Emmes

A Blueprint for Success in Cell and Gene Therapy Trials

Best Practices Drawn from Decades of Experience

Table of Contents

Introduction 03

BEST PRACTICE #1
Selecting the Right Trial Design 04

BEST PRACTICE #2
From Design to Data Insights: Building Better eCRFs 08

BEST PRACTICE #3
Maintain High Data Quality Throughout Your Trial 12

BEST PRACTICE #4
Prioritize Logistics for Patient Safety 16

BEST PRACTICE #5
Leverage Specialist Insights for Data Analysis 20

BEST PRACTICE #6
Regulatory Expertise and Robust Research Networks 23

BEST PRACTICE #7
Harnessing Technology to Improve Trial Outcomes 25

Conclusion 27

Introduction

Managing clinical operations for cell and gene therapy (CGT) trials, including those for graft-versus-host-disease (GvHD), is extraordinarily complex and highly specialized.

Ensuring a successful trial—one that runs smoothly, protects patients' safety, and produces quality data—requires a team of project managers, clinical data managers, biostatisticians, monitors, and pharmacovigilance specialists who are experienced in the therapeutic area.

This expertise goes far beyond being familiar with 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.

For GvHD trials, this means the team must understand how to stage and grade GvHD accurately.

Such detailed knowledge is essential to ensuring that the right data are collected; errors in data reporting are minimized; and the data are cleaned, analyzed, and reported properly. The necessary expertise cannot be gained "on the fly" without jeopardizing data quality and the development timeline.

There is no room for errors arising from the misunderstanding of the many intricacies and nuances associated with CGT treatment and data.

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

BEST PRACTICE #1

Selecting the Right Trial Design

Trials are, of course, a means to an end: clean, robust, conclusive data. It is therefore essential that those who understand the expectations for the data have input into the trial design and the protocol.

What precisely must the data demonstrate and how will it need to be presented? Our project leaders, clinical trial data managers, biostatisticians, and pharmacovigilance specialists can offer valuable insights to help ensure that the study will capture what is needed for regulators, health technology assessors, and payers. Their recommendations at this early stage can help prevent unnecessary complications and obstacles in later stages of the trial.

The best design for a given study will depend upon what is appropriate and feasible for patients and sites as well as on the existing standard of care (SOC). A product intended for a first-line setting will likely be tested against the SOC in a blinded, randomized trial. A treatment that will be introduced as a third-line therapy may, instead, be tested in an open-label, single-arm trial. Below are some examples of designs commonly used in CGT trials:

- A multicenter, double-blinded, randomized controlled trial that compares two therapies; patients randomly allocated at a 1:1 ratio to treatment arms
- A study that includes a safety run-in with staggered enrollment to assess for excess early toxicity; if certain toxicities occur, the safety run-in will be expanded; and once the final dose is selected, additional subjects will be enrolled with a potential for dose de-escalation
- A randomized, open label, multicenter trial with an initial, randomized, open-label, parallel-cohort run-in phase
- An open-label, controlled, multicenter, international, randomized study

CGT studies may be good candidates for adaptive trial designs that allow for changes based on interim analyses for efficacy or futility. It may be, for example, that based on early results a trial arm is shut down, that the sample size needs to be adjusted based on the treatment effect being seen, or that dosing must be adjusted. Any plan to adapt the trial would have to be pre-specified in the trial design.

The trial design should address the likely dropout issues that will arise should CGT patients need to move to a different therapy due to non-response or a worsening condition. In some situations, crossover designs can be considered.

BEST PRACTICE #1

Selecting the Right Trial Design

Ensure Practicality and Feasibility

When designing a CGT trial, a balance must be found between what is needed to achieve statistical rigor and what is possible and bearable for CGT patients, as they are generally in very poor health and must endure invasive procedures to receive CGT.

Sponsors should strive to minimize the burden on CGT patients by collecting only the data needed to answer the statistical question at hand.

Biostatisticians experienced in CGT trials can advise not only on what makes sense with regard to the data required but also on what is feasible in terms of sample size. This is especially important in CGT studies as the number of patients is usually small, which increases the value of every data point.

> Biostatisticians will determine the minimum number of subjects needed to achieve statistically significant results, taking into account a number of details such as subject withdrawals, randomization factors, recruitment realities, and enrollment rates in analogous trials.

Select the Right Endpoints

Failure to select the right endpoint can have disastrous consequences for any trial. Regulators might reject the protocol, causing a delay in the entire development program. Or worse, in the end, the data could fall short of what is needed to support approval and reimbursement.

In CGT trials the stakes are especially high, as endpoint selection is muddied by several realities—not the least of which is that these trials tend to be long-term studies. If a mistake is made in the design phase, it may not become apparent for years.

BEST PRACTICE #1

Selecting the Right Trial Design

Some challenges to endpoint selection in CGT trials include:

1 Confounding factors at play that can invalidate the link between cause and effect. Typically, patients taking part in CGT and GvHD trials are seriously ill, have endured arduous procedures as trial participants, and have a number of comorbidities. In CGT trials in particular, response variables are subject to multiple different factors with complex interactions. Therefore, it can be challenging to unambiguously define the endpoints that will measure the effect of the treatment being studied.

2 Safety and efficacy may be interwoven in the same endpoint, unlike in other therapy areas where safety and efficacy are separate measures. Because subjects in CGT trials are being treated for a serious condition, there is a balancing act to be made between toxicity and efficacy that doesn't exist in, for example, vaccine trials in healthy volunteers. Thus, statistically, there is not always a clean delineation between safety endpoints and efficacy endpoints; they map overlap.

3 Deep understanding of the space is required to be able to compute measures accurately, even when they aren't computationally complex. For example, while it is straightforward to define "complete response" as "the absence of GvHD systems without additional therapy," one must be clear on which medications count toward additional therapy. Such nuances need to be recognized and addressed within the protocol and reiterated in the Statistical Analysis Plan (SAP).

4 A generally very small patient population, making it harder to select an endpoint that can actually be demonstrated in a limited pool of participants.

At Emmes, we take a multi-functional approach to recommending the appropriate endpoints.

Our biostatistics, medical, and clinical operations teams work collaboratively to look at the possibilities from multiple angles and build on our institutional knowledge gained over decades to address any complexities at the design stage.

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BEST PRACTICE #2

From Design to Data Insights: Building Better eCRFs

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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, we enlist multiple functions in a joint effort to determine exactly what data will be collected, working backwards from the data points that will be analyzed to what questions or input will elicit those data points.

Our clinical data management team translates the desired data points into the information that research staff at trial sites will be asked to complete in the trial's data capture system.

Especially in stem cell transplant studies, not every point that will be analyzed can be written as a simple question or field for inclusion in the case report form. Questions such as "Did the patient consent to the study?" require just a simple "yes" or "no" response on the part of the clinical investigator.

However, a question such as "Did the patient experience a progression in acute GvHD at any point in the study?" involves applying a multi-tiered grading scale following multiple assessments at several different timepoints.

Example of how to 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. It is, therefore, critical that the severity of GvHD be assessed accurately and consistently.

The severity of GvHD is determined based on a grading scale applied to diagnostic criteria first recommended by the National Institutes of Health (NIH) Consensus Conference in 2005 and later amended in 20141. The grading system requires a clinician to look at each affected organ (skin, lower gastrointestinal tract, upper gastrointestinal tract, and liver) to answer very specific questions about the patient's condition.

[1] Lee SJ. Classification systems for chronic graft-versus-host disease. Blood. 2017 Jan 5;129(1):30-37. doi: 10.1182/blood-2016-07-686642. Epub 2016 Nov 7. PMID: 27821503; PMCID: PMC5216262.

BEST PRACTICE #2

From Design to Data Insights: Building Better eCRFs

Objectively Stage and Grade Acute GvHD

These answers are entered into the trial's electronic data capture (EDC) system and used to assign a stage to the disease (Fig. 1). Then, the scores are compiled to assign an overall grade for acute GvHD (Fig. 2).

If stipulated in the protocol, an Endpoint Review Committee (ERC) is set up composed of Emmes biostatisticians and data managers as well as the protocol chairs who review the clinical data that requires further clinical interpretation.

Acute GvHD is evaluated at multiple time points during the trial, and a patient's acute GvHD grade may change throughout the study.

An example of how a patient's acute GvHD grades may change throughout a transplantation study is having Grade 2 acute GvHD at Day 14 post transplant, then increasing to Grade 3 acute GvHD at Day 42 post transplant, and then back to Grade 2 acute GvHD at Day 80 post transplant. An example of how a patient's acute GvHD grades may change in an acute GvHD treatment trial is a patient having Grade 3 acute GvHD at enrollment, then Grade 2 acute GvHD at Day 28, and Grade 1 acute GvHD at Day 56.

Figure 1: Accute GvHD Staging — Criteria for NIH Method

ORGAN	CLINICAL MANIFESTATIONS	STAGING [e]
Skin [a]	Erythematous, maculopapular rash involving palms and soles; may become confluent Severe disease: bullae.	**Stage 1:** <25% rash **Stage 2:** 25-50% rash **Stage 3:** generalized erythroderma **Stage 4:** bullae
Liver [b]	Painless jaundice with conjugated hyperbilirubinemia and increased alkaline phosphatase.	**Stage 1:** bilirubin 2-3 mg/dL **Stage 2:** bilirubin 3.1-6 mg/dL **Stage 3:** bilirubin 6.1-15 mg/dL **Stage 4:** bilirubin >15 mg/dL
Gastrointestinal tract [c]	Upper: nausea, vomiting, anorexia. Lower: diarrhea, abdominal cramps, distention, ileus, bleeding.	**Stage 1:** diarrhea >500 ml/day or persistent nausea, vomiting, or anorexia[d] **Stage 2:** diarrhea >1000 ml/day **Stage 3:** diarrhea >1500 ml/day **Stage 4:** large volume diarrhea and severe abdominal pain +/- ileus

[a] Use 'Rule of Nines' or burn chart to determine extent of rash

[b] Range given as total bilirubin. Downgrade one stage if a cause of elevated bilirubin other than GvHD has been documented

[c] Downgrade one stage if a cause of diarrhea other than GvHD has been documented

[d] Downgrade upper GI one stage if biopsy result is negative, or if no biopsy done and GvHD is not an etiology, or if the biopsy is equivocal and GvHD is not an etiology

[e] Although GvHD will be assessed at every protocol-specified visit, GvHD will only be analyzed if it occurs after primary neutrophil engraftment. If GvHD is not an etiology for any organ, then GvHD is downgraded to stage 0.

Figure 2: Acute GvHD Grading — NIH Method

OVERALL GRADE	SKIN	LIVER	GUT
I	Stage 1-2	None	None
II	Stage 3 or	Stage 1 or	Stage 1
III		Stage 2-3 or	Stage 2-4
IV	Stage 4 or	Stage 4	

BEST PRACTICE #2

From Design to Data Insights: Building Better eCRFs

Developing the forms to collect data on staging and grading GvHD requires familiarity with the terminology experience and in studying the condition.

The learning curve is too great to entrust the work to those who don't know, for example, the precise definition of neutrophil engraftment as used in a given study.

Is it neutrophil recovery or is it neutrophil recovery and donor chimerism? Computing neutrophil engraftment correctly depends upon the context of the study.

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 from which to choose. Usually, the questions require only slight modifications from one study to the next, which is a significant timesaver.

> 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.

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BEST PRACTICE #3

Maintain High Data Quality Throughout Your Trial

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Maintain High Data Quality Throughout Your Trial

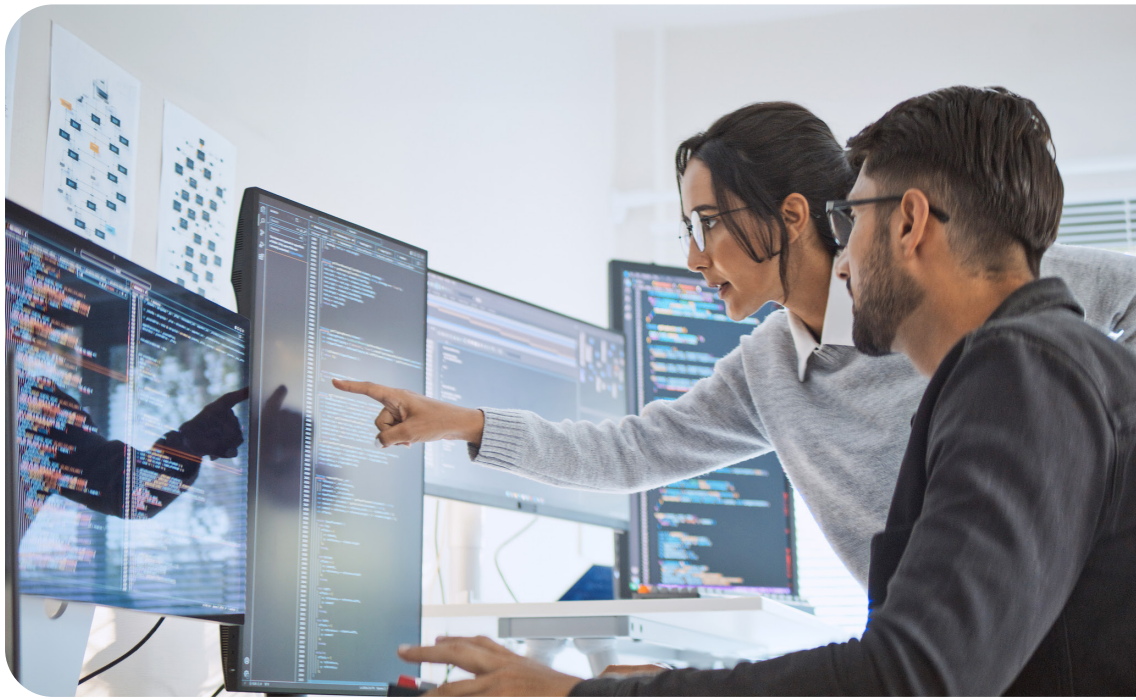
Thoroughly Prepare for Data Collection

As a best practice, clinical data managers should be given the opportunity to review every protocol before it is finalized. Their interest is in ensuring that the trial systems will be able record the data needed, particularly with respect to the number and timing of assessments and the acceptable window of opportunity for visits.

Based on how the schedule will translate into data in the system, they can advise how best to specify milestones in the protocol. For example, is “one month post-transplant” four weeks or 30 days? The answer makes a difference to how the system is programmed. Given their understanding of how the data will be analyzed, clinical data managers should also be heavily involved in designing the data collection tools.

The wording of questions/prompts in the case report form directly affects the quality and completeness of the responses captured; poorly written questions/prompts can confuse site staff and lead to instances of non-random missing data.

Additionally, to ensure that responses are accurate and comply with the study protocol, the data collection tools should be programmed with built-in edit checks that prevent data entry errors. These measures allow sites to enter data only with values that fall within predefined limits based on what is physiologically possible and that are consistent and logical. The system will not permit a temperature of 120° Fahrenheit to be entered, for example, but will permit certain other values that may not be considered “normal” in other studies but are within the normal range for patients receiving CGT.



> All clinical terms must be defined clearly, and everyone involved in providing, managing, and analyzing the data in CGT trials should share a common understanding of them. Misapplication of a term such as neutrophil engraftment (as discussed above) by anyone along the data flow would wreak havoc on the integrity of the data and its analysis.

BEST PRACTICE #3

Maintain High Data Quality Throughout Your Trial

Cleanse the Data of Discrepancies and Anomalies

Once the clinical trial database is created, clinical data managers must work closely with biostatisticians and safety experts to ensure that the quality, completeness, and integrity of the data are maintained throughout the life of the study.

Clinical data managers are tasked with exploring any anomalies and nonsensical data points identified by biostatisticians as they screen incoming data. Typically, the first check is performed after the first site submits data on the first few patients.

It is, of course, critical to spot any such discrepancies and anomalies before the data are submitted to regulators; when regulators find unexplained issues in the data, they will return the submission. Generating a response could be a simple matter of answering a question or updating a single data output. In the worst case, it could require the sponsor to re-run the analysis, potentially adding months to the development timeline.

> Good data managers also know what they don't know and can judge when they ought to turn to safety experts and others with clinical knowledge as well as biostatisticians to answer questions and advise them as a study progresses and data starts coming in.

Data managers responsible for reviewing the data and controlling its quality must have a solid understanding of the CGT protocol and the clinical processes involved to be able to distinguish between expected results and those that are cause for further exploration.

They must know, for instance, what toxicities are expected and which adverse events are unexpected. For example, what if a patient's white blood cell counts have dropped? At what point is the value outside of the normal range and no longer making clinical sense?

A knowledgeable data manager will be able to answer those questions given the patient's experience. It is imperative that data reviewers also be able to identify errors in grading as they will bias the study results and will not pass regulatory review.

Data managers must trace questionable data findings back to the source, have them corrected in the source data, and work to prevent recurrences. For example, the proper definition of engraftment is very specific, and could be misinterpreted by an investigator. Typically, to be considered platelet engraftment, the patient cannot have had a platelet transfusion within the past seven days.

If a patient is reported to have had platelet engraftment and also to have had a platelet transfusion six days earlier, there is an inherent conflict in the data. Either the answer to the question about platelet engraftment is wrong, or the transfusion record is wrong. In this case, the data manager would have to explore the issue with the site to arrive at the correct answer.

BEST PRACTICE #3

Maintain High Data Quality Throughout Your Trial

Centralized, On-Demand Data Monitoring

As data from various sources is increasingly being ingested directly into the EDC, simply running programmatic checks to catch transcription errors is insufficient to ensure that the data will be of the highest quality.

Much of the data is, in effect, source data and therefore is “clean”, meaning it could not have been copied into the system incorrectly. Nonetheless, there could be issues with the source data itself—issues that are too difficult to spot without the help of technology.

Emmes is developing a system that creates visualizations of trial data and uses machine learning and statistical methodologies to pinpoint data anomalies and outliers from across sources and multiple variables. Any unexpected, illogical, or questionable results are then flagged for investigation, and corrective action can be taken in a targeted and timely way.

Does the data from one source contradict that from another? Does the data from one site display an unnatural pattern? Is a change in a patient’s values or condition odd or unexpected? If, for example, a patient’s neutrophil count spiked in the lab data, but the patient reported outcome showed a decrease in neutropenia, the system will flag the discrepancy.

This centralized approach to data monitoring can be undertaken as the data comes in. This prevents issues from becoming systemic and ultimately speeds database lock.

Centralized Biospecimen Management

Tracking biospecimens manually as they move through a complex network of clinical trial sites, repositories, and central laboratories is inefficient and error prone. Samples are lost. The wrong samples are used. Samples are mishandled. And sample inventories can be depleted.

For trials meeting certain criteria, Emmes relies on GlobalTrace, a best-in-class system to maintain a central inventory of biospecimens and record the history of each specimen from the moment it is collected until it is no longer available. Regardless of the number of sites and their locations, GlobalTrace automates steps in the process, embeds quality control checks into the system, and offers visibility into samples across the clinical ecosystem.

By saving time at every step of the way in collecting, transferring, and tracking samples and by circumventing the need for a protracted reconciliation exercise prior to database lock, GlobalTrace successfully accelerates the trial timeline. And, by eliminating many opportunities for human error, the application helps ensure that all samples—and their assay results—can be used to prove the study’s endpoint.

BEST PRACTICE #4

Prioritize Logistics for Patient Safety

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Prioritize Logistics for Patient Safety

The patient journey in CGT trials is fraught with complex logistics that must be carefully coordinated between multiple stakeholders to ensure that every step in the process is timed, sequenced, and executed according to plan.

This responsibility is of the utmost seriousness, as any timing miscalculations or miscommunications could result in the unavailability of treatments to patients when needed. And, since many CGT therapies are individualized and manufactured for an "N" of one, there is no room for error when linking products to patients. The consequences of missed dosing or of misassigning a product would be devastating—and easily fatal— for patients.

Study managers and clinical logistics managers must work together to:

- Secure a manufacturing slot for the cellular product
- Schedule the patient's apheresis
- Coordinate with a specialized courier to transport both the extracted cells to the manufacturer then the cellular product to the site
- Ensure the site is ready to receive the cellular product and the patient has undergone the necessary pre-infusion procedures
- Confirm the site's receipt of the cellular product and that it has not been subjected to a temperature excursion
- Follow up to confirm that the patient received the infusion and is being monitored

> This work requires deep experience in the therapeutic area to be able to handle all of the interdependencies, risks, and contingencies. So much hinges on the proper transport, receipt, and storage of the patient's cells and the resulting cellular product that it is a best practice to rely on an automated system to streamline the supply chain and provide the instant visibility necessary for oversight of the process.

BEST PRACTICE #4

Prioritize Logistics for Patient Safety

The right software is critical to maintain a centralized inventory of both biospecimen and product, and to record the history of each as they move through the CGT supply chain.

It is important to have visibility into the disposition of every specimen in a trial, from the moment it is collected until it is administered to the patient (in the case of a cellular product) or no longer available (in the case of other biosamples). The right system can automate the steps in the process, embed quality control checks into the system, and offer visibility into who currently holds a specimen as well the full history of transfers and use.

Importantly, a centralized system spans the tracking systems at clinical sites, specialty labs, specimen repositories, shipping companies, and manufacturing facilities. Sponsors don't need to search disparate inventory systems to answer queries, monitor status, or reconcile data on specimen transfers; information on all specimen-related activities are captured in one place.

This eliminates the need to make multiple phone calls and collect reports from every entity in the system—steps that are not guaranteed to resolve issues. It also does away with the slow and error-prone work of reconciling transfer data between repositories and labs, and between labs and the trial's data center. Often, when this is done manually, discrepancies between clinical and laboratory data are discovered after the window of opportunity for further sample collection has closed.

BEST PRACTICE #4

Prioritize Logistics for Patient Safety

Reducing Risk through Automation

The right management and oversight software provide benefits at every step of cells' and cellular products' path over the course of a trial.

On-Demand Visibility

Good systems provide real-time visibility into the location of individual biosamples and cellular products as they are transported, manufactured, and stored, including a full history of transfers, specimen lineage, and issue management—all in one place. Search functions by attribute and location; plus, integration with EDC ensures closed loop tracking of specimens and cellular products, and enables search by characteristics of the study and its participants.

Patient Safety

Monitor the status of cells throughout the treatment journey so study managers can schedule key steps in patients' treatment and follow the protocol precisely, without delays or complications that could leave patients vulnerable. Temperature tracking and alerts on incoming shipments help prevent spoilage that could endanger patient treatment and retention.

Chain-of-Custody Preservation

Cell samples and products are bar-coded and scanned as they are shipped and received, leaving an audit trail and assuring provenance and linkage to a given patient.

Improved Quality

Reduce errors or omissions in specimen labeling and handling with a data repository featuring built-in quality checks, which also eliminates discrepancies between clinical and laboratory records, reduces errors or omissions in reporting laboratory results, and ultimately decreases the number of specimens that are lost, misidentified, or ruined.

Efficiencies

The best tools automate common specimen processing and cellular product tasks, eliminating manual tracking and reconciling of inventories and shipment manifests. Expediting and recording specimen-related activities can greatly reduce time spent querying specimen status, reconciling inventories and shipment records, generating sample picklists, and selecting specimens for analysis based on those picklists. When all specimen-related data is contained in one system and integrated with an EDC, end-of-trial record reconciliation is eliminated, saving time and effort and allowing earlier database lock.

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BEST PRACTICE #5

Leverage Specialist Insights for Data Analysis

BEST PRACTICE #5

Leverage Specialist Insights for Data Analysis

Data analysis in every study is prescribed in a Statistical Analysis Plan (SAP), which specifies the methods that will be used to analyze the data, draw comparisons, and deal with missing data.

The SAP is submitted to regulators, and while the initial SAP may be modified it must be finalized before the first analysis is conducted or before any unblinding occurs so as to not bias the study results.

Given the uniqueness of the statistical challenges and methodologies in CGT studies, the biostatisticians drafting and executing the SAP should be specialists in the therapeutic area.

Correct for Missing Data

Missing data—data points that are missing from the database because they weren't collected or entered—can result from many situations. In CGT studies, given their heavy patient burden, some amount of missing data is inevitable because:

- A patient missed a scheduled visit
- A patient did not complete a quality-of-life questionnaire
- Data collection form question was missed/skipped/had an exception granted
- A test, e.g., specific lab test, wasn't conducted at a specific visit
- A sample was destroyed
- A patient left the study before it was finished or was lost in follow-up
- An endpoint extended beyond the trial duration (such as a measure of overall survival when the patient was still alive at study close)

Procedures and statistical methodologies must be in place to address and account for missing data, especially as the study populations are so small. 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. Note: Data that is missing because a patient died and did not complete the study is not considered missing in the same sense and is treated in its own way.

BEST PRACTICE #5

Leverage Specialist Insights for Data Analysis

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

This technique is used to address 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.

Account for Small Patient Populations Statistically

The results derived from studies involving very small patient populations may not fit the normal distribution curve of results found in larger datasets. Statisticians must, therefore, use techniques/tests in their data analysis that may not be in common use in other therapy areas.

For instance, rather than the standard t-test, the Mann-Whitney U test can be used to compare results from two independent, small samples as it does not assume that the data will result in a perfect bell curve.

Similarly, small patient populations require an alternative to the commonly used Chi-square test, which examines whether the association between two variables is statistically significant. Fisher's exact test serves this purpose.

> Statisticians will often complete a sensitivity analysis to understand the impact of missing data, the underlying assumptions of missingness that are at play, and how the different techniques for dealing with missingness affect the results. All versions of these analyses are presented to regulators.

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BEST PRACTICE #6

Regulatory Expertise and Robust Research Networks

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.

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. 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.

BEST PRACTICE #7

Harnessing Technology to Improve Trial Outcomes

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. First, we are digitizing clinical trial protocols into structured data elements such as visit schedules, cohorts, and electronic case report form (eCRF) data elements. Our AI algorithms then use these data elements to find and re-deploy eCRFs and edit checks from more than 1,000 prior clinical trials and study builds. We can also use our AI algorithms to build new eCRFs and edit checks based on the digitized trial protocol. This approach minimizes human error and reduces build timelines by up to 30%. And with high quality, AI-predicted edit checks, it provides automated data cleaning functionality on Day 1, empowering sites to rapidly correct data issues.

Draft consent forms

Again, 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. Through our partnership with Datavant, we create a “token” or unique identifiers for trial subjects, linking data from various sources to our trial database. Our consent process includes approval to access this data for long-term follow-up studies.

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