



A Blueprint for Success in Cell and Gene Therapy Trials

Best Practices Drawn from Decades of Experience





Managing clinical operations for cell and gene therapy (CGT) trials, including graft-versus-host-disease (GvHD) studies, is complex and specialized. Ensuring a smooth trial that protects patient safety and produces quality data requires a team of experienced project managers, clinical data managers, biostatisticians, monitors, and pharmacovigilance specialists.

This expertise goes beyond CGT terminology; the team must have in-depth knowledge of the clinical procedures involved and the associated demands on, and risks for, patients. They must also be able to anticipate the appropriate clinical response. In GvHD trials, this includes accurately staging and grading GvHD.

Such knowledge ensures the right data is collected, minimizing errors and maintaining data quality throughout analysis and reporting. This expertise cannot be gained “on the fly” without risking data integrity and delaying development.

In over three decades of supporting CGT trials, Emmes has developed tried and true tools, methods, and processes that mitigate risks and speed trial operations. We appreciate the exigencies of clinical development in CGT for the benefit of patients and work to ensure that nothing stands in the way of advancing science toward that end.

Here we share the best practices we’ve used in successfully partnering with sponsors on more than 125 CGT trials.

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BEST PRACTICE #1 Selecting the Right Trial Design



The goal of a trial is to generate clean, robust, and conclusive data. This requires careful planning, and input from those familiar with the data's end-use to shape the trial design and protocol.

Emmes' project leaders and specialists ensure trials capture the necessary data for regulators, payers, and health technology assessors, preventing complications later in the trial. CGT trial designs must consider patient and site feasibility and the existing standard of care.

Examples of common designs in CGT trials include:

- Multicenter, double-blinded, randomized, controlled trials comparing two therapies
- Safety run-ins with staggered enrollment to assess early toxicity; adjusting enrollment and dose escalation based on results
- Randomized, open label, multicenter trials with parallel-cohort run-in phase
- Open-label, controlled, multicenter, international, randomized studies

Ensure Practicality and Feasibility

Designing a CGT trial requires balancing statistical rigor with what is feasible for patients, who are often in poor health and must undergo invasive procedures.

Biostatisticians help determine what data is necessary and feasible, especially in small patient populations where every data point matters. They also determine the minimum number of subjects needed for statistically significant results, considering withdrawals, randomization factors, and enrollment rates.

CGT trials may also benefit from adaptive designs, allowing for pre-specified changes based on interim analyses. These might include adjusting sample size, dosing, or even discontinuing an arm. The design should also account for patient dropouts as they may need to switch therapies.

Select the Right Endpoints

Selecting the right endpoints is critical to avoid regulatory rejection and delays in development. In CGT trials, endpoint selection can be particularly complex due to long timelines and other challenges. Mistakes made during design might not become apparent for years.

Challenges in Endpoint Selection

- 1 Comorbidities in CGT patients make it difficult to define endpoints that accurately measure treatment effects.
- 2 Safety and efficacy often overlap, requiring a careful balance between toxicity and efficacy.
- 3 Endpoints can involve nuances that must be carefully defined, as even small variations can affect the interpretation of results.
- 4 Small patient populations make it hard to select endpoints that show statistically significant results.

Emmes' multi-functional teams work collaboratively to recommend appropriate endpoints, addressing complexities from all angles.

From Design to Data Insights: Building Better eCRFs



Ultimately, the value of trial data depends upon the forethought, care, and discipline applied to its collection.

At Emmes, multiple functions collaborate to determine exactly what data will be collected, working backwards from the data points that will be analyzed to the questions that will elicit those data points.

The clinical data management team translates the desired data points into information for trial sites to input in the trial's data capture system.

Especially in stem cell transplant studies, questions range from simple “yes” or “no” answers to complex multi-tiered grading scales as those used to assess progression in acute GvHD.

This makes it essential to craft data collection tools that are not only scientifically rigorous but also user-friendly for sites.



Objectively Stage and Grade GvHD

GvHD is a secondary endpoint in stem cell transplantation studies and a primary endpoint in studies of treatments for GvHD, both acute and chronic—making it critical that it's assessed accurately and consistently. Developing the forms to collect data on staging and grading GvHD requires familiarity with the terminology and experience in studying the condition.

To streamline the collection process and control the quality of the raw data needed to stage GvHD properly, Emmes has developed very specific questionnaires and forms for investigators to use.

We have augmented and perfected them over a span of 20 years, amassing a full library of time-tested assessment questions to choose from. These are designed to require minimal modifications between studies, saving significant time. For any given study, the protocol team, safety managers, clinical data managers, and biostatisticians collaborate to recommend the forms that will best capture the necessary endpoints.



BEST PRACTICE #3

Maintain High Data Quality Throughout Your Trial



Thoroughly Prepare for Data Collection

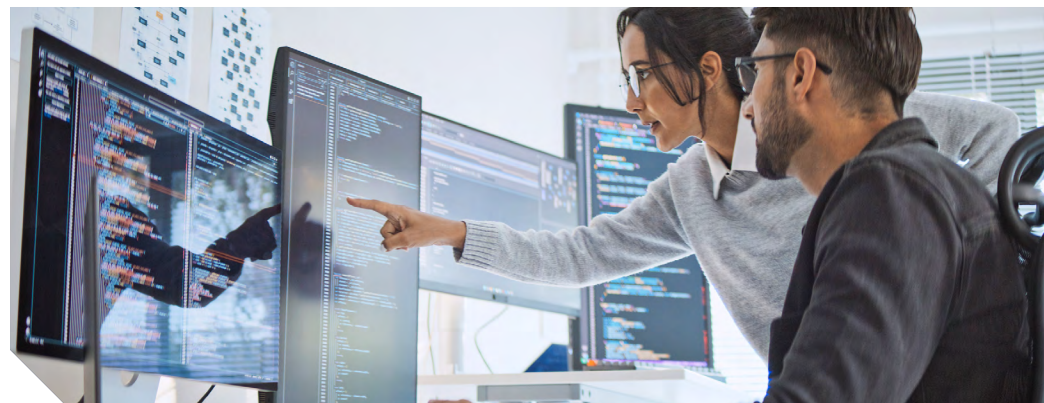
Clinical data managers should review each protocol to ensure trial systems capture the required data accurately. They can advise on specifying milestones that align with system capabilities, like clarifying if “one month post-transplant” means four weeks or 30 days. This precision ensures consistency across trial sites and supports accurate data analysis.

In addition to aligning protocols, effective data collection relies on well-designed questions in case report forms. Poorly phrased questions can confuse site staff, leading to non-random missing data, which ultimately impacts data integrity. Tools must include edit checks to prevent data entry errors, allowing only valid and logical values to be entered for CGT patients, reducing the risk of discrepancies and minimizing rework during later trial stages.

Cleanse the Data of Discrepancies and Anomalies

Data managers must also understand CGT protocol nuances to differentiate between expected and unexpected results. Their expertise is vital in resolving issues like determining whether a patient qualifies for platelet engraftment, which requires no transfusions within the past seven days. If a conflict arises—such as the data showing a transfusion six days prior—data managers must trace the issue back to its source and work with the site to correct it.

Ensuring that discrepancies are resolved quickly is essential to maintaining the accuracy of the data submitted to regulatory agencies and preventing delays in trial timelines.



Centralized, On-Demand Data Monitoring

As trial data increasingly comes from multiple sources, relying only on programmatic checks for transcription errors isn't enough.

Emmes is developing a system that visualizes trial data in real-time, leveraging machine learning and statistical methodologies to detect anomalies and outliers across various data sources. This system flags any unexpected, illogical, or questionable results for immediate investigation, allowing for quick corrective action. For instance, if a patient's neutrophil count spikes in the lab data but their reported outcomes suggest a decrease, the system will identify this inconsistency and alert data managers for further review.

By using this centralized, real-time data monitoring approach, Emmes ensures that issues are detected and resolved quickly, preventing them from becoming systemic. This not only maintains the quality of trial data but also accelerates database lock, reducing trial timelines and improving overall trial efficiency.



BEST PRACTICE #4

Prioritize Logistics for Patient Safety

The patient journey in CGT trials is complex, requiring precise coordination between multiple stakeholders to ensure every step is executed as planned. CGT therapies are individualized, meaning any errors in linking products to patients could have severe consequences.

Study Managers and Clinical Logistics Managers Must Work Together to:

- Secure manufacturing slots for the cellular product
- Schedule patient apheresis
- Coordinate specialized courier transport of extracted cells to manufacturers and then back to the site
- Ensure the site and patient are ready for infusion
- Confirm receipt of the cellular product, ensuring no temperature excursions
- Follow up to confirm the patient received the infusion and is being monitored

Centralized Inventory Management

A centralized system is essential for tracking biospecimen and product inventory. It provides visibility from collection to administration or storage, automating quality control and reducing errors, while providing real-time visibility into the supply chain.

This system spans clinical sites, labs, repositories, shipping companies, and manufacturers, consolidating all biospecimen data in one place and minimizing discrepancies between clinical and laboratory data.

Reducing Risk through Automation

- On-Demand Visibility** Good systems provides real-time visibility of biosamples and cellular products, capturing the full history of transfers, specimen lineage, and issue management in one system. Integration with EDC ensures closed-loop tracking and allows search by study or participant details.
- Patient Safety** Continuous monitoring of cellular products ensures critical treatment steps proceed without delays. Temperature tracking and shipment alerts prevent spoilage that could compromise patient care.
- Chain-of-Custody Preservation** Barcoding and scanning during shipping and receiving creates an audit trail, ensuring provenance of products and correct linkage to patients.
- Improved Quality** Built-in quality checks reduce errors in labeling and handling, eliminating discrepancies between clinical and lab records and minimizing specimen loss or damage.
- Efficiencies** Automating specimen processing and tracking eliminates manual tracking and reconciliation, speeds up shipment handling, reduces time spent querying statuses, and accelerates database lock.



BEST PRACTICE #5

Leverage Specialist Insights for Data Analysis

Data analysis in every study is prescribed in a Statistical Analysis Plan (SAP), which outlines the methods used to analyze data, compare results, and manage missing data.

The SAP must be finalized before the first analysis to avoid biasing study results. Given the complexity of CGT studies, the biostatisticians drafting the SAP should be experts in the therapeutic area.

Correct for Missing Data

Missing data can result from many situations. In CGT studies, given their heavy patient burden, some amount of missing data is inevitable for several reasons—like a patient missing a scheduled visit, incomplete quality-of-life questionnaires, or a sample that was destroyed. Procedures and statistical methodologies must be in place to address and account for missing data, because any missing data from a study involving a small population (which could be only a dozen patients) can have a tremendous impact on the results, biasing the interpretation of outcomes.

Account for Small Patient Populations Statistically

Studies involving small patient populations often don't fit the normal distribution curve. Biostatisticians use specialized tests such as the Mann-Whitney U test or Fisher's exact test to analyze results, ensuring statistical validity despite the small sample size.

Biostatisticians have various techniques for coping with missing values, and there is no “one size fits all” approach. Statisticians must apply the most appropriate methodology for each situation, choosing from among many options including:

✓ Last Observation Carried Forward

This method can be used when repeated measures have been taken over time. The last observed value prior to the missing value is used to fill in the missing value.

✓ Imputation

This involves replacing an absent value with one that fits into the pattern established by the existing data points.

✓ Censoring

Addresses a situation in which a value or observation is only partially known, either because the event occurs outside of the study period or because a value occurs outside the range of the measuring instrument.

Statisticians also perform sensitivity analyses to gauge the impact of missing data and ensure the techniques used for managing it don't distort the results. All versions of these analyses are presented to regulators.

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BEST PRACTICE #6

Regulatory Expertise and Robust Research Networks



Because the CGT field is advancing rapidly, staying current with regulations around the world requires a dedicated focus and will increase the likelihood of success with novel approaches to optimize the project development schedule.

Emmes maintains regulatory affairs staff around the world to advise on International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines and country- and region-specific submission requirements. Their expertise can be instrumental in developing a regulatory strategy, supporting trial operations, and preparing regulatory submissions.

Additionally, Emmes maintains close working relationships with the pre-eminent clinicians and key opinion leaders (KOLs) in the CGT space. These relationships afford us first-hand knowledge of any regulatory changes, serve as a resource for clinical knowledge, and give insight into developments and future directions in the field.



Emmes also collaborates with the Center for International Blood & Marrow Transplant Research® (CIBMTR), which is a research collaboration between the Medical College of Wisconsin (MCW) and NMDP (formerly the National Marrow Donor Program). We also work closely with the National Heart, Lung, and Blood Institute (NHLBI), part of the NIH.

Most notably, Emmes is a member of the Blood and Marrow Transplant Clinical Trial Network (BMT CTN) which coordinates clinical trials in cellular therapies across a large network of centers in the US.



BEST PRACTICE #7

Harnessing Technology to Improve Trial Outcomes

Emmes is committed to innovation and to adopting technology (including Artificial Intelligence [AI] and Machine Learning [ML]) to improve the efficiency of various processes in all trials, to include those in CGT and GvHD.

We have already begun or envision using technology to:



Build Studies with the Power of AI

Using natural language processing techniques (NLP) in combination with AI, our Veridix AI platform enables rapid study start-up. We are digitizing clinical trial protocols into structured data elements, finding and re-deploying eCRFs and edit checks from more than 1,000 prior clinical trials and study builds, and building new eCRFs and edit checks based on the digitized trial protocol. This approach minimizes human error and reduces build timelines by up to 30%.



Draft Consent Forms

Based on samples from analogous protocols, AI will be able to prepare the first draft of informed consent forms.



Improve Diagnostic Accuracy

AI and machine learning techniques can be combined to differentiate between pathologies and accurately classify disease. Continued research and refinement of AI-driven diagnostic models holds the promise of further enhancing diagnostic accuracy and expanding the scope of personalized medicine.



Prepare Reports

AI, using NLP, can be taught to pull information from patient narratives and prepare summary reports. Emmes is building an interactive reporting capability for on-demand custom reports, using NLP and AI.



Automate Patient Follow-Up

CGT patients must be followed for 15 years, a time-consuming process for sponsors and a burden for inactive trial participants. Emmes can use EHR data to automatically gather information on their health status, eliminating the need to track down trial participants for clinic or televisits.



CASE STUDY

Using Advanced Machine Learning to Improve Clinical Diagnoses

The National Heart, Lung, and Blood Institute's National MDS Natural History Study, spearheaded by Emmes, used advanced ML in an effort to redefine how myelodysplastic syndrome (MDS) is diagnosed.

By fusing AI and genomic sequencing data from 1,298 patients, we were able to create a sophisticated diagnostic classifier. Unlike traditional methods reliant on subjective pathology reviews, this AI-driven model analyzes mutational profiles from 18 genes to predict myeloid malignancy and differentiate MDS from other malignancies. Through meticulous development and training using ML, the classifier achieves unprecedented levels of accuracy.

Whether used independently or with traditional methods, the classifier has profound implications for patient care. It significantly reduces diagnostic discrepancies between local and central pathology reviews, ensuring consistent and reliable diagnoses.

Ultimately, it empowers clinicians to make more informed decisions regarding prognosis and treatment pathways.

Conclusion

CGT trials, including those measuring GvHD as a primary or secondary endpoint, are extraordinarily complex from a clinical operations standpoint—and in turn with respect to collecting, analyzing, and reporting the trial data.

One of the most effective strategies a sponsor can employ is to rely on a team of project managers, clinical data managers, biostatisticians, monitors, and pharmacovigilance specialists who have deep background in the therapeutic area and work collaboratively to recommend a successful approach.

Together, they can bring their past experiences, specialized knowledge, and commitment to innovating with technology to bear on solutions for trial design, data collection, managing data quality, data analysis, and regulatory compliance.

The stakes for all involved—patients, sponsors, and investigators—are too high to leave any detail to chance or to overlook a nuance. In this therapeutic area, experience and best practices most decidedly matter.

For additional information on our Cell and Gene Therapy services, please visit www.emmes.com