Thermo Fisher SCIENTIFIC

Whitepaper

Optimizing the cell and gene therapy patient journey through integrated CDMO and CRO partnership

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Adaptability

Executive summary

Cell and gene therapies (CGTs) provide the opportunity to transform medicine across diverse disease areas where there is significant need for new treatment options. Valued at $15.46 billion in 2022, financial analysts predict the global cell and gene therapy market will grow to $82.24 billion by 2032. Some of the key drivers for this growth include a robust clinical pipeline, new regulatory approvals, the development of innovative technologies to improve production, and strategic collaborations between biotech companies and research and manufacturing partners.[1,2]

Currently, the clinical trials process for these advanced therapies is complex, involving multiple touchpoints, various providers and locations, and significant costs—all of which can negatively influence the patient experience. Some of these challenges can be addressed through development and manufacturing strategies and patient-centered trial design, which fall under the purview of partner contract development and manufacturing organizations (CDMOs) and contract research organizations (CROs). Integrating development, manufacturing, and clinical research services reduces the complexity of managing multiple vendors and ensures consistency and quality control throughout development and clinical trial management. It also facilitates more tailored solutions to meet specific trial needs, enhancing trial efficiency and cost-effectiveness. Ultimately, this cohesive approach not only simplifies logistical and operational aspects but also centers on the patient experience, making clinical trials more accessible and less burdensome.

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Understanding the complex CGT patient journey

The path to participating in a cell or gene therapy clinical trial can often be convoluted and not universally accessible. Patients who live far from large academic centers or those with limited health literacy may never become aware of or fully understand the potential of investigational products being tested for their conditions. These factors contribute to recruitment and consent challenges, as well, and can be particularly important in underserved or marginalized populations where trial participation is historically low.[3] The process for patients who have access and are potentially eligible involves a series of assessments, consent forms, and preparatory medical procedures. Each step is critical, and the need for clear information and support is vital to help patients make informed decisions about their care.

The actual science behind developing and administering cell and gene therapies creates its own unique challenges. Long but critical manufacturing timelines, the need for on-demand manufacturing, the risk of serious adverse events, and long-term follow-up requirements can be particularly burdensome for patients and for developers, as can logistical considerations including the limited number of qualified clinical trial sites, patient travel, and required hospital stays. The costs and time commitments associated with these challenges make participation in these trials and receipt of these therapies impossible for many.[4]

An important step toward improving access and enhancing the overall patient experience is patient journey mapping as illustrated in Figure 1 below. This strategic approach helps therapy developers better understand the steps and touchpoints along the complex CGT patient journey that may provide opportunities for improvement.

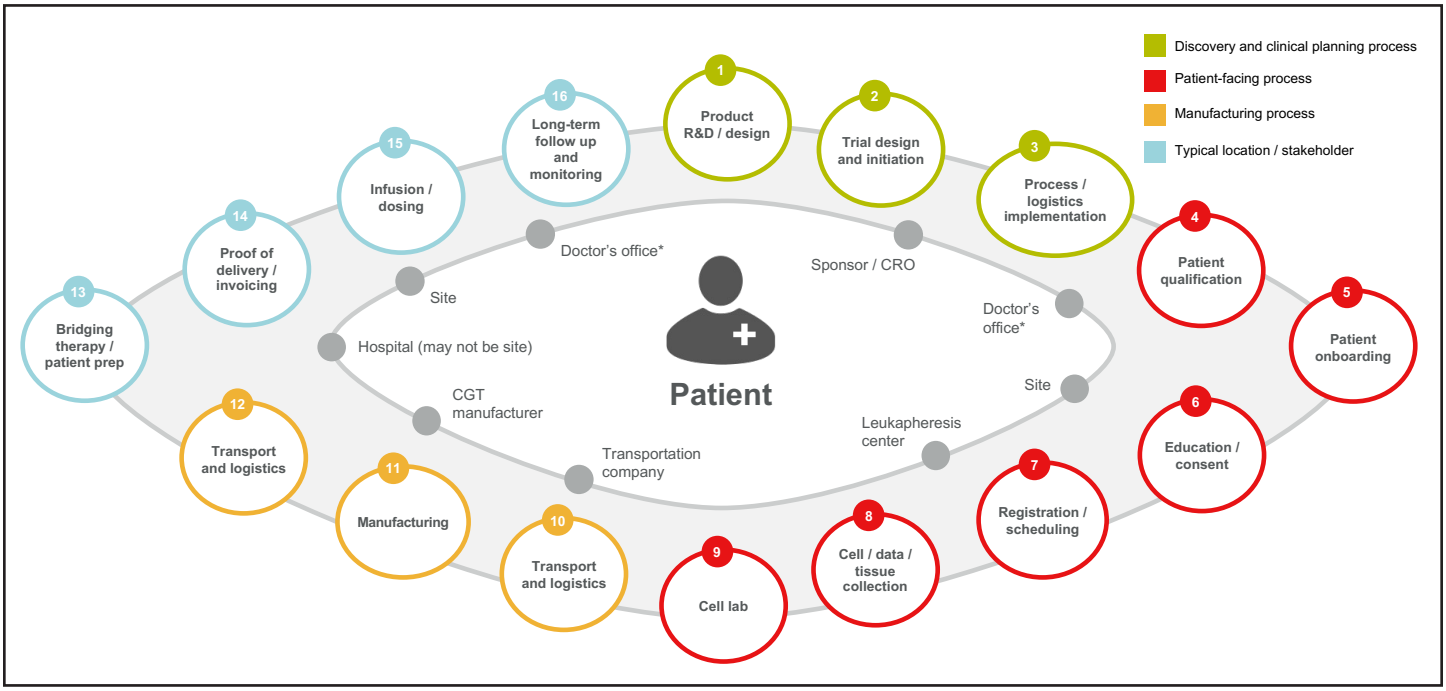

Figure 1: Current state of autologous cell therapy clinical value journey

The role of manufacturing in delivering cell and gene therapies to patients

Some of the challenges described above are directly associated with the complex manufacturing process and logistical network required to produce and deliver these treatments to patients. For instance, manufacturing delays in autologous cell therapies can postpone treatment initiation and affect entire treatment timelines, impacting patients with rapidly progressing diseases. A number of considerations that are unique to cell and gene therapy manufacturing can derail trial progress and influence the patient experience, including the following:

- *Supply chain complexity.* This is especially true for autologous cell therapies that have a circular supply chain in which starting materials from patients are used to generate and deliver the final product. In these situations, chain of identity/chain of custody and cold chain logistics are key. Any disruptions in supply could negate complicated logistical arrangements made by patients and families at various steps along the way.
- *Complex and specialized manufacturing approaches.* These are often labor-intensive and require substantial skill and training as many processes are manually performed by technical operators. There is currently a shortage of candidates with the specialized knowledge needed for cell and gene therapy processing, therefore competition for talent is fierce, often making it difficult for smaller biotechs to attract and retain qualified staff. Furthermore, new manufacturing technologies are continually emerging, which requires ongoing investment in staff training, making this a burden for smaller therapeutic developers to keep pace.
- *Challenges in scaling up from academic to commercial manufacturing.* Most CGTs originate in academic or small-scale labs where processes are often not designed for large-scale production. This transition to commercial-scale manufacturing poses significant challenges. Efficiently scaling up requires not only technological advancements but also a shift in process design and regulatory considerations. Addressing these challenges is crucial to meet the growing demand for these therapies and ensure their availability to a wider patient population.
- *Importance of robust quality control in manufacturing.* The inherent complexity of viral vectors and the biological variability of living cells necessitate stringent quality control measures in the manufacturing of CGTs. Establishing robust quality control methods and standards is vital to ensure product consistency, safety, and efficacy. Innovations in this area are essential to minimize variability, reduce costs, and shorten production timelines, ultimately leading to lower patient costs and faster access to therapies.
- *Navigating the evolving regulatory landscape.* Because cell and gene therapies represent a new frontier in medicine, the regulatory framework is continuously changing as regulatory agencies adapt their guidelines to address the unique characteristics and challenges. For manufacturers, staying abreast of these changes and maintaining compliance is crucial. This involves navigating complex regulatory pathways, engaging in proactive dialogues with regulatory bodies early and often, and ensuring that manufacturing processes meet the stringent standards set for safety and efficacy. Keeping pace with these regulatory changes is essential for timely market entrance and patient safety.

Future vision for cell and gene therapy clinical trial patients

Several opportunities exist to streamline the patient's clinical trial experience in the future and support them through this extremely difficult and emotional time in their lives. Fortunately, many of these opportunities are within the scope of influence of developers and their CDMO and CRO partners.

Awareness and participation strategies

Collaborations between developers, CROs, and patient groups are crucial in raising awareness of trials and new therapies. Data-driven approaches can identify suitable trial sites and patient demographics, ensuring trials reach a diverse and appropriate audience. Digital platforms and capabilities can also play a pivotal role in not only raising awareness of new trials and therapies, but also in maintaining a continuous connection with patients throughout their clinical journey.

By utilizing advanced data analytics, social media, and patient engagement platforms, developers and CROs can reach a broader and more diverse audience. For example, Thermo Fisher Scientific's approach, which combines data mining with access to a network of electronic medical records, exemplifies how digital tools can be used to establish treatment histories and identify suitable trial sites and patient demographics. This method helps to target the right patients and ensures that trials are accessible to diverse populations.

Additionally, digital tools can foster ongoing communication and support for patients enrolled in trials. This includes using patient portals for easy access to trial information, scheduling, and results, as well as leveraging telemedicine and mobile health applications for remote consultations and monitoring.

Innovative trial design

Future clinical trials should include patient input to address their unique needs and concerns. This could involve working with patient advocacy groups (PAGs) to redesign assessment schedules or streamline eligibility processes to reduce patient burden. In some cases, trial designers may work with patients to better understand endpoints that are specifically important to them.

Protocols may also be crafted to help patients determine eligibility as early as possible and avoid wasted time and unnecessary procedures. For example, pre-screening consent for a gene therapy trial could cover antibody testing only. The patient would only complete the full consent/assent process if they were deemed eligible based on the absence of neutralizing antibodies. Such patient-centric approaches ensure trials are more responsive and accommodating to participant needs.

Expanding access through wider collection site networks and decentralized trials

Geographic accessibility is a substantial barrier to clinical trial participation.[5] If the future of cell and gene therapy trials is to keep up with the increasing number of therapies and demand from patients, many more collection and trial sites will need to be established, not only at large academic centers, but also at community-based hospitals. Decentralized trials, where possible, increase access to patients and have the potential to bring much needed therapies to communities that have been previously underserved.

Innovative partnership initiatives can also improve access for patients. For example, Thermo Fisher Scientific's SiteCoach program offers training and tools to potential investigators to expand their eligibility to participate in clinical trials. In some cases, sites that are not fully qualified to conduct every aspect of cell or gene therapy trials may be able to lighten the patient travel burden by participating in specified aspects of the trial for which they are qualified. An increase in the number of trial sites can improve overall patient recruitment across a study by making them easier to reach.

Educational initiatives for patient empowerment

Given the complexity of cell and gene therapies, providing patients and caregivers with clear, understandable, and culturally sensitive information is crucial. Education should be comprehensive, covering therapy specifics, trial requirements, and potential risks, to empower patients in their treatment journeys. Characteristics of the patient population will determine the most appropriate formats for educational materials (e.g., brochures, decision aids, audio-visual components, etc.), but all materials should be developed and tested with patient/decision-maker understanding as the end goal.

Notably, cell and gene therapies require explanations of specific eligibility requirements and safety risks such as tumor lysis syndrome, cytokine release syndrome, viral shedding, or neurotoxicities. CROs and PAGs can suggest ways that materials can explain risks sensitively and effectively to patients with specific conditions. Showing empathy and managing expectations should be key objectives of any educational piece.

Comprehensive patient logistical support

A thorough understanding of patient needs is essential to provide effective support throughout the clinical trial journey. This includes addressing travel arrangements, financial assistance, and personalized scheduling to minimize the stress and inconvenience of trial participation. The specific needs of patients will vary from study to study and from patient to patient, but where possible, future clinical trials should account for all the ways in which the experience can be made easier for participants and caregivers. For example, patients may need financial or logistical support to arrange travel, including food and lodging or arrangements for care of other family members while the patient is involved in study procedures. Patients will need reimbursement for expenses, but some may need pre-paid cards for transportation, lodging, and travel expenses to avoid the burden of upfront, out-of-pockets costs associated with trial involvement. For studies that allow cross-border patient recruitment, sponsors may need to consider adding support for travel-related documentations, such as country-specific visas.

Implementation of best practices in cell and gene therapy manufacturing

Through accumulated experience in the development and manufacturing of cell and gene therapies, several key practices have been identified to help address the aforementioned challenges, ensure high quality standards, and contribute to enhancing the overall patient experience.

- *Rigorous materials and supply chain management.* Implementing a comprehensive materials management system is crucial. This involves strict control over raw materials, including thorough supplier qualification and validation processes, to guarantee their quality and traceability. Additionally, adopting dual sourcing strategies can mitigate supply disruptions, ensuring a consistent flow of necessary materials.
- *Consistent process control and monitoring.* Maintaining consistency and quality throughout the manufacturing process is vital. This is achieved by closely monitoring critical process parameters (CPPs) and key performance indicators (KPIs).
- *Integration of automation.* Where feasible, automation technologies such as automated bioreactors, cell culture systems, and robotic cell handling systems can reduce manual intervention, thereby minimizing operator errors while enhancing efficiency.
- *Quality by Design (QbD) approach.* Designing and optimizing manufacturing processes using a QbD approach is fundamental. This includes identifying and systematically managing critical process parameters and quality attributes, alongside comprehensive risk assessment and mitigation strategies.
- *Adoption of single-use technologies and closed systems.* Utilizing single-use technologies, such as bioreactors, bags, and tubing, helps reduce contamination risks and enables quicker batch changeovers. Similarly, implementation of closed systems where possible can minimize contamination risks from microbes and particulates.
- *Comprehensive personnel training.* Ensuring all personnel are thoroughly trained in processes, especially in aseptic techniques and adherence to Good Manufacturing Practices (GMP), is fundamental to the success of manufacturing. It is also important to develop robust and sustainable training programs with a “train the trainer” model. Additionally, creating alternative career pathways in the GMP ecosystem can help with employee retention.
- *Robust quality control and environmental monitoring.* Establishing full in-house Quality Control (QC) labs for extensive testing of both in-process materials and the final product is essential. Testing should cover identity, purity, potency, and safety/sterility. Regular monitoring of the manufacturing environment for contaminants helps maintain a clean and controlled production space.
- *Effective documentation and record keeping.* Maintaining thorough documentation and records throughout the manufacturing process is critical for traceability and regulatory compliance. This can also involve the development of risk management plans to anticipate and mitigate potential issues and maintain a smooth manufacturing process.
- *Validation and qualification of resources.* Ensuring that equipment, processes, and facilities are fully validated and meet regulatory and quality standards is essential for the integrity of the manufacturing process.

More than procedural necessities, these practices are integral to the safe, effective, and timely delivery of therapies to patients. Adopting these best practices can lead to overall cost reductions for both developers and patients, despite initial upfront investments in equipment and training.

For instance, cost modeling demonstrates that extensive automation and closed processing can significantly lower the labor-intensive expenses in autologous cell therapies. Full automation, when implemented at the right scale and with optimal parameters, emerges as the most cost-effective manufacturing approach.

A cost of goods comparison between an open process, a closed process as defined today, and a closed process of the future is shown in Figure 2. Cost of goods per unit goes from $200k to $97k to $66k, representing a significant reduction. The breakdown for each category of expense from the same study is shown in Figure 3. In summary, next-generation closed manufacturing technology could lead to a 30-35% reduction in cell therapy manufacturing cost per unit driven by better trained labor, greater clean room space efficiencies, and lower failure rates.[6]

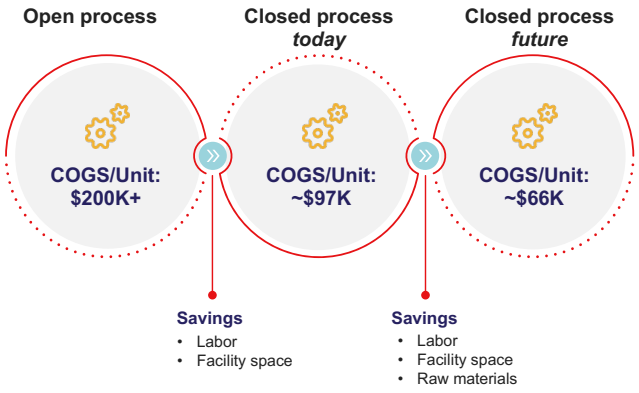

Figure 2: Potential reduction in cell therapy COGS per unit

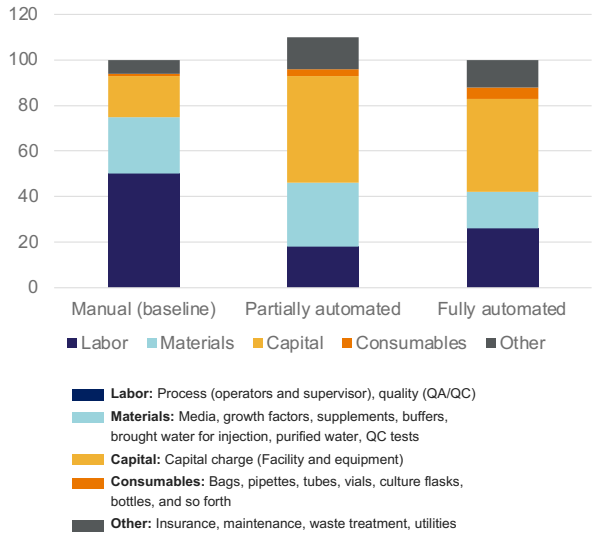

Figure 3: Summary of COGS breakdown per process

Even if manufacturers cannot fully automate immediately, gradual enhancements in automation should be strategically planned. This involves integrating modular systems that can be expanded and interconnected as the need for larger-scale production grows.[7]

Benefits of working with an integrated CDMO and CRO partner

By addressing industry challenges and implementing best practices, the future of cell and gene therapy clinical trials can become much more patient-centric, with opportunity for further optimization through partnership with an integrated CDMO and CRO provider. This enables a holistic approach to CGT trials, enhancing every stage of development and clinical processes. Integrated partners can provide comprehensive support from early development stages through commercialization, including access to GMP manufacturing capacities and predictable manufacturing timelines, which are crucial for the unique demands of cell and gene therapies (e.g., just-in-time solutions, on-demand manufacturing, etc.).

Integration also allows for the tailoring of manufacturing processes to meet the specific needs of clinical trials. This flexibility includes adjustments in batch size, customization for patient-specific treatments, and accommodating unique product requirements, all of which enhance the precision and effectiveness of therapies.

Reducing the number of handoffs across vendors simplifies logistics and optimizes supply chain management, resulting in more efficient timelines and cost savings. Better access to vendors and supplies through an integrated system leads to streamlined operations and improved pricing structures.

Another advantage of an integrated model is the feedback loop between clinical trials and manufacturing. Close collaboration with clinical researchers provides valuable feedback on patient outcomes and safety, informing improvements in product design, manufacturing processes, and quality control measures. This continuous loop of feedback ensures that products are constantly refined and optimized for efficacy and safety, while potentially reducing manufacturing costs.

Additional benefits include direct lines of communication, enabling proactive identification and resolution of potential delays or risks in manufacturing, and closer alignment with regulatory standards which reduces the risk of regulatory hurdles that can delay clinical development or commercialization. Additionally, enhanced data sharing between CDMO and CRO functions can reveal trends and opportunities for improvements in product quality and safety, as well accelerating time for product release and administration to patients.

Overall, an integrated CDMO and CRO approach represents a powerful model in cell and gene therapy development. This model not only streamlines processes and reduces costs but may also enhance the quality and efficacy of therapies, ultimately benefiting patients and accelerating the journey from clinical trials to market.

To learn more about Thermo Fisher Scientific's Accelerator™ Drug Development, 360™ CDMO and CRO solutions for cell and gene therapies, please visit:

Advanced therapy CDMO services

Cell and gene therapy CRO services

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