CLINOPS
Identifying and Overcoming New Hurdles in CGT Space

STRATEGY
A Biosafety Perspective on CGT Trial Operations

REGULATORY
Clinical Trial Modernization Raises FDA Compliance Issues

APPLIED CLINICAL TRIALS

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Volume 31 Number 10 October 2022

CELL AND GENE THERAPY TRIALS

The Problem with Decentralized Clinical Trials and How to Solve for Success

ON-DEMAND WEBCAST

Wednesday, September 7, 2022

Register for this free webcast at:
www.appliedclinicaltrialsonline.com/act_d/decentralized

Presenter

Bryan Lubel
Executive Vice President,
Connected Health
KORE

Moderator

Lisa Henderson
Group Editorial Director
Applied Clinical Trials

Event Overview

Decentralized Clinical Trials (DCT) is one of the hottest buzzwords in Life Sciences and Connected Health organizations today. Like any new approach, challenges and roadblocks are common and knowing how to solve for them will empower your organization to accelerate your trial deployment, speeding return of results and time to market. Join KORE to learn about the challenges and solutions in DCTs and advancing technologies to accelerate your success.

Key Learning Objectives

- Challenges, answers, & customer breakthroughs for DCTs
- How to overcome obstacles in the market
- Advanced technology for seamless DCTs
- Customer use cases and learnings for DCTs do's & don'ts
- Regulatory compliance insights

Who Should Watch

- Business and clinical professionals in the life science and connected health industry looking to deploy, manage, and scale their global DCTs

For questions email
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STAYING ON COURSE IN CGT SPACE

October is usually a time of adjustment for many of us. There's a noticeable change in the weather outside and it alters a lot of what we do in our day-to-day activities. At *Applied Clinical Trials*, we are also using October as a time to highlight adjustments—in the clinical trials industry, of course. This month's issue focuses on the unique operational challenges of cell and gene therapy (CGT) trials. Sponsors and CROs must be willing to adjust their practices to tackle these challenges as more and more CGT trial programs enter the space.

In addition to our usual columns in the News section, you will find a summary (page 11) of the Philadelphia, PA, region and its large presence in CGT research and development among US life sciences hubs. As a clinical trials publication based out of NJ, we must give a shout-out to our friendly neighbors across the Delaware River.

This month's main feature (page 14) sets the stage for our theme by providing a detailed look at some of the challenges and complexities that CGT trials present. Included are insights from industry leaders, who share their thoughts on this increasingly crowded playing field in drug development, as pharma, academia, and others pursue new opportunities to transform treatment through personalized medicine. Our next feature on CGT (page 26) offers a biosafety perspective on the clinical trial challenges associated with these products, and the potential advantages in working with an institutional biosafety committee to ensure regulatory compliance. Our third feature on CGT (page 30) focuses on how to handle biospecimens. The authors suggest partnering with biorepository and biospecimen logistics providers, which would open more time for researchers to advance the sciences behind the trials.

In other coverage this month, we explore planning and design strategies around trials for rare disease, drawing from lessons learned in Duchenne muscular dystrophy that can help sponsors and CROs improve the patient experience. Also included is a feature focused on rare disease indications in the oncology space (page 22), taking an in-depth look at enhancing enrollment in biomarker-driven trials targeting cancer subtypes. Thank you for reading.

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Mike Hennessy, Jr
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TOP 5 MOST-VIEWED STORIES ON SOCIAL MEDIA

1. Survey Results: GCP Quality and Risks in DCTs
   https://bit.ly/3SYh09n
2. Filling the Gaps in Clinical Trial Education, Literacy
   https://bit.ly/3rzUW8H
3. Redefining CRO Sourcing Model Terminology
   https://bit.ly/3rCjHBa
4. How Life Sciences Companies Can Strengthen Regulatory Submissions With External Control Arms
   https://bit.ly/3RJ2m4i
5. Start-Up Pharma Weathering the Inflation
   https://bit.ly/3CEABph

eLEARNING:
As clinical trial protocols become more complex, patient informed consent forms and processes become more complicated as well. Not only is it critical to effectively engage patients in the consenting process early to ensure protocol adherence and meet trial milestones, it's essential that their consent be tracked from initial screening through cohort or treatment group assignment and each subsequent amendment. In this webinar, IQVIA Complete Consent leaders will share how an eConsent solution can be customized to support these studies and high-risk patient populations.
https://bit.ly/3yo9coO

While it may seem prudent to include every single detail of a patient's medical history in a case narrative, an overabundance of information buries the salient points. It makes it difficult for regulators to assess the cause of the safety issue and runs the risk that irrelevant data will get pulled into the adverse event determinant. However, as this webinar explores, when authors take the time to combine a patient's relevant medical history with safety event details and focus on potential causes of the event, it is easy for regulators to understand what happened.
https://bit.ly/3rBBqbX

Lisa Henderson
Editor-in-Chief

The biggest obstacle to CGT innovation right now is in the manufacturing–"the process is the product"

Scientists Don't Ever Stop Sciencing

There are interesting things afoot in the cell and gene therapy (CGT) space. And not only what is tackled in our feature article on the risks and rewards of CGT trials, which is a hot take on the David vs. Goliath theme running through trial sponsorship for CGTs. With two recent FDA approvals for Bluebird Bio in back-to-back months, attention on CGTs and personalized medicine continues to grow.

At the recent DPHARM conference in Boston (https://bit.ly/3EEonyr), former FDA Commissioner Scott Gottlieb, MD, told attendees during his keynote that he was writing a book on the history of CGTs. Weaving the tale of Carl Jung, the University of Pennsylvania, and Novartis, Gottlieb noted the serendipitous events that almost failed—but ultimately succeeded—in bringing Kymriah, the first CAR-T therapy approved by FDA, to market.

But, as Gottlieb noted, the biggest obstacle to CGT innovation right now is in the manufacturing—"the process is the product." And, currently, FDA is not equipped to approve processes over products. Gottlieb explained that constructs currently exist within the agency to enable this change, but it needs a different framework. Ever the realist, Gottlieb foresees that this framework will be realized, albeit in an iterative process and may require an act of Congress to allow FDA to define the parameters for the process.

In our sister publication, *Pharmaceutical Executive,* this month, I wrote about the current state of research innovation hubs around the US. Cambridge/Boston, San Francisco, San Diego, Philadelphia all take top spots for leading-edge therapeutic innovations. (Also, see page 11 for more information on Philadelphia's CGT capabilities promotional campaigns). Juxtapose this against the current financial market in biotech, a market correction is underway. It's definitely not a chilling effect, but it is suggested that uncertainty around the manufacturing process and the regulatory implications of such is impacting investment due to an opaque regulatory model.

However, as we also know, and as stated in the main feature, scientists don't stop researching and seeking out the best for patients. One notes: "As a scientist, when you are doing something in biomed research, [the] goal is to translate bench work to the clinic for [the] wellness of people."

APPLIED CLINICAL TRIALS
EDITORIAL OFFICES
485 Route 1 South, Building F, Suite 210,
Iselin, NJ 08830 USA
+1 (732) 346-3080

EDITOR-IN-CHIEF Lisa Henderson, lhenderson@mjhlifesciences.com
GROUP MANAGING EDITOR Michael Christel, mchristel@mjhlifesciences.com
GROUP SOCIAL MEDIA EDITOR Miranda Schmalfuhs, mschmalfuhs@mjhlifesciences.com
ASSOCIATE EDITOR Andrew Studna, astudna@mjhlifesciences.com
SENIOR ART DIRECTOR Marie Maresco, mmaresco@mjhlifesciences.com
GRAPHIC DESIGNER Ariana Mexquititla, amexquititla@mjhlifesciences.com
WASHINGTON EDITOR Jill Wechsler

SALES SERVICES
EXECUTIVE VICE PRESIDENT, HEALTHCARE AND INDUSTRY SCIENCES Brian Haug
BHaug@mmhgroup.com
GROUP PUBLISHER Todd Baker tbaker@mjhlifesciences.com
SENIOR NATIONAL ACCOUNT MANAGER Cheryl Mahon cmahon@mjhlifesciences.com
DIRECTOR OF SALES Margie Rogers mrogers@mjhlifesciences.com
REGIONAL SALES DIRECTOR Vahé Akay vakay@mjhlifesciences.com
SALES SUPPORT COORDINATOR Kristi Stevenson kstevenson@mjhlifesciences.com

MARKETING SERVICES
PERMISSIONS/INTERNATIONAL LICENSING Alexa Rockenstein, arockenstein@mjhlifesciences.com
REPRINTS For requests, contact Todd Baker at +1 (732) 346-3002, tbaker@mjhlifesciences.com

CUSTOM PROJECTS
VICE PRESIDENT, CONTENT AND SPECIAL PROJECTS Colleen Hall chall@mjhlifesciences.com
DIRECTOR Robert Alaburda ralaburda@mjhlifesciences.com
MANAGING EDITOR Jeanne Linke jlinke@clinicalcomm.com
SENIOR EDITORS Megan Manzano mmanzano@mjhlifesciences.com
Shannon Stolz sstolz@mjhlifesciences.com
CUSTOM CONTENT WRITER Alissa Marrapodi amarrapodi@mjhlifesciences.com
DIGITAL PRODUCTION MANAGER Sabina Advani sadvani@mjhlifesciences.com
SENIOR PROJECT MANAGER, TEAM LEAD, INDUSTRY SCIENCES Anita Bali abali@mjhlifesciences.com
CIRCULATION AND AUDIENCE DEVELOPMENT DIRECTOR Stacy Argondizzo sargondizzo@mjhlifesciences.com

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COMMENTARY

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FROM THE EDITOR

NEWS AND ANALYSIS

BRAND INSIGHTS

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A CLOSING THOUGHT

Jill Wechsler
Washington
Correspondent

CLINICAL TRIAL MODERNIZATION RAISES FDA COMPLIANCE ISSUES

The shift toward greater use of remote data collection methods and innovative clinical trial designs has focused the attention of FDA officials on related challenges for ensuring the quality and accuracy of research reports and appropriate protection of research participants. In outlining a range of compliance issues important to drug development and oversight, Don Ashley, director of the Office of Compliance (OC) in the Center for Drug Evaluation and Research (CDER), recently addressed how an increasingly complex clinical research system raises issues for ensuring the reliability of research results and patient safety.

For many clinical trials, Ashley observed in a compliance policy presentation at the PDA/FDA joint regulatory conference Sept. 13, the COVID-19 pandemic encouraged the adoption of modern study approaches, creating new challenges in the process. These developments and the overall modernization of clinical trial design, operational approaches, and data sources have helped increase the speed and efficiency in developing medical products to treat serious diseases and conditions, Ashley acknowledged. He noted a shift to more pragmatic study designs, increased used of real world-data (RWD) and real-world evidence (RWE), and decentralized and point-of-care trial operations—developments that also generate concerns among regulatory officials for ensuring that clinical data can be relied on in making regulatory decisions.

Advancing quality

One approach for addressing the reliability of innovative research is for sponsors to adopt quality-by-design methods for clinical research operations, as is now widespread for drug manufacturing, Ashley proposed. This involves ensuring that trial design is adequate to answer the scientific question so that results are credible and resulting data is sufficiently accurate and reliable—fit for purpose—to support decision-making. When using digital technology to obtain study data, sponsors also should consider how to ensure that the rights, safety, and welfare of trial participants are adequately protected.

Ashley discussed these concerns about clinical trial data quality and reliability as part of a broader presentation at the PDA conference on how his office works to protect patients from poor-quality, unsafe, and ineffective drugs. Much of his presentation involved ongoing OC efforts to establish a modern drug supply chain security system based on enhanced methods for identifying and tracing drugs through national distribution operations. This initiative involves new licensing standards for distributors, changes in the National Drug Code, and implementation of an enhanced product verification system for 2023. Ashley further emphasized the importance of top corporate leadership in maintaining a robust state of control and a strong corporate quality culture to assure sustainable compliance and consistent production of high-quality drugs at a given facility in another presentation on Sustainable Compliance at the PDA/FDA conference.

These issues, including efforts to enhance clinical trial oversight to protect trial participants, are described in the OC annual report for 2021. The report highlights continuing FDA efforts to expand oversight of drug compounding and to bring criminal charges against manufacturers that fail to correct ongoing product contamination problems. It also describes compliance actions to ensure that clinical trial sponsors submit required results information to the ClinicalTrials.gov data bank and collaborations with other CDER offices to challenge misconduct and violations by research organizations. And it notes that OC's Office of Scientific Investigations (OSI) helped address challenges raised by expanded use of new research technologies in contributing to an FDA draft guidance published in January 2022 on Digital Health Technologies for Remote Data Acquisition in Clinical Investigations.

A PERVASIVE PATIENT FOCUS IN EU CLINICAL TRIALS AS NEW RULES FACE FINE-TUNING

The very first words in the European Union's new clinical trials regulation (CTR) are "In a clinical trial, the rights, safety, dignity, and well-being of subjects should be protected and the data generated should be reliable and robust. The interests of the subjects should always take priority over all other interests." And while the objectives of the regulation—now largely, but still not entirely, in force—also include to "stimulate the inclusion of as many member states as possible" in a trial, and to minimize "divergences of approach among different member states," the emphasis on the interests of trial subjects has been the dominant theme throughout its gestation, and continues as the fine-tuning is still being carried out.

The latest element in this fine-tuning is advice on how and when patient-facing documents have to be submitted in the course of seeking a clinical trial approval. It comes in the form of a late-September update to the guidance on the implementation of the CTR. This lengthy question-and-answer document, that already provides detailed practical information on how to meet the new requirements, has been further expanded to tackle this issue.

As it makes clear, patient-facing documents covers a wide field. Virtually any document presented to clinical trial participants during the conduct of the clinical trial falls into this category—questionnaires, patient diary, patient card, or patient-reported outcomes. And they have to be submitted as Part 1 of a clinical trial application. The submitted documents not only have to be in line with the language requirements for the trial protocol, but they must be provided to the trial participants "in a language understandable for the participants." It is up to sponsors to ensure the quality of all the translations, adds the guidance. Patient-facing documents that are linked to the endpoints of the clinical trial also have to be provided (together with the protocol) in Part 1 of the application, so they can be assessed during the Part 1 assessment.

The major exception to the obligation for early submission of patient-facing documentation is recruitment material or subject information sheets. It is not necessary to submit copies of the advertising material with Part 1 of the application, whether printed or in the shape of audio or visual recordings. Nor does the CTR require early submission of information given to the subjects together with the informed consent form before their decision over whether to participate in the trial. Recruitment material or subject information sheets are to be submitted in Part 2, "and no other documentation shall be submitted under these sections," intones the guidance gravely. "There is currently no legal basis in the CTR to request the submission of all patient-facing documents in the Part 2 documentation package and/or to require their translation," the guidance adds—with a certain ominous quality to the adverb "currently."

The process for fine-tuning is, in the best traditions of the EU, complex and ponderous, but though the EU mills grind slowly, they "grind exceeding small." The new guidance was discussed by the European Commission's expert group on clinical trials (CTEG), which brings together ethics committees and national competent authorities, and was then submitted for clearance to the Commission's clinical trials coordination and advisory group (composed of member state representatives) before it was published on Sept. 26.

In parallel to the strictures on material to be submitted before the trial, an intense discussion has been underway for over five years now on the requirements that will govern the lay summary of trial results—another requirement that the CTR imposes on all sponsors. Here, some official guidance has been published, in late 2021, based in part on a draft produced jointly by EU and US pharmaceutical companies, CROs, academic institutions, patient organizations, and nonprofit organizations, and reviewed and revised by the CTEG. But the 85 pages of this document are still not sufficient to answer all the questions if the various players are to discharge their duty satisfactorily.

Outstanding issues outlined by a multi-stakeholder workshop earlier this year include how to plan (and how to resource) the preparation, writing, review, patient engagement, translation, and dissemination that the obligation entails. Challenges also exist in meeting the simultaneous—but not necessarily compatible—requirements for readability and scientific rigor, or in arbitrating on the legitimate scope for interpretation in reporting results to lay audiences, or judging the adequacy of compliance with the rules. The obligation extends beyond the mere creation of a lay summary to disseminating it, and that too bristles with challenges over how it should be disseminated, where, by whom, and to whom, in what languages, and for how long.

Peter O'Donnell
Brussels
Correspondent

Barbara Lopez Kunz
President and
Global Chief
Executive, DIA

THE PULSE OF CLINICAL DEVELOPMENT TODAY FROM A GLOBAL PERSPECTIVE

The clinical trial landscape has changed significantly post-pandemic, and many industry experiences and strategies emerged at the Drug Information Association (DIA) 2022 Global Annual Meeting over the summer. In this interview, Barbara Lopez Kunz, president and global chief executive at DIA, discusses key themes influencing the current state of the clinical trials industry and its future.

Moe Alsumidaie: Post-pandemic, what are the most significant changes in drug and clinical development?

Barbara Lopez Kunz: We've all seen drug development evolve over the past few years, but the pandemic catalyzed some of the things we've discussed. It turned our talk into action, which we love, and hope will continue.

As the pandemic spread, we all faced the same challenge. As a result, international collaboration increased, and as part of this international exchange, formal work-sharing initiatives and dialogue emerged; there is a strong desire to use the pandemic response's flexibility and innovation to address unmet needs in other disease areas. This has been DIA's mission for nearly 60 years.

We've seen a few emerging trends. First, we see a sharper focus on including diverse patient populations in clinical research and development so that the solutions are effective for those who need them most. Pandemic urgency helped integrate clinical research into communities that may not have felt welcome or understood how to participate. While diversity inclusion has made strides, we still need to improve our outreach and integration of all communities.

Second, there is expanded collaboration; since it doesn't matter how effective therapies are if patients can't access them, DIA has brought in new players. Pharmacy benefits, reimbursement, health technology assessment, and other experts engage earlier in the drug development life cycle, so all perspectives work together.

Last, decentralized clinical trials (DCTs) have emerged quickly and are here to stay. Tufts University's Center for the Study of Drug Development showed that decentralized processes increase drug development efficiency. Our DIA Global Annual Meeting 2022 program included many DCT themes.

MA: What are some companies' DCT implementation challenges?

BLK: DCT adoption is a significant change, requiring the proper methods, tools, and training. DCTs will bring new challenges, such as ensuring appropriate training and delivery across sites and improving data collection and management. Until new approaches are solidified, drug development will use proven methods. As in change processes, some companies will move forward with decentralized trials while others wait for a larger mandate, monitoring understanding, process, training, and regulatory guidance. Clinical trials are the most time-consuming and expensive part of drug development, so process changes should reduce risk.

MA: Post-pandemic, what regulatory changes have you seen?

BLK: Regulators want to keep pandemic-era flexibilities. Regulators are accelerating changes in structures and processes to be more patient-focused. I'm seeing more patient engagement and patient-centric drug development now.

In the US, FDA published guidance on patient-focused drug development, including collecting patient input, identifying patient priorities, and developing meaningful outcome assessments. In Europe, the EMA (European Medicines Agency) endorsed the PREFER initiative's patient preference, integration, and drug development framework. The ICH (International Council for Harmonization) is working to harmonize data submission requirements for patient experience. Patient-centricity is entering countries' regulatory agendas. Asia, the Middle East, and elsewhere are seeing new patient engagement communities. DIA has long supported these efforts, and we're actively generating new patient engagement knowledge and learning opportunities for our community.

New data collection and analysis pose challenges throughout the drug development pipeline. Patient privacy, data ownership, and data integration will determine how we use these data to drive

R&D efficiency now and in the future. The EMA and HMA (Heads of Medicine Agencies across Europe) maintain a collaborative data-steering group to easily integrate big data and advanced analytics into their regulatory assessments. Signal detection uses analytics to automate case adjudication and identify false claims, adverse events, and illegal marketing. DARWIN-EU enables real-world data analysis and post-market surveillance and decisions. The FDA has seen a rise in AI/ML (machine learning)-related submissions in the US.

Clinical trials are the most time-consuming and expensive part of drug development, so process changes should reduce risk

MA: Where do you see clinical development headed in an uncertain world?

BLK: We›re all in transition. New COVID variants are emerging, and we're preparing a response. In addition to the pandemic, geopolitical issues, war, and unusual weather are causing health-related crises. We've made great strides in healthcare, and I'm proud of that, but we must continue collaborating and sharing our findings. We must create clinical trial designs that address our challenges. We must better prepare for collateral challenges, such as supply chain issues. Many companies and regulatory agencies must stabilize their supply chains to meet demand and launch new products. Global crises will persist.

As a neutral convener, DIA will continue to address these issues. And we'll keep putting patients first as a healthcare community. DIA's sharing and learning environment fosters ideas and creates momentum and practical ways to implement them. As new knowledge emerges, we revise and refine our learning offerings to ensure they offer the latest regulatory, clinical, and data science content our community needs.

MA: How is DIA supporting the future of clinical trials?

BLK: One DIA board member said years ago that we'd create it if DIA didn't exist. I couldn't agree more. In 1964, our founders couldn't have imagined how important a trusted, neutral, global platform would be for therapeutic development today. We knew years ago that we needed to improve access to DIA's knowledge, so we digitized all of our content and created a multi-year archive that we updated with new information. Creating a digital DIA was unrelated to recent crises. This work was done so that life science professionals worldwide could access the latest knowledge of science and policy. All stakeholders developing new therapies should use the latest information.

We've created a digital platform to keep clinical development experts like you informed and educated and to share what you've learned. In the early days of SARS-CoV-2, we launched the DIA Direct series to share China's experiences with healthcare delivery, drug use and repurposing, and clinical trials. This helped us engage thousands of members and stakeholders in knowledge exchange, accelerating the response to COVID. Today, we're publishing a new DIA Direct series on clinical trials and the Ukraine war. This series has helped clinical research and care communities in Ukraine share their experiences so others can learn and support them.

DIA offers regulators and the healthcare community a global, digital, virtual, and in-person neutral platform. We'll keep building strategies to prepare for the next disruption. You may remember that we presented a snapshot of the future of healthcare at DIA 2022. Next year's DIA Global Annual Meeting 2023 (in Boston) will focus on clinical research and healthcare challenges. This meeting's theme, Illuminate, aims to highlight the latest in drug development and our global collaborative network, which can transform individual professional expertise into actionable progress that benefits everyone.

Moe Alsumidaie, *MBA, MSF, is a thought leader and expert in the application of business analytics toward clinical trials, and Editorial Advisory Board member for and regular contributor to Applied Clinical Trials*

Critical Path Institute's Electronic Clinical Outcome Assessment (eCOA) Consortium

SURVEY INVESTIGATES BACKUP SOLUTION ADOPTION FOR ePRO SYSTEMS

The following is the second installment of a two-part series evaluating the use of backup solutions for electronic patient-report outcomes (ePRO) systems. Here, C-Path's Electronic Clinical Outcomes Assessment (eCOA) Consortium presents results from a survey issued to 15 sponsors who are members of C-Path's PRO Consortium and have a specific interest in eCOA systems. Twelve responses were received. The survey investigated backup solution adoption, justifications for solution selection, reasons why paper persists, and how backup data are evaluated.

General approach to backup solutions and justification for selection

When asked about their general approach to backup solutions:

- 4 sponsors include backup solution(s) in every trial.
- 2 sponsors include backup solution(s) for a specific subset of trials based on endpoint and/or indication.
- 2 sponsors provide backup solution(s) for only some trials but didn't specify the criteria.
- 2 sponsors have internal guidelines for backup procedures.
- 1 sponsor does not have any internal guidelines and delegates the decision to the clinical teams.
- 1 sponsor does not use backup solutions.

The primary electronic backup solution of choice for those that employ them was a web backup. Paper remains prevalent and is often used in combination with a web backup.

- 7 respondents selected web as the primary back-up (but some commented they use multiple backup solutions within a trial).
- 4 respondents selected paper.

Interestingly, web backups are not used in isolation in our sample. Multiple respondents indicated that web backup is not always accessible; limited connectivity or device availability could be factors, and even if accessible, the web-based solution may still be challenging for specific participant populations and/or assessments. In such cases, sponsors have used alternative methods such as bring your own device (BYOD), interviewer administration of assessments, replacement devices, and/or paper. Early discussions with clinical teams and sites to identify situations that necessitate a more flexible or tiered backup approach is advised (e.g., the combination of web and BYOD).

Prevalence of paper

As indicated, paper backup is used by some sponsors as a primary backup solution. Based on the survey, paper backup is mostly used to support site-based ePRO collection. The principal reasons for use were:

- Ease of use for sites.
- Site activation prior to eCOA availability, specifically in localized languages.
- Feasibility for specific therapeutic areas.

Evaluation of backup data

Most respondents agreed data captured via backup methods should be identified as such in the dataset. It was unclear from responses if sponsors uniformly conducted sensitivity analyses prior to pooling these data. Further discussion on backup data is necessary; it is important to know if sponsors see differences in the data and how they assess the relative level of quality between the data. It is evident from the survey that respondents consider it to be critical to reduce the amount of missing data; and employ a variety of backup solutions to ensure data completeness.

Takeaways

Although not generalizable beyond the survey respondents, the results indicate that there is no universal solution. Strategies may adapt to the trial's endpoint hierarchy, therapeutic area, and accessibility, and there is some desire for multiple options within a trial. Part 1 of this series suggested that with more flexible eCOA solutions, we may reduce the need for backups, specifically paper. Following the survey, we continue to champion the concept of flexibility. Respondents also acknowledged that what is planned is not always executed within the study. Clinical teams need immediate access to options such as web-based backup, BYOD, or replacement devices in order to pivot as needed, but this demands continued evolution of the eCOA systems used, inclusive of innovation in science, technology, device management, and technical support.

Authored on behalf of Critical Path Institute's eCOA Consortium by Lisa Charlton, Senior Director, eCOA, Science 37; Shelly Steele, Senior Scientific Advisor, eCOA, WCG Clinical Endpoint Solutions; Celeste Elash, Vice President, eCOA Science, YPrime; and Scottie Kern, Executive Director, eCOA Consortium

PHILADELPHIA SHINES IN CELL AND GENE THERAPY RESEARCH PURSUITS

A recent report commissioned by the Chamber of Commerce for Greater Philadelphia and researched by economic consulting firm Econsult Solutions, Inc. ranked the city No. 2 overall for cell and gene therapy (CGT) hubs (view here: https://bit.ly/3VaT3Nu). The analysis evaluated 14 US CGT hubs across five categories, including research infrastructure, human capital, innovation output, commercial activity, and value proposition. The only region to eclipse Philadelphia was Boston. New York and San Francisco ranked third and fourth, respectively.

According to the report, Greater Philadelphia researchers have been awarded at least $1 billion in NIH funding in each of the past five years. Focusing in more closely on research projects related to CGTs, more than $317 million in NIH funding has been awarded to Philadelphia investigators during that time period. Funding for CGT comprised 6% of total NIH funding in Philadelphia compared to a range of 0.7% to 5.2% in the comparison regions.

The volume of research funding is an indicator of the potential pipeline of discoveries and innovation that can be generated from basic academic research in the coming years.

In addition to the Pennsylvania city's second-place showing in CGT hub prowess, the Chamber of Commerce for Greater Philadelphia's CEO Council for Growth, along with its partners in the Cell and Gene Therapy Initiative, have released a new video (https://bit.ly/3EnUfXU) on the Philadelphia region's connected CGT startup ecosystem. Titled "Greater Philadelphia: Discovery Starts Here," the 90-second video animation shares a snapshot of several of the region's research institutions and a number of the CGT-focused companies that have licensed technologies.

The video highlights five of the region's leading research institutions: Children's Hospital of Philadelphia, Temple University, Thomas Jefferson University, University of Pennsylvania, and The Wistar Institute. It then shifts the focus to 15 companies that have direct links to one or more of those five research institutions. The video also distinguishes the organizations in four categories: emerging, privately held, publicly traded, or acquired.

> Categories evaluated were research infrastructure, human capital, innovation output, commercial activity, and value proposition

The 15 CGT companies highlighted in the video include: Adaptimmune; Aevi Genomic Medicine, Inc. (acquired by Avalo Therapeutics, Inc.); Cabaletta Bio; Carisma Therapeutics; Cartio Therapeutics; Imvax; INOVIO; Interius BioTherapeutics; KOP Therapeutics; Passage Bio; Renovacor; Scout Bio; Spark Therapeutics, a member of the Roche Group; Verismo Therapeutics; and Virion Therapeutics.

For more information on the video and the Chamber of Commerce for Greater Philadelphia's CEO Council for Growth, the full press release can be found here: https://bit.ly/3CCTU20.

—Applied Clinical Trials Editorial Staff

YPrime

Optimizing Decentralized Clinical Trials with Patient-Centric Tools

Decentralized clinical trial (DCT) models—clinical studies that use technology and processes or strategies to go beyond on-site locations—evolved in response to the COVID-19 pandemic. Although DCTs reduce the in-person contact required in traditional clinical trials, they pose unique challenges and require careful consideration in design, technology selection, and execution.

Pennsylvania-based software company, YPrime, offers cloud-based technology and expertise to help clients respond to these unique challenges. The patient insights and engagement team develops trial strategies and tools to keep patients more informed, boost compliance, and improve retention. Their scientific experts help focus on the endpoints and timepoints that answer the most important research questions and meet regulatory expectations. The data science team are leaders in building new protocol-specific integrations with other platforms, medical devices, and applications.

YPrime's technology solutions transform the design and execution of clinical trials, improving patient data collection, and simplifying clinical supply management.

As explained by Kelly Franchetti, Senior Vice President, Global Head, Patient Insights and Strategy at YPrime: "Technology solutions help to broaden opportunities for patients to participate in clinical studies, help sponsors and sites monitor the patients' progress in real time, and help maintain scientific rigor in the data-collection process."

Advanced outcome assessment

Using YPrime's electronic clinical outcome assessment (eCOA) technology, the company works with a trial sponsor to develop a therapeutically-driven solution that is easy for patients to use. YPrime's data-science team works with a trial sponsor to integrate a protocol with the eCOA. Plus, YPrime's scientific experts help a sponsor select endpoints that yield answers to a trial's key questions and provide regulatory compliance.

The resulting eCOA focuses on the patient experience. Patients can use their own devices to participate in a study. An easy-to-use and intuitive format keeps patients engaged and compliant. Plus, the cloud-based eCOA technology ensures data security.

The cloud-based foundation of YPrime's eCOA technology brings additional benefits to DCTs. For instance, near real-time data allows quality monitoring throughout a DCT and supports decision-making. Plus, YPrime's data-monitoring service warns a sponsor about safety and compliance issues.

Overall, YPrime's eCOA delivers cleaner data, enhanced clinical trial efficiency, increased site satisfaction, and improved patient compliance.

Interactive response technology

Interactive response technology (IRT) to manage all aspects of global patient randomization and clinical supplies can help reduce the complexities of designing for and executing on patient-centric clinical trials. YPrime provides best-in-class IRT solutions that ensure statistical integrity, reduce risk, and deliver submission-ready data at the end of every clinical trial. Flexible IRT designs can accommodate remote, hybrid, and onsite visit schedules, unique dispensation needs, and multiple direct-to-patient clinical supply shipping models.

Patient insights and engagement

YPrime works with patients, care partners, healthcare providers, patient advocacy groups, and payers to develop the most meaningful and beneficial relationships with all stakeholders in a DCT. In terms of working with patients, for example, YPrime interacts with family and patient advocates—even collecting information on attitudes and emotions—

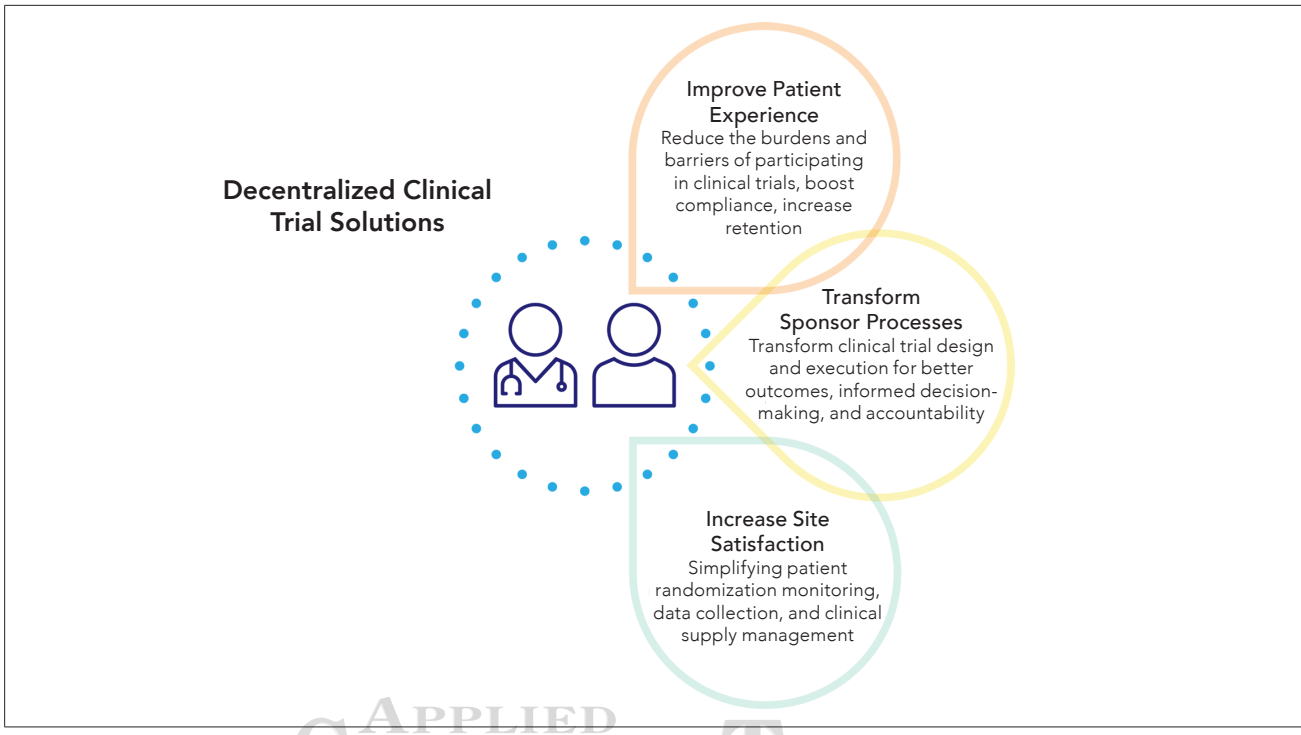


FIGURE 1. The three core advantages of decentralized clinical trials

to determine what matters the most in their daily lives as well as treatments.

Based on this information, YPrime can test hypothetical protocols—from patient education through data collection—and possible patient-reported outcomes. By combining the patient information and test protocols, YPrime can design a DCT that optimizes methods of outreach and supports patients with adherence—all tuned to the needs of specific patient populations.

Plan for success

The most successful organizations and studies align the protocol, patient type, and therapeutic area through a collaborative effort with partners, minimizing burdens and risk, while maximizing the effectiveness of the technologies applied. The patient journey needs to remain at the heart of designing technologies and strategies for patient-centric trials.

Near real-time data allows quality monitoring throughout and supports decision-making

"Patient-centric clinical studies are a critical outgrowth of the digital health revolution, giving patients an active role in the drug development process, from clinical study design through to expanding treatment opportunities for more patients," says Mark Maietta, President, YPrime. "Clinical trial technology can bring transformative benefits but requires deep understanding of the entire process and the lived experience of patients who navigate that journey."

Christine Bahls
Freelance Writer for Medical, Clinical Trials, and Pharma Information

The Risk-Reward Proposition for CGT Clinical Trials

As activity in this space grows, so do the hurdles in moving these products forward

Cell and gene therapy (CGT)—its risks and promises—are succinctly summarized in this description of clinical trial number NCT01129544, a Phase I/II study in children born with X-linked severe combined immunodeficiency (SCID-X1), an inherited, rare, and life-threatening disease. The eight-person trial, which began in May 2010, continues today. The following paragraph has been edited.[1]

Gene transfer is still research for two reasons. One, not enough children have been studied to tell if the procedure is consistently successful…. [And] we are still learning about its side effects and doing gene transfer safely. In previous trials, five children developed gene transfer-related leukemia; four are in remission; one died.

If the above information has stifled the research community's scientific curiosity about CGT, it is not evident. Evidence from numerous sources—ClinicalTrials.gov, the Alliance for Regenerative Medicine (ARM), FDA—are chock-a-block with studies, trials, and figures showing these therapies' popularity. In the second quarter of 2022, 3,633 such treatments were in development, up from 1,745 in May 2021. The vast majority are in the preclinical stage.[2,3]

Some sources are revealing more.

Stephen Majors

Most indicate that academics now have a remarkable presence in the CGT development space, including sponsorship. Last year, for the first time, ARM included sponsorship figures in its twice-annual industry report.[4] Academic- and government-sponsored trials far exceeded industry for sponsored trials in CGT. Stephen Majors, senior director for public affairs, ARM, says the alliance knew of academia's presence for the past few years, but only was able to get data this year from its partner, Global Data.

Less reliable, but still noteworthy, are data from ClinicalTrials.gov: for active Phase I trials, industry has 89; "others," which covers academia and government, have 50. Industry enrollment for Phase I is 172; others, 116. Phase III is one for others, eight for industry.

A little disruption in pharma's corner of the world? It seems that way. While basic bench to preclinical to clinical trial has long been the traditional route to FDA approval—and no one interviewed for this article suggested a reroute—what it does imply is that pharma members have some competition from the spin-offs and academic biotechs that historically they have absorbed.

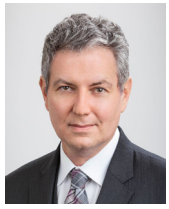
"There are suspected trends that we are watching," says Majors. As to whether academia's presence in this spot can be called a trend depends on one's definition of what a trend is. The Centers for Disease Control and Prevention (CDC) considers changes over a number years to determine a trend; financial investment firms typically evaluate over a two-year period. Considering that CGT companies raised $23.1 billion in 2021, 16% more than 2020,[3] the answer to the above question could be, maybe.

The CGT space is still immature, according to Mike Rea, founder of Protodigm, a self-described exploratory research organization that partners with biopharma clients on alternative development and commercial solutions. Physicians need time to be comfortable with these therapies, notes Rea, so they may not be used on a regular basis.

Arthur M. Feldman, MD, PhD

For example, physicians have to understand how to deliver the gene, agrees cardiologist Arthur M. Feldman, MD, PhD, whose lab worked on a heart failure-related mutation in BAG3 for decades.

Last month, the company he founded, Renovacor, agreed to be acquired by Rocket Pharmaceuticals.[5] "We are asking physicians to do something they never did before and to understand a very different set of information, including risk/benefit discussions that they didn't learn about in medical school," he says. Feldman is a Laura H. Carnell Professor of Medicine, Division of Cardiology, and a member of the Center for Neurovirology and Gene Editing at the Lewis Katz School of Medicine at Temple University.


Chris Learn

Chris Learn, Parexel's vice president of cell and gene therapy, is unequivocal regarding academia's increased presence in the drug development space focused around these treatments. He cites MD Anderson and Moffitt Cancer Center as two institutions that are sponsoring their own trials. "The lines are really blurring here," he tells *Applied Clinical Trials*. "It is indisputable."

The numbers

The following is a look at how academia is showing up in various reports.

In its 2022 report[4], ARM separated sponsorship, type of therapy—gene, cell-based, and tissue engineering—and trial phase. What these data show are industry far exceeding academic and government sponsored trials for gene therapy, while for cell therapy alone, the reverse is true: 656 cell therapy trials for academic and government, and 424 for industry. For gene therapy, there are 84 for the academics and government, and 222 for industry. In a later report, ARM found non-industry trials dropped.

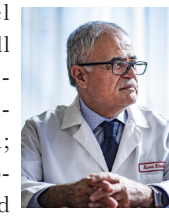
Pharma Intelligence's Pharma R&D Annual Review does not break down trials by their sponsors. It does, however, break down what's in the pipeline in various categories, including by the number of therapies per company, and by disease type.[6] In numbers captured prior to March 2020, the analysis reported 1,849 companies with a single drug in its pipeline, up from 1,633 in 2019, comprising more than half of all drug companies. As for types of therapies, gene therapy was in third place, the same spot it occupied in 2019. (Cancer-related therapies occupy the top spots.) Overall, biotech therapies in the pipeline increased by 13.2% in 2020 over 2019—6,135 vs. 5,422. Cellular therapy, the field in which academia is dominating, rose to 14th place, up from 33.

A decades' long tale of the heart

In 1982, Feldman was a resident in the cardiac care unit at the Johns Hopkins Hospital in Baltimore when he took care of a 22-year-old woman, a native Pennsylvanian, who was dying of heart failure. "Sadly, we didn't have drugs with which to treat her," he recalls. Feldman's involvement with the case and the woman's family led to his career as a cardiologist, he says. Twenty years later in Philadelphia, he was asked to see a heart-failure patient in consult, who turned out to be the aunt of the younger woman. It would take almost another 10 years until the technology became available to identify the genomic anomaly in this family. Here, a genetic variant that is produced by one of two alleles causes the protein product to be unstable. The result: the cell removes it, so the person with the variant has just half the amount of required protein.

> We are asking physicians to do something they never did before and to understand a very different set of information

BAG3 is an interesting protein that is found in the heart, the skeletal muscles, and the nervous system, including the brain. Its function is to help remove degraded and misfolded proteins, stop apoptosis or programmed cell death, and maintain the structure of the skeletal muscles. A missing allele isn't the only genetic cause for heart failure, Feldman said. Other patients, while having the correct amount of DNA, have a point mutation–a single amino acid–in half of the produced DNA. That single letter is the wrong amino acid in the specific site in the protein.


Kamel Khalili, PhD

Around this time, Kamel Khalili, PhD, Laura H. Carnell Professor, and chair of the department of microbiology, immunology, and inflammation; director of the Center for Neurovirology and Gene Editing; and director of the Comprehensive NeuroAIDS Center, Lewis Katz School of Medicine, Temple University, had created a method by which he could excise the HIV virus from patients using the new technique of CRISPR-Cas9.

Khalili believes that BAG3 may be involved in the pathogenesis of HIV-1 in brain diseases and protein quality control caused by viral infection as well as several other disorders, including Alzheimer's disease and dementia. BAG3 changes

I think it is just the beginning. Academia will put their futures in front of them. Why put all your sweat equity into it … and not have any fiduciary benefit of the approved product?

the homeostasis of the cell, he says. "The only solution is to fix the cell." Khalili has used CRISPR technology to excise the viral genome in both small and large investigational animals and has recently started a Phase I trial to test the safety of the new gene-editing treatment. Khalili, too, started a company, but Temple holds the license. In the case of Renovacor, it was granted the license by Temple.

"As a scientist, when you are doing something in biomed research, [the] goal is to translate bench work to the clinic for [the] wellness of people. We are doing long hours and long days because we want to help. We are trying to see if discovery can help people," says Khalili. "I know my limit, I stop at business aspects. My interest is to discover research which can help populations."

Was Feldman happy with his business experience? "As a company gets bigger, others join the team who fulfill other roles, like acquiring funding or developing the actual product," he says. "Releasing the control reins are difficult." But if it speeds up the timeline to get an approved product into the clinic, "then it's all worth it," he adds.

Researchers such as Feldman and Khalili, says Kaspar Mossman, PhD, director of communications and marketing at QB3, a University of California biotech accelerator, are normally not deeply interested in business. He notes the new flagship space in UC Berkeley called Bakar Lab. So far, it has 25 companies, one-third from university labs. "They collaborate, they share equipment, [at times] they merge," Mossman tells *Applied Clinical Trials*.

And, he adds, "Academics tend to be very smart individuals. The more time they spend in business, they learn stuff and become serial founders," says Mossman. "They are honest about not wanting to be a CEO."

In terms of business, the academics' employers are also pretty smart. The huge bugaboo with CGT commercialization is the manufacturing process—the need for an apheresis unit, ultra-cold storage, and regulated cell processing facilities.

Some institutions are building their own manufacturing facilities to more easily meet the increasingly complicated standards pertaining to regenerative medicine production. Harvard, MD Anderson, Moffitt, the University of Pennsylvania, and the University Hospital of Liege in Belgium[8] all have or are planning to build their own facilities.

Pros and cons

As for how academia's presence impacts the traditional pharma space, those interviewed cited pros and cons. More research is better, more companies vying for venture capital funding is not. But more trials mean more competition among similar therapies, which, says Majors, is a good thing.

"We need experimentation," adds Rea. If left to pharma, he says, the research wouldn't happen. "Smaller biotechs are taking the risk." Over the last 10 years, Rea believes pharma has been slow in the risk-taking department. Once upon a time, pharma didn't have many competitors. Now, with many numerous smaller companies with viable assets, willing to accept a smaller net profit, the competition is creating some angst. "Pharma can't project everyone's movement," says Rea. "The gene/cell therapy landscape [for products] is huge."

Likely adding to the angst: Those smaller biotechs are getting financial help. Between April 4, 2021, and June 24, 2021, of 23 start-up financing deals, 19 involved academics.[2]

Learn's viewpoint is different. He says there are too many players out there, and while large pharma may be averse to risk, "I really do believe what we are witnessing are simply market forces that have played into this." There is so much cash coming in, he continues, that "people can be blinded by the pitfalls." The CGT area, he adds, is "bloated" and he says the industry needs an overall strategy.

Learn doesn't think that academia's presence in the CGT space is a flash in the proverbial pan. The enthusiasm to find cures is real, and some re-

search institutions have the endowments to see the trials through. "I think it is just the beginning," says Learn. "Academia will put their futures in front of them. Why put all your sweat equity into it … and not have any fiduciary benefit of the approved product?"

In Pharma Intelligence's 2020 Pharma R&D Review, its author questioned the wisdom of so many drugs, overall, in the pipeline—4,001 added in 2018 and 4,730 added in 2019, for a total of 17,737 drug candidates. "[A]re the industry's eyes getting too big for its belly? Unless it can continue to provide [approved therapies] then a certain degree of control in the pipeline might be advisable," the report stated.[6]

And now to costs. While no one doubts these cures change lives, the question of access persists. FDA's approval of Bluebird Bio's second therapy this year, branded as Skysona, for early but active cerebral adrenoleukodystrophy, is expected to cost $3 million. Learn doubts that payers are jumping up and down to get Skysona on their formularies.

It's still a "fairly dicey business proposition" for companies to invest in this field, Steven Pearson, MD, president of the Institute for Clinical and Economic Review (ICER), said recently.[8] There's "still a risk" that next-generation therapies will not flourish "even in developed countries' health systems," he added.

One positive development in the US, however, occurred late last month when Congress reauthorized the Prescription Drug User Fee Act (PDUFA) for the next five years, 2023-2027. The action maintained FDA's authority to collect fees from manufacturers and keep and recruit agency staff to review the increased number of CGT applications. Majors says most of FDA's review of CGT products involves scalability and consistent reproducibility in the manufacturing process, which, of course, means traveling.

According to a Senate press release[9], FDA is seeking to hire at least 320 new staff members. In a statement, Pharmaceutical Research and Manufacturers of America (PhRMA) said a "modern regulatory framework supported by PDUFA helps ensure patients have timely access to lifesaving medicines."

Keeping pace

PDUFA reauthorization aside, there is little argument that the field of CGT, from research and drug discovery through commercialization, is advancing rapidly. In turn, so are the unique operational and manufacturing challenges that these therapies present. This reality may thin the currently crowded playing field in CGT going forward, with those sponsors and partners best prepared to deliver on the numerous touchpoints required separating from the pack.

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Rare Disease Clinical Trials: Strategies Learned from Duchenne Muscular Dystrophy

Approaches sponsors, CROs, and investigators can take from the DMD experience

Mary P. Kotlarczyk, PhD
Project Manager in Clinical Operations, TRiNDS

Ana K. Christensen, MPH
Director of Strategic Solutions, TRiNDS

Michael G. Kelly, PhD
Chief Scientific Officer, CureDuchenne

Lauren P. Morgenroth, MS, CGC
Chief Executive Officer, TRiNDS

Delivering successful outcomes in rare disease clinical trials requires special attention to study planning, patient recruitment and retention, collaboration, and management. The R&D track record in one disease setting in particular, Duchenne muscular dystrophy (DMD), has shown this to be true. DMD is an x-linked genetic disorder affecting an estimated six in 100,000 individuals.[1,2] It is characterized by mutations in the dystrophin gene that cause progressive weakness due to muscle cell damage as a result of routine physical activity. Over the last 10 years, drug developers have completed multiple successful clinical trials in DMD, leading to regulatory approvals of mutation-specific drugs in the US and Europe.[3]

With a long history of active engagement and interest in clinical trials, DMD clinical care, sites, and communities are uniquely positioned to support clinical study success. Patient groups have brought together clinicians, regulators, and nonprofit organizations to collaborate on various research, clinical, and funding initiatives. As a result, standard clinical care guidelines for DMD are being implemented around the world and have continued to evolve since initial publications on respiratory care in 2004.[4-7] In 2018, FDA published industry guidelines for DMD drug development,[8] and, today, the landscape is crowded with multiple sponsors conducting competing clinical trials in global multicenter networks. While each new trial has its own specific needs, past success of DMD clinical studies can offer valuable strategies sponsors, CROs, and researchers can draw upon today.

Seek supportive input, relationships

As DMD illustrates, it is important to consider all available resources when planning a rare disease clinical trial. First, consider if there is regulatory guidance specific for the disease space, as such guidance can inform key trial design decisions about the patient population and outcome measures. When planning international rare disease trials, regulatory agencies may have conflicting preferences and requirements to be addressed—and clinical care for rare diseases can be vastly different, particularly if there is no established standard of care. Even within the same country, sponsors cannot assume a patient in one location is receiving the same type of care as one in another; patient priorities and available support options can vary greatly across communities.

Sponsors and CROs should, therefore, seek to develop relationships with existing academic and medical networks as well as patient organizations during the trial-planning stages. This will allow them to connect with potential investigators and better understand patient perspectives on clinical trial participation. In addition, these relationships can be particularly valuable for understanding the variable regional landscapes. For example, in the case of DMD, the Duchenne Natural History Study[9,10] was conducted by the Cooperative International Neuromuscular Research Group (CINRG), and its datasets have been a key part of the success of many DMD trials.[11] Natural history data for rare diseases can be used to inform sample size estimation and outcome measure selection, and, in some cases, serve as a comparator group for investigational trials.

Nevertheless, despite these tools, sponsors of trials targeting rare diseases inherently face operational challenges—the first being practical decisions around whether even investing in clinical development is reasonable, given the landscape of known competitors with late-stage or approved products. As DMD has shown, if the development space is crowded, there is more competition for a limited participant pool. And, fundamentally,

healthcare providers, patients, and families need to perceive a new investigational therapy as worthwhile relative to other experimental or approved treatments. Clinical sites can become overburdened with operating too many studies for too few patients. Sample sizes in rare disease trials are typically smaller than those for more chronic, widespread conditions; optimizing data collection and minimizing missing data are even more critical with a small study population. To that end, sites may need additional resources to adequately manage participant follow up and trial assessments. Patients, for example, may need assistance with transportation and accommodations if they live far from a site.

Sponsors should also consider engaging specialized CROs with experience in conducting rare disease trials. These organizations may have connections with sites and patient groups to potentially help bolster recruitment. And their experienced data managers can design case report forms appropriate for the patient population, particularly when standard values in healthy populations are not in alignment with those found in the patient setting. It is important as well for sponsors, when determining outcome measures for rare disease trials, to engage with subject matter experts who have experience standardizing outcome measures across the patient population. Primary outcomes in rare disease studies should be ones that are likely to change and have clinical meaningfulness tied directly to the investigational drug; rather than outcomes that represent disease progression.

Equipped to educate

Patient recruitment and retention is, of course, critical to the chances of a successful rare disease trial. Recruitment planning begins with understanding the clinical and social contexts of eligible participants. Given the inclusion and exclusion criteria of the study protocol, sponsors and CROs should define what an eligible participant's symptoms are and how they impact daily life, where the person lives and receives care, and the knowledge level of the individual in regards to research and interventions concerning their condition. This portrait can guide site selection and recruitment strategy, and aid in the development of educational tools. At the patient level, investigators can be better prepared for participants' expected levels of science and health literacy during recruitment and the informed consent process. In turn, at the study level, sites and CROs may be more apt to set aggressive recruitment goals, use proactive recruitment tactics, and work compassionately with participants.

Regardless of interaction point, patient advocate organizations, such as CureDuchenne in DMD, are playing ever-expanding and critical roles in helping prepare patients for clinical trial readiness through education and outreach. CureDuchenne collaborates directly with sponsors and researchers to fund, advise, and help accelerate the drug development process. Further, its centralized data hub, CureDuchenne Link, has been built to support researchers by combining clinical data, biological samples, and patient-reported data for individuals with DMD and Becker muscular dystrophy, factoring in female carriers, which are very rare in both, as well. The platform facilitates data sharing, which is important to advancing a deeper understanding of the disease and accelerating research closer to a cure.

CureDuchenne also conducts regular workshops and webinars to keep the community informed on the latest scientific developments in DMD research, including status and participation in clinical trials. The group also educates on best practices to extend ambulation, and offers guidance on disease management and care. While DMD may be better positioned for drug development than other rare diseases, there are several approaches sponsors, CROs, and investigators can take from the DMD experience and apply into any rare disease clinical trial.

First, evaluate the available resources

- Natural history data: Select endpoints and outcome measures based on the natural history data. Leverage natural history study protocols to develop methods for outcome measure collection. If natural history data is not available, investment in this area is critical and will support multiple future clinical trials.
- Standardization of clinical care: Clinical trials will struggle to meet endpoints if the clinical care is variable. Design protocols to align with published clinical care guidelines for consistency across sites. Development and publication of guidelines increases the chances for success.

Next, recruit collaborators

- Site selection: Select sites with the experience and capacity to successfully conduct the trial. Choose sites to provide adequate geographic

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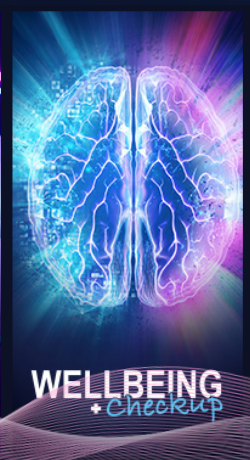

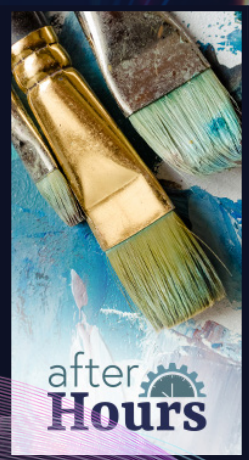

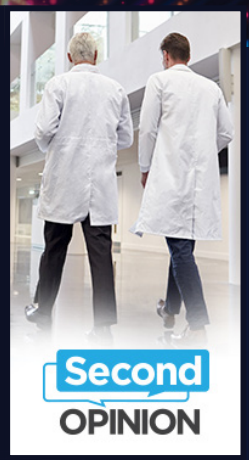

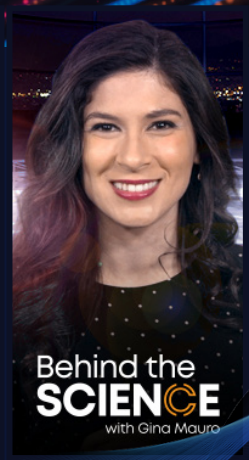

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coverage with the provided travel support. Prioritize sites that can provide excellent customer service to participants throughout the study.

- **Advocacy groups:** Engage with patient advocacy groups early. Once oriented to the study, they will be invaluable partners to help educate families, find eligible participants, and resolve unexpected problems.
- **Global community:** Most rare disease clinical trials will need a global network to succeed. Engage with regional partners to better understand the clinical context in their geography.

Finally, build in recruitment and retention up front

- **Recruitment plan:** Set aggressive recruitment goals and motivate sites to actively find participants and engage with them about the protocol. Work with advocacy groups and clinical networks to drive referrals and meet recruitment goals.
- **Build consensus:** Sponsors and CROs may need to educate each other about the intricacies of conducting a smaller clinical trial in a rare disease. Stakeholders may need to reset expectations of what a "large" clinical trial might be in a given disease or therapeutic area. Building internal consensus supports setting effective strategies.

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Esther Mahillo
Vice President, Operational Strategy and Feasibility, Precision for Medicine

Enhancing Enrollment in Biomarker-Driven Oncology and Rare Disease Trials

Integrated approaches can help enhance recruitment plans

Oncology accounts for 27% of all clinical trials conducted since 2017. Compared to other therapeutic areas, oncology trials are more resource-intensive and less efficient, requiring an average of 16 clinical sites to enroll a median of just 31 patients per study. In fact, average enrollment duration for oncology trials is two times longer than for all diseases combined (22 months vs. 11 months).[1]

Yet research interest remains high, with oncology accounting for 45% of all planned studies from Q4 2021 to Q4 2024. Nearly half of these are Phase II studies and almost 40% include countries in North America, while 35% are being conducted in Asia.[2] As of July 2022, among the 19,700 new drugs in the pipeline, 6,731 (34%) are for cancer. This robust development activity spans over 20,000 organizations across 116 countries. Interestingly, 72% of these oncology trials are sponsored by companies outside of the top 50 pharmaceutical organizations and 67% are for rare and orphan disease indications.[1]

Among the more than 1,500 potential oncology biomarkers that have been identified in the preclinical setting, approximately 700 are involved in the active or planned clinical trials in oncology. Over 60% of these studies are for immuno-oncology drugs, with the remainder for targeted therapies.[3]

The rise of personalized medicine has been driven by biomarkers, which have enabled researchers to understand the science behind mechanism of action and have been used to target recruitment. More than one-third of all drugs approved by FDA since 2000 have been personalized medicines, demonstrating that biomarker-driven approaches help optimize treatment impact and improve patient outcomes.[4] In fact, a recent analysis of 9,704 development programs from 2011 to 2020 found that trials employing preselection biomarkers have a two-fold higher likelihood of approval, driven by a nearly 50% Phase II success rate.[3]

The value of biomarkers is not limited to the clinical trial setting. Rather, biomarkers play a critical role throughout drug discovery and development, bridging preclinical and clinical studies. Incorporating biomarkers into programs requires careful choreography—from collecting biological samples and analyzing them in decentralized or specialty labs to generating data that will be integrated with other clinical information to support decision-making. It may also require a broad spectrum of logistics and laboratory management capabilities for handling a range of sample types.

Challenges of biomarker-driven development

Table 1 on the facing page provides a sampling of FDA-approved biomarker-driven therapies. A key challenge of integrating biomarkers into development programs is selecting the right biomarker. Often, the frequency of the biomarker of interest is very low. The same or similar biomarker may be present in multiple tumor types at varying frequencies, as is the case with HER2 amplifications in breast and gastric cancer. Biomarker frequency may also differ among races and ethnicities—it may also change as the disease progresses. For example, EGFR exon 20 T790M alterations increase in frequency in patients with non-small cell lung cancer who have become resistant to previous lines of therapy. Consequently, selecting the right biomarker is akin to finding a needle in a haystack.

Case study

Precision for Medicine was involved in an oncology cell therapy study, where eligibility was based on the expression of two biomarkers. The first biomarker was expression of human leukocyte antigen (HLA)-A*02:01 and the second was a tumor type expressing a certain cell receptor on at least 80% of cancer cells. Precision for Medicine performed

Boosted by Biomarkers

Biomarker	Therapy
EGFR exon 19 deletions & EGFR exon 21 L858R alterations	TK inhibitors
EGFR exon 20 T790M alterations	Osimertimib
ALK rearrangements	Alectinib, brigatinib, crizotinib, ceritinib
BRAF V600E	Dabrafenib, trametinib
MET	capmatinib
HER2 amplification	Trastuzumab, ado-trastuzumab-emtansine, pertuzumab
PIK3CA	alpelisib
KRAS/NRAS	Cetuximab, panitumumab
BRCA 1/2 alterations	Olaparib, rucaparib
FGFR2	Pemigatinib, infigratinib
Homologous recombination repair (HRR) gene alterations	olaparib
TMB ≥ 10 mutations per megabase	pembrolizumab
NTRK 1/2/3 fusions	larotrectinib
MIS-H	pembrolizumab

TABLE 1. EXAMPLES OF APPROVED BIOMARKER-DRIVEN THERAPIES.

SOURCE: Precision for Medicine

an analysis and found that the prevalence of HLA-A*02:01 varied among geographic regions, with a prevalence of 38.5% to 53.8% in Europe and 16.8% to 47.5% in North America (see Figure 1 on next page).[5] Based on this finding, we recommended conducting this clinical trial in Europe.

Analysis of the expression of the cell receptor of interest showed that expression levels varied not only by tumor type, but even by subtype or demographic (see Table 2 on page 25).

We used these findings to project the number of patients and samples that would need to be screened in order to enroll 36-40 study participants. Our assumptions were that 30% of patients screened would have HLA-A*02:01 expression and 10% of those patients would have ≥80% biomarker expression, and 50% of those would meet all the inclusion criteria for the study.

Based on these assumptions, it was determined that HLA analysis would need to be performed on approximately 2,500 blood samples and immunohistochemistry would need to be performed on about 750 tumor tissue samples to reach the enrollment target.

A key challenge of integrating biomarkers is selecting the right biomarker. Often, the frequency of the biomarker of interest is very low

To increase the efficiency of this study, the Precision for Medicine team implemented various strategies for streamlining the recruitment process:

1. **Identifying where potential patients are located.** In addition to evaluating epidemiology data, we searched the databases of not only our global clinical site network but also our biospecimen repository, for patients who might be eligible for this study. We partnered with organizations, including commercial next-

Biomarker-Expression Eligibility

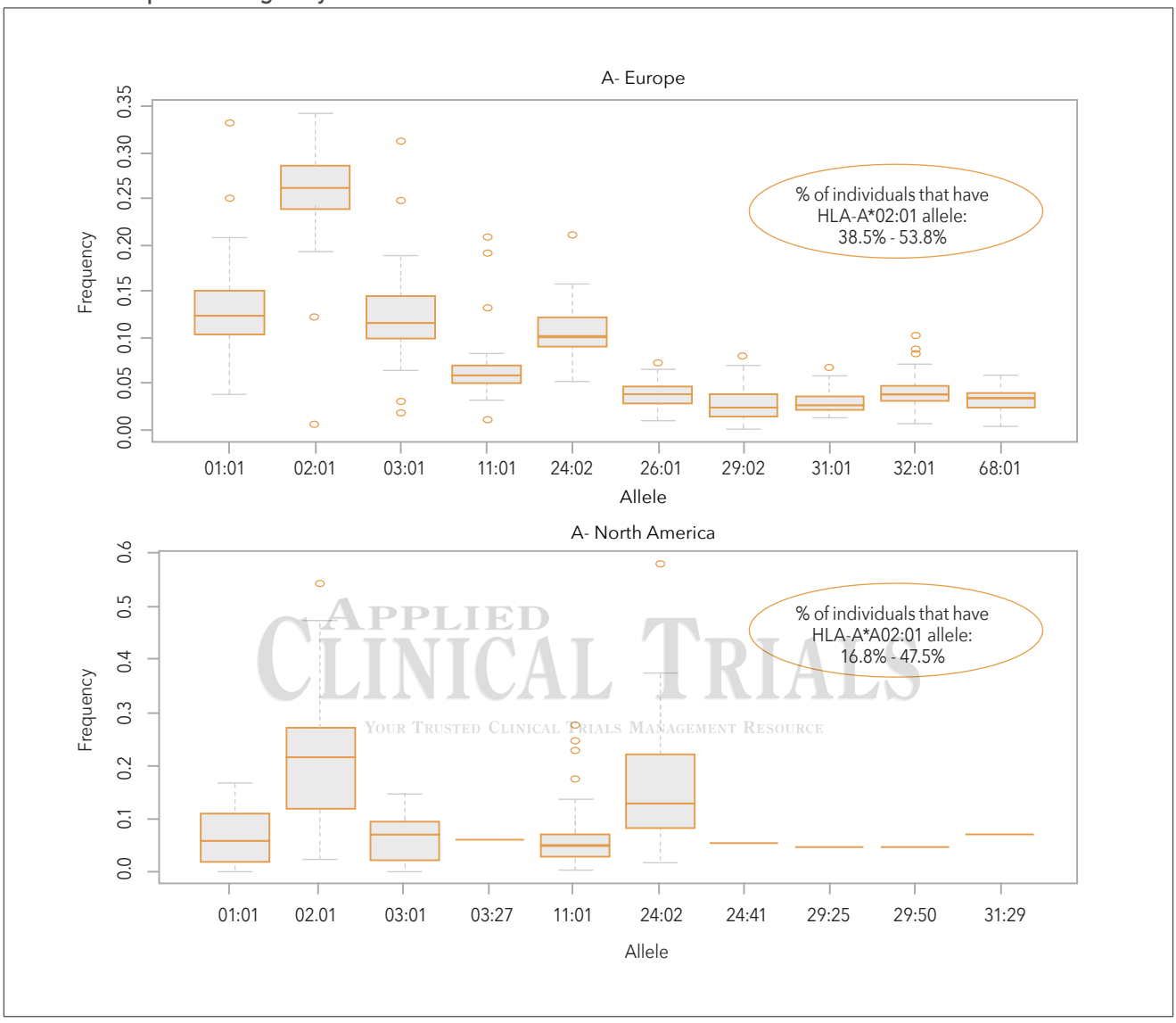

FIGURE 1. THE PREVALENCE OF HLA-A*02:01 VARIED BY REGION, HELPING TO TARGET WHERE TO CONDUCT THE STUDY.

SOURCE: Precision for Medicine

generation sequencing (NGS) laboratories, that have access to site networks and examined ICD-10 claims data. We also leveraged strategies such as advertising to proactively attract potential patients.

2. **Identifying the best sites for enrolling patients.** To identify and qualify sites, we leveraged our global clinical site network and key opinion leaders and evaluated sites based on various criteria, including previous experience and competing studies in a similar patient population that might interfere with recruitment. We also assessed the regulatory landscape to understand the nuances involved in conducting the study in different regions or countries with regard to compliance with advanced therapy medicine product guidelines or data protection regulations and access to health data.
3. **Enhancing patient enrollment.** Performing a pre-screening study that is separate from the core clinical trial can help to increase efficiency and enrich the patient funnel. One option for this study was to perform a pre-screening study to analyze blood samples for

Pre-screening Snapshot

Indication	Subtype	Biomaker expression
NSCLC	NS	70%-80%
Melanoma stage IV	NS	51%
High-grade endometrial cancer	Endometrioid endometrial cancer grade 3	93%
	Serous and clear cell carcinomas	86%
Breast cancer	NS	50.8%
	Medullary	33%
	TNBC	69.2%
Glioblastoma	All	37.8%
NSCLC	<60 years old	21%
HNSCC	NS	69.8%
Papillary thyroid carcinoma	NS	36.5%
Ovarian cancer	Serous cystadenocarcinoma	53.7%-77.8%
Bladder cancer	NS	22%-60%
Liver cancer	NS	80%-69.9%
Pharyngeal tumors	NS	70%
	Nasopharyngeal	31.1%
Neuroblastoma	NS	44%
Oral squamous cell carcinoma	NS	80%
Gastric cancer	NS	32.5%
Renal cell carcinoma	NS	20%

TABLE 2. BIOMARKER EXPRESSION VARIES BY BOTH TUMOR TYPE AND SUBTYPE.

SOURCE: Precision for Medicine

HLA-A*02:01 expression. Sites were also provided access to EHR Connect, Precision for Medicine's proprietary data mining tool, to assist in the identification of potentially eligible patients. Concierge services were also offered to help ease the burden of study participation, and other decentralized trial strategies were deployed to enhance enrollment.

As oncology clinical research evolves toward personalized treatment of patients in niche populations, a biomarker-driven approach to drug discovery and development is required. With new biological targets frequently having a low level of prevalence, it is important for researchers and developers to look for more innovative approaches to patient identification.

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Daniel Kavanagh, PhD, RAC
Senior Scientific Advisor, WCG

A Biosafety Perspective on Operational Challenges in Cell and Gene Therapy Studies

The benefits of working with an institutional biosafety committee in CGT research

A rapidly growing portion of clinical trials involve cell and gene therapy (CGT), or human gene transfer. These studies involve administration of living cells and/or genetically modified DNA or RNA to clinical trial participants. In 2022 to date, the Alliance for Regenerative Medicine has identified 2,093 active clinical trials in this category, testing products from 1,369 cell, gene, and tissue-engineering therapeutic developers.[1] Examples include: regenerative medicine products derived from pluripotent stem cells, immune effector cells engineered to express chimeric antigen receptors (e.g., CAR-T cells), genetically engineered oncolytic viruses, and viral vectors expressing therapeutic transgenes to treat inherited or acquired disease. Importantly, within the CGT category, certain operational considerations apply only to cellular therapies or only to gene transfer therapies, and some apply to both.

When research involves potentially infectious or transmissible agents, genetically modified DNA or RNA, or biological toxins, it should be evaluated for potential risk to research staff, the general public, and the environment. Biosafety is the field of practice dedicated to assessing and mitigating these risks, and biosafety oversight at many research centers is provided by an institutional biosafety committee (IBC). *The NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*[2] are issued by the National Institutes of Health (NIH) and mandate IBC approval for certain clinical trials prior to initiation. For research subject to the NIH guidance, the approving IBC must be registered with the NIH, and each such IBC registration pertains to a unique institution or clinical trial site.

Historically, each NIH-registered IBC was administered by the respective research institution, usually the university or academic medical center, and the bulk of research under review by these committees was basic science or preclinical studies. More recently, biosafety oversight for many clinical trials has been provided by central commercial IBC service providers, who can manage the IBC registration for multiple sites selected for a multicenter trial, for example.

Whether or not IBC review is mandatory for a particular study, certain biosafety considerations are recommended in the interest of responsible conduct of research. In the sections ahead, we will summarize these considerations in terms of NIH requirements and best practice recommendations.

Study-level biosafety considerations for sponsors

The NIH guidance requires that IBC approvals be issued for each clinical trial site or institution. This means that there are no study-level approvals under the guidance; nevertheless, there are many ways that clinical trial sponsors can facilitate best practices and efficient IBC approvals. If biosafety considerations are addressed in an investigational new drug (IND) application, they can inform preparation of study documents that are distributed to investigators and review committees. These documents may include the protocol, investigator's brochure (IB), pharmacy manual (or administration manual/product handling instructions), and draft informed consent form (ICF).

Under the current version of the guidance, IBCs are not required to review the ICF; however, institutional review boards (IRBs) and IBCs may collaborate to identify and address third-party risks to participants and close contacts or family members, and these considerations may affect IRB approval. Review and consultation with a biosafety professional during the drafting stage of these documents can enhance their utility and facilitate efficient site-level approvals. For example, where appropri-

ate, protocols should include plans for shedding assessments in the schedule of events. Also, the IRB should realistically address potential third-party risks and summarize existing preclinical or clinical shedding data.

A key document for biosafety review in multicenter clinical trials is the sponsor pharmacy manual, or equivalent product handling instructions. The pharmacy manual provides an opportunity for the sponsor to instruct sites and investigators on the safe handling of study agents. The pharmacy manual can also help to inform the site selection and study start-up processes whenever special equipment, such as a biological safety cabinet (BSC) is required. Clinical trials of non-biohazardous drug products often involve the use of laminar flow hoods for drug preparation. However, laminar flow hoods are generally not approvable for preparation of biohazardous products. BSCs (e.g., Class II A2 BSCs) are designed to protect the sterility of the drug product and the safety of the clinical staff and are required for some but not all CGT research. IBCs consider biosafety requirements under both the NIH guidance *and the Biosafety in Microbiological and Biomedical Laboratories* (BMBL) handbook.[3] Depending on the study, drug preparation at a site may also be subject to rules relating to current good manufacturing practices (cGMP), US Pharmacopeia (USP) 797, or USP 800 requirements. Collaborative review by pharmacists and biosafety professionals during the drafting stage of the pharmacy manual can harmonize operating expectations and facilitate site regulatory submissions and clinical trial initiation.

When it comes to site selection, there are a variety of considerations that specifically apply to CGT research. As mentioned, for gene transfer research, sites should either have an IBC registration with the NIH or be willing to become registered. Facilities and equipment required for a protocol should be specified in the respective pharmacy manual or equivalent, and prospective sites should be evaluated to see whether that equipment is available on site, or if purchasing, installation, and certification are required (all of which require time to complete). For cellular therapies, sites with demonstrable expertise in clinical operations may undergo a rigorous evaluation to become certified by the Foundation for Accreditation of Cellular Therapy (FACT).[4] On the other hand, for many CGT products, it is possible with expert assistance to enable naïve sites to undertake advanced therapies research—an important consideration as sponsors seek to engage with underserved communities and diverse patient populations.

Does My Study Require IBC Approval?

The *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* include detailed information specifying when institutional biosafety committee (IBC) review of a clinical trial is required. Clinical research subject to the NIH guidance requires IBC approval if it meets the definition of human gene transfer (HGT) research per guidance section III-C-1. HGT research is defined as administration to a human research participant of an investigational product containing genetically modified DNA or RNA (with certain exceptions for molecular sequences that are very short or genetically inert).

HGT research is subject to the NIH guidance when specific types of funding apply at the level of product development, sponsor, study, or clinical trial site. In addition, the guidance recommend voluntary compliance even in cases where funding does not apply.

Biosafety considerations at the site level

For a site with limited experience in gene transfer clinical trials, preparing to conduct research with advanced therapy or gene transfer products may seem like a daunting challenge. IBC review ensures that proposed research activities are compliant with federal biosafety requirements. Clinical staff often report that working with an experienced biosafety professional helps them feel confident about their approach to CGT study start-up and execution.

For any site, the first step in securing IBC approval is to ensure that there is an IBC registered with the NIH for that site. For sites using a commercial IBC service, the registration is generally administered by the commercial service provider on behalf of the site. Once registered with NIH, the IBC may be maintained indefinitely, so a new registration for each new study is not required.

Once the NIH registration is filed, then site staff can begin working with the IBC to secure approval for the first protocol. In general, each clini-

cal trial protocol requires separate IBC approval. In contrast to IRB reviews, which are focused on protecting clinical trial participants, IBC reviews are focused on protecting clinical staff, visitors, the public, and the environment. When reviewing a clinical trial, an IBC will consider numerous factors, including the proposed biosafety level (i.e., BSL-1 or BSL-2) for the research and the equipment, training, and procedures to be used in safe conduct of the research.

As mentioned, a key item of equipment for many (but not all) gene transfer procedures is a BSC, and the most used type is Class II A2. Many research pharmacies are already equipped with this type of cabinet for general use, even without gene transfer research experience. Class II A2 cabinets draw clean air from the surrounding environment via a HEPA filter and then blow clean, HEPA-filtered exhaust air back into the workspace. When properly used, this design will both protect the investigational product (IP) from contamination, and protect clinic staff from unintentional exposure to the gene transfer product. BSCs require certification by an expert inspector prior to initial use and at regular intervals after installation.

In general, IP preparation at clinical trial sites does not require rooms with special airflow or negative pressure to comply with biosafety requirements. However, in certain cases, sponsors or sites may determine that ducted evacuation of exhaust air is needed, in response to special requirements relating to cGMP standards or the use of volatile compounds. These designs may involve Class II B2 or Class III BSCs, which channel air into exhaust ducts. Designing facilities to maintain balanced airflow in the presence of ducted BSCs requires a very significant increase in expense and setup time compared to regular Class II A2 operations. Any such facility should be carefully designed in consultation with architects, HVAC engineers, and biosafety professionals to minimize expense and delays.

Sites preparing for IBC approval should ensure that there is a biosafety standard operating procedure (SOP) appropriate for each protocol under review. The SOP should clearly delineate how the IP is received, stored, transported, prepared, administered, and disposed of, in addition to describing planned response to spills, exposures, and other unexpected events. Spill response for an IP that may contain viral vectors, infectious agents, or bloodborne pathogens requires careful planning. It is important that staff trained on the SOP response are available to respond at any time that spills may occur.

It is also important to ensure that risk to patients and visitors not enrolled in the study is minimized, especially in clinical contexts such as cancer centers where many patients are likely to be immunocompromised. Depending on the study agent, it may be advisable to segregate enrolled participants from other patients, especially during dosing and infusion, when spills or accidental release of IP is most likely. Sites can benefit from planning ahead to identify infusion areas where participants can be kept separate during dosing.

Compliance and expectations

Clinical research with products containing genetically modified DNA and RNA is a rapidly growing area, and includes some of the most promising new advanced therapies. Most sites, even those with little or no experience in this area, can conduct these studies safely when they partner with experienced biosafety professionals. In many cases, the sites will be required to seek IBC approval, which not only ensures compliance with federal guidelines, but also helps ensure that investigators and staff understand best practices and expectations for safe and responsible conduct of gene transfer research.

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Real-World Data Networks: Automating & Reducing the Burden of Clinical Studies and Registries

ON-DEMAND WEBCAST

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Event Overview

Real-world data networks are changing how data is collected and leveraged for evidence generation. A tech-enabled platform approach can significantly automate and reduce the burden of clinical study programs and registries, improve site and patient engagement and lower costs.

Join Dr. Richard Gliklich, CEO of OM1, as he discusses this new research model, its benefits and special considerations, including:

- Automating data collection with specialized treatment centers and KOL sites
- The value of reusability and meeting multi-stakeholder requirements, including regulatory
- Enhancing understanding of unmet needs and patient experience
- Accelerating product differentiation with RWE

Key Learning Objectives

- Discuss opportunities for and benefits of using real-world data networks for conducting clinical research
- Identify applications for meeting multi-stakeholder requirements
- Explore use cases for generating evidence and demonstrating differentiation

Who Should Watch

- Life sciences senior managers and executives with responsibilities in conducting clinical studies and registries and in roles such as R&D, clinical operations, clinical affairs, medical affairs, real-world data, real-world evidence, strategy and innovation functions.

Presenter

Richard Gliklich, MD
Chief Executive Officer
OM1

Moderator

Andrew Studna
Associate Editor
Applied Clinical Trials

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Radha Krishnan
Global Director, Biorepository Operations and Strategy, Avantor

Managing Biospecimens in Cell and Gene Therapy Trials

Pursuing new tools and capabilities in sample logistics, storage, and data analysis

One of the most powerful and significant developments in medical therapies in the past decade has been the maturing of cell and gene therapy (CGT) treatments. Cell therapies such as CAR-T and TCR-T offer transformative outcomes for challenging diseases. Recent cell therapy approvals and the growing number of clinical trials are accelerating the process from discovery through clinical trials to commercial manufacturing and delivery.[1]

Gene therapies can provide significant—and possibly curative—benefits to patients who have genetic or acquired diseases. Through the direct expression of a therapeutic protein or by restoring the expression of an under expressed protein, gene therapy uses vectors to deliver gene-based drugs and therapeutic loads to patients.

While the approvals for treatments for rare diseases are certainly early wins, the impact of gene therapies will significantly expand as approved treatments are administered to larger patient groups and studies expand to address diseases that are broader reaching—for example, with treatments for multiple myeloma, leukemia, and other forms of cancer.[2]

Biospecimen management challenges

Compared to more standard biopharmaceutical clinical trials, there are unique challenges associated with managing biospecimen samples during trials of CGTs. One of the most critical challenges is properly and safely managing the specimens taken from each patient, since those specimens can actually be used to create the therapy and must be returned with absolute safety to the patient for treatment.

CGT trials, while following their own specific workflows, are generally carried out in similar stages. Cell therapy can be allogenic when produced from cells that are collected from a healthy donor and shipped to a clinical site to treat a patient. Alternatively, there can be autologous therapy, where the biological material is from the patient and is transferred to a biomanufacturing site for genetic modification, and then returned and administered to the patient the sample was taken from.

Although each trial is unique, the major workflow steps are relatively similar. First, genetic or cell-based disease states and potential therapeutic pathways are identified by researchers and the trial design begins to be developed.

Once a trial is designed, trial participants need to be identified. Unlike other biopharmaceutical trials, CGT trials tend to have much smaller patient populations. Biospecimen cells are collected from these patients and need to be transported under the most stringent safety and cryopreservation conditions in coordination with regulatory requirements.[3] This includes having well-established cold chain logistics that manage and document each specimen's condition to ensure that no temperature-related degradation occurs.

Each specimen is then used to biomanufacture the therapeutic cells—either through modification of the cell genome (for cell therapy) or through creation of the viral vectors to deliver gene-based drugs and therapeutic loads to the patients. These temperature-sensitive therapies must then be carefully thawed, with minimum impact on viability and functionality, to be delivered to the patient by the clinical trial team at the investigative sites.

In addition, as part of the clinical trial, portions of the specimens need to be set aside, before and after biomanufacturing, for various testing requirements. Tests like qPCR, ELISA, flow cytometry, and others are critical to conducting the analysis of the therapeutic steps being studied, so proper storage (short-term and long-term) needs to be fully managed.[4-5]

Proper management of aliquoting biological samples is also a critical element in biospecimen management for these trials in order to mitigate risk of cell deterioration from freeze-thaw cycles. Many research centers require aliquoting to generate sub-samples for distribution to third-party laboratories and clinical partners. Since the source biospecimens from each patient are so much smaller in actual quantity, extraordinary care is

needed at every step of biospecimen management not to lose any biological material.

Finally, biospecimen management for CGT trials must include support for stable, multiyear storage. With the administration of gene therapy products into a patient, there is a possibility of delayed biological events that demand the collection of data for a longer period. The therapeutic changes that patients experience due to genomic modification often need to be tracked for 10 to 15 years, so long-term cryogenic storage of the modified cells is a critical element for supporting the trial.[6]

As CGT trials expand, it is important for the industry to investigate and fully understand the best practices researchers should follow for managing living/active samples during CGT clinical trials, especially given some of the unique processes described earlier.

Along with management during the active trial, it is also crucial to long-term biorepository and sample management to ensure your biospecimens are secure and safely stored. These best practices include having a thorough appreciation of the regulatory factors to consider when managing the type of data generated by these trials.

Due to the sensitive nature of this personalized kind of medicine, researchers need to work very closely with regulatory agencies to fully understand and plan the trials according to established protocols. Gene therapy developers have access to expedited approval pathways such as Regenerative Medicine Advanced Therapy (RMAT) designation in the US, PRIority MEdicines (PRIME) designation in the EU, and SAKIGAKE designation in Japan.

Biorepositories address management obstacles

Leading biorepository providers across the globe are responding to the heightened complexities and risks of biospecimen management in CGT trials. They are building on established sample logistics, storage, and management tools to address these unique challenges more fully. Concerns include:

- Preserving the specimens from collecting the cells from patients through cell therapy manufacturing and delivery to them. Unlike other treatment regimens, the specimen is also the therapeutic pathway—its safe preservation, management and storage is critical to the progress of the clinical trial and ultimate demonstration that the therapy can be successfully applied.
- Rigorous cold chain transport logistics to ensure cryopreservation at multiple stages. This requires detailed, multifactor tracking of each sample so that it is clearly and permanently associated with a specific patient at every point of exchange and every process step, including ancillary steps associated with clinical testing and long-term storage.
- Detailed familiarity with requirements and compliance: All clinical practitioners and personnel from biorepository logistics and storage organizations need to be thoroughly grounded in the strict protocols established for each trial and demonstrate how their procedures comply; since CGT therapies are so new, and patient risk is elevated, biorepository operations have a special duty to manage any biospecimen management safety concerns.

The relative newness of CGT programs at major life sciences research institutions has led, in some instances, to a preference for keeping all aspects of clinical trials within a single research organization or network of researchers.[7,8]

Because the relatively small size of the target patient in a given geographical region is as small as one-tenth the number of patients participating in traditional clinical trials, it has created the need for multiple locations worldwide for conducting clinical trials or having the patients travel for getting the clinical treatment. As a result, researchers tend to set up their own biorepositories, biospecimen management systems, and model industry best practices to maintain sample integrity and traceability across the sample management ecosystem.

While the desire for comprehensive control would seem to make sense, there are distinct advantages to working with expert biorepository operations to manage all key aspects of biospecimen capture, transport and storage. GxP or "good practice" quality guidelines and regulations with leading service providers assures proper storage for the viral vectors and cells so they have the traceability and consistency.

These include creating rigorous chain-of-custody procedures with advanced biospecimen digital documentation and tracking tools that tightly associate each specimen with its source patient throughout every exchange. They have established meticulous biospecimen collection and registration procedures that are flexible enough to adapt to specific clinical

trial procedures, patient populations, manufacturing locations and regulatory protocols.

Biorepositories are also customizing their cold-storage logistics and transport procedures to support CGT biospecimens. This includes tracking shipments in real time using automated tracing software and GPS-based tools, as well as working with clinical researchers to minimize transport times from the site of specimen collection to therapeutic manufacturing and specimen storage locations.

Leading biorepositories have also made extensive investments in large-scale, custom-built cryogenic storage facilities. These plants offer storage temperatures ranging from cryogenic -196 °C and ultralow -80 °C to refrigerated and controlled room temperature storage, offering researchers much greater flexibility. These specialized systems are continuously monitored and typically include multiple backup systems to prevent accidental specimen loss due to outside events or local power failures. Some of the leading biorepository providers have sited these state-of-the-art facilities in multiple locations worldwide to enable CGT trials with global footprints and patient populations to work with a single biospecimen management provider.

There are biorepository and biospecimen logistics providers who are actively investing in more robust, expert biospecimen data management systems. Just like their operational procedures, these tools have been developed and continually improved through hands-on experience managing millions of samples for a wide range of research applications.

These material management systems give instant digital access to comprehensive data of biospecimens that have been transported and stored, allowing researchers to efficiently manage biospecimen inventory, submit work requests, and generate standard or custom reports.

In addition, they are further developing these systems to satisfy evolving regulatory requirements for CGT clinical trial data management, since the conditions of the biospecimens at all stages of transport, biomanufacture, and storage need to be exhaustively documented.

Working with expert biorepository organizations and outsourcing biospecimen collection, cold transport logistics and both short- and long-term storage provide CGT researchers with a proven resource that can help prevent error, protect patient safety, and help make CGT trials more efficient.

An effective path forward would include increased collaboration between professional biorepository operations and clinical trial researchers. By fostering true working partnerships, these experts can educate researchers on the risks associated with imperfect or poorly planned biospecimen logistics; especially with multisite trials, they can work to refine standardized procedures and tools used to collect, secure, document, and transport specimens to reduce the risk of error or inefficiencies.

Streamlining and standardizing biospecimen management can ultimately help reduce costs, minimize rework and simplify many clinical trial management tasks often carried out by researchers. The advanced data management capabilities also provide a powerful foundation for conducting advanced data mining and analysis of trial and biospecimen data to augment other research results.

Most importantly, working with biorepository experts to handle these critical tasks will free researchers to focus their valuable time and efforts on advancing the science CGTs.

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What the Future Looks Like for Clinical Data Leaders

Katrina Rice
Chief Delivery Officer, Data Services, eClinical Solutions

The data manager has evolved into a data steward, the confident leader who owns and guides the modern data strategy

The industry-wide jump in data complexity, digitization initiatives, and volume of data sources, propelled further by the pandemic, requires new approaches to clinical data management. A 2019 study by the Tufts Center for the Study of Drug Development found 75% of life sciences organizations still using SAS and Excel to integrate and analyze data. Over 80% of respondents reported data management activities as time-consuming and labor intensive. The study also reported a 40% increase in last patient, last visit (LPLV) to database lock cycle times for companies with five or more data sources and concluded that contending with disparate data sources was contributing to longer database lock cycle times.

Since 2019, the trends impacting clinical data have only accelerated, due in part to adoption of decentralized clinical trial (DCT) models that enable increased remote data collection and greater utilization of local labs. Amidst this disruption, digital and analytics-based modern data management is now an imperative. Here are three ways clinical development leaders can approach this data management evolution by aligning people, process, and technology.

The rise of the data steward

Today, few would deny the importance of a data strategy. The current data environment is too complex not to have one. Most clinical data is generated from sources external to electronic data capture (EDC), and trials routinely average eight or more data sources. The traditional role of the siloed data manager, focused on cleaning and querying listings of EDC data is in the past. But in its next iteration, data management has even more value to offer. Its role has evolved continuously, becoming more technically advanced and growing in responsibility and complexity over the last 20 years. We've heard it asked, is the data manager becoming a data scientist? I would argue no. Instead, the data manager has evolved into a data steward, the confident leader who owns and guides the modern data strategy.

This new paradigm demands different skills, too. The data manager as data steward applies a breadth of knowledge across clinical development, from data management to quality and regulatory. They collaborate with clinical operations, programming, and biostatistics with enough professional knowledge of each to enable cross-functional empathy, ensuring all data stakeholders can get what they need from the data. This modern data manager looks at the whole picture the data tells across all data sources, connecting it to their knowledge of the data strategy for the trial. They apply their technical skillset to the many different systems used in development to support evolving protocol requirements and ensure that technology aligns to process improvements in support of accelerated timelines.

Empower data management

Variety in acquisition technologies creates flexibility to choose what is best for trials and participants. For clinical data infrastructure and analytics, this means interoperability is critical. Centralized data platforms can increase the quality of data deliverables and reduce manual work, positively impacting cycle times. Integrated clinical data platforms ingest and organize all sources and structures of data. They must have the ability to serve all their users, not solely the data manager. Data stewards maximize the use of these types of foundational tools that automate end-to-end data flows and enable greater collaboration and faster time to insights.

Risk-based optimization

It's one thing to have technologies and another to drive their use and adoption. For the data steward, upskilling team members and training in technologies is key. It's important to consider technology as organization-led and supported from a top-down approach. Involve teams across functions in re-engineering processes around the technology. It's not about bringing technology in, but about maximizing its use for the greatest efficiency gains.

Value is recognized when teams adopt and apply these tech-enabled approaches within their data strategy framework. Self-service analytics focus attention where it's meaningful and create collaboration opportunities among colleagues from a single source of truth. Teams can identify issues, see what has been reviewed, and detect trends and outliers in need of discussion. This approach avoids teams waiting until the end of the trial to integrate data, risking rework due to missed insights or outliers.

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