Fortrea

CELL AND GENE THERAPY WHITE PAPER

Fortrea's cell and gene therapy operational solution.

Introduction

Delivering a successful cell and gene therapy (CGT) trial requires many coordinated operational solutions spanning site selection and patient recruitment to monitoring and long-term follow-up. As our team at Fortrea has gained experience and contributed to the advancement of both FDA-approved gene replacement therapies and FDA-approved cell therapies, we have established a dedicated infrastructure and expertise in the CGT arena.

To help emerging biotech and large pharmaceutical sponsors execute their CGT studies, this white paper shares our insights, lessons learned and best practices. Learn from Fortrea clinical trial team members and subject matter experts as they discuss their strategies for advancing complex CGT studies, such as autologous/allogeneic cell therapies, neoantigen DNA vaccines and T-cell engager therapies.

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1. Cell and Gene Therapy (CGT) studies: smart CGT study execution

Fortrea Senior Director, Project Management

Question: What can a Fortrea partnership offer to companies wanting to expedite the safe delivery of their oncology CGT to patients and obtain quality data to support each step of their clinical development plan to market?

Answer: At Fortrea, we engage with the sponsor early in the journey, listening and offering tailored CGT operational solutions to meet the needs of the study protocol and the selected patient population. Our key priority is to ensure our services will complement the sponsor's expertise and capabilities. The study's operational strategy, as well as risk and mitigation plans—created by a CGT subject matter expert (SME) team—are reviewed and flexibly adjusted on an ongoing basis by regular assessment to ensure incorporation of environmental changes.

We follow our standard CGT processes and train the sites to ensure successful patient enrollment and navigation of the logistics by leveraging our expert logistics team and specialist vendors. Those processes reflect learnings from our CGT portfolio, experience with pre-IND (Investigational New Drug Application) discussions with regulators and complex patient treatment pathways on CGT studies.

Our focus on patient recruitment, safety and quality data draws on our deep experience and decades of success from our medical, safety and operational CGT teams. We offer specific decentralized clinical trial (DCT) solutions and patient-centered materials to help reduce the burden and support the patients throughout their CGT study, especially during the long-term follow-up (LTFU) part of a study. To support the CGT development journey, we also offer pre-clinical, laboratory solutions as well as regulatory and commercialization expertise.

2. Optimal CGT study design

Fortrea Associate Director, Project Management

Question: What considerations should be made when optimizing a CGT protocol?

Answer: The design of early-phase clinical trials in CGT differs from that of other trials due to the distinctive elements involved; these include a patient population's inclusion/exclusion criteria, specialized screening procedures, cell or tissue collection, lymphodepleting or bridging chemotherapy, slot availability and manufacturing considerations, safety management and long-term monitoring requirements.

The inclusion and exclusion criteria requirements of CGT studies can be restrictive or challenging for study recruitment. Patients are often excluded for any viral infection or autoimmune disease due to risk of reactivation. In addition, in CGT studies that require patients to go through apheresis and a lymphodepletion regimen prior to infusion of the CGT, the patient must continue to meet all inclusion/exclusion criteria.

In some trials, the time between cell collection and product administration can be lengthy (up to two months), and although a patient may meet the study enrollment criteria when the tissue or cells are first collected, the patient may no longer meet those criteria at the time of product administration. Close communication and review of protocol criteria among the sponsor, investigator and medical monitor along with rigorous review of the patient's history and medical

records by the investigator and site staff is crucial to ensuring patient viability for the duration of the study participation. Detailed communication and eligibility review should be outlined in the medical plan.

For autologous products or patient-specific allogeneic donor products, unique product lots are manufactured for each subject and potentially for each dose a subject receives. For such products, the inability to control factors such as subject-to-subject variability can contribute to product complexity. Some CGT products may take several weeks to months to produce, limiting the availability of manufacturing capacity and the number of patients who can receive treatment. Fortrea logistics coordinators work closely with the lab responsible for the study's drug manufacturing along with the Fortrea clinical team to closely coordinate and communicate among the site, sponsor and manufacturing teams regarding cell shipment. In addition, the logistic coordination team works closely to understand if/when there are delays to manufacturing that could impact the patient.

Another critical consideration of CGT studies is safety management and the monitoring of specific safety issues that may be anticipated with CGT products. Such safety issues might include acute or delayed infusion reactions, autoimmunity, graft-versus-host disease, new malignancies, transmission of infectious agents from a donor or viral reactivation. There are often complex management requirements of the toxicities associated with CGT studies as well as more frequent safety events (Cytokine Release Syndrome [CRS] and neurotoxicity events).

Managing complex safety monitoring often involves:

- Offering standardized training to sites
- Establishing clear communication pathways
- Defining response time for sites to the clinical medical monitor
- Engaging the investigator through close contact with the medical monitor
- Training patient caregivers to manage toxicities outside the clinic setting
- Optimizing medical comorbidities

Because the CGT products are designed to achieve permanent or lasting effects long after the dose administration is complete, monitoring of the safety profile and pharmacologic activity is required for a substantially longer period than traditional studies. Regulations mandate LTFU on patients to identify late-stage effects. Design of the long-term assessments should be made with the patient burden in mind, for example, by:

- Reducing visits and/or implementing remote visits (annually if possible)
- Keeping assessments to a minimum
- Using real-world or decentralized means for data collection

Fortrea has developed a decentralized clinical trial adapted solution to reduce the patient burden of participating in trials and accommodate patient needs. This can include physician televisits to electronic collection of eConsent, patient diary data (electronic patient-reported outcomes (ePRO), electronic clinical outcome assessments (eCOA) and protocol visits performed at the patient's location.

3. Patient-centric solutions
Fortrea Senior Director, Project Management

Question: How can patient-centric solutions support the success of a CGT clinical trial?

Answer: Our team's primary goal is to improve patients' lives by bringing them life-changing therapies in a compassionate way. Our dedicated global Patient Recruitment and Engagement team provides added support from the start to ensure that we engage patients and their families while supporting sites to appropriately consent, educate and maintain compliance with protocol requirements.

In CGT studies, which often experience a high screen failure rate, the process of screening and eligibility needs to be explained to patients so they not only understand the reasons they may be suitable for the trial but also understand the reasons they may not be suitable—both can be life-changing. The patient study journey, including the LTFU, can be complex. We need to help patients understand what is involved and know that we consider their desires and needs as their condition progresses. We believe that retention starts at consent, ensuring the patient has a clear understanding of the study rationale and the requirements upfront, is motivated to commit to the study and is educated on the importance of compliance for the overall study success. We provide the information in a patient-friendly way, which can include:

- A combination of study awareness materials and educational tools
- Tailored informed consent media
- A study welcome pack
- A study overview flip chart
- A visit calendar

Other bespoke materials can be created depending on the trial and genetic counseling can also be organized.

Presenting the study effectively to patients will be paramount to successful study delivery. At Fortrea, we make sure our outreach communication and patient-facing materials are all developed to be inclusive. We work with sites to promote diversity in their recruited patients by addressing implicit bias and ensuring all study communications are inclusive in their language (health literacy and learning preferences) and visuals (representative of the patient population). The Fortrea team can also support sponsors to develop a race and ethnicity diversity plan that helps enroll participants from underrepresented populations as recommended by regulators.

4. Regulatory expertise

Fortrea Senior Manager, Regulatory Submissions

Question: How do you navigate the complex labyrinth of the CGT regulatory process?

Answer: Our regulatory team at Fortrea supports all regulatory activities—from conception of a regulatory strategy for CGT studies, including all necessary competent authority interactions and discussions, to submission and evaluation of market authorizations, as well as post-approval activities globally. We have a proven track record of success in global regulatory submissions in the CGT field and regulatory agency interactions, such as:

- Scientific advice discussions
- Discussions before the Clinical Trial Application [CTA]
- Orphan drug designation negotiation
- Pediatric plan development

Our regulatory SMEs are managing a constantly evolving CGT regulatory environment across North America, Europe and Asia Pacific. While we follow the standard regulatory process in participating countries, trying to proactively streamline an approval timeline, we also carefully assess differences in how the product modality is perceived and treated by local agencies.

The Fortrea team supports our CGT sponsors through pre-CTA meetings with national authorities that do a thorough review—especially if there has not been any scientific advice interaction initiated well in advance of the CTA submission. In some countries, assessment of the GMO (genetically modified organism) component is done as part of the CTA, but in most countries, this is done via a separate submission.

Additionally, therapies that allow expedited approval pathways require a sound understanding of the best ways to implement an efficient clinical development plan. The Fortrea regulatory team designs adequate regulatory strategy to reinforce the justification for expedited development of CGTs to the authorities. We are focusing on unique features of the CGT, patient population involved and on an application of these to the clinical studies in each targeted malignancy. The regulatory team proactively addresses key topics usually questioned by regulatory agencies and ethic committees/institutional review boards; these topics include:

- Manufacturing and safety aspects of the CGT
- Management of leukapheresis if involved for autologous products
- Blood and tissue procurement processes
- Administration of product within a short time window
- Post-infusion follow-up (with a focus on the patient's safety in the CTA/Investigational Medicinal Product Dossier [IMPD] submission letter and package to avoid questions and comments from regulators and prevent possible delays in the approval process)

Each study and CGT product is unique, and the regulatory team determines the appropriate regulatory strategy for each country participating in a study, considering the regulatory framework in all regions involved as well as the availability of CMC (Chemistry, Manufacturing and Control)/IMPD documentation for all regions involved.

5. Cell journey: logistical orchestration

TrakCel Project Manager

Question: Why has cell orchestration become so common within the CGT sector and how does TrakCel's OCELLOS solution addresses challenges in the cell journey for autologous therapies?

Answer: OCELLOS is a cell orchestration platform (COP) and as such was initially developed to safeguard both chain of identity (COI) and the tight timelines within the personalized cell therapy supply chain. When early cell therapy products such as Dendreon's PROVENGE® were being reviewed for commercial launch, the FDA stated clear concerns around the orchestration of the fragile supply chain managing patient-specific products with a short shelf life that required very specific shipping and handling. These concerns went on to significantly delay the drug approval until Dendreon could demonstrate sufficient, robust tracking methodology and infrastructure within the supply chain to assuage fears that large-scale production of the therapy was unviable.

Electronic orchestration systems have now become the de facto norm for most of the CGT sector, particularly as trials scale up, as most developers acknowledge that the supply chain processes are too complex and unwieldy to orchestrate manually without vast amounts of paperwork and admin support, both at the time of processing and at the point of audit.

Technology is no more a sector to stand still than CGT, and recent years have seen general expectation of how technology can support supply chains increasing greatly. From live tracking to online portals for booking and scheduling logistics, there are many tools that when brought together give supply chain teams better visibility and control. Personalized CGT can draw benefits from this as it allows stakeholders to manage the critical steps in the therapy journey closely, ensuring each patient is delivered their therapy safely and quickly. To harness this technology, the integration landscape is becoming critical, and it is undoubtedly a challenge for therapy developers who may be using many third-party systems as well as various business systems that hold data critical to progressing the therapy journey. Consequently, secure and robust data connectivity is becoming a big focus for many clients.

While technology progresses rapidly, the changes in the CGT landscape over recent years have been staggering, with more methodologies and treatment types coming to trial, each with their own supply chain steps and models. Second-generation COPs like OCELLOS have evolved alongside the industry and are built to allow them to precisely match the processes of the therapy they support.

Each OCELLOS deployment begins with a detailed discovery phase where the therapy process is mapped, and all the elements that are going to be written into automated workflows are documented. Third-party integrations are scoped, and detailed user profiles for each of the stakeholders within the supply chain are created and married with access and data permissions to keep the system and the data within safe and secure. Through this process, the client support team works alongside the therapy developer to understand where custom configuration or steps may be required. An example of this was an autologous gene editing therapy targeting genetic blood disorders, which required multiple apheresis collections to generate sufficient cell volumes. Each collection needed to be treated independently but run in tandem with a second cell collection process that made for a particularly complex chain of identity (COI) and chain of custody (COC) as multiple lots will eventually combine into a single infusion.

The OCELLOS solution was configured to accept and track these multiple apheresis collections via unique apheresis IDs relating back to the patient identifier and lot number, tracking information such as cell counts through the manufacturing process. Retaining the information for these individual lots, such as that relating to the transit, manufacturing and storage of the various lots and the

final combined therapy is necessary as part of the audit trail for the patient. In this case, the OCELLOS scheduling system also helps healthcare providers offer clarity to patients that are managing multiple appointments, and mapping the relationships between prescribing healthcare centers and corresponding apheresis centers made the process simpler for healthcare users booking these appointments.

To facilitate ease of use for all users in the supply chain, the dashboard, which the apheresis center users see, shows all the patients, even those from multiple treatment centers. This results in a COP with a standard infrastructure, making it cost-effective to own, support and develop as therapy needs change, with a custom configuration that maps it to the process precisely.

TrakCel has been able to support many therapies that have quite specific needs, such as repeated patient screenings, multiple indications or patient groups, cell matching cycles or multiple collections of starting materials. The ability to automate these steps into a process that guides users through the right steps in the right order ensures critical information is in place and distributes information over the supply chain as needed in real-time—a critical process to successfully managing these therapies with time-critical logistics.

6. Cell journey: Phase I dose escalation studies

Fortrea Clinical Trial Lead

Question: What logistic solution can you offer to small Phase I dose escalation studies involving CGTs with a limited patient population?

Answer: As described above, in complex studies such as autologous cell therapies but also other types of CGTs (e.g., DNA vaccines, T-cell engagers), logistical oversight and management of the product delivery to sites are critical. Each step in the process—from scheduling a patient visit to processing and transporting biological samples, tracking manufacturing, conducting Qualified Person (QP) Release and getting samples back to the investigative center—is crucial for patient safety and successful execution of the CGT study.

Given our experiences on small Phase I studies with limited patient population/sample size, we offer simple, lean solutions that are robust at the same time, involving our logistic coordinator— who takes full responsibility for all steps in the process for sample and CGT product management—and all participating vendors contributing to the logistic solution.

The logistic coordinator develops a comprehensive process map for logistic management of apheresis, blood/tissue samples and the final CGT product. Additionally, the coordinator, jointly with our clinical research associate (CRA) team, conducts a “dry run” to test the shipment process for all participating sites to ensure the site team is comfortable and confident with the processes required for shipping of cells/tissue or receiving and storing product at a site.

For cell therapies, the Fortrea team involves our partner service, QuickSTAT, who are particularly experienced in frozen shipment supply of clinical specimens for clinical trials and support our projects delivering cryopreserved CGT products to our clinical sites. The logistic coordinator within our clinical team serves as the main point of contact for sites to order investigational product and oversee management of the timelines for fulfilling the orders of frozen specimens. By accessing QuickSTAT technology, the logistic coordinator supports timely coordination of apheresis with available manufacturing slots for studies with autologous CGTs.

The availability of open manufacturing slots serves as the basis for the leukapheresis dates as well as the screening periods. The logistic coordinator communicates availability of a manufacturing slot, as well as communicates shipping announcements of blood samples or availability of CGT. The manufacturing site informs the logistic coordinator about intermediate and final results of the manufacturing process; this information is shared with sites by the logistic coordinator.

Prior to the delivery, the site must ensure that the appropriate staff members are available to receive the cell therapy and that the staff members receiving the cell therapy have subject source documents containing demographic information to be able to confirm the subject identity. Every step in this process is tracked and documented by the logistic coordinator, and data are shared with all stakeholders involved in the process.

7. Selection of right CGT sites: performance and quality

Fortrea Senior Project Manager

Question: How do you ensure the correct CGT sites with all required capabilities (autologous/ allogeneic studies) are selected for a CGT study, sites that deliver patients, data and quality?

Answer: One of the most important factors to ensure success of a CGT study is identifying the "correct sites" with the required capabilities (e.g., apheresis), access to the patient population defined by a protocol, and the capacity and resources to participate in the study. Our key strategies in the site selection process at Fortrea involve utilizing a smart feasibility assessment approach that taps into our broad knowledge base of preselected sites. This includes current and historic work experience, startup and submission processes and timelines, and performance data derived from our systems focusing on patient numbers and data quality.

Once the preselected site list has been finalized, the site outreach process is initiated with the establishment of confidentiality agreements. This process can be very lengthy with numerous legal reviews, but with our network of partner sites, this process is expedited due to the previously established agreements. The next step in the outreach process is the development of a feasibility questionnaire sent to the sites along with the protocol or protocol synopsis. The principal investigator and the site staff can carefully assess their ability to perform complex procedures that are a part of a CGT study.

Each cell and gene therapy trial is unique. We create, together with the medical monitor and clinical team lead (CTL), a detailed feasibility questionnaire that documents the patient pathway reflecting all requirements of the CGT and the protocol. Each site must demonstrate they have access to the targeted patient population and the understanding that some CGT studies require very complex prescreening steps, which may include:

- Human leukocyte antigen typing/profiling
- Lymphodepleting chemotherapy
- Rechecking subject eligibility before actual dosing
- Coordinating all processes defined by the study protocol

We also consider the needs related to:

- Managing apheresis (autologous products)
- Storing the cryopreserved allogeneic therapy
- Securing support from all other departments required (lab, pharmacy, transplant center, surgical department)
- Managing resources to closely monitor patients 24/7 during treatment and the post-infusion period

Once the site has completed the feasibility questionnaire and indicated they are interested in participating in the study, the project team evaluates the need for a pre-study visit (PSV), which may be performed if the site:

- Is new with a limited historic data set
- Has undergone substantial changes from the previous PSV
- Has not participated in a Fortrea study recently

Our goal in the site selection process is to ensure—together with the sponsor, medical monitor, CTL and CRA—that we have clearly identified the correct sites that can quickly enroll eligible patients into a study. Whether we are supporting a Phase I dose escalation study with multiple cohorts and basket design or larger Phase II CGT study, we must also mitigate all risks that could potentially delay enrollment.

8. Streamlined CGT startup process

Fortrea Startup Project Manager

Question: Can you describe what startup tactics you apply to complex CGT studies?

Answer: We start by mapping out the local site process for all selected CGT sites with our local teams. This involves the submission and approval requirements, timeline, contract negotiation, and additional internal site approvals that contribute to overall approval timelines. We prepare the necessary documents for submission to various types of committees involved.

On a weekly basis, we share a progress update with the detailed site-level plan and the submission process with the sponsor and the vendors involved in the planned site activations. Due to experience gained during the COVID-19 pandemic, we are accustomed to responding to a rapidly changing environment. We can be very flexible and suggest nonconventional ways of delivering our startup tasks. These coordinated efforts help streamline site activation for the selected sites as we hold weekly teleconferences with study coordinators at sites and quickly answer any questions to gain understanding of how to best promote rapid site startup.

In addition to the mapped individual site submission and activation plan, we provide for autologous CGT products' personalized logistics for each site. Oversight is provided by the logistic team, which accounts for study-specific processes and requirements of the cell therapy involved. We ask our sites to commit to early contract negotiation, submission deliverables and activation timelines. Relationship building is key; therefore, before initiating the startup process (after we receive a site approval from a sponsor) our startup team schedules an introductory call with each investigator participating in a study, which establishes site-specific details around the process, timelines agreed with a site and study startup deliverables.

9. Site training and support: addressing site-level complexities

Fortrea Clinical Trial Lead

Question: Can you describe strategies you implement to ensure adequate site training on CGT trials?

Answer: To ensure sites are adequately trained on CGT trials, the Fortrea team provides comprehensive training to sites during the site initiation visit (SIV) and throughout the trial, as needed.

Due to the complexity of CGT trials, sites often face challenges in understanding the protocol requirements, screening procedures, Investigational Medicinal Product (IMP) preparation and dosing scheme, associated adverse events (AEs) and critical sample collections.

The Fortrea team is well versed in developing site-ready training toolkits, which provide several key considerations for CGT studies. These tools include Fortrea CGT templates/checklists, mapping the process of conducting patient visits, sample collections and a "dry run" (e.g., apheresis shipment, IMP delivery). The Fortrea team also develops a patient treatment pathway document to ensure compliance with all protocol-required activities such as screening, patient treatment and follow-up of the associated AEs. The sites, along with any departments involved in study conduct, receive training material on:

- Signs and symptoms associated with the infusion of the T-cell product
- Education on the AEs of cytokine release syndrome and neurotoxicity
- Grading of AEs
- Data entry in the electronic data capture (EDC)
- Collection of critical samples

Additionally, the Fortrea CRA team proactively assists sites in understanding which samples are required and where they are shipped.

Fortrea also recognizes challenges sites may face during staff turnover. The team creates a subject tracking tool and sample collection tool and proactively reminds sites of upcoming subject visits and critical sample collections that will take place. This streamlined process aids the site in preparation for the upcoming visits and collections and ensures continued quality of the study, even during staff changes. Fortrea CRAs offer support to the new site staff by checking in and assessing if further training is needed using comprehensive and easy-to-understand materials to review with the sites and document accordingly on training logs. These training materials can also be used during regular monitoring visits, as needed.

10. Patient recruitment: CGT strategies and limiting factors

Fortrea Associate Director, Project Management

Question: Can you describe how you proactively manage patient recruitment in CGT studies, especially in situations when recruitment has not gone according to the initial recruitment plan and projection?

Answer: The ability to find, recruit and retain patients in CGT clinical studies—very often involving rare patient populations with high screen failure rates and later-line treatment options—is becoming increasingly challenging and expensive. The recruitment effort in our CGT studies requires a strong collaboration between our Fortrea project team and the sponsor (operational and manufacturing teams) and cooperation of all functions, all of which contribute to efficient and effective patient screening processes, enrollment and retention planning. The project manager is ultimately responsible for the execution and delivery of a project, ensuring all resources and tactics designed to ensure recruitment and retention are effectively utilized. With clinical trial lead (CTL), the project manager develops a study-specific recruitment plan that includes all key strategies to recruit patients in cohorts and dose levels in a timely manner, and identifies suitable recruitment vendors, as necessary, to support the recruitment strategy and for any contingencies. CTLs and CRAs then create a tailored site-level recruitment plan for each site.

Several contingencies can be considered for inclusion in a CGT recruitment plan. These include:

- Referral networks for each participating site supporting prescreening of rare patient population
- "Booster" recruitment calls and visits conducted by Fortrea medical monitors and/or CRAs (with optional sponsor attendance)
- Increased monitoring frequency
- Lessons-learned investigator Webex meetings with principal investigators presenting their patient cases and site recruitment tactics (with our project team supporting content development for those meetings)
- Ad hoc tumor board meetings scheduled with a focus on study patient population
- Regular teleconferences where sites can provide feedback directly to Fortrea project management, CTLs and the sponsor
- Ongoing site education and sharing of study-related materials and publications developed for conferences or other events
- Study reference tools and fact sheets, which are available for site initiation visits, can be provided to referring sites as well

The Fortrea clinical team, including the CTL and CRAs, liaise proactively with sites, Fortrea project management and the sponsor if recruitment is behind. They can help implement contingencies based on triggers (e.g., a site without a screened subject one month after activation, high screen failure or dropout rate, issues in patient dosing) defined in the recruitment plan. It is critical to account for these possibilities, especially if the CGT manufacturing process offers only a limited number of manufacturing slots monthly; in such a case, Fortrea needs to ensure every available manufacturing slot is utilized.

Thorough site identification and principal investigator engagement is essential during feasibility. Sufficient and robust site education also supports recruitment as eligible patients may be rarely seen and site teams need to understand where to identify potential patients. There is always a limited patient population defined by CGT protocols; therefore, implementation of referring healthcare professionals equipped with key study information is a must.

In our experience at Fortrea, the best way to increase recruitment, compliance and retention is regular contact with the study team. Regular contact means frequent and meaningful discussions sharing advice on recruitment challenges the site is facing, as well as providing support, lessons learned from other successful sites, educational materials, motivational tips and appreciation. This is how we guide our CRA team interacting with sites and ensuring a site's attention to a study.

11. CGT medical monitoring
Fortrea Senior Medical Director

Question: How is your medical team supporting CGT programs?

Answer: The Fortrea medical team appreciates the fast pace of CGT clinical development and rapidly evolving environment with frequent protocol amendments. To deliver scientifically valid recommendations to a sponsor in this area, we have established a team of medical directors dedicated to oncology CGT. The team includes physicians in the Americas, Europe and Asia Pacific, with expertise in CGT for both hematologic malignancies and solid tumors.

With a deep understanding of immunology and oncology, the team uses shared experience to support projects with CGTs. This ensures the continual integrated medical-scientific oversight of CGT studies, enabling us to deliver these in line with the sponsors' timeline, scientific and quality expectations. Our medical team provides a range of services to sponsors with a heavy focus on CGT products and related topics and on strategies allowing our sites to successfully enroll required patient populations according to a protocol, supporting sponsors with dosing decisions and data reviews.

Each study has a dedicated medical director who is focused on providing continuous medical oversight, ranging from study planning, support of protocol development through enrollment and all other parts of the study life cycle. The medical director regularly interacts with the sponsor and investigative sites to discussing protocol requirements, review eligibility of individual patients, and monitor the patient journey through the study, including dosing, safety monitoring, tumor response and LTFU to ensure the desired study endpoints are met. The interactive team approach of our oncology CGT medical team throughout the study ensures that any potential issues that often plague CGT clinical studies are identified and managed early before they become a problem that could impact subject safety or the ability to meet the study objectives or timelines. This involvement results in improved subject safety together with improved medical-scientific validity and quality of protocols and data.

12. Clinical database and data cleaning
Fortrea Director, Project Management

Question: Are there any specifications to think of when building the database for CGT? How do teams prepare for numerous data sweeps?

Answer: Our Data Management (DM) team uses the existing CGT Case Report Form (CRF) Library and CRF modules validated for specific indications, which help streamline the database build. Also, when building the database, the team encourages programmable deviations to assist with capturing all that occurs and flagging trends.

For CGT studies, it is imperative for the experienced CGT clinical team to assist with database testing and help identify potential holes within the database build. Flexibility in the initial database build must be one of priorities for the DM team considering the high number of amendments, frequent changes in the CGT database related to new cohorts added, protocol design revisions and other changes impacting the database structure.

When approaching data sweeps (safety cohort reviews, publications, development safety update reports, interim or final analysis), the team needs to proactively manage availability of site staff and come to an agreement on data cleaning timelines. After completion of the first data sweep, the team reconvenes to determine trends in data, queries and update CRF guidelines to assist sites and teams with future data sweeps.

Prior to database locks, the team should work to have principal investigators reset passwords at least a month in advance to mitigate a risk of a database lock being delayed due to missing investigator signatures. The team needs to ensure sufficient time is dedicated to data cleaning planning and phone discussions with sites to walk through queries and questions during these sweeps.

Our clinical team understands the intense burden on the sites for data, especially in the first few months of each patient's participation in a CGT study (screening, treatment and post-dosing periods generate significant amount of data) and during dose escalation, with frequent data reviews. The sites, data management and clinical teams must ensure the data are current for all the required data reviews to support important study decision-making processes. We are implementing reporting and data tracking solutions to define the most efficient and effective data cleaning strategy, transparently sharing the plan with a sponsor and sites. This strategy enables us to review the patient data earlier and streamline an overall data delivery timeline.

13. Site monitoring: CGT complexities

Fortrea Clinical Research Associate

Question: Can you describe how the complexities associated with monitoring a CGT clinical trial affect the approach to site management and monitoring?

Answer: When working on CGT studies, specifically autologous cell therapies or gene therapies with complex dosing schemes, there are numerous points of contact and systems that are needed for the efficient and effective delivery of manufactured cells/product to a patient. Points of contact include, but are not limited to, the apheresis nurses, the study coordinator, study nurses, cell infusion staff, lab sample shipping staff, data coordinators, and, of course, the principal investigator and co-investigators.

Beyond the points of contact, there are typically several systems being used. This can include central imaging, various central and specialty labs with specific shipping instructions, the EDC database, the manufacturing slot scheduling platform and shipment tracking.

With systems also comes access requests; there is quite a bit to balance as a CRA. Therefore, staying organized is one of the most important factors to being successful. Organization can come in various forms, but we have found it most helpful to ensure that the Clinical Trial Management System is up to date with contact information and study roles for all site team members. Central tracking for site staff is also useful in tracking credentials and protocol training to ensure information is up to date at each monitoring visit.

In addition to organizational skills, developing a close relationship with the site eases communication and decreases response time. Taking the time to learn each site's processes for monitoring and understanding the workflow within the site's institution can save headaches once patients are being dosed. We know that each site works a little bit differently and it's our job as the CRA to keep them aligned with the protocol.

For tracking new potential patients, open, proactive and regular communication is key. Cell therapy studies that have a prescreening phase can be challenging to track. Often, the prescreening process is managed outside the EDC database and it is critical to collect the information from sites in a timely manner. The Fortrea team has created a thorough patient tracker for patients in prescreening who are pending eligibility confirmation and have not yet moved on to the screening phase of the study. Keeping track of patients ensures that not only do we have control over the flow of patients to manufacturing and dose escalation slots, but we can also track our alignment to study enrollment goals.

To obtain screening updates, we typically send out a weekly recruitment email requesting updates on patients in prescreening or any potential new patients. We then follow up on individual subjects with sites and patients ready for the next manufacturing slot. In addition to weekly emails and ad hoc discussions, we work to meet with the site coordinator at least biweekly via Webex. This gives us the opportunity to work through any issues they're having with patients, EDC and data entry, local and central lab results, pending site action items, etc. The meetings can be as short as five minutes, or it can be as long as an hour. Again, open communication and developing a relationship with each site makes CRA life much easier and helps to keep all sites satisfied and successful in terms of patient enrollment.

The treatment scheme in CGT studies may differ significantly for various cell therapies or gene therapies. A good example would be a CAR T study where patients are typically treated with CAR T-cells only once or twice during their treatment phase and the majority of study monitoring visits occur within the first 28-56 days of the patient screenings. This means a bolus of data entry for sites, which also translates to a significant amount of SDV for CRAs when a patient is enrolled/dosed.

Additionally, the likelihood of a patient experiencing a severe adverse event (SAE), adverse event of special interest (AESI), or dose-limiting toxicity is exponentially higher within these first few weeks, which also contributes to the large amount of data. Therefore, our CRA approach is to proactively schedule monitoring visits in anticipation of a patient being dosed and schedule the visits with increased frequency for a few months following patient dosing to ensure that SDV backlog does not build up. Additionally, sending the site metrics with pending data entry and queries will also help keep the site on track to meet data entry goals. For our studies, sites are typically sent metrics on a weekly/biweekly basis and every day before planned data extracts.

Since many of our CGT studies are early phase studies, there are numerous cohorts as we try to identify the Phase II dose, which means a high number of data extracts to review data for individual cohorts. This requires proper planning and open communication with sites. Sending sites metrics on a weekly basis, planning out monitoring visits and ensuring that ongoing action items are addressed in a timely manner means that sites are not unprepared for the high frequency of data extracts.

Furthermore, in cell therapy studies, there are typically sponsor-specific forms that must be completed for each patient in addition to numerous eligibility checkpoints: pre-apheresis (or blood/tissue collection), pre-chemo conditional therapy, after bridging therapy and pre-infusion/dosing. Having an understanding for what is expected to be collected at monitoring visits is critical. Reviewing these forms, providing them in a timely manner to a sponsor and ensuring that they meet ALCOA+ guidelines is necessary at each monitoring visit, and such forms are often utilized as a source for SDV. As with any protocol, it's also important to ensure that the CRA knows the AESIs, AE/SAE monitoring window, dose-limiting toxicities (DLT) definitions and the specified treatment for expected AEs, such as cytokine release syndrome and neurotoxicity.

It's essential that the CRA verifies patients are receiving the treatment specified in the protocol when applicable to ensure patient safety. Patients may experience numerous AEs, so it's imperative for a CRA to take the time to comb through electronic medical records to reconcile data with the AE log and EDC to ensure all safety data are being captured appropriately.

While our site management and monitoring approach is not all encompassing, it provides a glimpse into some of the complexities a CRA may experience throughout a CGT study. There is a lot to keep track of, including moving parts, so it's important to stay organized, have open communication with sites, and take the time to learn the protocol and processes.

14. Central and bioanalytical laboratories for CGT studies
Fortrea Senior Director, Project Management

Question: How can assay development timelines affect First Patient In timelines? Are there benefits to using central versus local labs?

Answer: It's important to get an early draft of the schedule of assessments so that the lab team can start to provide feedback on which unique assays will need to be developed and validated. This is especially important for first-in-human studies where the assays support inclusion/exclusion criteria. For assays that are exploratory or are used to support endpoints, it may be possible to collect and hold the samples until validation is complete.

For central versus local labs, the simple answer is: it depends. For Phase I, we usually recommend that as many assessments as possible are performed locally. Because there are usually unique assays needed to support CGT studies, there will invariably be some that do not make sense for local labs to perform; therefore, central specialty labs must be utilized. For Phase II and III studies, it is recommended that everything except safety labs be performed centrally to ensure consistency in laboratory data presented to regulators later.

15. Long-term follow-up: a key part of the CGT development process
Fortrea Project Manager

Question: How are you managing LTFU parts of your CGT programs in terms of patient retention, tracking, etc.?

Answer: Patients who have received genetically modified investigational product under a study protocol should be asked to roll over upon either premature discontinuation from, or completion of, a study and participate in an LTFU part for up to 15 years after their dosing. LTFU data reporting is required by agencies (both FDA and EMA), so LTFU protocol compliance is key. However, it can be difficult to achieve if, for example, physicians are looking to the next possible treatment for their patients. In addition to the regulatory requirement and collection of safety data, survival and disease progression as important endpoints require thoughtful planning from the outset of a study.

This begins with active site management and continued engagement throughout the life of the study. Learning the nuances of how each site will handle LTFU can also help your team plan how to maximize compliance from the sites, the patients and, most importantly, the patients' caregivers. For instance, if a site typically assigns a single coordinator to handle LTFU patients on a given study, a CRA can coordinate with that team member to establish a regular update process, as well as reminders for patients with upcoming LTFU visit windows.

Another process that sites can implement is the use of telemedicine and electronic patient outcome forms. This allows for greater patient retention due to the unnecessary burden of travel, allowing for better patient quality of life. Sites, patients and CRAs can also use a shared portal to gather, complete and extract data in real time. Trust can be established on both sides through clear expectations and predictable communication, which creates an effective partnership with sites.

Our project team and a sponsor need to secure commitment from sites participating in a CGT study to adhere to LTFU protocol requirements at the time of patient discontinuation by emphasizing the regulatory expectations, data needs (focusing on safety) and benefit to the wider patient community by collecting long-term data. In our current CGT programs, patients are living well into and beyond the planned LTFU periods. As a result, some CGT portfolios have decided to roll over multiple studies into a unified LTFU (non-treatment standalone) study. It is important to review the particulars of this rollover process and then establish best practice guidelines with each site. Some studies may require a separate consent form prior to entering the LTFU period; if this is the case, this discussion needs to take place with the patients not only at the onset of the main treatment study but immediately when transitioned to the LTFU part.

Overall, the key to efficient delivery of both LTFU data and rollover to LTFU protocols is establishing guidelines with our sponsors as early as possible. In some cases, sites may be asked to bring patients in early for an "unscheduled" visit to expedite transition to an LTFU protocol. This requires proper planning and coordination operationally at the individual patient level across both treatment and LTFU parts of the CGT programs.

16. The role of an experienced CGT study team

Fortrea Project Manager

Question: Can you explain how you prepare your teams to conduct a CGT trial? How are your teams benefiting from shared experience across Fortrea?

Answer: Our CGT team at Fortrea is made up of both established SMEs, as well as the future leaders of tomorrow. To ensure that all CGT teams are equipped with the best knowledge and experience available, Fortrea has enlisted a core team of CGT experts who share their expertise across the CGT portfolio. This is done through training seminars and training sessions when initiating a new CGT protocol, as well as through numerous guidance documents detailing best practices and lessons learned from previous or ongoing studies. Fortrea has also gone to great lengths to ensure that all team members involved in a CGT trial are given training through real-life scenarios taught by the experts who have lived it.

Providing continual support and guidance shows the team that we are invested in their growth and development in an area of constant change and upheaval. Conveying these shared experiences forms the cornerstone of our best practice education and ensures future studies stand on the building blocks established from our prior experience.

In our partnership with sites, we can provide training to help walk the site team through the unique study processes, from data management, through safety reporting, to Investigational Product (IP) logistics and more. We want to ensure sites have the tools needed to enable smooth, clean delivery for the patients and our data. This should include a thorough review of site capabilities during pre-study visits (PSVs), as well as review of site regulatory complexities, mapping out the timing of leukapheresis, blood draws, tissue, shipment, management of different types of CGT products (autologous, allogeneic, gene therapies or DNA vaccines), IP administration and more within the site.

We then assist at any step of the process to adjust as necessary if accommodations need to be made or if changes arise from protocol amendments, as we've witnessed an average of eight protocol amendments per study across our CGT portfolio. Providing training and support for our CRAs when a study is rolled out or during an amendment is also key. The CRAs are the link to the sites, and being able to assist a site shows engagement and the importance of the site's work. By establishing clear lines of communication through the sponsor, Fortrea team and site, we ensure the appropriate stakeholders receive the information they need, when they need it—without delay.

17. Vendor management on CGT studies

Fortrea Senior Director, Project Management

Question: For those functions that aren't directly provided by Fortrea, how can sponsors be assured that the right external vendors are selected and held accountable for these complex studies?

Answer: Our vendor selection process places quality and accountability at the forefront. It is important specifically in the complex CGT study environment with multiple vendors involved contributing with data to key decisions at the patient or study level (e.g., screening process, pharmacokinetics/pharmacodynamics or imaging data). The clinical sourcing team takes the lead on negotiating the contract terms and scope of work specific to each CGT protocol.

The clinical sourcing team also manages performance of each vendor at the enterprise level. For our contracted vendors, there is a robust qualification/requalification process governed by Fortrea standard operating procedures. The project manager and the Fortrea delivery team are responsible for day-to-day oversight and performance tracking at the project level, which ensures the study's operational solution is well orchestrated across all vendors involved by transparent communication and our governance process. This includes tracking deliverables and managing weekly, monthly and milestone key performance indicators. Specific vendors needed for CGT studies vary but commonly include premium courier services, central imaging, specialty labs and a logistics platform provider as well as typical vendors such as printers, EDC and meeting planners.

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