

# Clinical Researcher

**The Authority in Ethical, Responsible Clinical Research**

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## **Getting Down to Business in Clinical Research**

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## Clinical Researcher

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EXECUTIVE DIRECTOR'S MESSAGE

**Be Inspired, Be Informed, Be Connected**

Susan P. Landis, Executive Director of ACRP



Have you ever seen how, in movies or television shows, the swift passage of time may be represented by a quick shot of the pages of a calendar whipping by as if being blown in a hurricane wind? That's what it feels like for the staff and volunteers of your Association as we rush to put all the pieces together for [ACRP 2023](#), speeding along with the force of an irresistible southbound express train aimed at the immovable starting date of April 28.

However, this isn't our first rodeo, as the saying goes, and with the logistical help and managerial advice of our [sponsors](#), [hotel partners](#), vendors, and meeting planners both onsite and offsite, we aim to deliver nothing but the finest eye-opening moments, educational content, and networking opportunities possible for every stakeholder in the clinical research enterprise who attends.

I find it hard to believe that, after four earlier ACRP conferences in Texas dating as far back as 1985 (thrice in San Antonio and once in Houston), this will be our first-ever visit to Dallas, with all its history, culture, and attractions lying in wait for us. We look forward to seeing many fresh and familiar faces as we strive to inspire, inform, and connect you with one another during our time in the "Big D." It will be a homecoming of sorts for me, as I once lived in Dallas for nine years. In fact, I met my husband there—we were both working at *The Dallas Morning News*—and we got married at [Old City Park](#).

**Inspiration**

ACRP 2023 will inspire you to greatness. Join us as we spotlight your contributions to advancing health, connect you to purpose, and motivate you to be your best. Among the many opportunities we hope you will find inspiring at ACRP 2023, we invite you to:

- The Signature Series Session on [Women in Clinical Research: Perspectives of Progress](#) at 7:50 a.m. on Saturday, April 29
- A special presentation on [Disrupting Healthcare Through Innovation: My Personal Story, A Brief History, and Endless Gratitude](#) from Courtney Burnett, MD, Physician, Writer, and Brain Cancer Thriver, at 2 p.m. on Saturday, April 29

- The Signature Series Session on [The Intersection of Diversity, Equity, and Inclusion in Clinical Research: Strategies for Moving from Intentions to Actions](#) at 7:50 a.m. on Sunday, April 30
- The Signature Series Session on [Sound Off on DCTs](#) at 2 p.m. on Sunday, April 30.
- The Signature Series Session on [Sparks, Signals, and Success: Bringing Dedication to Disruption](#) at 7:50 a.m. on Monday, May 1

## Information

ACRP 2023 will deliver gold-standard education, along with expertise and insights to support your professional development and ensure quality and integrity in the clinical research process. The session-sized learning at ACRP 2023 has been organized into the following “[Content Journeys](#)” for your convenience:

- [Study Management & Conduct](#)
- [Regulatory Trends & Compliance](#)
- [Leadership & Career Growth](#)
- [Workforce Development](#)
- [Technology & Future Trends](#)

Although you are more than welcome to do so, you don’t have to stay on a single journey throughout your time in Dallas, so feel free to explore wherever the spirit calls you.

## Connection

ACRP 2023 will connect you to the people and resources you need to be successful in clinical research. No other event offers more opportunities to share kinship, knowledge, and fun with your community. You will have many chances for making and reinforcing connections with your new and old colleagues at such events as:

- The [Opening Night Celebration](#) for networking in the Expo Hall from 5 p.m. to 7 p.m. on Friday, April 28, for your first chance to meet with more than 100 leading-edge organizations and suppliers
- Additional [Expo](#) hours from 9 a.m. to 2 p.m. and from 4:30 p.m. to 6 p.m. on Saturday, April 29 and Sunday, May 1, including receptions both evenings starting at 5 p.m. (breakfast and lunch are served in the Expo Hall Saturday and Sunday)
- A variety of half-hour long “Small Talk” opportunities on focused topics scattered throughout the schedules on Saturday and Sunday (see the [full schedule](#) for details)

**See You There!**

PEER REVIEWED

## **Electronic Source Reduces Protocol Deviations Compared to Paper Source in Clinical Trials**

Ryan Chen, BA; Calvin Nash, BA; Nicole Mastacouris, MS; Garrett Atkins, MPH; Daniel Dolman; Jonathan Andrus, MS; Raymond Nomizu, JD



Web-based clinical research software solutions that let sites configure data templates to specific trial protocols and capture data against those templates in a clinical setting are known as electronic source (eSource) solutions. eSource leverages the use of edit checks and other technology innovations to reduce the incidence of protocol deviations in clinical trials compared to paper source (pSource). While many sites have not yet transitioned away from the traditional pSource model, eSource may

represent an efficient systematic alternative to this traditional method. To investigate the effect of eSource at the site level, we report the study of protocol deviations using a commercial eSource solution vs. site-generated pSource across three independent study sites within a large network.

### **Background**

Source data were first defined in section 1.51 of the International Council for Harmonization's Good Clinical Practice (ICH-GCP) guide as the original data in records and certified copies of original records of clinical findings, observations, or other activities used for the evaluation of a clinical trial. Source documents are defined in section 1.52 of the ICH-GCP as the original documents or records that store source data. Source data are fundamental to trials as they are analyzed to establish study outcomes. Attempts have been made to provide guidance on source document generation and completion since source data ultimately become core study data.

In compliance with federal and state law, this documentation should be attributable, legible, contemporaneous, original, accurate, enduring, available and accessible, complete, consistent, credible, and corroborated.{1} These standards were created to protect human subjects and safeguard study integrity. Despite industry standards, some sites struggle to meet all source criteria; in fact, source documents are the most commonly cited document type in findings during monitoring inspections and audits.{2} Therefore, additional consideration is needed to improve initial source document accuracy and reliability.

### **The State of the Industry for Paper vs. Electronic Source**

Like source, the case report form (CRF) is an electronic or paper tool used to collect and store clinical information associated with clinical research protocols. Unlike source, CRFs are typically a secondary data reservoir designed to standardize data collection across multiple sites as specified by the sponsor.{1,3} CRFs are designed by the study stakeholders to capture required endpoints while source is the responsibility of the investigators. Typically, sites transcribe data from site-captured source templates into the CRFs, and sponsors then perform source data verification (SDV) to confirm the accuracy of the CRF transcriptions against the underlying source before locking the CRF data and extracting for statistical analysis.

Presently, electronic CRFs (eCRFs) are auditable digital records of clinical investigation data that can be systematically captured, reviewed, managed, stored, and analyzed.{3} The flexibility of the eCRF and its potential integrability into other medical technological platforms—like the electronic medical record (EMR)—eliminates transcriptional errors during eCRF data entry.{4}

The pharmaceutical industry has largely migrated from paper CRFs (pCRFs) to eCRFs in response to issues of data quality and cost efficiency.{5} Multiple studies have demonstrated a substantial improvement in data quality via a reduction in data entry errors when eCRFs were implemented over pCRFs.{6–8} eCRFs allow sponsors and sites to perform point-of-entry logic checks and auto-query generation, which result in faster turnaround times for query resolution.{8–10}

A more efficient query resolution process translates into shorter post-recruitment study times and reduced study costs due to financial mitigation in data management and site monitoring processes. eCRFs offer several additional advantages, such as instantaneous data submission, ease of handling, and overall efficiency.{7}

## **Making the Case for eSource**

Use of eSource may offer significant advantages over pSource models. Electronic documentation offers greater accuracy, accessibility, security, and efficiency, and may help reduce the deviation burden of clinical research sites. Benefits of the transition from paper to electronic documentation can be modeled by the industry move from traditional paper models to digital systems.<sup>{3,6–8}</sup> This can result in improved workflows, reduced cost, and increased productivity, making electronic documentation a preferable option for many organizations. The transition to eSource may yield similar benefits and should be explored.

Despite these benefits, the adoption of electronic documentation can pose a challenge for facilities that have streamlined their workflow based on pSource models. The implementation of new electronic systems may require significant changes in established practices, potentially causing disruptions and resistance among personnel accustomed to traditional methods. Moreover, facilities that have adopted the eSource model may face integration challenges when attempting to incorporate their records into eCRFs required by study sponsors. This may be exacerbated by the fact that few eSource models have permission for direct transcription, making it difficult for facilities to transfer their data seamlessly into eCRFs. These challenges may be particularly severe for facilities that have limited experience with electronic systems.

To date, no studies have compared the effect of pSource to eSource on protocol deviation rates at the site level. To understand the benefits of eSource, we looked at a group of research sites that were transitioning from pSource to an eSource model and studied the impact of each methodology on the rate of protocol deviations observed with each method.

## **Methodology**

We focused on a commercially available eSource solution (CRIO) being used by a study site network, Benchmark Research, that performs third-party data collection for clinical trials in the public and private sector. As of 2020, this network had helped its clients conduct more than 1,000 clinical trials and interface with more than 40,000 participants, contributing to the development of new vaccines and medical therapies worldwide.<sup>{11}</sup> The network's central office services encompass performing study visits and monitoring data entry to sponsors' eCRFs.



We analyzed the anonymized data gathered by the network from three of its large clinical trial sites (in New Orleans, La. and Austin and Fort Worth, Texas) from January 1 through March 22, 2022. During this period, all three sites were in the process of transitioning from pSource templates to eSource templates. Because the sites preferred not to change source data methodology mid-study, each site during this period had a mix of studies using each data collection methodology. The network configured its own study templates using the aforementioned eSource product's built-in configuration modules, which allows sites to build their own schedule of events and configure questions, instructions, and edit checks based on sponsor protocols. No sitewide hardware system upgrades were necessary to facilitate the transition to eSource, as the product is accessible in web-based browsers.

All clinical trials being conducted at the sites during this period were reviewed. Only in-person visits were considered. During this period, the network's central office had in place numerous mature processes governing the identification and classification of protocol deviations. All protocol deviations were identified in a running study-specific protocol deviation log. The network's quality assurance (QA) team then reviewed each deviation and classified them as either site-generated or other-generated. Site-generated deviations are those whose root cause was in site performance, and which were not previously approved by the sponsor. Since the network already reviews source completion as part of its QA protocol for sponsors, no additional clearance was necessary to access eSource.

In our study, we reviewed the protocol deviation logs across all trials. Trials implementing the eSource solution served as the experimental group and trials using pSource served as the control group. The number of site-generated protocol deviations in both models were compared. The number of protocol deviations per completed study visit was the endpoint. Completed study visits served to calibrate across the relative volume of work performed.

The rate of protocol deviation (RPD) was calculated by dividing the total amount of site-generated protocol deviations by the total number of visits performed. Percent reduction of RPD was calculated as the percent difference (see Table 1).

**Table 1: Deviation Rates in pSource vs. eSource**

	Source method	Total Visits	Total Deviations	Deviation rate (as percentage)	Reduction
Site 1	Paper	695	10	1.44%	
	CRIO	2394	16	0.67%	54%
Site 2	Paper	1022	8	0.78%	
	CRIO	1766	8	0.45%	42%
Site 3	Paper	1197	11	0.92%	
	CRIO	1312	10	0.76%	17%
Total (Weighted Avgs)	Paper	2914	29	1.00%	
	CRIO	5472	34	0.62%	38%

A one-tailed, two proportion Z test was utilized to determine if using eSource significantly decreased the RPD as compared to pSource. All samples are independent and simply random. The null hypothesis states that the use of eSource does not reduce the RPD. The alternative hypothesis states that eSource decreases the RPD. A significance level of 0.05 was used ( $\alpha = 0.05$ ). Figure 1 demonstrates the formula used to calculate the Z-score for the two proportion Z test.  $\hat{P}_1$  represents proportions from sample 1 and  $\hat{P}_2$  represents proportions from sample 2.  $\hat{p}$  represents the total pooled proportion from both samples.  $n_1$  represents the sample size of sample 1, and  $n_2$  represents the sample size of sample 2.

**Figure 1: Two Proportion Z Test Formula**

$$Z = \frac{\hat{P}_1 - \hat{P}_2}{\sqrt{\hat{p}(1 - \hat{p})\left(\frac{1}{n_1} + \frac{1}{n_2}\right)}}$$

**Results**

The use of eSource decreased the RPD across all sites. At site 1, the RPD using pSource was 1.44% while the RPD with eSource was 0.67%; there was a 54% reduction in deviation ( $Z=1.9574$ ,  $\alpha=0.05$ ,  $P<0.025$ ). At site 2, the RPD was 0.78% and 0.45% with pSource and eSource, respectively; there was a 42% reduction in deviation ( $Z=1.1108$ ,  $\alpha=0.05$ ,  $P=0.1335$ ). At site 3, the RPD was 0.92% with pSource and 0.76% with eSource; there was a 17% reduction in deviation ( $Z=0.4305$ ,  $\alpha=0.05$ ,  $P=0.3336$ ).

The weighted RPD with pSource across all three sites was 1%, while the weighted deviation rate of eSource was 0.62%. There was a 38% reduction in deviation rate when eSource was used as opposed to traditional pSource ( $Z=1.8879$ ,  $\alpha=0.05$ ,  $P=0.02938$ ).

## **Discussion**

The use of eSource platform consistently decreased site-wide deviation rates compared to when conventional pSource was used. Using data from three participating sites, the calculated weighted deviation rate significantly decreased when eSource was used compared to when traditional pSource was used between a set period. The statistically significant decrease in weighted deviation rate demonstrates that eSource use leads to an overall decrease in RPD.

While the decrease in weighted deviation rates was statistically significant using a one-tailed two proportion Z test, this was not always the case at each independent site. At site 1, the reduction in deviation rate was statistically significant at 54%. The reduction in deviation rate at site 2 was not statistically significant at 42%. The reduction in deviation rate at site 3 was also not statistically significant at 17%. While the RPD from eSource use may not be statistically significant at sites 2 and 3, the baseline RPD rates with pSource use are already so low that the observed site-level improvements with eSource implementation may be difficult to quantify as significant. Site 1 also had nearly double the number of visits implementing eSource compared to sites 2 and 3; this may demonstrate that the efficacy of eSource is tied to the degree of experience a site has working with it.

A nearly 40% reduction in the rate of protocol deviations due to the use of eSource could benefit clinical trials at the sponsor and patient level by improving data quality and patient safety. The improvement in data quality is consistent with the eSource solution's features, such as real-time edit checks and visit window calculations which are designed to automate and flag error-prone processes. The site network's QA team attributes the drop in deviations to these automation features.

Furthermore, eSource improves patient safety by protecting patient privacy. Recommendations for best practices in anonymizing patient-level clinical trial data include the ability to standardize processes across data holders, practically delivering large volumes of data, and cost

efficiency.<sup>{ 12}</sup> eSource addresses all of these criteria due to its practicality, which allows a cost-efficient way for different parties to access large quantities of data simultaneously in a secure manner. eSource can further improve cost efficiency by decreasing the downstream effects of protocol deviations, such as prolonged data-cleaning times and associated costs for corrective action plans. The resources spent on these tasks could be reinvested by the sponsor and study stakeholders into other aspects of clinical research.

In addition to decreasing the rate of site deviations, using eSource offers many other advantages over pSource. The site network's QA team reported several advantages from using eSource over pSource charts. When pSource is used, quality control (QC) often requires having site staff scan paper charts and e-mail them to QC personnel, who in return annotate those scanned documents and then return the annotated scans to the site. After the sites correct the errors, the sites must then scan and e-mail back the corrected paper templates for review. Multiple cycles of this process may occur, which can exponentially increase the time spent on these clerical tasks. Furthermore, there is often a delay between data capture and data QC due to the administrative time required to scan and send in paper documents.

By contrast, QA teams can review the eSource platform directly to review the source data shortly after they are collected, or even in real time during an ongoing study visit, and then issue electronic queries for the site to resolve. The site network's system, for example, has built-in change management, so that changed source is highlighted for successive review. Since all data are electronic, multiple stakeholders can view the data at the same time, across geographies, enabling more efficient global workflows.

### **Further Considerations**

Several logistical and administrative challenges may limit the transition to an eSource model. One of the key challenges is the burden associated with initial implementation, as it requires the necessary hardware, software licenses, and network resources. Additionally, sites must train their research staff on the new systems to ensure that legal, regulatory, and quality standards are met, especially during the transitional stage. Sites with smaller volume may find the initial costs of eSource system licensing and personnel training to be uneconomical.

It is also important for study sites to consider the cost efficiency of adopting eSource systems in their circumstances; large-volume sites, such as those that generate a high volume of documents, may benefit more from the transition to digital documentation models than smaller sites. This is because the costs associated with managing paper-based documentation, such as printing, quality assurance, storage, or transportation, can be significant for organizations with large volumes of data. As a result, sites with greater recruitment volume are most likely to benefit from the eSource model, while smaller sites are less likely to experience a significant mitigation of data management costs.

It is important to note that, currently, there is no standardization in the utilization of eSource systems for clinical trials. A study site's choice in software may or may not easily interface with a sponsor's computer systems. While this lack of standardization and potential lack of compatibility may introduce challenges, it may also allow study sites to select software that best suits their needs. As the standardization of eSource systems evolves, it may help simplify the process of choosing eSource systems and improve clinical trial workflow.

## **Limitations**

While this study provides valuable insight, several limitations should be noted. The level of protocol complexity for each study was not assessed and used as an independent variable for analysis. Greater protocol complexity scores could potentially lead to more deviations compared to studies with lower protocol complexity scores. Additionally, we did not consider the number of patients per study, which may be associated with an increased rate of protocol deviations due to a larger volume of study visits. Diagnostic and laboratory data values were not considered as metrics for protocol deviations, as these types of data are usually procured from external contract research organizations and automatically transmitted to the sponsor's eCRF.

## **Conclusion**

eSource platforms may offer a cost-efficient, reliable alternative to traditional pSource documentation models in clinical trials. Besides improving data quality and patient safety, eSource platforms simplify other processes in clinical trials such as recruitment, the QA process, and stipend management for patients. It is important for independent study sites to consider the

cost efficiency of implementing eSource systems; recruitment rates, data management cost analysis, software licensing, and hardware requirements may limit access to eSource platforms depending on site volume. As the landscape of eSource systems evolves, more research is needed to identify other independent variables that may influence the effectiveness of such solutions.

## Disclosures

Jonathan Andrus and Raymond Nomizu are currently affiliated with Clinical Research IO (CRIO). Garrett Atkins and Daniel Dolman are currently affiliated with Benchmark Research. Benchmark Research is a third-party firm which provided data to CRIO for this study, and has no financial gain from the research being conducted.

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## The Top Life Sciences Trends Shaping 2023: An Outlook from Ireland

Jane Lyons



*As the life sciences sector evolves, being on top of new trends and regulations is essential for success. By navigating the complexities of risk-based systems, leveraging cutting-edge technologies, and prioritizing their supply chains, companies in Ireland can remain at the forefront of the industry in 2023.*

### **The Adoption of Artificial Intelligence and Big Data in the Sector**

The life sciences sector has been undergoing an immense transformation, driven by the adoption of artificial intelligence (AI), machine learning (ML), and natural language processing (NLP), and by the exploitation of “big data” sources in new and powerful ways. These new technologies and practices are enabling companies to restructure their business models, reduce human error, increase efficiency and performance, and bring innovative products to the market much faster. This has led to the emergence of a new “pharmaceutical intelligence” that has allowed the industry to move away from traditional, slow-moving, and costly processes. AI is increasingly important in drug discovery and development as well as clinical trials, operations, pharmacovigilance, and many other areas.

The life sciences sector is increasingly leveraging technology across its operations, and this trend will continue in 2023 with more collaborations and partnerships between pharmaceutical, biotechnology, and medical device companies and information technology (IT) vendors. Through these collaborations, advanced technologies tied to AI and big data are being employed



to develop personalized and targeted medicines, ultimately leading to more effective treatments for diseases like cancer and immune deficiencies. This will also allow companies to utilize advanced computational models to find better treatments more quickly while also reducing costs associated with drug development. This trend has already begun and is only likely to grow as companies continue to invest in advanced analytics and data-driven decisions.

### **Blockchain Technology: The Future of Data Transparency**

Blockchain technology is quickly becoming one of the most important trends in the sector, offering a secure and easy way to share data across organizations. This technology provides all parties with an up-to-date and accurate view of the supply chain and other datasets, which is essential for maintaining robustness in the manufacturing process. While blockchain is commonly connected to cryptocurrencies, its uses extend far beyond financial transactions, and the technology is being adopted across the sector to increase transparency and security.

One of the most valuable aspects of blockchain is that transactions on a blockchain network are stored permanently and are viewable by all participants, making it difficult for fraudulent activities to go unnoticed. This helps to ensure that sensitive data, such as patient information or drug safety standards, remain secure and trustworthy. The technology also offers a more efficient and cost-effective way to handle transactions confidentially. In addition, increased research and development in personalized medicines are driving more demand for blockchain technology. With personalized medicines, the need for data accuracy and integrity is paramount, as decisions are made with individual patients' health in mind. These factors highlight that the need for secure data sharing has become more important than ever in the sector.

### **Bringing Innovations to Market**

The digital revolution in the sector is poised to take a huge leap forward in 2023. We have already seen how the adoption of digital technologies into clinical trials enables decentralized readouts and mobile phone applications for patient participation, allowing for more efficient and cost-effective clinical trials that span multiple regions. This could drastically reduce the time, cost, and resources associated with clinical trials. At the same time, Industry 5.0 will build upon

the principles of Industry 4.0 to take production processes to a new level of human-centricity. This could lead to more personalized medicines tailored to individual patient needs and help companies develop more effective treatments for certain patient groups.

At the same time, the sector is closely following advancements in digital health technology and their applications in healthcare. Wearable technologies such as fitness trackers, heart rate monitors, and smartwatches are becoming increasingly popular and allow users to track their health more accurately than ever before. Wearables also have the potential to revolutionize healthcare in clinical trials, providing data that are more accurate and reliable than traditional methods of monitoring patients.

Another component is “connected health,” which refers to the use of digital technologies for healthcare, including mobile health (mHealth) and telehealth applications. Connected health has a wide range of potential applications, from providing patients with more convenient access to care to enabling healthcare providers to better monitor patients’ health. In 2023, technologies that power wearable devices and support connected health are likely to become increasingly popular as companies continue to invest and explore the possibilities of leveraging them for healthcare purposes from remote monitoring to clinical decision support.

### **Ensuring Safety and Efficacy with CSA and CSV**

Computer software assurance (CSA) and computer systems validation (CSV) are two distinct areas of compliance that companies must consider when developing new computer systems for use in drug manufacturing and other related processes. CSA is a set of standards for ensuring the safety and efficacy of computer systems used in drug manufacturing, while CSV involves validating the computer systems themselves. We expect to see a rise in CSA and CSV as companies continue to invest in computer-based technologies and strive toward meeting regulatory standards.

The adoption of cloud computing has also enabled companies to bring their products to market quickly while maintaining compliance and quality standards. This has allowed for the acceleration of innovation in the sector and is expected to become even more prominent in 2023.

## An Evolving Regulatory Landscape

The regulatory environment is becoming increasingly interdependent and globalized. Companies are looking to leverage overseas approvals to increase efficiencies while ensuring quality and safety standards are met. This is especially true as the trend toward incorporating AI, cybersecurity, and data analytics into healthcare products is rapidly growing. In response, new regulations have been created to evaluate the quality, safety, and efficacy of these products.

In particular, European Union (EU) companies must pay attention to Medical Device Regulation (MDR) and *In Vitro* Diagnostic Regulation (IVDR). For example, the IVDR sets out specific requirements for software used as a medical device. These regulations stipulate the necessary steps for the design, development, and fulfillment of products that are considered “software as a medical device” (SaMD), from concept to market entry.

The release of new guidance from the Medical Devices Coordination Group (MDCG), operating under the European Commission, and any transitional arrangements must also be considered. The U.S. Food and Drug Administration (FDA) has introduced an electronic Submission Template and Resource (e-STAR) program to support companies in developing and reviewing new medical devices, which provides an interesting opportunity.

### Did You Know...?

- ❖ The [Health Products Regulatory Authority](#) is responsible for the assessment of clinical trials with medicinal products in Ireland.
- ❖ You can see how many active clinical trials are running in Ireland, according to CenterWatch, by [clicking here](#).
- ❖ A partial list of contract research organizations currently active in Ireland can be found [here](#).
- ❖ The [Irish Pharmaceutical Healthcare Association](#) works to create a suitable environment for the conduct of clinical trials in Ireland through the [Health Service Executive Clinical Trial Indemnity Form](#) and model Clinical Trial Agreement.
- ❖ The [Clinical Research Platform](#), a network of clinicians and supportive parties across the primary care and hospital divide, with interest and experience in performing clinical trials, is based in Dublin and works with more than 40 trial sites and deals with sponsors across Europe.
- ❖ Since 2017, [Cancer Trials Ireland](#) has led an industry-supported drive to raise public awareness of clinical trials.

## **New Requirements for Safety and Quality**

The continued interest in RNA-based therapies such as gene therapy and nano-extracellular vesicles is driving innovation within CMC biologics. CMC, short for chemistry, manufacturing, and control, defines the characteristics, safety, and consistency between batches of a pharmaceutical product. Ultimately, the goal of CMC within the biologics space is to ensure that pharmaceutical products can meet or exceed specifications throughout any step of the production process.

This goes hand in hand with revisions to EU pharmaceutical legislation which are providing opportunities to improve the supply chain and reduce drug shortages. The use of electronic product information and the web-based human variation electronic application form on the Product Lifecycle Management portal is also becoming more prevalent, particularly for centrally authorized products. Finally, the mandatory use of the Clinical Trials Information System for clinical trial applications in the EU is increasing, ensuring that safety standards are met.

At the same time, the newly revised EudraLex Annex 1, published in August 2022, has brought a much-needed shift in regulatory expectations. Instead of simply providing what is considered acceptable and not acceptable, companies must now provide risk-based rationales for decisions made with patient safety when it comes to manufacturing processes. This brings with it several challenges for organizations that are not at the same level of maturity when it comes to quality risk management systems.

To ensure readiness by the August 2023 deadline, companies should first evaluate their current level of compliance with Annex 1 regulations and identify any gaps between current status and the regulatory expectations. This assessment should include all areas of sterile manufacturing and should involve a cross-functional team to ensure everyone involved is aware of how the new Annex 1 will impact their areas of expertise.

## **Early-Phase Modeling to Inform Strategic Decisions**

By 2023, early-phase modeling (EPM) is expected to become a standard component within companies' development processes. The EPM process involves key evidence gathered from the early stages of product development to support and inform decisions around pricing and

reimbursement as well as market positioning. This helps to ensure that companies understand a product's potential before releasing it to the public, increasing the chances of successful reimbursement and anticipated pricing.

EPM not only helps to keep companies informed of a product's potential, but also allows them to become more aware of any gaps that may need attention. The process provides information on how a product will be accepted in the market, helping to predict whether there are likely to be any regulatory or health technology assessment questions or concerns. This is especially helpful for the developers of more complex therapies and medical devices, as timely evidence gathering can help to demonstrate a product's potential to investors and encourage further investment in advanced therapy medicinal products.

### **Capitalizing on 2023's Technology Trends**

The rise of advanced technology such as AI will revolutionize how the life sciences sector manages supply chains in 2023 and beyond. Companies will be able to leverage AI-driven analytics to predict customer demand and proactively adjust supply chain operations. Companies must prioritize sustainability in their supply chain operations. Among other considerations, this means investing in green production methods and ethical sourcing.

For the foreseeable future, the sector will be shaped by advances in technology, globalization, and quality compliance. Companies that fail to prepare for these challenges will find themselves left behind by their more nimble competitors.



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RULES & REGULATIONS

## Recommendations for Navigating New Regulations on Decentralized Clinical Trials

Neta Bendelac



Traditionally clinical trials have been conducted at specific clinical trial sites, to which patients had to travel. However, over the last three years, the demand for decentralized clinical trials (DCTs) has spiked, and a consensus has emerged that [DCTs will become permanent fixtures](#). The aim of DCTs is to make it easier for patients to participate in clinical trials by reducing the need to travel to central trial sites. This approach has the potential to make clinical trials available to a wider demographic of participants and reduce drop-out rates.

While decentralization might increase the accessibility of clinical trials to participants, regulatory bodies, including the European Medicines Agency (EMA), have recently published recommendations that aim to facilitate the conduct of DCTs while safeguarding the rights and well-being of participants, as well as the robustness and reliability of the data collected.

### Challenges and Considerations

One unique challenge to DCTs is managing investigational medicinal product (IMP) integrity. The EMA suggests that when sending IMPs to a participant's home, it is essential for logistics providers and vendors to have a contract in place outlining how the product is handled and shipped. This is an area in which the industry should strive to achieve better visibility and drug integrity. Additionally, while not considered a requirement, through digital solutions such as barcodes, logistics providers can verify that IMPs are dispensed at the appropriate time, ensuring that the correct product is used in the study and that the integrity of the product is maintained.

The EMA has also recommended that sponsors further consider the storage and administration of IMPs at the participant's home when designing a DCT. Patients should have sufficient measures at home to ensure the IMP's inclusion and exclusion criteria are adequately met. For example, appropriate storage conditions should consider temperature controls and unexpected light exposure. To maintain the safety and efficacy of a product, digital sensors can be used to monitor environmental indicators such as temperature, humidity, vibration, and light. If a patient does not have proper conditions to store a product, then local pharmacies can be utilized as an alternative to shipping the IMP directly to the patient's home. In that case, the pharmacists should be trained to dispense the IMP using the correct protocol.

DCTs should also require drug-centric procedures that consider recall actions in case a return is necessary. If a drug is unexpectedly compromised, it is essential to have a plan for how IMPs will be collected. Real-time tracking can report precisely where IMPs are located until the product is delivered. Recording data is just one consideration to take into account when designing a study that involves proper recall procedures when administering an IMP at a patient's home.

With this in mind, it is also essential to inform patients participating in the trial that third-party vendors will use their data to correctly and safely send an IMP to their homes. This information should be explicitly stated in the consent process, and participants should be made aware of their rights and any potential risks associated with using their data in this way.

The EMA further recommends that healthcare professionals still be involved in preparing and administering an IMP, even in a decentralized setting. When a participant self-administers an IMP, there should be step-by-step instructions to ensure the correct and safe use of the product. In addition, electronic instructions via accessible methods, such as QR codes, should be considered.

## **A New Mandate**

In the United States, regulations such as those included in the recently passed [Public Law 117-328](#) (otherwise known as the 2023 omnibus appropriations bill) have recently gone one step further, no longer recommending certain procedures, but mandating clinical trials create diversity

action plans. The outbreak of the pandemic accelerated the implementation of digital technology, resulting in a significant increase in the use of digital solutions including mobile health tools and tele-healthcare in clinical trials (e.g., video consultations), health data analytics (e.g., data processing systems that support bioinformatics modelling), and digital record systems.

Once stakeholders are confident that technologies are adequately validated, selection based on scientific and ethical considerations can be presented to regulators in accordance with applicable legal and regulatory frameworks. The possibilities are virtually limitless, and in the context of trial participation and access to medicine, technologies could assist in:

- Reducing assessment times and hence increasing patient compliance
- Improving access to individuals with rare diseases in remote settings
- Making reasonable adjustments to allow equal access for individuals with disabilities
- Enabling patient engagement from marginalized groups with a preference for remote access

## Conclusion

It is critical for sponsors to work closely with regulators to ensure DCTs are conducted safely and in compliance with all regulatory expectations. In the coming years, recommendations such as those posed in this article by EMA will further allow DCTs to advance, teaching sponsors lessons and revealing the full benefits of this novel approach. Stabilizing guidelines and encouraging the use of digital tools will drive continued adoption and innovation.



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ON THE JOB

## Clinical Data Management: From Back Office to Center Stage

Richard Young



*As clinical science advances, data professionals will lead in trial optimization by solving a Rubik's Cube of people-, process-, and technology-related challenges.*

After more than two years of scrambling to adjust to rapid-fire changes in clinical trial operations, life sciences are moving on to address new challenges. More companies are developing long-term plans for their clinical programs, while sponsors strive to become more efficient and make technology less burdensome for patients and research sites. Those on the leading edge are working to unify data and connect more closely with partners. The goal is to speed up access to information and improve patient value.

At the same time, the science driving clinical trials is changing rapidly. Trials that were once one-dimensional are now multidimensional, with [more varied data sources](#) being considered daily. Adaptive designs are now being used in basket and umbrella studies; for example, [adaptive trials](#) for sickle cell disease and beta-thalassemia treatments involving CRISPR. In some cases, trials are amended after every patient visit, driving a more performant study and protecting patient safety.

These approaches are still considered novel, but will likely become more familiar over time. The same applies to trials involving more automation and new strategies leveraging artificial intelligence (AI). Will our existing data infrastructure be able to handle them?

## **Linear Approaches Won't Work for Multivariate Problems**

As an industry, we have to stop thinking linearly about clinical trials. Instead, we should examine them from the people, processes, and technology perspective. I think running a trial today is akin to solving a puzzle: a Rubik's Cube. For those unfamiliar with a Rubik's Cube, the once phenomenally popular game introduced in the 1980s requires players to rotate six squares that come in six different mixed-up colors as part of an overall cube up and down and back and forth until each side of the cube is a single color—all without disassembling or damaging the cube in any way.

Imagine that one side of the cube represents patients, another sites, another regulators, another data management, another clinical research, and another statistics (and that is leaving out other potential sides for pharmacovigilance and medical writing).

The first thing you will appreciate about the cube is that you can only see three sides at any time, no matter how you orient yourself or the cube. Consequently, when you make a change, you have no idea what impact that change will have on the other three sides outside your vantage point.

However, like any good clinical trial, there is an additional complexity to consider because you are not the only person trying to solve the Rubik's Cube. Imagine other people are trying to solve it at the same time. Do your moves work in concert with or against those of the other players? Are they undoing your good work? Are they making things easier or better for you?

If we accept this analogy of a Rubik's Cube, our next thought is to review whether we are solving this effectively, or if at all. As we explore the growing complexity of clinical trials, another idea comes to mind—what if, rather than solving the Rubik's Cube, we are unintentionally making it even more complicated?

Rather than nine pieces per side, what if there are 16 or 25; what if the puzzle is no longer a cube but a dodecahedron? The truth is that, instead of solving this puzzle, we're only making it larger and more complicated. This is where clinical data professionals come in and why the industry needs to move from merely managing clinical data to thinking more strategically and adopting science-based approaches.

For years, the clinical data manager's role has been invisible. Practitioners reconciled and cleaned data quietly in the back office, separated from colleagues in clinical operations and other departments. It is time for a change.

### **New and Changing Roles in Clinical Data**

With data and scientific complexity changing trial design and execution, clinical data specialists are moving from the back office and taking centerstage. Clinical data managers are now helping to solve some of the most challenging problems, such as optimizing protocols, improving trial flexibility for patients, and collaborating across functions. As Mayank Anand, outgoing Chair of the Society for Clinical Data Management (SCDM), put it, “Who else will be able to clean the terabytes of clinical data that the industry is currently generating?”

I recently discussed the evolution of clinical data management with Mayank and Luis Torres, head of programming and the full-service provider business program at Labcorp Drug Development, in the [State of Digital Trials podcasts](#).

As Mayank recalled, clinical data management has often been an accidental career path for those who had studied life sciences, biotechnology, or genomics-related fields in graduate school. He said that data professionals took a back seat for years in strategic planning and business meetings.

Similarly, Luis shared recollections of his first job during the paper days of clinical data management. “Ten or 12 of us worked on manual clinical data entry and similar tasks in a room that we called Guam because it was so isolated from the other departments and so hot from the computers we used,” he said.

As their professional careers took off, both saw how vital data management would become to improving clinical trial efficiency. This became clear once companies adopted electronic data capture systems. Now, 20 years later, disruptive changes necessitated by the pandemic have made it an exciting time to work in the field.

Luis sees data managers becoming the “glue” that holds trials and their many varied stakeholders together. Mayank agreed, adding that the ability to bring different groups together, understand other perspectives, and develop a cross-functional approach to optimizing trials is already improving results at companies that include GSK.

## **Taking on the Cube**

Cross-functional problem solving and adopting a “we” rather than an “I” approach to technology selection is crucial to trial success today, said Mayank. Teams can be as large and varied as needed without bogging down decision-making, as long as a decisionmaker has been designated to move processes forward.

In the future, having standardized practices across the industry will also improve efficiency, commented Luis, who appreciates the work that SCDM has been doing in this area. Currently, contract research organizations may use their own standard operating procedures in some situations, those of their customers in others, or some hybrid of the two. He noted that industry-wide standards and guides promise to clarify best practices and help the industry advance.

SCDM has also become a global voice for clinical data specialists, said Mayank. The society provides a forum for discussion and debate as the role of the data specialist and clinical data continue to change.

## **Conclusion**

The industry is clearly moving from data management to data science as strategies evolve and data professionals’ roles become more prominent. Closer collaboration between clinical data and clinical operations and more cross-functional efforts involving other stakeholders should accelerate study advances in the future.



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TRIALS & TECHNOLOGY

## **Clinical Trial Technology: A World of Opportunity for Entrepreneurs with the Right Mindset**

A Q&A with Sam Whitaker, Co-Founder and Co-CEO of Mural Health



By 2027, the clinical trials software market will be worth an estimated \$2.1 billion,<sup>{ 1 }</sup> making it one of the world's fastest growing technology sectors—and fertile ground for start-ups with ways to make research safer, faster, or more efficient.

But what is it really like to operate in this highly specialized space, what challenges can entrepreneurs expect to encounter, and how quickly will they, realistically, be in a position to cash out?

Helping us explore these topics is Sam Whitaker, founder and CEO of multiple clinical research technology companies. These include [Greenphire](#), which launched the first patient payment system in 2008, and his latest venture, [Mural Health](#), a patient management platform that aims to make it as easy as possible to take part in clinical trials.

**You founded the first clinical trials payment financial technology (fintech) company back in 2008. How did that come about?**



When I was at college, I did some work at Pennsylvania Hospital and wanted to go to medical school. For one reason or another, that didn't happen. I decided to major in philosophy, because I enjoyed flexing my brain to think about abstract problems, and after graduating in 2002, I became an investment banking analyst. I soon realized that didn't really suit my personality, and ended up working at

a fintech start-up, Ecount, just outside Philadelphia.

It was here that I came up with the idea of developing a technology that would help pharmaceutical companies make payments to clinical trial participants. It came from a combination of the experience I had at the start-up, and my work at the hospital when I was a student.

**How did you make the jump from working at a fintech to starting a company in the clinical trials space?**

I knew I wanted to start a company—that I didn't want to work for somebody else—and I had experience in payment technology. My idea was to build a software that would increase the value of technology beyond just moving money from point A to point B and was designed to meet the needs of one specific industry. Today, you would call it a “vertically integrated payments business,” but that terminology didn't exist at the time.

People often ask me how I identified clinical research as an opportunity, but it wasn't really like that. In fact, when I made a list of the industries that could benefit, drug development was number nine. Our main requirement was that we had to be first. We didn't just want to “make a better mousetrap,” because while it may have been easier, it would have been less interesting. When we looked into clinical trials, we saw that no one had done what we wanted to do before. That was enough for us to make that commitment and move forward.

I read an article once that compared the way entrepreneurs and MBA graduates work. It said that an MBA graduate is like a chef who finds a recipe then goes to the store to buy all the necessary ingredients. An entrepreneur, however, goes into the kitchen, takes an inventory of the

ingredients that are already in the cupboards, and works out what they can make with them. The process of starting that first business was very much like the later scenario. We checked the shelves, saw what we had to work with, and then created something new.

### **What were the biggest challenges and how did you overcome them?**

There is a certain amount of agility that is needed to be successful, and definitely a component of luck, but the most critical skill to have is problem solving. At the start of this journey, we had challenges being fired at us from all angles: from vendors, clients, employees, regulators, and investors, so we got very good at solving problems.

In the early days, we had to convince the industry that what we had created was even necessary. I remember one of our earliest investors saying that patient payments weren't an issue. But my point was that just because you are not hearing about it doesn't mean that people are fine with the status quo—they just don't know any better. It is like the difference between snail mail and e-mail. This was an opportunity to operate in a more efficient way and we had to demonstrate that.

We worked with a couple of sites to find out exactly how patient payments were being made. We found many manual steps, within many painfully bureaucratic processes that, in aggregate, were costly to universities and research sites, and had a negative impact on user experience from the participants' perspective. No one had ever quantified that or tried to solve the problem, so there were some people our solution would resonate with, and others who just wouldn't believe that it was an issue.

I think this is true with all kinds of innovation, especially within the clinical research space, and “expect to demonstrate value” is something I would say to anybody wanting to enter this space.

### **What makes a clinical research technology start-up successful?**

As we were outsiders coming into the space, we were able to look at things a little differently. The way we approached development was unique at the time, and probably still is now.

The sponsor is the one paying for the product, but the site and, more importantly, the patient are the ones using it. If they do not like using it, they will not stick with it, and, eventually, the

sponsor won't use it either. From a design perspective, then, we saw the patient as our primary user and the site as our primary business user, which made the sponsor of tertiary importance. We focused on delighting users, which in turn created more value for the customer.

It's different from what has been done in the past, but I think it is exactly what we should all be doing in this space. Many clinical tech businesses still tend to be very client focused, and I think that is a mistake.

### **What does a successful exit look like in this space?**

We had three exits along the way. We started it late 2007/early 2008, and in 2011 we sold some stock to the venture capital firm we were partnered with, which was a relatively small, but really meaningful, moment in our lives. I left the business in early 2016, and the management team grew it from there, before the final exit in July 2021.

It was 13 years, start to finish, but if you look at companies that have gone from "zero to hero" in this space, a decade is probably a good estimate. I think Greenphire took a little longer because we were the first in the area, so it took us a while to define the space and get the industry on board.

Because it is so highly regulated and specialized, I don't believe this space will accommodate a hyper-growth business. Often, raising a ton of money is a mistake because it is very hard to get the exponential, top-line growth you might get in a more generalized, cross-vertical tech space.

Of course, there are always exceptions, but I think 10 years from start-up to exit in this space is a good rule of thumb.

### **What's next for you?**

I have co-founded a new patient management platform, Mural Health. We all know that recruitment and retention are huge problems in clinical trials, so we want to make taking part as easy as possible for the volunteers.



The vision is to manage all of the touchpoints between a patient and a clinical trial, but we can't do that from day one, so we are focusing on four areas that all embrace the participant-first mentality. We are launching with a next-generation payment solution, an in-app transportation feature, robust two-way communication, and participant analytics. That means the app will periodically ask the participant about his or her experience in the study, so that, longer term, sites and sponsors will be able see who is at risk of dropping out and take action.

Again, we are focusing on the end-user—on the patient and the site—even if they are not the ones paying for the technology. Because if you cannot satisfy the end-users, you will never satisfy the sponsor.

## **Reference**

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**Sam Whitaker** is from suburban Philadelphia, Pa., (Delaware County) and is a graduate of the University of Pennsylvania.

## A Primer on the Importance of Recruitment and Retention in Clinical Trials

Tiffany Ashton, MAS



It is not a surprise that clinical research professionals who are involved with patient recruitment for a clinical trial widely consider enrollment to be one of their most challenging and stressful job responsibilities. Just read these statistics:

- 19% of clinical trials were closed or terminated due to failure to recruit enough participants, which is detailed in the study discussed [here](#).
- More than half of ongoing clinical trials struggle with patient recruitment. Depending on the type of trial, this number can climb up to 85%, as mentioned in [this article](#) on the National Institutes of Health (NIH) website.
- [According to Atlant Clinical](#), 15% to 40% of enrolled participants drop out of their trial prior to completion.

Study recruitment and retention are very important parts of each study because a study cannot move forward without participants. However, depending on the study, it can be extremely difficult to find enough willing and eligible participants. In addition, since patients can choose to withdraw consent at any time, retention efforts are integral for a study to continue.

## **What is Patient Recruitment?**

Patient recruitment is when sponsors, contract research organizations (CROs), study sites, or recruitment companies use strategies to try to connect with patients who may be eligible for their clinical trials. These recruitment strategies are usually based on methods that have been successful in previous studies.

Recruitment is a long process that generally takes more time than any other step of the trial. It begins with research about the patient population and the creation of a plan for outreach. It continues by connecting with potential participants, determining if they are interested and eligible, and moving forward with the consent process.

[This article](#) from Advarra offers helpful visuals and information about patient recruitment and enrollment.

## **Why Patient Recruitment is Crucial to the Success of a Clinical Study**

There are many reasons someone may choose to participate in a clinical trial. Some patients believe they may receive better treatment or that their results may help others. While both may be true, enrollment continues to be a struggle in the majority of research studies.

When the initial recruitment strategies do not produce their intended results, the study team is responsible for brainstorming new ideas to boost recruitment.

Recruitment delays cause increased stress for study team members due to the pressure they often receive from the sponsor to advance recruitment and make up for lost time. The sponsor is at risk of losing a lot of money due to delays, and its priority is to fund a successful clinical trial.

When recruitment is delayed, the trial can be affected in the following ways:

- Budget overspend
- Extended timelines
- Inability to properly analyze the investigational drug or device

Negative impacts caused by recruitment delays may lead to the failure of the clinical trial. This is why patient recruitment is crucial to the success of a clinical trial—and why it is at the forefront of the responsibilities for multiple individuals on a research team.

### **What is Patient Retention?**

Patient retention is defined [here](#) by the NIH as “the strategy and tactics designed to keep participants [who are] enrolled in clinical trials from discontinuing participation and dropping out.” The NIH says these three things are needed for a successful patient retention strategy:

- Treating participants with respect
- Being considerate of the participants’ time
- Quickly identifying and overcoming retention challenges

On a clinical trial, patient retention begins when a trial’s enrollment numbers are met. The next goal for a study team is to ensure the highest number of patients complete the study by keeping them actively involved (and retained) through regular communication and check-ins.

It is important for various members of the research team, but most importantly the clinical trial manager and clinical research associate (CRA), both working on behalf of the sponsor, to closely monitor retention rates and initiate risk mitigation strategies if/when retention rates decline.

Risk mitigation strategies are generally discussed early in the study initiation phase of a clinical trial as study team members have a general idea of the retention challenges they may face. However, they must be amenable to adjusting along the way for new, unexpected challenges.

### **Why Patient Retention is Critical for Each Clinical Research Trial**

Patients have the right to withdraw their consent from, or drop out of, a clinical trial at any time. Patients should never be coerced to stay in a trial.

Instead, it is important for research site staff to carry out patient retention strategies in their daily work and communicate concerns and challenges to the CRA.

When too many patients drop out of a trial, the trial is at risk of being “underpowered.” An underpowered study does not enroll enough participants as indicated in the protocol in order to draw a quality conclusion.

[According to the NIH](#), underpowered trials are an issue because in order to keep the trial going, the sponsor may have to expand the number of sites, increase budget allocations, and/or eliminate certain tests from the protocol.

Similar to recruitment delays, patient retention issues and underpowered trials may lead to budget excesses, delayed timelines, and reduced quality of results.

Low patient retention rates can cause a clinical trial to fail. This is why it is important for study teams to make patient retention a priority throughout a study.

### **The Role Clinical Trial Managers Play with Study Recruitment and Retention**

Recruitment and retention are two of a clinical trial manager’s main job responsibilities during the study conduct stage. These managers deal with many challenges throughout a clinical trial, and study recruitment is widely considered to be among the most taxing parts of the role.

A clinical trial manager helps drive recruitment and retention strategies and troubleshoots when initial targets are not achieved. He or she needs to be proactive, regularly track the numbers, and work to identify new recruitment and retention strategies to help the study stay on target.

Clinical trial managers can develop a subject recruitment and retention plan (SRRP) for site staff to complete and revise as necessary throughout the trial. Through the SRRP, site-based recruiters and managers can outline:

- Recruitment projections each month
- From where they intend to recruit patients
- Anticipated barriers and recruitment strategies
- Site-specific retention strategies

The SRRP allows both the site staff and the clinical trial manager to track progress in real time and make swift changes if needed.

Even though recruitment and retention are extremely important for the clinical trial manager role, these functions are not often part of the training received when someone is promoted to the role or takes it on at a new company. Lack of training and understanding of recruitment and retention can make these job responsibilities even more challenging. That's why they should be discussed in detail in training courses for aspiring and current clinical trial managers that cover key strategies used to manage clinical trials from study initiation to study conduct to study close-out.

### **Strategies for Patient Recruitment and Retention**

We are going to leave you with some tried-and-true recruitment and retention strategies for saving time, boosting recruitment, and managing retention:

- Clinical trial managers should ensure that patient compensation is in line with industry standards and Fair Market Value.
- CRAs should schedule booster visits with sites separate from monitoring visits to discuss in detail any recruitment or retention challenges and create a plan of action.
- Site staff should check the patient schedule each day and flag potential matches for recruiting studies.
- Site staff should prioritize positive patient experiences in their recruitment and retention efforts.

[Click here to receive a free download](#) that includes more details about the four tips above as well as six additional recruitment and retention tips that can be used to lead your study to success.

### **Conclusion**

The overall goal for a clinical trial is to conclude the study on time, within budget, and with high-quality results. The key is to recruit and consent as many eligible patients to the study as needed to ensure the trial's enrollment goal is met as quickly as possible. By focusing on the patient and providing a positive patient experience, you are more likely to both recruit and retain participants for your study. Recruitment and retention are a team effort—and when we work together toward a common goal, we are more likely to achieve success.



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GOOD MANAGEMENT PRACTICE

## Factors for Ensuring a Successful Launch and Market Access for Specialty Drugs and Novel Cell or Gene Therapies

Dea Belazi



For the multitude of scientists, researchers, and professionals who are immersed in drug research and development (R&D), clinical trials, regulatory approvals, and other aspects of pre-commercialization, product launch dates seem too far off in the future and may not require immediate focus. However, whether the drug is first-to-market or a new indication, its launch, market access, and commercial success rely heavily upon careful consideration of the challenges as early as before Phase I—prior to the clinical trial phase, or about four to six years into development. This is a significant departure from legacy launch plans, which are now proving woefully inadequate for introducing a specialty drug or novel cell or gene therapy (CGT) in an increasingly complicated and challenging marketplace.

Establishing proof of concept, creating value throughout the product lifecycle, and realizing the full potential of the therapy, from the day of launch and beyond, requires manufacturers to dedicate as long as three to four years of effort about mid-way into the development process.<sup>{1}</sup> Since it takes an average of 10 years to develop a potential new medicine<sup>{2}</sup> for treating a complex condition or rare or orphan disease, strategic go-to-market planning can never begin too soon. The fallout of risks from delaying the planning for a CGT could be disastrous, resulting in a significant waste of time and money when the product fails to gain the acceptance of healthcare professionals or achieve optimal reimbursement.



## **Launch Preparation Across Critical Business Functions**

A carefully executed strategy enables manufacturers to address and overcome challenges, ensuring seamless product launches, improved medication access, and enhanced clinical outcomes for patients.

### *Capture Critical Data Supporting Payer Negotiations*

Gathering the right clinical data and developing a safety profile during the drug development process not only helps to optimize pricing on the day of launch, but also impacts payer negotiations. Data collection is highly valuable because the disease burden is often not quantified for rare subpopulations indicated for CGT or certain orphan drugs. Data are also needed to engage in outcomes-based contracts and establish the causal relationships between the disease and outcomes.

To establish product safety, manufacturers must create a holistic projection of the product's durable pipeline success and assess the direct financial impact on the payer through analyses of data that address:

- Dosing regimens
- Treatment durations
- Route(s) of administration
- Patient population size
- Specificity on the eligible patient population
- Benchmark prices
- Number of patient lives affected
- Long-term outcomes and real-world evidence supporting payers with early visibility into the total health system costs related to a particular disease

An astute payer negotiation team is a “must-have” in market preparation to ensure patient access to therapy and determine pricing and reimbursement at the time of launch. This requires a team of individuals with experience, expertise, industry contacts, and a track record of success for negotiating pricing strategies that work for the manufacturer and the health plan or self-insured employer group.

### *Optimize the Supply Chain*

Demand forecasting should begin as early as three years before the actual launch to ensure that patient-specific doses are delivered just in time to sites of care. Many manufacturers look for clean, actionable, real-time data from one source for integrated support and collaboration. They also contract for exclusive drug distribution services with entities that specialize in rare diseases, since specialty medications and CGTs often require special handling, such as refrigeration, overnight delivery, and shipment tracking.

A distributor that focuses on this market sector has the experience to coordinate third-party logistics for warehousing or shipping, providing patients with uninterrupted therapy and access to medications they need when they need them most. Manufacturers appreciate this exclusive distribution model not only for significant cost savings, but also the assurances that the therapy itself is readily available since there is little room for failures, bottlenecks, or delays throughout the supply chain.

### *Streamline Care Continuum*

One of the most important tasks is to anticipate requirements and barriers for healthcare professionals to communicate with insurance providers and external pharmacies. With a goal to streamline communications between clinicians, patients, and pharmacy, manufacturers should have methodologies and technologies in place that notify doctors if a patient is noncompliant with taking medication on schedule or as prescribed.

The prior authorization process is yet another area for attention, underscoring the important role of healthcare professionals as medication prescribers who provide vital assistance to ensure that a particular drug qualifies for coverage under the terms of the pharmacy benefit plan. Any breakdown or disruption in this communication channel will seriously compromise patient access to treatment and negatively impact outcomes.

### *Prepare Clinicians for Specialty Drugs, CGTs*

Healthcare professionals typically deal with fewer specialty patients—and even fewer rare disease patients—which may make it more challenging to diagnose rare diseases. One survey{3} sought to promote understanding of these challenges, with findings that are consistent with small patient populations for each disease: lack of rare disease education and symptom awareness were the most common issues.

Healthcare professionals can also benefit from a clear understanding and awareness of medication costs, methods for communicating financial information with patients, and tools to help patients access necessary therapies and avoid missed doses or treatment lapses. While these professionals may be most familiar with “specialty” drugs, cell and gene therapies are not as common, largely because their practices may not include rare disease patients who would benefit. For these reasons, it is critical to provide full support for the therapy itself by offering evidence-based information and frequent updates.

The market is changing, emphasizing the need for clinician education that will be critical to market access. More than 900 Investigational New Drug applications{4} to the U.S. Food and Drug Administration (FDA) for ongoing clinical studies of gene therapy products are under way, and the agency is predicting it will be approving from 10 to 20 gene therapies per year. Cancer{5} is expected to be a big focus of specialty drug development and the current oncology pipeline is expected to add more than 100 new drugs in the next five years, which includes treatment through cell therapy, RNA therapy, and immuno-oncology treatments.

### *Identify Financial Solutions*

As healthcare costs rise for both patients and payers,{6} new financing models such as value-based pricing and innovative financial offerings are being developed to address the high costs of novel treatments for payers. The introduction of customizable copay assistance programs is instrumental in helping to break down financial barriers to patient access of therapies.

Since the high list prices for specialty therapies aren't likely to change, such as \$3.5 million for Hemgenix, the new hemophilia gene therapy,{7} the demand grows for better financing mechanisms that address a payer's fiscal responsibilities to these exorbitantly expensive products and lower out-of-pocket costs to patients. Risk-sharing mechanisms between pharmaceutical companies and payers are being introduced to proactively remove financial barriers, enhance medication access, and optimize outcomes.

One innovative program allows the extraordinarily high one-time costs of gene therapies and other expensive medications to be converted into smaller, predictable payments over time for payers. Another option is the outcomes-based pricing approach, such as the one employed for Zynteglo,{8} the blood disorder beta thalassemia with a list price of \$2.8 million per treatment. In the case of Zynteglo, the biotech will refund up to 80% of the drug's cost if it is not effective for the patient.

Innovative and specialized copay assistance solutions that support existing copay card programs help to ensure full transparency of transactions that guard against fraud, provide complete manufacturer oversight of copay fund usage, and protect the safety and security of funds. The most attractive options are programs that are compliant with the Centers for Medicare and Medicaid Services for eliminating financial barriers to accessing treatment and offer the benefits of block-chain technology to provide data security. When these capabilities are embedded into the program, they effectively minimize risk and assure that patients receive the full benefits of copay funds.

## **What's Ahead**

Life sciences companies are increasingly entering the rare disease space, with the market expected to grow{9} at a compound annual growth rate of 12.8% between now and 2030. Despite this growth, more than 90% of the 7,000 known rare diseases lack a treatment option.

Launching a specialty drug into the market not only requires additional planning and preparation time, but also expertise that differs from launching a drug used by a considerably larger population. Emerging and small to mid-size manufacturers do not typically have in-house capabilities for implementing end-to-end solutions that span the entire product lifecycle—from

pre-commercialization/clinical trials through launch and market access—prompting many to work with a single-source solutions partner that provides customized programs to meet these challenges.

Through this approach, a company eliminates the need to engage with multiple vendors, eases administrative burdens, and collects purely actionable data from one source. An all-inclusive vendor that offers white-glove support and service will accelerate all processes and enable manufacturers to reach drug launch milestones. A strategic approach requires a patient-centric focus, progressive thinking, and careful attention to details as they impact patients, payers, and providers.

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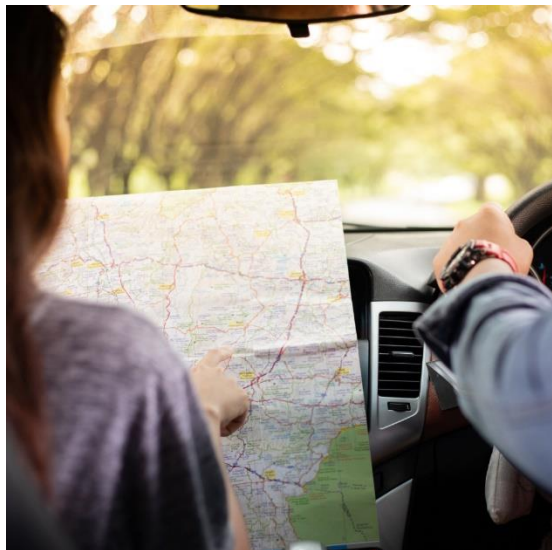
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## Twists and Turns on the Winding Road of Digital Therapeutics: From Product Development to Approval to Access

Joel Morse, MBA



The pandemic has produced a series of seismic shifts across broad aspects of our lives, upending so much of what we had previously taken for granted. One example in healthcare is the sudden growth of digital therapeutics (DTx). DTx revenue in the U.S. is expected to reach \$11.2 billion by 2030, while the [global DTx market](#) is projected to reach \$56 billion in just two year (up from a forecast of \$9 billion). Much of this growth can be traced back to the start of the pandemic, when the U.S. Food and Drug

Administration (FDA) fast-tracked several DTx products to provide options for an increased number of patients with anxiety and depression at a time when traditional, in-person treatment methods were less available. In April 2021, too, the FDA loosened [regulations](#) surrounding approval of digital mental health tools to hasten their time to market.

### Facing Challenges and Making an Impact

Today, the uses of DTx have expanded beyond mental health and their benefits are making a lasting impact across therapeutic areas, demographics, and pandemic limitations. Innovation across the DTx sector represents a critical new frontier for healthcare and an important opportunity to provide patients with a new kind of modern care. Further, as more of Generation Z enters the healthcare marketplace, these progressive approaches can expect to be welcomed with open arms. For a generation that often conducts much of its daily activity on smartphones

and puts a high premium on convenience, healthcare companies that prioritize digital and embrace innovation will be more likely to see success.

Unfortunately, however, innovations relating to the commercialization of DTx have lagged those of the digital products themselves. Instead of coming to market with relative ease, many DTx have been mired in processes that were originally designed for more traditional therapeutics, such as drugs, and ill-suited for the products that are being developed by DTx companies.

“One of the exciting things about new technology as well as one of the challenges is that it really opens up new ways to develop products and then to commercialize them,” said Mike Rosenbluth, PhD, CEO at Swing Therapeutics, a DTx company founded in 2019. “The question we need to ask is how we adapt those processes for the new intervention. A lot of the processes of developing a drug are not relevant for what we’re doing in DTx.”

Thankfully, there are early signs of an evolution taking place in the development and commercialization of DTx, starting with the utilization of decentralized clinical trials (DCTs). DCTs saw a major uptick when COVID-19 struck, and sponsors had no other choice but to conduct their studies remotely. Even as pandemic restrictions lifted, the benefits of DCTs remained. For instance, hybrid and decentralized trials improve patient enrollment both in speed and in diversity by allowing sponsors to target patients without geographic limitations. Well-crafted digital engagement can reach potential participants where they regularly engage with content, capturing their interest and seamlessly bringing them into the vetting process. As a result, DCTs are often more effective at obtaining highly engaged participants that better represent the patient population than the traditional, brick-and-mortar trials.

## **DTx in Development**

Swing Therapeutics is trialing two DTx products for the treatment of fibromyalgia, a chronic pain condition. “We’re working to expand access to clinically validated treatments to help patients when and where they need it,” explained Rosenbluth. “Right now, there are over 10 million people in the U.S. with fibromyalgia yet only about 5% have access to behavior therapies, so we are working to get this product out to all patients in need.”



Since the therapeutics being studied are digital, a decentralized trial is a natural fit. Fundamentally, a DTx is software rather than a pill or injectable, so there is no physical distribution of medicines. There are no physical logistics—no shipping, storing, chain of control, cold storage, or biohazards, plus endpoints can be captured within the DTx application itself, making DCTs ideally suited for DTx studies whether seeking regulatory approval or consumer and payer confidence. Further, because a DTx is also the data collection device, manufacturers often save costs from not needing extra technologies like an electronic patient-recorded outcome to capture data in a clinical trial. DTx trials also benefit from the many other documented advantages of a DCT, including those related to patient recruitment and enrollment.

In the Swing study, for example, the company leveraged a virtual site and was able to recruit on average 10 times the number of enrolled participants vs. those recruited from each of the study's 22 other traditional sites that started recruiting at the same time. Without geographic restrictions, the virtual site could recruit nationwide, and the convenience of a decentralized trial incentivized more patients to enroll and participate in the comfort of their own homes, rather than in traditional clinical settings outside their comfort zone.

Concerns that the lack of face-to-face contact puts virtual sites at a disadvantage seem to be unfounded, based on the Swing study. “Actually, I would say that the [DCT patients have] been more engaged in terms of their participation than [those at] other sites in our study,” Rosenbluth said.

There is also the added benefit of reaching participants who might be new to the clinical study process, and a better representation of the population who might benefit from the new therapeutic. “In a lot of clinical trials, there is a database where you can find a narrow set of people who are active trial participants rather than someone who might be more representative of the overall population and participating for the first time,” added Rosenbluth.

### **Aiming for Approval and Beyond**

Yet even with these positive developments, the overall processes required to commercialize DTx products remains frustrating, and gaining FDA approval, an already arduous process, is hardly the final hurdle toward achieving success. Instead, it is often just the beginning; DTx companies

are then faced with a series of potentially crippling obstacles, from the battle for visibility and market access, to tackling payer- and reimbursement-related issues. Companies also face systemic institutional challenges that include steep learning curves and a lack of awareness from many healthcare providers, who often have entrenched practices about the traditional therapies that they prescribe to their patients.

A traditional pharmaceutical company might spend between \$200 million and \$300 million to launch a new product, bolstering it with expensive initiatives such as wide-ranging patient support programs, enormous sales and marketing teams, and comprehensive advertising strategies. For the vast majority of DTx companies, such elaborate and expensive product launches are simply not possible. As a result, innovative therapies that might have already cost millions of dollars to research and develop often never successfully reach their markets. This is an unfortunate and unnecessary failure that ultimately leaves patients with fewer options.

For DTx companies to be profitable, or even sustainable, the path to commercialization must be altered and streamlined. DTx companies can help themselves by providing strong, evidence-based data on the efficacy of their therapeutics as well as by developing innovative and less costly ways of educating and enabling physicians to prescribe digital therapeutics and get reimbursed. “We’re committed to evidence development and demonstrating that our products are clinically effective,” Rosenbluth said. “The industry needs to build on a solid foundation of evidence so that digital therapies can be adopted as standard of care.”

### **Paving the Way for Access**

Swing’s cognitive behavioral therapy mobile application, known as Stanza, is commercially available under the FDA’s Enforcement Policy for Digital Health Devices. In addition to being available by prescription, Stanza is available through Swing Care™, an affiliated, physician-owned telemedicine clinic established by Swing Therapeutics to enable broader access to its product and place it in the context of a holistic care pathway. “We are working to find patient-centered ways to provide widespread access to our product and the holistic care patients need. We expect to expand Swing Care to more areas of the country in 2023,” concluded Rosenbluth.

The various pivots that were necessitated by the pandemic over the last few years offer a clear road map for how we can begin to take innovative approaches toward leveling the playing field of healthcare—from developing new therapeutics to ensuring equitable market access.

Decentralized approaches and new technologies are the lynchpin, but require close collaboration with regulators, physicians, sponsors, payers, and patients. Without taking bold steps now, we risk potentially muting the impact of important new therapeutics and preventing critical care from reaching those who need it the most.



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## Dose Optimization: Getting it Right for Vulnerable Populations

Justin Hay; Frank Engler



Pandemics amplify existing strengths and vulnerabilities—not only highlighting who are among the at-risk populations in our society, but also bringing to prominence strengths and weaknesses within healthcare systems and drug development processes. Advancements in vaccines and antivirals were carried out at unprecedented speed during the COVID-19 pandemic using exciting, new technologies, and there are now a slew of enquiries, reports, and (hopefully) “lessons learned” from those experiences. But is dose optimization one of these teachings?

### Hindsight is Perfect

In theory, dose optimization is a relatively simple concept—make sure a drug’s dose delivers the best balance between risk and benefit for the patient—yet in practice it is a different story. Dose optimization has never been perfectly spot on, with dose changes to labels occurring in one of about every five small molecules and in about one of 10 for biologics.<sup>{1,2}</sup> For small molecules, most label changes are related to safety and due to the dose being too high. However, safety does not appear to be the driving issue for biologics, where label changes are mostly due to patient convenience and related to efficacy.<sup>{1,2}</sup>

Understanding the drug’s dose-exposure-response relationship is key to justifying the dose on the label.<sup>{3,4}</sup> For monoclonal antibodies targeting COVID-19, this is especially important.

## Opportunity Knocks But Once

As with other therapeutic fields, such as oncology {5}, there is an absence of dose-response data available for pandemic medicines, albeit for different reasons. Pandemics demand that decisions are made quickly and require medicine development programs and approvals to be ruthlessly efficient because, initially, there is an imminent, unmet need for treatments and later they need to keep pace with the evolution of the viral target. While the doses selected may be justified, are there opportunities to ensure they are optimized even with only limited data available?

## Double-Edged Sword

Modelling and simulation have played critical roles in our understanding of the pharmacology of COVID-19 therapies. Their applications range from describing the population pharmacokinetics (PK), to investigating possible dosing regimens and exposures in pediatric populations, to highlighting potential drug-drug interactions using physiologically based pharmacokinetic (PBPK) modelling. Modelling and simulation have also been crucial to dose justification for monoclonals, helping to determine whether the level of antibody is reaching sufficient levels quickly enough in the target tissue and for long enough to offer protection.

However, the challenge for COVID-19 therapies (and indeed many other anti-infectives) is that variants cause big headaches for research and development, especially for the monoclonals targeting an ever-changing spike protein or non-conserved surface antigen. *In vitro* neutralization curves have been critical to our understanding of the susceptibility of variants to monoclonals, with modelling and simulation providing a critical link between the IC<sub>50</sub>, the IC<sub>80/90</sub> (should it be calculated or measured?), the plasma-to-target-tissue ratio (should it target the lower or upper respiratory tract?), the target threshold, the variability in the PK, and ultimately understanding whether there is enough drug at the site of action.

A handful of monoclonal antibodies have received authorization in the European Union (EU) for the treatment and/or prevention of COVID-19—among them, regdanvimab (Regkirona), casirivimab/imdevimab (Ronapreve, known as REGEN-COV in the U.S.), sotrovimab (Xevudy) and tixagevimab/cilgavimab (Evusheld). Others have received opinions under Art.5(3) in the EU or Emergency Use Authorization in the U.S.

Interestingly for Evusheld, at the time of initial approval, there were limited clinical data supporting the use of tixagevimab and cilgavimab against the newly circulating omicron variant.{6} Regulatory agencies advised that a 600 mg dose, rather than the initially studied 300 mg dose, was needed for pre-exposure prophylaxis of COVID-19 based on the levels needed to neutralize the omicron variant *in vitro*. Insensitive variants have already knocked casirivimab/imdevimab, sotrovimab, and bamlanivimab/etesevimab out of the race.{7,8} This story is bound to be repeated in the future with a plethora of emerging variants on the horizon.

Meanwhile, there are many new monoclonal antibodies against COVID-19 in development, but making sure that medicines are safe and effective is a time-consuming business. Going forward, is there enough time to wait for a confirmatory clinical trial to tell us whether a monoclonal against COVID-19 (still) works? Or is it enough to rely on some clinical data—modelling the *in vitro* data, combining them with assumptions of human physiology, and simulating target concentrations in target populations? Is this pushing the limits with regard to bridging nonclinical and clinical development? Regardless of what the answers are, it is important to make sure that any underlying assumptions used for modelling and simulation are robust and accurate.

Recently the U.S. Food and Drug Administration and European Medicines Agency (EMA) hosted a joint workshop{9} to discuss this exact topic with some interesting take-home messages regarding the use of surrogates of clinical efficacy like viral load, neutralization titers, and PK/pharmacodynamic modelling and whether these can be used to predict or support clinical efficacy. It is hoped these discussions can be leveraged to bring forward monoclonal therapies in a rapidly changing world. Not only will this help us with the further development of therapies for COVID-19, it also will hold us in good stead so we can be prepared for the next pandemic and meet any unmet need as quickly as possible.

## **Eye On the Target**

Even though we may have put COVID-19 somewhat behind us, and it does not make the headlines as much anymore, there are many lessons to be learnt or perhaps re-learnt from it. While for many, COVID-19 may result in a mild sniffle and a cough, for the

immunocompromised for whom vaccination may not lead to an adequate immune response, COVID-19 still lingers as a significant threat to their health, and it is for them that we need to make sure that we get the dose right.

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## **EU Adopts New Approach to Medical Device Regulation Deadlines**

Clare Huntington, MSc



With thousands of outstanding conformity assessments for medical device certification under the Medical Device Regulation (MDR) and limited capacity to manage these within the transition period, concerns over widespread product shortages in the European Union (EU) market have been growing.

To mitigate this risk, the European Commission (EC) proposed an extension of the transition period.

European Health Commissioner Stella Kyriakides noted that “the transition to the new rules has been slower than we anticipated,” and pointed to several contributing factors:

- The COVID-19 pandemic
- Shortages of raw materials caused by the Russian invasion of Ukraine
- Low notified body capacity

It has been estimated that 23,000 devices and 1,500 *in vitro* diagnostics (IVDs) certified under the previous directives had not yet transitioned to the new regulation, and these certifications were likely to expire in May 2024 and May 2025, respectively.

As the end of 2022 approached, it became clear that, with just 36 Notified Bodies designated for medical devices and only eight for IVDs, there would not be sufficient capacity to maintain existing products on the market and bring new products and innovations to EU markets.

This created the potential for shortages of life-saving medical devices for patients, which Kyriakides noted was “a risk that we cannot take.”



## **Rethinking the Deadlines**

With these concerns in mind, Kyriakides proposed at a meeting of the Employment, Social Policy, Health, and Consumer Affairs Council in Brussels that an amendment be introduced to the MDR to postpone the transitional deadlines.

This targeted amendment was proposed to include staggered deadlines, depending on the risk of each device, and would be subject to certain conditions to ensure they apply only to devices that do not present any unacceptable risk to health and safety. These devices should also not have undergone significant changes in design or intended purpose. Furthermore, manufacturers are expected to have undertaken the necessary steps to launch the certification process under the MDR.

## **Following Developments**

On 16 February 2023, the EU Parliament adopted the proposal, which the Council adopted on 7 March. The final step before full acceptance was publication in the Official Journal of the EU (OJEU), which was actioned on 20 March 2023.

Under this new Regulation, (EU) 2023/607, most devices certified under the previous Medical Devices Directive (MDD) or Active Implantable Medical Devices Directive (AIMDD) may be placed on the market until:

- 31 December 2027 for Class III and IIb implantable devices except sutures, staples, dental fillings, dental braces, tooth crowns, screws, wedges, plates, wires, pins, clips, and connectors; or
- 31 December 2028 for lower risk devices (Is, Im, IIa, remaining IIb devices not covered by the point above), as well as devices that were Class I under MDD and require an assessment by a notified body for the first time under MDR.

The extension also applies to devices with certificates that expired between 26 May 2021 and the date of publication, on certain conditions.

First, the manufacturer and the notified body must have signed an agreement for the conformity assessment of the device covered by the expired certificate, or a device intended to substitute that device before the expiry of the certificate. Second, a national competent authority has granted a derogation.

### *Conditions to be met to qualify for the extension*

There are a few conditions the devices and manufacturers must meet to be granted an extension. These include that the devices must continue to comply with MDD/AIMDD; that there are no significant changes in the design and intended purpose; and that the devices do not present an unacceptable risk to patients, users, third parties, or public health.

There are also requirements that manufacturers implement a quality management system as described in MDR article 10(9) before 26 May 2024. In addition, the manufacturer (or authorized representative) must have applied to a notified body for the conformity assessment of these devices, or the devices intended to replace them before 26 May 2024, with the agreement signed no later than 26 September 2024.

### *Specific arrangements for post-market surveillance*

Despite the extension, the requirements for post-market surveillance, market surveillance, vigilance, registration of economic operators, and devices described in the MDR apply, replacing the corresponding requirements of MDD/AIMDD.

The notified body that issued the certificate under MDD/AIMDD continues to be responsible for the surveillance of these devices, unless the manufacturer has a written agreement that the notified body responsible going forward, if different, will continue such surveillance.

The transfer of responsibility between the two notified bodies must occur before 26 September 2024 and should be clearly defined in an agreement between the manufacturer and the two notified bodies.

### *Specific arrangement for Class III custom-made implantable devices*

The requirement for Class III custom-made implantable devices to obtain a certificate from a notified body has been postponed until 26 May 2026, as long as the manufacturer has submitted an application to a notified body before 26 May 2024 and has signed an agreement no later than 26 September 2024.

## *Removal of the time limit for placing medical devices and IVDs into service*

In addition to the latest date for placing devices on the market, the MDR and *In Vitro* Diagnostic Regulation (IVDR) both introduced a date until which devices could legally be made available or put into service (26 May 2025 for medical devices, between 26 May 2025 and 26 May 2028 for IVDs). All of these deadlines have been removed by the new regulation, meaning that the devices that have been legally placed on the market can continue to be made available.

The EC believes that this decision will help with the continued supply of medical devices, giving manufacturers and notified bodies more time to work on the MDR implementation. Most importantly, it assures the safety of patients via the post-market surveillance and market surveillance obligations.

### **Next Steps**

Even after publication of the delay, a number of questions remain. Furthermore, some challenges experienced as a result of the implementation of the MDR have not been addressed, such as challenges facing innovative products, including devices with a significant change or that are new to the market.

The EC has prepared a Q&A document that seeks to provide guidance on practical aspects relating to the implementation of Regulation (EU) 2023/607. It is expected that this will be updated regularly in the coming months. It provides feedback on the following subjects:

- Scope of the extension of the MDR transitional period
- Evidence of extended transitional period
- Conditions to be fulfilled to benefit from the extended MDR transition period
- Appropriate surveillance to be performed by Notified Bodies
- Deletion of the “sell-off” date

Even with the delay now in force, the advice remains the same: companies should continue to transition to the MDR and IVDR as soon as they can. This will allow them to focus on marketing and improving their products. Moreover, there may be future bottlenecks with Notified Bodies as the new deadlines approach, and companies that are ready to transition will be in a better position to market MDR/IVDR-approved products globally.

## Resources

Press release from 6 January 2023—Public health: more time to certify medical devices to mitigate risk of shortages [Public Health: medical devices \(europa.eu\)](#)

Regulation (EU) 2023/607 of the European Parliament and of the Council of 15 March 2023 amending Regulations (EU) 2017/745 and (EU) 2017/746 as regards the transitional provisions for certain medical devices and *in vitro* diagnostic medical devices [https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L\\_.2023.080.01.0024.01.ENG](https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2023.080.01.0024.01.ENG)

Q&A on practical aspects related to the implementation of Regulation (EU) 2023/607 amending Regulations (EU) 2017/745 and (EU) 2017/746 as regards the transitional provisions for certain medical devices and *in vitro* diagnostic medical devices [https://health.ec.europa.eu/system/files/2023-03/mdr\\_proposal\\_extension-q-n-a.pdf](https://health.ec.europa.eu/system/files/2023-03/mdr_proposal_extension-q-n-a.pdf)



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OVER THE TRANSOM

## **Getting Down to Business in Clinical Research**

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Although we do not typically spend much time dwelling on the dollars and cents of drug and device research and development (R&D) in the pages of *Clinical Researcher*, if anyone needed a reminder that ours is not an arena for contestants who are risk averse or cash strapped, they got one in a big way in March. When Silicon Valley Bank (SVB) [collapsed](#), it at least badly rattled, if not entirely took down, the hopes and dreams of more than a few biotech borrowers who were counting on it to help them bring their products-in-

development to life in an era when the financial outlook for many (especially smaller players) in the industry was already questionable.

Life goes on, however, and in this issue's pages we offer up a variety of perspectives on ways to improve, broaden, and deepen the business aspects of the clinical research enterprise for the benefit of all its stakeholders. Included are welcome contributions from Ireland and the European Union on some big-picture topics, and focused columns that bring us valuable glimpses into such corners of our realm as patient recruitment and retention, data management, digital therapeutics, decentralized trials, dose optimization, and more.

Keeping in that vein, here are some excerpts from recent announcements of and opinions on other corporate movings and shakings in the rough and tumble research business world (no endorsements implied).

## Partners to Leverage *In Silico* Modeling and Simulation for Rare Disease Therapies

Premier Research, whose mission is to help biotech and device companies take ideas from concept to commercialization, and Italy-based InSilicoTrials, which focuses on artificial intelligence (AI) and computational modeling and simulation (CM&S) to accelerate development of new therapies and medical devices, [have partnered](#) with the intention to create safer, faster, and more efficient pathways to regulatory approval for rare disease treatments.

They say that, with regulatory support for CM&S advances making possible the full or partial substitution of virtual patients for live ones in certain circumstances, *in silico* trials can enable simulated synthetic control or treatment arms, inform strategies for patient enrollment, and more efficiently predict the safety and efficacy of novel drugs and medical devices, particularly in rare disease research. The partnership aims to emphasize smarter *in silico* study design resulting in more effective preclinical review of trial design parameters and faster submission-ready studies.

“Modeling and simulation combined with AI is the most effective way to innovate the R&D process in drug development,” InSilicoTrials CEO Luca Emili said. “Computational models and AI are true game changers because they enable sponsors to dramatically accelerate the development of new medicinal treatments, improve the safety of medical products, and significantly cut R&D costs.”

### Is the Medical Breakthroughs System Broken?

Medical research saves lives, yet it is too slow, causing much death and needless suffering, writes Dr. Simon N. Whitney, author of the [new book](#), *From Oversight to Overkill: Inside the Broken System that Blocks Medical Breakthroughs—And How We Can Fix It*. Whitney says the problem is that the review system—created for good reason, to protect the safety of patients participating in research—is out of control, with institutional review boards (IRBs) imposing complex, draconian conditions that stifle and delay medical advances. In addition to being a physician, Whitney is a medical ethicist and a law school graduate.

Whitney sees regulation as an essential part of modern life, but maintains that regulations need to reflect real-world research if they are to serve their mission. The book’s argument—driven not by

ideology, he says, but by the hope of relieving suffering and avoiding premature death—uses case studies of how vital breakthroughs for treating heart attacks, premature births, and kidney stones have been delayed, forcing (according to the author) doctors and patients to settle for less-effective treatments.

The regulatory system Whitney describes is largely beyond the public’s awareness, unlike the work of the U.S. Food and Drug Administration, whose approvals of medical treatments are often prominently reported by news outlets. In contrast, IRB rulings on the ethics of medical research at universities and research centers are overseen by the federal Office for Human Research Protections, which Whitney contends urges them to follow restrictive approval practices that delay and damage research without meaningfully protecting research subjects.

### **Driving Health Equity in Clinical Trials**

Jumo Health, a provider of age-appropriate, culturally sensitive medical education, in March [announced](#) that, together with the I Choose Life Foundation (ICLF), it has expanded its health equity service line to include the recruitment and retention of people of color in clinical trials. To guide their pharmaceutical and biotech customers as they endeavor to develop culturally responsible medications, Jumo Health and ICLF have amassed a national network of more than 2,000 churches that primarily serve Black congregations. Those churches, which are located across the United States, have more than 500,000 members in total. This group offers rare access to a community that is historically underrepresented in clinical trials. While approximately 14% of the United States population is Black, the community only makes up approximately 5% of clinical trial participants.

“[We explain] difficult medical concepts in ways people can understand and act upon,” stated Kevin Aniskovich, President and CEO of Jumo Health. “With a keen understanding of health literacy, how various communities consume information, and the importance of storytelling, we ensure that people can ‘see themselves’ in the information provided; critically important when serving communities that have been historically overlooked by government and industry.”

“There’s no reason that my community accounts for 14% of the United States’ population yet we are only 5% or less of those participating in clinical trials,” shared Tony Wafford, President and

CEO of ICLF. “Over 70 years ago, Dr. Martin Luther King Jr. said, ‘Of all the forms of inequality, injustice in healthcare is the most shocking and inhumane.’ The Black community can no longer be left behind when it comes to culturally competent education, recruitment, and Black retention in clinical trials and research. Through this partnership...we’re going to turn that narrative around! My goal is to make the Black community self-conscious agents of [its] own health and wellness.”

### **In Other News...**

Germany-based PharmaLex group, a provider of specialized services for the pharmaceutical, biotechnology, and medical technology industries worldwide (and recent contributor of several articles to *Clinical Researcher*), has [announced](#) its intention to merge with Cpharm, a provider of pharmacovigilance and medical services in Australia and New Zealand. The merger expands PharmaLex’s footprint in the region through Cpharm’s capabilities in drug and device vigilance, while offering complementary services and expanding the service portfolio of both companies. For the past 20 years, Cpharm has provided a range of pharmacovigilance, safety and risk management, medical information, material review, and patient program services to support clients ranging from start-ups to top-10 multinational pharmaceutical companies.

Infectious diseases like COVID-19, HIV, and battlefield wound infections cause illness and disruptions that threaten health and military readiness across the nation. To help foster collaboration in the field and share best practices, the Uniformed Service University’s Infectious Disease Clinical Research Program (IDCRP) [hosted its first annual Science Symposium](#) in March. IDCRP is the top resource for the U.S. Department of Defense to readily identify and assess infectious disease risks, providing clinical research to help shape best practices and policies. It is also a global multicenter, collaborative clinical research network dedicated to reducing the impact of infectious disease threats in the Military Health System, improving care of the warfighter, and ensuring the military community is ready to respond whenever and wherever the next infectious disease outbreak occurs.

BSI Life Sciences, a specialist in software for life sciences, and Ledger Run, Inc., a technology company focused on optimizing clinical operations in the areas of site budgeting and payments, [announced](#) a new partnership in February. Through the partnership, the companies say that BSI Life Sciences’ Clinical Trial Management software BSI CTMS™ and Ledger Run’s ClinRun™ platform will streamline and enhance clinical operation budgeting and payment processes with an intelligent approach and seamless integration.

