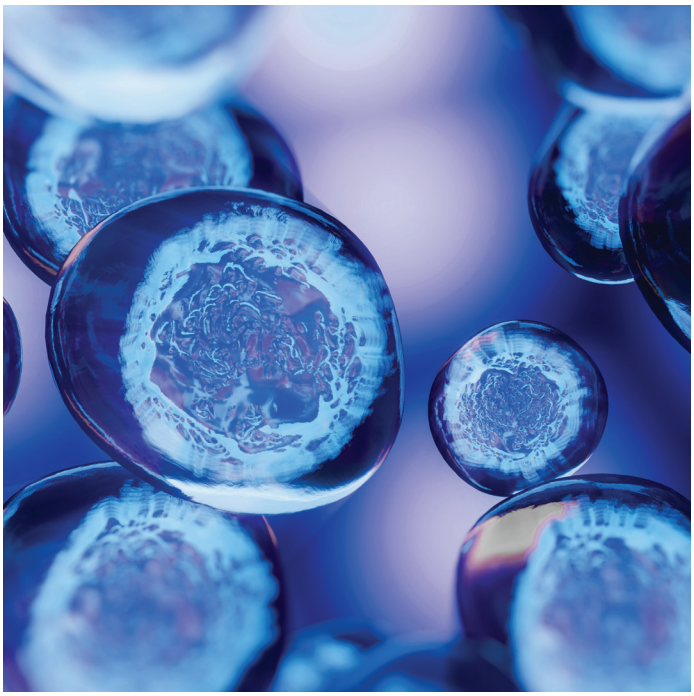
LESSONS LEARNED IN EMERGING CELL AND GENE THERAPIES: A HOLISTIC APPROACH TO CLINICAL DEVELOPMENT

Cell and gene therapies hold tremendous potential to advance patient care and treatment of many diseases.[1] This is reflected in the rapid growth of the regenerative medicine space, predicted to hit $39.33 billion by 2023 with the fastest growth expected in cell therapy.[2] The Alliance for Regenerative Medicine reports that over 1,000 clinical trials were underway worldwide in 2019[3] in the areas of gene therapy, gene-modified and cell-based immuno-oncology, cell therapy and tissue engineering, while 987 regenerative medicine companies were in operation.

Despite the rate of growth and investors' interest, many cell and gene therapies do not complete the journey from laboratory bench to commercialization. Success is dependent on a chain of interconnected decision points along the way, and a weak link can result in a failed clinical program.[1,4]

Because of the steep learning curve, cell and gene therapy companies often benefit from the assistance of experienced clinical partners who help ensure each step in the product development process is in place to efficiently move to the next stage. Centralizing these critical activities within a cross-functional team of experienced experts who work seamlessly together can be a key differentiator, allowing sponsors to accelerate clinical trials and thoughtfully plan for long-term goals such as marketing product approval.



Sponsors who develop cell and gene therapies typically need to find partners — such as clinical research organizations (CROs), consultants, laboratories — to help advance their therapy. Because of the added complexities of working in this space, there are inherent benefits to working with a partner who brings a full-service and integrated approach to ensure efficiency across medical, regulatory, and operational considerations and requirements.

Each of these areas that are critical to successful product development — medical, regulatory and clinical operations — face a unique set of challenges.

Partnering with an integrated team of experts who work collaboratively — not in individual organizations or departmental silos — gives sponsors the best chance of achieving their clinical development timelines and program success.

Here, we provide insight into some of the challenges faced in developing cell and gene therapies, as well as guidance for overcoming these hurdles.

MEDICAL CHALLENGES: MAKING THE LEAP FROM LAB TO CLINIC

Solid science — backed by evidence of safety and the promise for an unmet medical need — is at the core of a successful clinical development program. Medical experts vet the initial therapeutic hypothesis, identify the product's market niche, advise the sponsor on trial design, and fine-tune protocols. "This level of expertise facilitates movement and accelerates the speed of the trial so that key milestones are met," said Dr. Blythe Thomson, Senior Medical Director at Medpace, a CRO with deep experience in advanced therapy clinical development. "This can't be emphasized enough when companies are looking to get into the clinical arena."

A well-vetted study design is a critical link in the chain toward success. Coordinating logistics between harvesting cells, manufacturing the therapy and delivering it seamlessly to the correct patient is always complex. The level of complexity increases exponentially when scaling up from an academic trial in a single laboratory to a global, multicenter trial. Peggy Kaiser, a nurse practitioner at Medpace, said "academic protocols often need to be streamlined to reduce logistical complexity and successfully make the leap from single lab to marketable product."

When the protocols are achievable, establishing consistency across sites is another challenge. Sponsors must ensure that investigator training is comprehensive and consistent, and that acute and long-term side effects are appropriately managed. Communication breakdowns can occur when working across sites, particularly among people who have not previously worked together.

Starting with a clear roadmap, identifying and remaining cognizant of long-terms goals and staying mindful of both endpoints and patient safety throughout the clinical development process are critical strategies.

It is common for sponsors to underestimate timelines for approvals, infrastructure requirements and the level of investigator training and experience needed across global centers. For these reasons, many companies benefit from partnering with a clinical research organization that has been through the process many times before.

Partnering with a knowledgeable intermediary is also key in translating local best practices to a global multicenter trial. Having physicians at the trial site who can explain and train investigators on the protocol ensures that the study design is translated correctly across multiple sites and that the protocol is respected.

When working with gene and cell therapy companies, a partner can facilitate communication across the multisite team, ideally on the phone versus email or text. The partner should check in with investigators at the various sites to ensure the trial is proceeding according to protocol.

"It is important to include medical monitors who understand the toxicities associated with the treatment that are due to the cell therapies versus those that are disease related or are related to treatments in the past," said Ann Woolfrey, senior medical director at Medpace. "They are able to help manage variations in real time that were not anticipated by the protocol."

Finally, while the clinical trial and product are important, patient safety must be the top priority. "When teams struggle to meet an artificial deadline, that's when things fall apart," said Dr. Woolfrey.

"If Sponsors always remember the patient and their safety comes first, decisions will become clear."

OPERATIONAL CHALLENGES: PLANNING, PRACTICING AND COMMUNICATING

In order to achieve a zero-error rate during clinical development, sponsors must think through every operational aspect of the protocol, making sure processes are robust and pressure-testing them prior to starting the trial. When designing study protocols and selecting trial sites, it is critical that sites and partners have the appropriate infrastructure and capabilities upfront to ensure milestones are met.

One of the operational challenges often faced by sponsors is issues with investigational product supply and management logistics. For example, due to manufacturing constraints and the product's short shelf life, clinical sites need adequate storage, such as appropriate freezers, biohoods, and qualified cell infusion units/centers as well as appropriate processes to manage the product and monitor the patient.

Cell tracking between investigational, manufacturing and clinical sites is also critically important, and the chain of custody and chain of identity must be meticulously tracked in real time. "There are many steps that must be executed perfectly, and when different vendors are involved, communication is a particular challenge," said Aaron Logue, Sr. Associate Director in Clinical Trial Management at Medpace.

An example of a pressure test used by Medpace is a mock transport. This process is used to fine-tune cell tracking before a trial, and these exercises have shown that communication is the most important differentiator between a successful process and one that can be broken. They also help reveal whether sites have the infrastructure and capabilities in place for conducting a trial.

As with medical considerations, a strong team, communication, and clarity are the keys to success in clinical operations. Partnering with all study personnel early results in a tightly managed team set up for success.

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Experienced teams know that selecting vendors and sites recognized as top performers is important. Logue notes that working with one vendor, rather than multiple vendors, can help companies stay on track with key milestones. "If everyone is working together, we can quickly identify potential risks and mitigate them, and as a team we work together regularly so we know our best practices."

REGULATORY CHALLENGES: ENGAGE EARLY AND PLAN FOR THE LONG TERM

Due to the cutting-edge nature of many products and myriad of regulatory guidelines and expectations that vary between regions and countries, it is important for sponsors to work with development experts who understand the regulations and how to forge partnerships with regulatory agencies.

Furthermore, considering the complexities of these products, regulatory barriers can cause long delays in the initiation of clinical trials, particularly for global multicenter trials that require additional approvals for genetically modified organisms (GMO). While timelines may vary across regions, effective partnerships with regulatory experts with a strong scientific background and working knowledge of manufacturing, nonclinical, and clinical considerations for these products can optimize timelines for clinical trial initiation.

Oftentimes, failure to plan appropriately due to a lack of understanding of the required data for clinical trial approvals is a common issue. Unlike traditional programs, there is not a one-size-fits-all development approach for cell and gene therapies. As such, to prevent derailed timelines and delayed achievement of milestones, regulatory planning is critical early on to understand the needs of a program and ensure phase-appropriate manufacturing, nonclinical, and clinical data is in place to maximize the effectiveness of the clinical program.

Program flexibility is key, and a well-thought out development strategy with a clear picture of the entire clinical development plan will allow for efficient progress through development milestones. Adopting a global perspective, even if the company initially plans to confine trials to one region, is also a best practice to ensure program flexibility in the future.

With the complexity of the product, it is of critical importance to have a clear understanding of how the nonclinical, manufacturing, clinical pharmacology, and clinical pieces come together to ensure regulatory requirements are addressed to ensure patient safety. As such, early engagement with regulatory agencies through existing mechanisms such as advanced therapeutic medicinal product classification certification procedures, innovative task forces, scientific advice, and pre-submission meetings are advised to facilitate clinical development and study initiation.

Partnering with regulators is critical, especially when smaller companies are faced with the manufacturing challenges, nonclinical hurdles, and complex clinical trial designs. Furthermore, market access strategy should also be proactively considered in later phase programs. For example, it is recommended that sponsors include market access or health technology assessment endpoints in their Phase 3 clinical program, particularly related to reimbursement in Europe.

Early consideration of development targets and planning with the end in mind is a key contributor to program success.

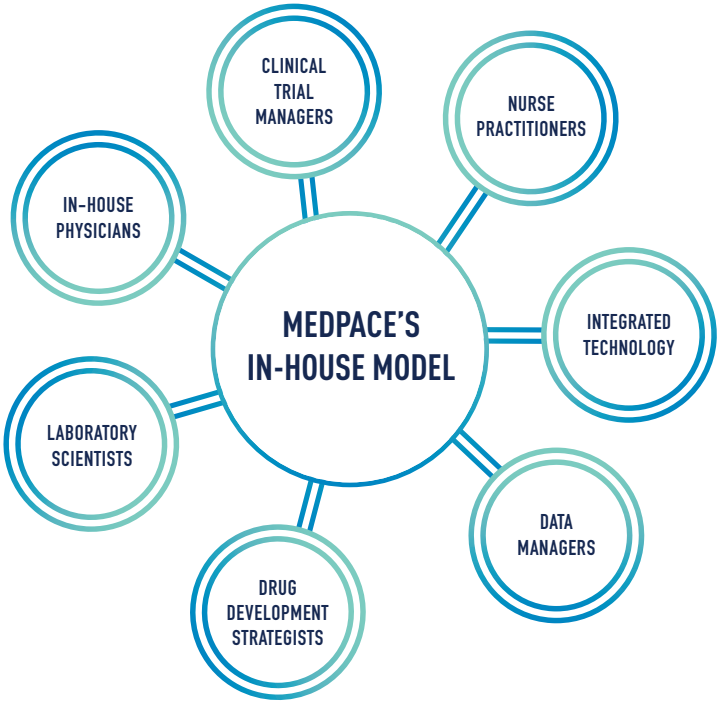
ADVANTAGES OF A HOLISTIC, INTEGRATED APPROACH TO CLINICAL DEVELOPMENT

Medical, operational, and regulatory aspects of the clinical development process function as links in a chain. Given the interrelated nature of these areas of expertise, advancing promising medical therapies is best accomplished by a cross-functional team that is expert in advanced therapy development.

Medpace is an example of a clinical research organization that brings a holistic, full-service approach to development and has been deeply involved in advanced therapies. When a team of medical, operational, and regulatory experts work together, they are able to accelerate clinical development and help sponsors avoid the barriers in this many-step journey from lab to market. Additionally, extensive experience and relationships with clinical sites, vendors and regulators help facilitate complex, global trials.

In Medpace's model, in-house, cross-functional teams provide industry and scientific experience and expertise from:

- Physicians who collaborate with sponsors to provide hands-on leadership as they design, execute and monitor clinical programs
- Clinical trial managers who manage recruitment, study startup and trial execution, and who have experience in project management for many types of studies
- Nurse practitioners who provide a positive patient experience and partner with data managers, research teams and clinical sites to ensure the protocol and data flow match the clinical process
- Interactive response technology systems experts who ensure processes are error-free
- Data managers who streamline data capture fields and optimize sites' ability to get it right the first time
- Regulatory affairs and drug development strategists who are familiar with global regulatory frameworks and country-specific requirements and can advise sponsors on the best ways to work with regulators to maximize development efficiency and program value
- A global team of hands-on laboratory scientists who actively engage with your study team throughout the entire clinical development of a drug



As advanced therapy clinical development becomes more complex, a holistic, multidisciplinary team working in unison offers the best advantage to biopharma sponsors who want to bring their scientific advances to trial and ultimately to patients. It is the high-touch competencies of communication, teamwork, coordination, collaboration and extensive experience that make the difference in attaining milestones and accelerating progress to meet sponsor goals and bring important, innovative therapies to the patients who need them.

FULL-SERVICE CLINICAL DEVELOPMENT

Medpace is a scientifically-driven, global, full-service clinical contract research organization (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 local regulatory and deep therapeutic expertise across all major areas including oncology, cardiology, metabolic disease, endocrinology, central nervous system and anti-viral and anti-infective.

SOURCES

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