off on choosing the countries where they will activate trial sites until after they have made decisions about factors such as labeling, packaging and preclinical studies. Doing those activities before considering the location of a clinical trial creates the risk that they will all need to be redone to comply with regulations in the target market.

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“Requirements vary greatly from country to country. What we see in most cases is that the sponsor has no overall regulatory strategy. Where do you want to market this product? That key driver of the strategy needs answering,” said Jan Ohotski, Regulatory Submissions Technical Advisor at Medpace.

Considering country-specific requirements too late in the process can lead to setbacks such as the rejection of clinical trial applications. Such setbacks are hard to fix if the product has not been developed in line with the local regulations. Major revisions to raw materials, excipients, product specifications and most often to how a product is manufactured could be needed.

Strategies for Success

Aligning the overall product development strategy with regulatory, clinical operations, manufacturing and supply chain requirements is essential, as is an awareness of common pitfalls for cell therapy trials. Sponsors that run into one of the pitfalls risk delays in site activation, recruitment and trial completion. The best way to mitigate that risk is to recognize and respond to the challenges early in the R&D process.

1) Bypass Rate Limiters in Study Setup by Planning Ahead

Early planning is critical to cell therapy success and the strategic timing can surprise sponsors. For example, cell therapy clinical trial sites want to review investigational product or cell therapy manual during startup, earlier than is typical for other modalities. Details in the manual have big implications for trial management and can elucidate unexpected challenges for sites. Equally, sponsors are best served by considering how IP is handled and fits into site processes long before first patient. Further, to develop the cell therapy manual, the sponsor must have a clear understanding of how the cell therapy will be tracked to comply with regulatory requirements. Partnering with an experienced CRO can help sponsors avoid pitfalls in developing the cell tracking system and the cell therapy manual.

“Medpace has a lot of experience building cell tracking processes and cell therapy manuals. We have a very experienced operational team, including experts who previously worked at sites with apheresis and cell therapy infusion centers and who work routinely with logistics, drug depot and manufacturing vendors. We have developed many study-specific cell therapy manuals that provided detailed clinical



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and operational instructions for the sites, including how to handle the product, prepare the product for administration, administer the product—intravenous, intravesicular, etc—as well as how to accurately document the chain of custody and identity at each critical juncture in the flow of the product through their systems. We also have the clinical experience to identify gaps in the cell tracking process or in the cell therapy manual such as what clinical supplies and equipment should be provided to the site,” said Elizabeth Shepherd, Clinical Trial Manager at Medpace.

2) Develop the Global Marketing Strategy Early

Developing the global marketing and regulatory strategy ensures sponsors understand the requirements in each target market. Again, sponsors need to gain this knowledge early. Sponsors need to have a clear picture of their clinical trial before they start site selection. It is essential to start the process early as the insights will shape which sites are selected and whether those sites are equipped and licensed to run the trial.

Sponsors can reduce the risk of regulatory setbacks through strategic engagement with the authorities. While the FDA and EMA, as regulators of major markets, are key stakeholders, sponsors should also talk to other relevant agencies, in line with their product development strategy. Manufacturing of the product and design of the trial should be discussed with GMO authorities, when required.

Site-specific review bodies such as U.S. Institutional Biosafety Committees may need to approve a study prior to site initiation. Similar review bodies exist in other countries such as in Australia and the U.K. In countries such as France and Spain, additional national bodies also need to approve studies as part of the GMO submission process and a license to procure, use, import and export cells and tissues is required for clinical sites, infusion sites and pharmacies handling cell-based products in Germany and the U.K., amongst others. Finally, an additional site license is often required for activities classified as manufacturing.

An assessment of regulatory readiness can reveal whether a project is likely to encounter problems. Assessments entail the review of submission documents in light of national and regional guidelines, as well as consideration of site-specific



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cell and tissue licenses required for product handling, import, export and manufacturing and country-specific documents required for GMO submissions in markets including Australia, Brazil, Canada and Japan.

3) Form a Dedicated Management Team to Track Processes

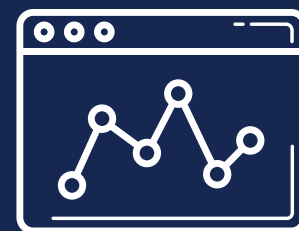
Operationally, sponsors need a system for tracking cells from donor to patient using a distinct code that is traceable throughout the chain of custody and tied to all records pertaining to that product. The tracking system needs to be provided to the recipient of the goods in writing before distribution and be able to cope with the complex, multi-stakeholder cell therapy supply chain.

While the supply chains of autologous and allogeneic therapies differ, both pose considerable challenges for tracking systems. The tracking challenges contribute to the logistical complexity of cell therapy trials. Sponsors need to ask questions specific to the modality, such as: if manufacturing must start within 24 hours of leukapheresis, is that logistically feasible based on-site locations and transit options? How will critical communications be shared with all relevant stakeholders?

Given the complexity, a dedicated management team should be considering every risk and ensuring there are processes in place to address the threats, as well as managing the various stakeholders and how each will communicate as necessary.

4) Integrate Management of Clinical Operations and Regulatory Affairs

The regulatory strategy must connect to the operational strategy, something sponsors can achieve by working with a full-service CRO that is aligned internally and understands global variations in requirements surrounding the development of cell therapies. Connecting regulatory oversight to operational planning ensures items such as the IP labels and logistics comply with local regulations. This interaction would also ensure that all auxiliary labels needed for IV bags and syringes are created in advance, designed and reviewed by the regulatory team.



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Partnering for Cell Therapy Success

Full-service CRO Medpace has extensive experience of cell therapy development. Medpace's team of physicians, many of them full professors, have led advancements in the field and have now shared their knowledge with the CRO's customers across tens of cell-therapy studies in the U.S., Europe and Asia Pacific.

The deep experience has given Medpace a robust strategy for avoiding and mitigating the risks related to common pitfalls that are faced by its cell therapy customers. Medpace's unique system equips it to help sponsors pose and answer questions that are critical to the management of cell therapy challenges and considerations.

This expertise has enabled Medpace to create a cell tracking process that seamlessly manages the many changes in custody along the cell therapy supply chain. Sponsors that partner with Medpace gain access to the tracking process and cell therapy expertise.

The cell tracking capabilities are part of a broader package offered by Medpace. The full package covers regulatory, site assessment, feasibility, training and metrics, startup, investigator relations and medical monitoring. By partnering with Medpace, sponsors can access the full suite of services, enabling them to bypass the pitfalls of cell therapy development and accelerate the licensing of life-changing medicines.



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About Medpace

Medpace is a scientifically-driven, global, full-service CRO providing Phase I-IV clinical development services to the biotechnology, pharmaceutical and medical device industries. Medpace's mission is to accelerate the global development of safe and effective medical therapeutics through its high-science and disciplined operating approach that leverages regulatory and therapeutic expertise across all major areas.

YOUR CRO PARTNER FOR CELL & GENE THERAPY CLINICAL DEVELOPMENT

Medpace has contributed to over 130 Advanced Therapy clinical trials. Our experienced team of experts take an active role in the field and are at the forefront of rapidly changing clinical and regulatory developments.

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