



Oncology and hematology studies

Key considerations for overcoming the complexities of oncology and cell therapy clinical trials

Seven critical factors that impact success

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Executive summary

Oncology clinical trials in general — and cell therapy trials in particular — are complex undertakings that present significant regulatory, operational and patient recruitment challenges to drug developers. And for the patients who participate in these trials, the therapies under investigation may present their last hope. With potentially life-saving therapies at stake, time is of the essence. Sponsors developing new cancer therapies are better positioned for clinical trial success when they partner with an experienced provider of oncology and cell therapy clinical research solutions. Ultimately, a trusted partner enables drug developers to accelerate timelines, mitigate risks, reduce patient burden, and achieve success with complex protocols, more safely and efficiently.

Positioning oncology trials for success

Oncology clinical trials are surging ahead of other therapeutic areas in terms of clinical activity volume, but a higher level of activity does not necessarily translate to a higher success rate. According to data from the U.S. Food and Drug Administration (FDA), oncology drugs have an overall 3.4% approval rate¹, with a vast majority of therapies often failing to gain approval due to drug efficacy or toxicity issues.

Beating the odds and getting therapies to the patients that need them requires sponsors to improve operational efficiency with innovative trial designs, strategies for early-stage decision making, and the early selection of candidate drugs with a high likelihood of success.² Many drug developers partner with a contract research organization (CRO) that offers the expertise and resources that are essential to overcoming the challenges associated with complex oncology trial protocols, including those for small molecules, immuno-therapies, and cell and gene therapies.

This white paper explores key considerations for sponsors navigating these complexities with the support of a dedicated CRO partner. By leveraging proven experience in devising and implementing clinical trial development strategies for complex oncology trials — including cell therapy trials — drug developers gain the perspective needed to successfully navigate:

- Barriers to enrollment and intense competition for qualified sites and patients
- Rapidly changing standards of care and clinical strategies, including an increased acceptance of innovative trial designs and master protocols
- Regulatory and payor requirements that necessitate higher data volume and collection and long-term follow-up



Seven key considerations for navigating the complexities of oncology and cell therapy clinical trials

Oncology and cell therapy trials involve many competing elements that must be prioritized to ensure these treatments get to the patients who need them. The intricate process can be convoluted, requiring sponsors to manage a delicate balancing act of many complicated factors — all of which have a bearing on trial success. Giving careful thought to and effectively planning for each of the following considerations enables drug developers to navigate challenges and enhance positive outcomes for their oncology and cell therapy treatments.

1. Understanding the patient experience and enrollment barriers

While drug development for other therapeutic areas may last, on average, eight years, oncology development extends for roughly 12 years, according to a report by the Tufts Center for the Study of Drug Development.³ The elongated timeline is a consequence of complex protocols, the larger footprint of the studies and the need to generate a higher volume of data. For cell therapy studies, the FDA advises sponsors to conduct long-term follow-up studies for an additional 15 years to monitor for any delayed adverse events.⁴

This extended timeframe impacts the overall patient experience, as participating in an oncology or cell therapy clinical trial presents a significant burden to patients and their caregivers. Beyond the long-term time commitment, sponsors must consider several additional factors that affect enrollment and how a patient engages with the study — provided patients have knowledge of and access to the study.

Trial participation is not universally accessible, even for the patients who would benefit most from being involved. Patients who live far from academic centers or have limited health literacy may not be aware of or fully understand the potential of investigational products (IP) being tested. These obstacles contribute to recruitment and consent challenges, as well, and particularly impact underserved or marginalized populations whose trial participation is historically low.⁵

The process for patients who have access and are potentially eligible involves a demanding series of assessments, consent forms, and preparatory medical procedures. This is especially true in early phase trials, which require participants to undergo pharmacokinetic and pharmacodynamic assessments. Each step is critical for generating the information that is needed for the study.

Clear communication and steadfast support are vital for patients to understand their role in the trial, know why certain tests are being done and empower them to make informed decisions about their care.

With the right CRO partner in place, sponsors gain an extension of their team that brings deep expertise and added empathy to the patient experience — especially in an early phase study. At this point in the drug development process, the experience for patients is complex, as sponsors work to capture as much information about them as possible in a short amount of time. An experienced CRO partner, like the PPD™ clinical research business of Thermo Fisher Scientific, will advise on which information is necessary to capture and make recommendations regarding operational factors, determining the best schedule of events for patient visits and assessments. Reducing or eliminating unnecessary visits and tests can be mutually beneficial for patients and sponsors — minimizing the patient burden and lowering sponsors' operating costs. Relying on a CRO to manage such administrative responsibilities allows sites and sponsors to spend more time focused on offering an optimal patient experience.

An expert CRO also reduces site burden and the administrative responsibilities of site staff through the implementation of digital and decentralized trial solutions that further improve the patient experience and drive operational efficiency. Our digital and decentralized solutions offer strategies for infusing hybrid and decentralized solutions into studies. Our experts provide sponsors with the breadth and depth of experience needed to deploy mobile sites, home health care visits, wearables and more — making patient participation more viable and less cumbersome.

2. Keeping pace with rapidly evolving standards of care and complex protocols

The standards of care in oncology clinical trials are continually evolving as research, technology and methods of patient-centricity advance. Add to that the changing regulatory environment — especially for first-in-human studies — and it is unsurprising that sponsors struggle to move their trials forward.

A critical step in advancing early phase oncology and cell therapy clinical trials is assessing the safety and potential efficacy of a new drug by determining the maximum tolerated dose (MTD), while minimizing patients' exposure to infra- or supra-therapeutic doses. As adaptive designs gain prominence, the way drug developers make this determination is changing. Sponsors must identify which method works best for their therapy — and which patients will benefit most. Various models are available that provide different approaches for achieving the MTD and offering the best experience to patients.

Model-assisted designs

Model-assisted designs, including Bayesian optimal interval (BOIN) and modified toxicity probability interval (mTPI) designs, have gained popularity as they outperform the traditional 3+3 design.⁶ Because BOIN and mTPI are governed by decision rules based on pre-specified target toxicity levels, they can better identify the correct MTD while offering increased flexibility with the cohort size. However, there are limitations, and these designs are best suited to trials testing four or fewer dose levels.

Continual reassessment designs

For trials needing to test more than four dose levels, the continual reassessment method (CRM) design is more efficient and typically requires a smaller sample size and shorter study duration. A CRM design models the probability of observing a dose limiting toxicity and continuously refines it during the course of the study. A key advantage is that all data from all dose levels are used to update the MTD estimation. The model is frequently updated and improves with accruing data, leading to better, more precise answers and increasing the chance of treating study patients around the MTD.

Bivariate CRM designs

Bivariate CRM designs facilitate the identification of the optimal biological dose based on a risk-benefit tradeoff between toxicity and efficacy. This design offers a dose escalation pathway for new immuno-oncology drugs, which have vastly different safety and efficacy profiles than cytotoxic chemotherapies.

Project Optimus

The FDA launched Project Optimus, an initiative to reform the dose optimization and dose selection paradigm in oncology drug development.⁷ This guidance addresses the challenges drug developers face and encourages the incorporation of a more comprehensive understanding of dose response and long-term tolerability, enabling them to make better informed decisions regarding the dose selection for their oncology compounds.

Dose optimization can occur within a seamless development program with careful planning, according to the FDA. Sponsors should seek a CRO with demonstrated experience collaborating with drug developers to choose the best design to accurately and cost-effectively determine a MTD. This allows studies to confidently move into Phase II as quickly as possible. As leaders in early phase oncology studies, our clinical, biostatistics and regulatory experts have extensive experience partnering with sponsors to successfully incorporate innovative and adaptive trial designs — often leading to cost savings and accelerated timelines.

3. Navigating intense competition for qualified sites

In a survey of drug developers, 42% ranked the increasing complexity of clinical trials as a top challenge facing their organization — the No. 2 challenge overall, surpassed only by patient recruitment.⁸ The number of cell therapy-accredited sites is limited, and the finite resources available at these sites are overburdened by the growing number and complexity of cell therapy trials. This scarcity creates an environment in which sponsors must compete for access to these sites and their resources, making securing partnerships with accredited sites a crucial factor in ensuring timely and efficient clinical trial execution.

Identifying, training and qualifying non-traditional research-experienced sites

Opportunities exist for drug developers to increase the number of accredited sites by identifying, training, and qualifying non-traditional research-experienced sites to run cell therapy clinical trials. At present, these sites are not equipped to manage complicated trials and lack the infrastructure necessary to provide the current cell therapy standard of care in their own communities. The establishment of additional cell therapy trial sites can be achieved with a focused effort on expanding the network of qualified sites and providing comprehensive training and support to ensure their readiness.

Increasing the number of community sites

The lack of community sites also fuels the competition for qualified sites. Many patients prefer to receive treatments in their own communities, where they are comfortable and have support systems in place. However, access to groundbreaking cell therapies is often limited to specialized centers, which can be far from patients, requiring travel and extended stays away from home. To overcome this, drug developers can establish partnerships with academic centers and community sites, facilitating the collaboration needed to expand access to innovative therapies and reduce the burden on patients and their caregivers, who would otherwise have to travel long distances for treatment.

Challenges in finding the right sites for oncology and cell therapy drug developers begin with identifying sites that have Phase I experience, along with enrollment capabilities to meet recruitment goals. The PPD clinical research business has longstanding relationships with a vast site network and the proven ability to meet enrollment goals. As an experienced provider of clinical research solutions, we understand site selection must be targeted, and possess the know-how to innovate when circumstances require a creative approach. And once sites are selected, we leverage our technology platforms — including artificial intelligence that taps into proprietary metrics — to combine extensive patient recruitment and site performance data with predictive models and advanced analytics.

When sites with cell therapy experience aren't accessible, an ideal CRO partner will respond to the challenge by training more sites to support these complex studies. Our clinical research experts implement strategies to identify, train and qualify non-traditional research-experienced sites and increase the number of community sites. For more sites to provide these capabilities, we know collaboration is needed between cell therapy experienced CROs, sponsors, academic sites, payors and regulators.

To that end, our SiteCoach training program provides solutions for:

- Next-generation cell therapy-experienced oncologists at academic sites who are considering careers in communities without cell therapy expertise
- Community oncologists, site staff, research nurses and study coordinators who want on-site training sessions at academic sites, the lessons from which they can bring back to their community hospitals
- Hospital administrators who are willing to get the training necessary to bring complex cell therapy treatments into their hospital systems
- Community sites that need assurance from insurance carriers that they will receive adequate reimbursement for standard of care comparator arm treatments and for cell therapy treatments given as standard of care

4. Finding the right patients

Attracting and retaining the ideal patient population requires targeted strategies to raise awareness among patients and health care providers about the potential benefits of participating in oncology and cell therapy trials. When devising these strategies, it is important to remember that although these therapies may represent the last hope for patients to gain access to life-changing treatments, attitudes toward them vary.⁹ The right CRO partner will offer comprehensive support and enable sponsors to overcome barriers to enrollment with solutions tailored to alleviate patients' concerns. Our patient concierge services and collaborations with patient advocacy groups are just some of the resources available to ensure the right patients are aware of and enroll in studies.

Leveraging biomarkers for patient selection

Identifying the right patients early on in immuno-oncology studies — particularly those who are likely to respond favorably to treatment — is crucial for the success of these trials. By determining biomarkers that can accurately predict patient response, sponsors can better prevent and manage toxicities associated with these therapies, enabling better patient outcomes more quickly.

For meeting recruitment goals for trials using or requiring biomarkers, Thermo Fisher's OncoPrint platform offers state-of-the-art technology for fast profiling and next-generation sequencing of key biomarkers and comprehensive genomic profiling, ensuring the right patient population is participating in the trial. As an added bonus, sophisticated data-mining tools like OncoPrint enable drug developers to consolidate and streamline workflows, providing a 24-hour turnaround time, higher sensitivity and potentially higher detection yield — and, most importantly, better patient outcomes.

5. Implementing a cohesive approach to operations and logistics

Other operations and logistics considerations must be prioritized concurrently with site selection, patient enrollment, and study design, including the chemistry, manufacturing, and controls (CMC) process for the IP. Sponsors are encouraged to engage with a CMC-authoring subject matter expert as quickly as possible to ensure a validated, reproducible process is in place. Further, a CMC gap and risk analysis is advised to define the best strategy for overall development and manufacturing.

When it comes to the operational elements of complex autologous therapies, the smallest hiccup — logistically or operationally — can have enormous downstream effects on the patient and the trial. The cold chain requires a deep understanding of the robust global infrastructure needed to

successfully transport cells between locations and provide just-in-time delivery to patients. Unlike small molecules or antibodies, there isn't a backup if something goes wrong with the manufacturing, storage or administration of the therapy. These living cells must be precisely managed to maintain optimal potency — they can't be frozen and thawed at random.

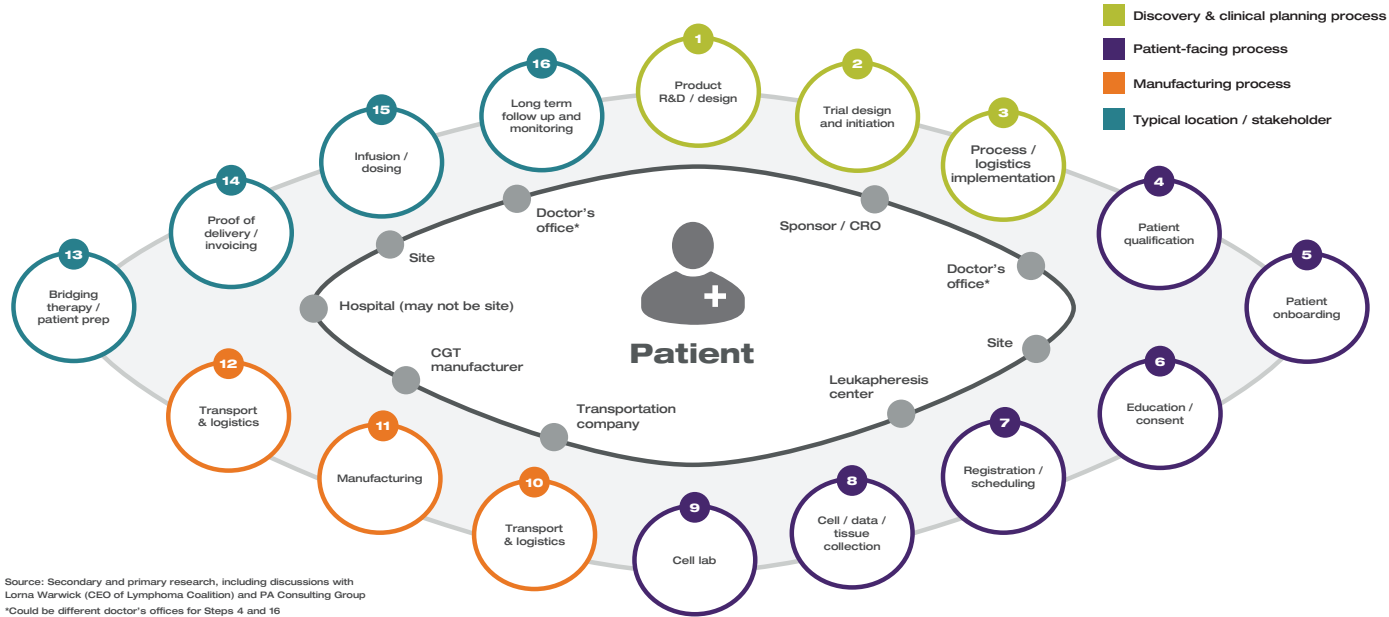
Additionally, the vein-to-vein time is long for autologous cell therapies using viral vectors for gene modifications, considering manufacturing and the time it takes to get therapies back to patients. This may result in the need for bridging therapies while patients wait for their cells to be delivered. Some patients may develop disease progression during this time and never receive their manufactured cells, demonstrating what's at stake with the time-sensitive nature of these therapies. And while some allogeneic therapies can alleviate some of these challenges, sponsors may need guidance for how to incorporate these into their trials.

Because manufacturing and administration of the therapies are so nuanced, drug developers should seek expertise in managing these elements to avoid delays to studies' timelines and detrimental effects on the overall success of the study and, potentially, patient outcomes. A CRO partner with a built-in contract development and manufacturing organization (CDMO) can enable sponsors to seamlessly integrate development,

manufacturing and clinical research services. This reduces the complexity of managing multiple vendors and ensures consistency and quality control throughout IP development and clinical trial management. This combination also facilitates more bespoke solutions to meet specific trial needs, enhancing trial efficiency and cost-effectiveness.

Like the PPD clinical research business, the Patheon™ pharma services of Thermo Fisher Scientific support sponsors in ensuring success with IP availability, especially to meet the critical first patient in milestone. Together, we work with sponsors to provide best-in-class CRO and CDMO services, while always keeping an eye toward the future. For instance, we are actively innovating to find manufacturing approaches that increase cell therapies' potency with a longer duration of antitumor activity and without increased toxicities.

Those working in our dedicated clinical logistics monitor role possess a deep understanding of global logistics for the shipment of vein-to-vein autologous therapies from the manufacturing site into the clinical sites — providing a unique benefit to sponsors and patients. This highly trained specialist is an expert in logistics, entirely focused on safeguarding and maintaining the critical chain of identity, chain of conformity and chain of custody for these therapies.



6. Understanding the need for higher data volume and collection

The personalized approach of oncology and cell therapy treatments necessitates detailed, patient-specific data collection to assess the impact of the IP on each participant. The consideration of factors such as patient characteristics, disease state, immune response and treatment outcomes requires a substantial volume of data.

Because of the unique nature of oncology and cell therapy trials, rigorous monitoring for potential adverse events — including both acute and long-term toxicities — must be prioritized. Robust safety monitoring requires comprehensive data collection on adverse events, laboratory values, and other safety parameters to ensure patient safety and to accurately assess the risk-benefit profile of the investigational therapy.

For example, cell therapies involve the manipulation and administration of living cells to patients — which can have complex and diverse mechanisms of action — so it's imperative to understand the behavior, persistence and function of these cells. Extensive data collection is essential for evaluating their safety, efficacy and long-term effects. Further, FDA¹⁰ and European Medicines Agency (EMA)¹¹ guidelines often mandate extensive data collection to ensure the scientific validity and regulatory compliance of the trials.

Biomarker analysis is often incorporated to identify patient subgroups that may benefit from specific treatments or to assess treatment response. This analysis involves collecting additional data, such as genetic or molecular profiling, to better understand the underlying biology and enable personalized treatment approaches.

With the support of an experienced and knowledgeable CRO, sponsors are better positioned to navigate the complexities of the shifting data volume and collection standards. The data and real-world evidence experts of the PPD clinical research business empower drug developers to effectively manage and collect the volume of data required for all phases of oncology and cell therapy clinical trials. Our efforts ensure that sponsors conduct trials efficiently, maintain data quality and meet regulatory requirements.

7. Navigating stringent regulatory and payor requirements

Regulatory bodies and payors are on the receiving end of much of this collected data, through the submission of regulatory documents that include Investigational New Drug applications, Investigational Medicinal Product Dossiers and New Drug Applications.

Beyond these submissions, regulators require long-term follow-up studies for oncology and cell therapy studies to collect extensive data on patient outcomes, including disease progression, survival rates, adverse events and quality of life measures. This data is typically collected over an extended period — up to 15 years or longer, depending on the IP — to capture the long-term effects of the treatment.

Payors play a significant role in determining the reimbursement and coverage of oncology and cell therapy treatments. Before providing coverage, payors require detailed evidence of the long-term benefits and cost-effectiveness of these therapies. The long-term follow-up data is essential in demonstrating the sustainability of treatment outcomes and to justify the economic value of these interventions.

Payors and health authorities have increased their expectations, demanding more and better evidence of a product's value, safety and effectiveness. Sponsors are wise to seek scientific advice from regulatory authorities and experts who have access to regulatory intelligence early in the drug development process. By doing so, they can align their trial designs, endpoints and data collection strategies with regulatory expectations, reducing the risk of regulatory hurdles and delays later in the process.

As a provider of clinical research solutions with a team dedicated to data collection and real-world evidence, we are equipped to provide sponsors with the expertise needed to navigate regulatory guidance and guidelines and create submissions that move their products forward. And to supplement data from sponsors' studies, we extract valuable insights from more than 100 data sources across more than 20 countries in North America, Europe, South America and Asia.

Choose the right provider of clinical research solutions to overcome complexities and achieve success

The complexities of oncology clinical trials aren't going away, but strategies exist to enable sponsors to overcome them, allowing them to make critical decisions faster and with more accuracy. A strong CRO partner — like the PPD clinical research business — empowers drug developers with the end-to-end solutions and capabilities they need to alleviate challenges and realize safer and more cost-effective oncology and cell therapy studies, with speed.

With lives on the line, we offer expertise in managing the operational elements of complex therapeutics. This experience prevents delays in study timelines and contributes to the overall success of the trial — and provides the best opportunity for, patients to prolong their lives.

You don't have time to lose

Let's work together to overcome your trial's complexities. Get started now at ppd.com/oncology.

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