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New Destinations in Clinical Research: You CAN Get There from Here

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With the end goal of reaching a sustainable environment of high-quality, inclusive, compliant, and impactful studies and research roles, contributors to this issue invite you to explore the theme of "New Destinations in Clinical Research: You CAN Get There from Here." Eye-opening layovers and side quests along the way will consider adventures in career development, hiring practices, political influences, data management, study design, and more for the clinical research enterprise.

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The Industry Shift Toward Decentralized Clinical Trials: Impacts on Quality Management, Participant Outcomes, and Data Management

Casey Halle, MCR; Esther Chipps, PhD, RN, NEA-BC, FAONL

Decentralized clinical trials (DCTs) have emerged in popularity in the clinical research industry in recent years. Advantages and disadvantages to this clinical trial operations model are described here through the lens of quality management, participant outcomes, and data management. Furthermore, U.S. Food and Drug Administration (FDA) guidance on DCT operations is summarized as related to each of the corresponding deliverables. DCTs are not intended to replace the traditional site model, but can be used in conjunction with traditional site models to diversify enrollment and data. Overall, this review serves as an observation on decentralized trial impact on industry trends, sustainability, and outcomes.

Background

Traditional clinical research trials are conducted at research sites such as academic hospitals, outpatient research clinics, or private provider offices. This is referred to as the standard “brick and mortar” site model, which has lost popularity in the new age of DCTs. There is no central site or location in the DCT model, allowing subjects to participate from within their own homes. In this model, access to a clinical trial is brought to the participant by way of telehealth, mobile healthcare staff, and shipment of clinical visit supplies and investigational product. The decentralized model increases healthcare access and equity in clinical trials, as it does not discriminate participation based on proximity to an enrolling traditional site location. (Apostolaros et al., 2019)

The decentralized model has existed for slightly more than a decade, with Pfizer sponsoring the first fully decentralized trial in 2011. (Petrini et al., 2022) The model surged in popularity in the wake of the COVID-19 pandemic beginning in 2020, and its success has led to the long-term sustainability of decentralized trials. However, there are advantages and disadvantages to this model of clinical trial delivery, as described in the following sections.

Quality Management

FDA Guidance

Despite such trials being piloted more than a decade earlier, the FDA did not release formal guidance on "[DCTs] for Drugs, Biologic Products, and Devices" until May 2023. This document also serves as a reference for hybrid or partially decentralized trials, where only certain activities are conducted remotely. Primarily, the guidance states that regulatory requirements for decentralized trials are identical to those used for traditional onsite clinical trials. Standard requirements regarding documentation, adverse event management, and licensing of staff and laboratories must be followed. All regulatory documents are required to be in the investigator site file (ISF) and maintained physically and/or electronically. (FDA, 2023)

When deciding if a trial is appropriate for the decentralized model, the FDA recommends considering whether the investigational product or device is simple to administer or use, has a well-characterized safety profile, and does not require complex medical assessments. On the other hand, investigational products with complex administration procedures, high-risk safety profiles, or are in early development may need in-person supervision by investigators at a trial site.

This guidance does not specifically state what phase, indication, or formulation of products are not recommended. However, it can be inferred that Phase I and II trials are not well suited for decentralization, as safety is a main endpoint of consideration in those trials. Phase III and IV trials are more appropriate for use in decentralized trials as safety profiles are better established, and further efficacy or post-marketing surveillance data are being collected. Investigational products such as gene therapy, biologics, and devices that are injected or implanted are not suitable for decentralized trial use. (FDA, 2023)

To assess the appropriateness of decentralized trial utilization, product safety profiles are used to consider the risk of hypersensitivity, abuse potential, and the type of trial (such as dose escalation). Additionally, the FDA only recommends investigational products with high stability through shipment excursion and long shelf lives as suitable for decentralized trial use. Only devices that can be used over the counter are considered suitable for decentralized trial utilization. Devices that would be used in ambulatory or hospital settings are not recommended for decentralized utilization. As required with any trial, accountability and documentation of all investigational products and devices shipped and received are required, and centralized distribution of these products is recommended. (FDA, 2023)

Digital Tools

The execution of successful decentralized trials relies on the use of many digital applications and tools. One of the most popular digital applications, although not exclusive to decentralized trials, is electronic consent (eConsent). eConsent forms are regarded as positive as they are easy to file, retrieve, and reference. (Petrini et al., 2022) However, eConsent forms can also pose challenges to certain populations, including the elderly, those with low technology literacy, or those without a personal device.

The digitization of eConsent can improve the quality of the informed consent process by providing prospective subjects with a user-friendly platform to reference before the consent visit, along with digital education material. (Harmon et al., 2023) Per the FDA guidance, eConsent forms must contain the site investigator's contact information for research questions and to report any research-related injuries. Furthermore, eConsent forms are also used to notify subjects of all bodies that will have access to their digitized trial data and personal health information. (FDA, 2023)

eConsent forms require institutional review board (IRB) approval, just the same as physical consent forms, and it is essential to ensure the digital modality used is in compliance with the Health Insurance Portability and Accountability Act (HIPAA). (Apostolaros et al., 2019) eConsent platforms must have data security measures and safeguards in place to ensure forms and subject personal health information (PHI) are confidential and secure. (Petrini et al., 2022)

Real time date and time stamps can also improve the quality of the informed consent process for accurate signature information. The United States and the FDA consider electronic signatures legally valid, and eConsent signatures are no exception. (Vayena et al., 2023)

Digital clinical trial assessments are commonly known as electronic patient-reported outcomes (ePROs) and electronic clinical outcomes assessments (eCOAs). Active reported outcomes include participants directly entering data into survey forms at scheduled time periods. This improves data quality because participants can truthfully answer questions with no reporting bias or perceived pressure from study staff. This allows participants to take a more active role in the trial while promoting retention. (Petrini et al., 2022) Therefore, ePRO and eCOA can improve quality by allowing participants to take more ownership and authority of their data reporting in an easily accessible digital location.

ePRO and eCOA reports do require review for quality control by study staff to ensure that data collection is accurate and complete. Additionally, the use of digital assessments can increase enrollment retention due to convenience to participants, and can improve compliance and quality of study data collection. (Norman, 2021)

Review Boards

Decentralized trials utilize fewer IRBs because regulatory documents and patient-facing materials are standardized across the study, without site-specific differences. (Noman, 2021) Central IRBs are utilized and can improve data quality with standardized approval processes, communications, and timelines. Central IRBs also reduce redundant resubmissions to multiple IRBs at the site level. This reduces costs while improving the ability for sponsors to pivot based on trial needs, and to submit protocol amendments with streamlined timelines. Overall, central IRBs improve data quality in DCTs with standardized approval, communication, and adaptability to evolving trial needs. (Noman, 2021)

Participant Outcomes

DCTs utilize telehealth, mobile healthcare providers, and central labs to conduct clinical research visits. This method allows subjects to have more flexibility over trial participation schedules to

reduce the burden of travel, work, etc. The FDA guidance also praises decentralized trials for the ability to expand access to participation and improve clinical research diversity and robust data collection. Therefore, enrollment and retention in clinical trials can be superior in the decentralized model. (FDA, 2023) In this model, investigational products are shipped to subjects' homes from central pharmacy or device vendors. Additionally, mobile healthcare providers can travel to participants' homes to collect and ship labs, perform exams, and complete drug accountability. (Vayena et al., 2023)

While the use of telehealth allows the investigator and the subject to be in different physical locations, the investigator still must be licensed in the states in which the subjects reside. For example, some decentralized clinical research companies will have investigators licensed in several states, including up to all 50 states in the U.S. This allows for subjects to be recruited and enrolled in all states for DCTs in accordance with investigator licensing regulations. However, this also requires close regulatory monitoring of all investigator state licensing and expiration dates in order for renewals to be managed on time and in compliance with legal and regulatory guidelines. (Apostolaros et al., 2019)

Participant experience on a trial can also be improved in more ways than just convenience in the decentralized trial model. For example, comfort levels in the home and investigational product education and adherence training in the environment in which the product will be used can improve subject confidence and adherence. Additionally, DCTs require more subject responsibility with remote reporting of adverse events, with training of methods and technology to report these events. This training for self-advocating can assist with participants feeling more autonomous and comfortable with participating in the decentralized trial. (Apostolaros et al., 2019)

Decentralized trials do come with some drawbacks to participants. Primarily, the remote investigator is likely a provider they have never met and who is not well acquainted with their medical history. Subjects may feel less comfortable sharing their medical history and current condition with a new provider, and the relationship may be limited to medical record review and standard clinical trial outcome reporting. Additionally, there can be limitations based on states where investigational products cannot be shipped directly to subjects. Lastly, subjects may not be

able to participate based on investigator licensing limitations and mobile healthcare provider travel restrictions, such as in more remote states with lower populations. (Apostolaros et al., 2019)

Case Study

STOPCoV, a recent study that highlights the successful implementation of the DCT model, was developed to assess the long-term antibody response of preventative COVID-19 vaccines, and to collect data to inform booster decision analysis. This study utilized remote recruitment, eConsent, ePROs, at-home sample collection devices, and satisfaction surveys. Overall, this decentralized study demonstrated the ability to quickly recruit, enroll, and complete the clinical trial with a diverse and satisfied participant pool. The performance metrics of this study included: 95% of the participants were satisfied with their participation in the decentralized trial, 90% of participants viewed the eConsent and ePRO as easy to use, and 37% of participants reported enrolling as a result of the convenience of completion in their home. This study highlights alignment with FDA guidance with post-marketing surveillance data being collected, digital tool utilization, and enhanced recruitment and enrollment performance metrics. (Ravindran et al., 2023)

Data Management

Introduction and Utilization

Clinical trial data are paramount to both the sponsor and the FDA in determining if an investigational product shows statistical significance in terms of safety and efficacy. Important considerations must be made to secure data collection and management to protect the proprietary data for sponsors, and the safety and privacy of the participants in the trial. (Petrini et al., 2022)

With decentralized trials being conducted without a central site or location, the way in which data are collected, integrated, and utilized has been transformed from traditional clinical trial models. DCTs are also referred to as digital trials because they operate with all data collection online throughout recruitment, enrollment, and closure of the clinical trial. (Harmon et al., 2023) The FDA has also provided guidance on software considerations for sponsors in a decentralized

trial, in that it can be used on a variety of platforms and support multiple trial operations. The FDA states that tablets, cell phones, and personal computers can be utilized for operations in decentralized trials; however, this must be outlined in the sponsor's data management plan to account for all methods of data collection and platform utilization. (FDA, 2023)

Beyond the aforementioned eConsent and ePROs, recent digitization processes that are standard in decentralized trial conduct include smartphone applications and wearable technology. (Harmon et al., 2023) Some electronic data collection is active, such as signing consent or completing ePROs where the participant actively answers questions and completes the data collection fields. Other data collection can be passive, including data collected from consented wearables, such as heart monitors. Additionally, participants must be informed of the risks with electronic data collection and management, and details about who will have access to the participants' data must be disclosed. (Petrini et al., 2022)

HIPAA and the FDA

When participants utilize technology that collects PHI, data security precautions must be in place. (Petrini et al., 2022) The aforementioned HIPAA does not define the terms of decentralized or virtual clinical trials. (National Academy of Sciences, 2019) However, research is defined as a systematic investigation and DCTs can reasonably be categorized under research operations. Additionally, HIPAA regulations do apply to all of the clinical trial data collected by the investigator, regardless of whether they originated from a participant's smartphone or a study-issued device. (National Academy of Sciences, 2019)

Leonard Sacks, Associate Director for Clinical Methodology with the FDA, has stated that existing regulations need to be applied to the data that remote technology produces in the interest of patient safety, privacy, and data integrity in technology-enabled decentralized trials. (National Academy of Sciences, 2019) It is critical that participants are adequately informed at the time of consent of the intended use and risks associated with their data collection in any clinical trial model. Data integrity and safety must be considered during all phases of the clinical trial. Furthermore, the risk of unintentional data disclosure or breach of privacy are real-world threats

to PHI and data. However, training and precautions can be well implemented in attempt to avoid these occurrences, and are equally important among all clinical trial models. (Petrini et al., 2022)

Monitoring

Monitoring is just as important in decentralized trials as in traditional models, in order to assure complete and quality trial execution. Source data in DCTs, where the clinical trial data are initially recorded, are entered into an online source data collection form. Data are then entered or integrated into larger electronic data capture (EDC) systems where queries can be generated on large datasets. (National Academy of Sciences, 2019)

The FDA requires sponsors to ensure proper monitoring of an investigation, as highlighted in the DCT guidance. (FDA, 2023) With the emergence and popularity of DCTs, a parallel relationship has emerged in decentralized risk-based monitoring. In the FDA guidance for industry, risk-based monitoring with reduced source data verification (SDV) has become more widely acceptable as opposed to conventional 100% SDV requirements. (FDA, 2013) Risk-based monitoring has grown in popularity with DCTs as centralized online source documentation and EDCs allow for large dataset trend analysis. (Williams et al, 2021)

Closing Thoughts

DCTs have gained popularity in the industry with the ability to recruit more participants from diverse geographical areas more quickly and with less burden to participate. This has caused innovation and adjustments in the operations of data, quality, and participant experiences. There are advantages and disadvantages to decentralized trial delivery; consideration of FDA guidance must be taken into account for the suitability of this model based on the clinical trial model, phase, and indication. It is prudent during protocol development and study design for assessment of appropriate use in the decentralized model. This is not an all-encompassing review of DCTs, as new protocols, treatment methods, and delivery models are constantly evolving in the industry. This is an overview of main deliverables and how decentralization impacts those outcomes.

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Insights into the Clinical Research Associate Career Pathway

Anthony Chew, MS

In clinical trial operations, clinical research associates (CRAs) serve as the primary liaison between study sponsors and sites by monitoring and verifying data to ensure accuracy and adherence to protocols. They collaborate with investigators, conduct site visits, and maintain strict documentation to guarantee the integrity of a trial. The CRA position, while highly sought after, is also one that many professionals have difficulty obtaining, despite there being many job openings for the role in the industry. This dilemma was noted in a recent *Clinical Researcher* article by Meghan Francis and Andrew Pucker,{1} which looked at how even CRA hopefuls with a graduate degree and experience at the site level may find difficulty securing a position as a CRA, due to the fact that many companies desire someone with at least two years of experience in a direct role as a site monitor. Of course, to gain experience as a site monitor, one must first be hired into the position of a CRA, hence the Catch-22 nature of the situation experienced by many.

The Survey

On April 1, 2024, an electronic survey conducted as part of the author's graduate school studies was distributed to approximately 2,000 individuals who were either currently a CRA or held a previous position as a CRA. The survey was a combination of multiple choice and free response questions that investigated information such as the background of the CRA, the type of employer that initially hired them, the training process that the new CRA underwent, and any advice that they might have for aspiring CRAs (see Table 1). After one week, 59 qualified CRAs and former CRAs had completed the survey. Among the respondents, experience in the clinical research

field ranged from two years to more than 25 years, with the average experience being nine years in the field. Thirty-six of these respondents were current CRAs whereas 23 were former CRAs who had since moved on to a higher position.

Select respondents were chosen for a follow-up interview to further explore their experiences and how they shaped the clinical research professional that they are today. Interviewees were selected with the objective of having a diverse set of CRAs of different experience levels and exposure. For example, one CRA was selected for their experience as a clinical research coordinator (CRC) prior to being employed at a large contract research organization (CRO), whereas another CRA was selected for their experience as a clinical trial assistant (CTA) at a small sponsor start-up. Those interviewed were asked to weigh the advantages/disadvantages that their specific experience gave them, as well as to further clarify some of their responses provided in the initial survey.

Table 1: Survey Questions and Response Options

Question	**Response Type/Options**
First and Last Name (Optional)	Free Response
Preferred E-mail Address (Optional)	Free Response
How many years have you spent as a CRA?	Free Response
How many years have you spent in the field of Clinical Trial Operations as a whole?	Free Response
Current Job Title	Free Response
Current Employer (Optional)	Free Response
Please list the name of your employer who gave you your first experience as a site monitor. (Optional)	Free Response
Was this employer who gave you your first experience as a site monitor a sponsor or a CRO?	Multiple Choice: • Sponsor • CRO • Other: (Free Response)

What was the approximate size of the organization at which you were employed for your first experience as a site monitor?	Multiple Choice: • 1-200 Employees • 201-500 Employees • 501-1,000 Employees • 1,001-5,000 Employees • 5,001+ Employees
Please select the option that best describes the pathway you took in becoming a CRA.	Multiple Choice: • A. CTA for sponsor/CRO --> CRA • B. CRC for site --> CRA • C. Internal Company Transfer • D. CRO Bridge Program • E. Other: (Free Response)
If you selected C, D, or E in the question above, please use the space below to clarify. If you selected A or B, simply put N/A.	Free Response
Please describe the training/qualifications process you underwent for your first experience as a site monitor. How did you go from having no experience to becoming qualified and performing an independent monitoring visit?	Free Response
What are three important skill sets you believe would be important for becoming or working as a CRA? Explain what you did or are doing to develop/hone these skill sets.	Free Response
Do you have any other advice for someone looking to break into the clinical research field?	Free Response
I am looking to schedule a 20-minute Zoom interview with individuals who are willing to further share their clinical research career experiences. Are you open to being interviewed?	Multiple Choice: • Yes (If so, please ensure you provide your email in question 2) • No (Thank you for participating in this survey!)

Who is Hiring First-Time CRAs?

Large Organizations

Results showed that most respondents (72%) obtained their first position as a CRA at a larger organization (1,001 employees or more). According to those who were interviewed, a benefit to beginning their career as a CRA at a larger company is the robust systems and training protocols in place. “Being trained at a bigger company was great for me, because bigger companies tend to have better processes in place [in terms of] better systems: they’re a little more organized…,” commented a respondent who first began their CRA career with Quintiles (now IQVIA). A current CRA had similar remarks: “The benefits of coming into a large organization that’s been around for awhile would be that they have a very systematic way of doing things. This is the plan. This is how we’re going to train you—whatever it may be—because they have a large quantity of people. They have a very established way of completing training and running through [all the trainees].”

CROs

CRAs who began at a CRO had slightly more representation (49%) in the survey, as opposed to those who began at a sponsor organization (44%). A small minority of respondents began at an academic institution/hospital (see Figure1). CROs are companies that are contracted by the sponsor to perform specific trial tasks, such as site monitoring. Often, CRAs who are employed at CROs will simultaneously work on multiple trials for different sponsors at once (defined as a “full-service alignment”; working with only one sponsor is referred to as a “sponsor-dedicated alignment”).

One CRA recalled how working in a full-service alignment allowed her to observe various processes between companies and focus on which processes work best. They remarked that the training process for CROs was the “gold standard.” Indeed, the article by Francis and Pucker outlined this gold standard by recounting the growing practice of CROs to develop training programs that bridge the gap in experience for less-experienced CRAs.{1} A CRA who recently completed such a program with Premier Research compared the primary motives of a CRO as

being one that prioritizes the development of the employee, versus the primary motives of a sponsor being one that prioritizes the product.

To elaborate, providing quality personnel (including CRAs) is essential to the success of the CRO, because the quality of their personnel determines the size of their customer base. As such, one viewpoint suggests that a CRO has more motivation than a sponsor organization to put more resources and training into developing quality CRAs.

The consistency of the qualification process amongst CRAs who began at a CRO was reflected in the results. For those who went in-depth about the training process, respondents of different CROs including IQVIA, PPD, ICON, and more had all cited similar training processes despite having no relation to one another. These training processes included classroom learning and online modules/certifications; as well as in-person observational training, which may have included shadowing senior CRAs on a monitoring visit and accompaniment on the new CRA's own initial monitoring visits before being "signed-off" by their supervisor.

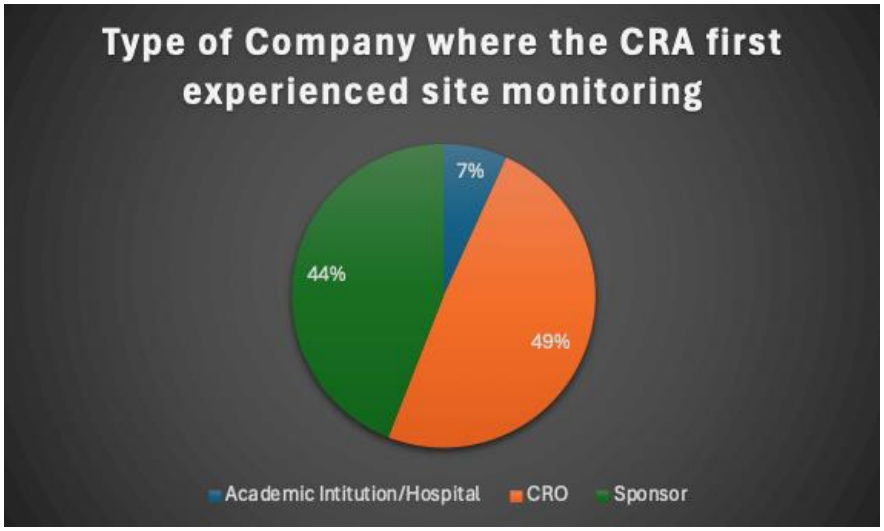
CRA training on the sponsor side yielded more inconsistent responses. While there were many respondents who indicated having experienced some sort of observational training, there were also multiple responses that indicated having only been assigned an online module and protocol review prior to conducting their first visit and then learning from experience going forward. One respondent stated that they received "no formal training." Even more concerning than the inconsistency in qualifications was the inconsistency in the positions themselves. One respondent had indicated their current title as that of a "Clinical Research Associate II" for a sponsor organization, but also indicated that they did not perform onsite monitoring as part of their duties, nor had they been trained on such.

Still, respondents suggested that there were various benefits to being employed at a startup. One respondent who began his career as a CRA at such an organization described their experience as one that had great risks but one that was also rewarded with greater experience: "You have to wear many hats at a startup. That exposure, in and of itself, gives you a lot more opportunity to get experience in different sections of the clinical trial. You might do things in study start-up, you might do things in monitoring, and you might also get exposure to things like budgets and

contracts. So you can get all that experience, all at one time, at a smaller company as a startup. If you go to a bigger company, they already have a structure. They already have training programs for your CRAs to go through, and most of that is going to be focused on monitoring."

A respondent who is now in a director-level position shared similar sentiments. While starting with a smaller company was not great for their career as a CRA, it provided much cross-functional knowledge in the biotechnology industry as a whole. It also gave access to more personalized mentoring—even in terms of receiving feedback from the company's vice president at the time.

Figure 1: Type of Company Where the CRA First Experienced Site Monitoring



Options Leading Down the CRA Pathway

More than two-thirds of respondents were observed to have held positions as CRCs or as CTAs prior to their career as a CRA (see Figure 2). The Association of Clinical Research Professionals (ACRP) offers a "Ready, Set, Clinical Research!"{2} toolkit recognizing these two positions as common entry points into the field of clinical research. CRCs support, facilitate, and coordinate the daily research activities on the site end. On the sponsor end, CTAs provide administrative and project tracking support for the clinical trial.

Starting as a CRC

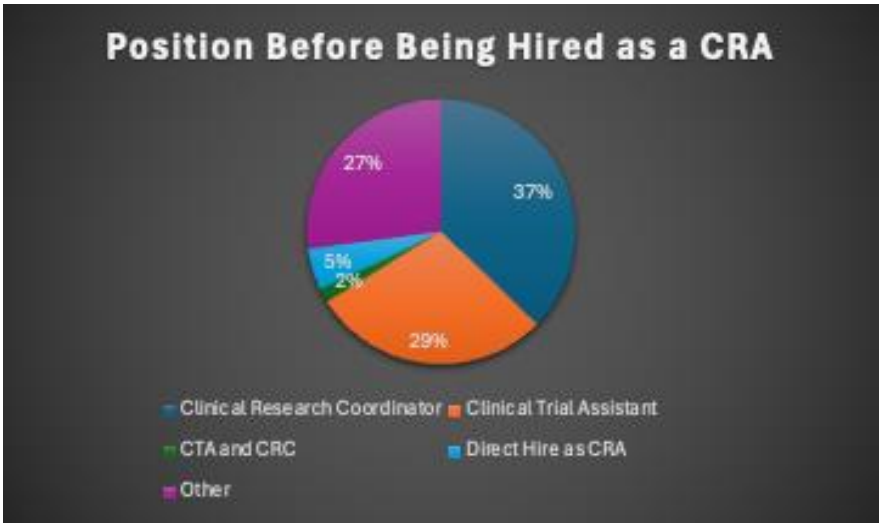
Among the respondents who were former CRCs, almost one-third cited their experience as CRCs to have played a major role in helping become an effective CRA. One such respondent highlighted their experience as a CRC as one that allowed them to have a greater understanding of what goes on at the site and have greater empathy for the site personnel when mistakes occur.

Another respondent placed emphasis on the industry knowledge their experience as a CRC gave them: "You're able to build a really solid foundation of the regulatory requirements at the site level: Building an ISF (investigator site file) and becoming familiar with all the different essential documents that you need to collect for all your investigators." They also recognized how directly interacting with both the patient and the site investigator developed their communication skills as well as their knowledge of the oncology field as a whole, such as the process of obtaining and reviewing pathology scans.

Starting as a CTA

Respondents who had experience as a CTA also indicated its benefits. For one, beginning their career as a CTA provided the best quality of work as well as had more direct access to upward mobility—specifically when employed by the sponsor: "When you work for sponsors directly, you're able to decide to work on something you care about, and you get to be a lot more invested in the projects you're on. On the CRO side, you get to see a lot of different studies, you get to be involved in a lot of different things. But also you don't get a lot of choice about what you're working on. I'd say the same is true as a CRC. I do think one benefit of being a CRC is that if you're interested in going into the medical field, that can be a really good bridge, because you're working with patients and physicians in a clinical setting. But there's less of a job ladder. [For example, a CRC] is never going to become the PI (principal investigator)... there isn't quite as much room for [direct] upward mobility." Since they are on the sponsor end, a CTA has the potential option to be promoted into the CRA position, whereas a CRC must leave their current employer to advance into a CRA position.

Figure 2: Position of the Employee Before They Were Hired as a CRA



Relevant Skills

Characteristics related to communication skills (40 responses related to "communication," "soft skills," "relationship building," etc.) and attention-to-detail (31 Responses) were listed by most respondents as important for being an effective CRA (see Figure 3). These traits were verified as directly applicable to the position of a CRA amongst the interviewees. For one respondent, communication is a core aspect of maintaining a good relationship with the site so as to "work together with them and not against them." They also highlighted attention-to-detail as the "core of what monitoring is," including tasks such as reviewing the ISF, regulatory documents, or source data verification.

Figure 3: Word Cloud Diagram of the Essential Skills that CRAs Considered Important for Their Position

Takeaways for the Aspiring CRA

Limitations of the survey were its anonymity and sample size. To encourage more CRAs to respond to the survey, certain questions (such as those pertaining to the respondent's current or past employers) were considered optional to preserve confidentiality. This prevented any analysis on the specific organizations that the CRAs were employed by. Moreover, future studies could strive to obtain a higher number of respondents (N>59) to gain a clearer landscape of the CRA position.

It should be noted, however, that the purpose of this survey was not to provide a definitive judgment of where or how CRAs are hired, but rather to point the aspiring CRA in the "general direction" and offer insight as to the advantages and disadvantages that each type of experience provides.

While there is no "wrong" pathway to become a CRA, the responses would suggest that the ideal pathway to becoming a CRA is to start out as a CRC, then join a large CRO as a full-service alignment CRA, and then to secure a CRA position with a sponsor. This pathway optimizes the ability for the potential candidate to receive as much experience as possible—first to understand what goes on at the site, then to receive training that is consistent with the industry at a CRO, and finally to understand trial operations at a higher level with the sponsor.

Obviously, this is easier said than done. Some professionals may have trouble even obtaining the CRC position. When asked if they had any advice to give to the aspiring CRA, respondents recommended finding ways to gain experience in the clinical research field, networking, and becoming more educated in the field.

If one is unable to gain direct clinical research experience, the next step would be to develop the relevant skills that are important for the CRA, such as demonstrating communication skills, attention to detail, and any other skills listed in Figure 3. For respondents who did not have CTA or CRC experience, this might have meant working in the laboratory, handling the clinical samples themselves, and demonstrating the ability to adhere to the protocol of the trial.

Networking is also a valuable tool for aspiring clinical research professionals. For those who are already employed at an organization that conducts clinical trials, sometimes all it takes is to "just ask," as one respondent phrased it. This might entail a 30-minute call about what clinical trials are about, or you may even have the opportunity to shadow someone on their daily tasks. For one respondent, the importance of networking is found in seeking good mentors that will help you grow.

As far as education goes, there are a variety of courses, certificates, and certifications{3} from for-profit or higher education sources of learning, ranging from small extension programs to undergraduate or graduate degree offerings. Probably the most obvious early step involves becoming certified in GCP (Good Clinical Practice); however, there are additional courses that are available that can further immerse one's knowledge in specific topics such as site monitoring or trial management.

Clinical research is still a developing field, and while the pathway to becoming a CRA can be frustrating, the experiences of today's CRAs demonstrate that persistence can pay off.

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PEER REVIEWED

The Future of Multi-Omics in Cancer Clinical Trials

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This article delves into the role of multi-omics in enhancing cancer clinical trials, highlighting its promise against the backdrop of frequent trial failures encountered in oncology research and limited success of precision medicine. Multi-omics, by analyzing genetic, proteomic, and metabolomic data, aims to personalize cancer treatment, addressing obstacles like data inconsistency, tumor diversity, and therapy resistance. However, integrating multi-omics into cancer trials presents significant challenges, including variance in data regulations, complex data analysis methodologies, ethical hurdles around patient consent, and logistical hurdles in trial management. This discussion advocates for improved trial designs, effective data handling, and robust patient safety measures. It emphasizes the need for collaborative efforts across the scientific community to navigate these challenges and to enable holistic integration of multi-omics in cancer clinical trials, thereby advancing precision oncology.

The Global Cancer Crisis: Reevaluating the Clinical Trial Landscape

Ten million people die each year due to cancer.{1} Our efforts to treat cancer on a global scale —through radiation, chemotherapy, surgery, and targeted therapies—have often felt like drops in the ocean. Research conducted by MIT reveals that about 97% of trials in oncology end in failure.{2} This daunting statistic not only highlights the immense challenge at hand, but also raises critical questions about the trajectory of our current cancer research methodologies and, more importantly, about the precision drugs which have been long thought as the final frontier for cancer.

Foundations of Precision Medicine in Oncology

Precision medicine at its core is the idea of tailoring treatments to fit an individual's unique genetic profile. It involves the detailed analysis of a patient's tumor at the molecular level, to identify specific genetic mutations or biomarkers that drive the growth and spread of cancer. This comprehensive molecular profiling enables oncologists to select treatments that are most likely to be effective against the unique characteristics of each patient's cancer. While precision medicine has been around for awhile, one might ask about what their success rate has been so far, and what kinds of challenges are being faced in clinical trials targeting cancer through precision medicine.

Milestones and Roadblocks in Targeted Cancer Therapy Studies

In the realm of precision oncology, there have been remarkable achievements that showcase the potential of targeted treatments. Notably, Imatinib has shown a 95% response rate in treating chronic myeloid leukemia patients, extending their quality of life by an average of nine years.{3} Similarly, Venetoclax has been effective in 80% of cases involving chronic lymphocytic leukemia , and CAR-T therapy, specifically Tisagenlecleucel, has demonstrated a 62% remission rate at 24 months for patients with acute lymphoblastic leukemia.{3}

Despite these advances, the broader impact of precision medicine on cancer care remains modest. A *JAMA Oncology* study highlighted that only about 8% of cancer patients are eligible for precision medicines, with merely 5% likely to benefit from them.{3} This underscores a significant gap between the potential and the actual reach of precision oncology, pointing to the need for broader application and accessibility of such treatments in the oncology field. This discrepancy raises a crucial question about what kinds of obstacles are hindering the holistic implementation of precision medicine in clinical trials for oncology.

Barriers to Success in Precision Oncology Clinical Trials

Data Fragmentation

Precision medicine trials in oncology are facing several hurdles that make personalized cancer treatment a complex goal to achieve. First off, the lack of standardized genetic testing across the more than 150 research sites working on this front in the U.S. leads to significant inconsistencies in the data we rely on to develop precision treatments.{4} This fragmentation is a significant barrier to advancing precision medicine, as it hampers our ability to draw definite conclusions from these clinical trials. This diversity underscores a pressing need for standardized sequencing methods and data formats to ensure reliability and comparability of results across different platforms and studies.

However, data fragmentation is not the only challenge we face in precision oncology trials, since the tumor profiles are as diverse as the data themselves.

Tumor Heterogeneity and Drug Resistance

One of the primary challenges in precision oncology is the heterogeneity of tumors. Tumor heterogeneity refers to the variation found within a single tumor, as well as between tumors in different patients, in terms of genetic, epigenetic, and phenotypic characteristics. This diversity is not only present among the different cells within a single tumor (intra-tumor heterogeneity), but also across multiple tumors within the same patient (inter-tumor heterogeneity) and among similar tumor types across different patients. This inherent heterogeneity of tumors, which can vary significantly between primary and metastatic sites within the same patient, makes it challenging to evaluate the efficacy of targeted treatments in oncology trials.

Furthermore, the rapid development of resistance to targeted therapies is a pressing concern. As tumors evolve, they can become resistant to treatments that were initially effective, leading to late-stage failures in precision oncology trials. Compounding these issues, the sheer volume of data generated by genetic testing requires sophisticated data analysis methodologies, yet the existing infrastructure for bioinformatics analysis often struggles to keep pace.

Traditional Trial Designs Limiting Precision Oncology

The design of the vast majority of precision oncology trials still follows a traditional format that does not fully embrace the holistic principles of precision medicine. This conventional approach, coupled with the slow development of new drugs compared to the rate of genetic target discovery, restricts the availability of innovative treatments for evaluation in these trials. Finally, precision oncology trials are heavily dependent on data sharing principles, and yet this is the same principle that has been entangled in a web of legal, ethical, and technical hurdles.

Overcoming these challenges is key to unlocking the full potential of precision medicine in oncology trials, making it a critical area of focus for researchers and clinicians alike. This is where multi-omics might come in handy, but what exactly is multi-omics?

Multi-Omics: A Cornerstone for Precision Cancer Trials

In precision-focused cancer clinical trials, multi-omics represents the comprehensive analysis of the genes (genomics), proteins (proteomics), and metabolites (metabolomics) within a cancer cell or tumor environment. This integrated approach provides a holistic view of the tumor's molecular landscape which is essential for developing personalized treatments. By leveraging multi-omics, researchers can match therapeutic strategies with the specific biological context of each patient's oncology profile, potentially leading to more effective and targeted interventions.

Further, multi-omics has the potential to address the below-mentioned challenges we see in precision oncology trials.

Overcoming Tumor Heterogeneity

The presence of tumor heterogeneity in precision oncology trials means that a treatment found to be effective for one part of the tumor, or one patient's tumor, might not be effective for others. This complexity can lead to difficulties in predicting how different patients will respond to the same treatment, making the design and execution of clinical trials a challenging task. This is where multi-omics can help.

For instance, in trials for novel breast cancer treatments, multi-omics allows for the precise categorization of breast tumors into specific subtypes based on genetic mutations and deeper insights into active biological pathways. Consequently, this enables the identification of cohorts of patients whose tumor profile resonates with the molecular signature targeted by the therapy under investigation, allowing for treatments to be specifically tailored to the molecular characteristics of this cohort.

Such a level of resonance addresses key challenges in precision oncology trials, notably improving patient selection and enhancing treatment efficacy, and thereby improving the success rate in these trials. Here, multi-omics not only accelerates the development of effective treatments, but also minimizes the time and resources spent on less promising therapeutic paths in these trials.

Still, tumor heterogeneity is not the only core challenge for precision oncology trials—we must also consider the problems raised by drug resistance.

Identifying and Overcoming Drug Resistance

Drug resistance remains a significant obstacle in cancer trials, often leading to the failure of initially effective therapies. This phenomenon occurs when the cancer cells undergo genetic mutations that enable them to survive and proliferate despite the presence of therapeutic agents designed to inhibit or kill them. Multiple cancer studies have shown that it often contributes to the 95% failure rate that we see in oncology trials.{5}

Multi-omics offers a pathway to understanding and overcoming this challenge. Consider a trial for a new lung cancer drug where patients begin to show resistance after initial success. This phenomenon can lead to late-stage failures when drugs no longer work as expected in these trials. Multi-omics analysis can be employed to investigate the resistance mechanisms at play.

For example, genomic sequencing might reveal mutations in the cancer cells that deactivate the drug's target. Proteomic analysis could uncover alternative signaling pathways the tumor exploits to survive. By integrating these insights, researchers can identify biomarkers indicative of emerging resistance. This enables the adaptation of trial protocols to include combination

therapies designed to block both the primary target and the alternative pathways identified, offering a strategic approach to circumvent drug resistance in these trials.

Refining Clinical Trial Design with Multi-Omics

Finally, multi-omics data can help us transform the design of precision-focused cancer clinical trials. By analyzing the genomic data of tumors within the given cohort of patients, researchers could identify specific mutations that are predictive of a positive response to the treatment being tested. Proteomics could further differentiate patients based on the protein expression profiles associated with those mutations, while metabolomics might offer additional clues about a tumor's environment that influence drug efficacy.

This stratification allows for the design of a trial where only patients with the molecular profile likely to respond are enrolled. Additionally, multi-omics can monitor for early signs of treatment efficacy or emerging resistance, enabling real-time adjustments to treatment plans. This not only increases the trial's chance of success, but also accelerates the development of personalized treatment strategies.

By integrating genomic, proteomic, and metabolomic data, multi-omics enables researchers to not only improve the accuracy in assessing long-term therapeutic effectiveness, but also increases the likelihood of trial success by ensuring treatments remain effective against evolving tumor profiles. This helps us build the next generation of robust models for precision oncology trials.

Integrating Multi-Omics into Precision Cancer Trials

While multi-omics presents a promising avenue for enhancing precision-focused cancer clinical trials, its adoption comes with a set of complex challenges spanning clinical trial execution, patient considerations, data regulation, ethics, and safety.

Clinical Trial Execution Challenges

The sheer complexity of integrating genomic, proteomic, and metabolomic data necessitates powerful analytical tools and an advanced level of expertise, posing substantial logistical and financial challenges. How can a trial efficiently process and analyze millions of bytes of data within a reasonable timeframe and budget, especially in oncology, where the rate of progression of the disease is exponential? Moreover, adapting trial designs to accommodate the complex insights provided by multi-omics data demands a modern techno-clinical infrastructure that many institutions may not have in place today, potentially limiting the speed and scope of these trials.

Patient-Centric Considerations: Consent and Incidental Findings

From the perspective of patient engagement, integrating multi-omics raises important questions about consent and the handling of incidental findings. For instance, in a breast cancer trial let's say we employed a multi-omics approach to customize treatment plans based on the genetic, proteomic, and metabolomic profiles of individual patients. However, this comprehensive analysis may inadvertently reveal genetic markers that not only inform the current treatment strategy, but also indicate susceptibility to other hereditary conditions, such as mutations in the BRCA1 or BRCA2 genes, which significantly increase the risk of breast and ovarian cancers.{6}

How should researchers disclose this information to the participant without adding unnecessary stress while ensuring they are fully aware of the findings?

The challenge begins with ensuring informed consent is truly informed. Traditional consent forms might not adequately capture the breadth of potential discoveries multi-omics analyses can unearth, including those with implications beyond the immediate focus of the trial. This raises critical questions about how to effectively communicate the possible outcomes of such analyses to participants, ensuring they understand the potential for findings that could affect their health in ways unrelated to the cancer being treated.

These scenarios underscore the need for clear communication and ethical guidelines to navigate the balance between research objectives and patient rights in these trials employing multi-omics.

Data Regulation, Ethics, and the Path to Collaboration

The management of the extensive datasets generated by multi-omics analyses presents another layer of complexity—navigating complex data protection regulations and ethical considerations, especially when data are shared across international borders.

For instance, a multi-omics cancer trial spanning several European countries will need to tackle the challenges related to compliance with the General Data Protection Regulation (GDPR). The GDPR rightly sets stringent standards for the processing of personal data, including genetic, proteomic, and metabolomic information, which are central to multi-omics trials. The challenge is, each European country has its own national legislation that implements GDPR, tailored to its specific legal and cultural context.{7} This variation poses a substantial challenge for the management and operation of clinical trials that span these jurisdictions.

Addressing these challenges, initiatives like the Cancer Cell Line Encyclopedia (CCLE) offer a blueprint for standardizing and centralizing anonymized data in precision oncology.{8} The CCLE, a collaboration among the Broad Institute, the Novartis Institutes for Biomedical Research, and the Genomics Institute of the Novartis Research Foundation, has detailed the genetic and pharmacological profiles of more than 1,000 human cancer cell lines.{8,9} This resource includes fully anonymized and standardized transcriptomic, epigenomic, proteomic, and metabolomic datasets, and is freely available to the oncology research community.

This model demonstrates how anonymizing and standardizing data can mitigate privacy concerns and facilitate data sharing in compliance with regulations like GDPR. It underscores the importance of collaboration among stakeholders to harmonize data handling, protecting patient data integrity and streamlining data flow throughout a trial's lifecycle. Thus, researchers must design trials with robust informed consent processes and secure data protocols that comply with GDPR across all involved jurisdictions, ensuring participant data protection against unauthorized access or transfer.

Safety Concerns with Targeted Therapies

Finally, the application of targeted therapies derived from multi-omics analyses introduces safety considerations that must not be overlooked. The precision of these therapies, while a boon for treatment efficacy, requires a thorough understanding of potential side effects and interactions with existing medications. For example, a therapy targeting a specific genetic mutation in colorectal cancer might inadvertently affect other cellular processes, raising concerns about adverse events (AEs) and serious adverse events (SAEs) in these trials.

This scenario underscores the necessity for comprehensive clinical validation and diligent monitoring throughout the trial phase. The identification and management of AEs and SAEs is paramount to maintaining participant safety and the integrity of the trial. Rigorous preclinical studies and early-phase trials are essential to anticipate potential off-target effects and interactions with conventional treatments. Moreover, once a trial is underway, continuous monitoring and real-time reporting mechanisms for AEs and SAEs ensure swift response strategies to mitigate risks to participants.

Conclusion

In conclusion, multi-omics presents an unprecedented opportunity to advance precision oncology clinical trials, promising to significantly improve the personalization of cancer treatment. This approach, however, introduces a spectrum of challenges, including data integration complexities, ethical concerns, regulatory hurdles, and patient safety concerns. The question then arises: How can we effectively leverage the potential of multi-omics while ensuring the integrity and safety of clinical trial processes?

It necessitates a concerted effort from a broad coalition of stakeholders—researchers, clinicians, ethicists, and regulatory authorities—each committed to navigating these challenges with diligence and foresight. Pushing the boundaries of what's possible in cancer treatment through a unified effort while holding patient welfare as our north star is how we'll truly make a difference in these trials—for we're not just navigating the complexities of precision medicine; we're redefining the very essence of cancer treatment for generations to come.

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RECRUITMENT & RETENTION

Diverse, Inclusive Clinical Research Begins with Optimized Trial Design

Faith Holmes, MD; Kristen Snipes, CCRA

Diversity in clinical research has become a hot topic in recent years, with heightened attention leading to dramatic changes in the regulatory framework. The U.S. Food and Drug Administration Omnibus Reform Act of 2022 (FDORA) is one of the most notable.{1} This landmark legislation has broadened the scope of diversity considerations in clinical trials.

FDORA mandated diversity action plans for clinical trials, requiring sponsors to establish and justify diverse patient enrollment goals and outline strategies to achieve them. This regulatory shift underscores the industry's growing recognition of diversity's critical role in ensuring the efficacy and safety of medical treatments across the whole population.

Now, just over a year since FDORA's implementation, the industry's perspective on diversity has undoubtedly evolved. However, despite this increased awareness and regulatory push, many long-standing challenges persist. The same barriers that have historically hindered diverse participation in clinical research continue to pose significant obstacles.

These persistent barriers are reflected in clinical trial participation statistics. Approximately 10.6% of participants are Black/African American compared to representing 12.6% of the U.S. adult population. Hispanic/Latino representation in clinical trials is approximately 11.6%

compared to 16.7% of the population. Conversely, White participants are overrepresented, making up 77.9% of trials and 74.1% of the population.{2} Although numerous factors contribute to these statistics, the most crucial one is arguably the ongoing lack of minority accessibility to research.

While this piece focuses primarily on racial and ethnic diversity, it's important to note that the regulations and diverse practices discussed in general also encompass sex, gender identity, age, socioeconomic status, disability, and other demographic factors.

What Factors Limit Clinical Research Access for Racial and Ethnic Minorities?

Understanding and addressing disparities in research access is crucial for improving clinical trial participation among racial and ethnic minorities. Two major hurdles stand out: 1) lack of trust and knowledge of clinical research and 2) barriers related to distance and time commitments.

The Trust and Knowledge Gap

Forty-one percent of Americans know nothing about clinical research, and 91% have never been invited to participate in a study.{3} Even among those aware of trials and invited to participate, very few consent to join. Many patients, especially those in traditionally underrepresented groups, fear being treated as "guinea pigs," doubting that researchers prioritize their well-being.

This distrust is rooted in significant historical examples of minority exploitation, including the Tuskegee Syphilis Study (1932–1972),{4} the Guatemala Syphilis Experiment (1946–1948),{5} and the San Antonio Contraceptive Study (1969).{6} Beyond these historical traumas, many minority patients have concerns about receiving care from providers outside their communities. This apprehension can stem from several factors:

- **Cultural insensitivity**: Healthcare providers from different cultural or ethnic backgrounds may lack understanding of the specific needs, values, and practices of minority communities, leading to poor communication and inadequate care.
- **Implicit biases**: Unconscious biases among healthcare providers can result in discriminatory practices, affecting the quality of care received by minority patients.
- **Social and cultural stigma**: Presenting with certain health conditions or seeking help outside the community may carry stigma, deterring individuals from engaging with unfamiliar providers.

Physical Barriers

The geographic distribution of clinical trials presents another significant obstacle. Seventy percent of all clinical trials worldwide occur at just 5% of research sites, and most trials primarily draw patients from within 40 miles of their sites.{7,8} While this distance might seem manageable to some, it can be insurmountable for others. Lack of insurance, transportation issues, and financial constraints can make even relatively short distances a significant hurdle.

Time is also a major factor, including not only travel but also time spent at the site. If visits are long and/or frequent, participating while juggling other responsibilities and commitments may be difficult.

The combination of mistrust, lack of knowledge, and physical barriers limits research involvement among minority populations. This not only increases costs and prolongs timelines, it also compromises the validity of clinical data, as they fail to represent the diverse population that will ultimately use the treatments.

How Can We Increase Minority Access to Research Participation?

Innovative trial design is key to improving research accessibility, specifically through the concept of optimized trials, defined as virtual clinical trials designed to create ideal conditions for both patients and sponsors. Patients have simple, effective, and comfortable access to research as a care option, while sponsors can quickly and easily enroll and retain eligible, engaged patients.

This approach to trial design prioritizes patient experience and accessibility, which in turn can significantly increase access to research participation for traditionally underrepresented communities. By reimagining how clinical trials are conducted, optimized trials have the potential to break down many of the barriers that have historically limited minority participation in research.

Patient Trust

All patients, but especially those from racial and ethnic minority communities, ideally will develop trust and rapport with their regular medical providers. In a perfect scenario, they feel at ease and are familiar with interacting with these professionals and their teams in accessible, well-known settings.

Optimized trials boost patient understanding of and confidence in clinical research by enabling participation through trusted healthcare providers, referred to as "Healthcare-First sites." These locations include hospitals, doctors' offices, pharmacies, and other facilities where patients regularly receive care, and which can also function as research sites. Ideally, Healthcare-First sites receive support in their research efforts through infrastructure, training, technology, and expert insights.

As most patients rely on their healthcare provider for clinical trial information, Healthcare-First sites increase patient knowledge of research.{3} These sites allow patients to participate in trials with their own well-liked healthcare providers, who are more likely to understand their backgrounds and to be part of their communities. This in turn increases patients' trust in clinical research.

Physical Barriers to Research Participation

Optimized trials' use of Healthcare-First sites also helps overcome the physical barriers to research participation for underserved communities. Because these sites are where patients already go for care, they are easily accessible while considering insurance status, transportation access, and financial constraints.

However, there are still instances where trial opportunities aren't accessible via a Healthcare-First site, patients do not have existing relationships with providers, or patients' commitments or physical conditions make even brief site visits challenging. Optimized trials address these common barriers by integrating Healthcare-First sites with remote research solutions such as home visits, wearable devices, telehealth consultations, and other innovations. Taking a hybrid approach further emphasizes the patient's experience and supports diverse participation in clinical trials.

Patient Identification

Optimized trials increase research diversity by aiding in diverse patient identification. While traditional clinical trial enrollment processes can be effective, they may not easily support patient identification based on demographics such as race, ethnicity, geography, or disease severity.

Conversely, optimized trials use Health Insurance Portability and Accountability Act–compliant electronic health record (EHR) data and artificial intelligence (AI)–powered analytics to target and engage with specific patient groups. The process typically starts with experts using AI technology to search an abundance of EHR data from hospitals, major health systems, and healthcare-based sites, identifying previously untapped patients. Then, careful review of each patient's medical records makes it possible to identify only those who fit the trial criteria.

Embracing an Era of Optimized Trials

Research diversity is not only a matter of fairness; it's fundamental to producing robust, inclusive, and impactful treatments that benefit all people. While there is still significant work to do in reducing the barriers that stand in the way of inclusive research, the industry can make substantial progress by implementing optimized trials.

Simply put, when clinical trials achieve greater diversity, they accelerate progress in medical research and treatment development. Optimized trials represent an effective way to achieve this ideal outcome, addressing long-standing issues of accessibility, trust, and representation in clinical research.

As we move forward, the widespread adoption of optimized trials could play a crucial role in democratizing access to cutting-edge medical research. By breaking down barriers and creating more inclusive research environments, we can ensure that the benefits of scientific advancement are accessible to all communities.

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ON THE JOB

Hire with Caution: Background Checks May Not Catch Applicants' Fakery

Angela Roberts

It can be difficult to find qualified and motivated candidates for clinical research job openings who are following all the rules. So, when competition gets so cutthroat that an entire shadow network of fake references springs up to help foist illegitimate new hires on short-staffed or over-eager employers via trickery, caution should be the hiring manager's byword.

When the topic of how to identify fake job applicants comes up, I am constantly asked, "But why not just call and verify past employment?" That seems like a reasonable question. By all means, you should do background checks—but such checks and employment verifications aren't always going to protect you from candidates whose resumes are littered with details of fabricated positions and achievements.

Yes, There are Fake Companies

Never assume the companies listed on candidates' resumes are real businesses. "Fake companies" can have folks who will answer the phone and "verify" employment. We first noticed this trend in 2010, when clinical research associate (CRA) candidates from certain would-be previous employers consistently failed our competency assessments. As we dug deeper, we realized the companies didn't exist, and that the candidates were fake job applicants who were using these bogus companies to represent monitoring experience they didn't really have.

To date, we have identified 47 of these phony companies, with an additional 119 classified as highly suspicious. The trend of candidates using fake companies on their resumes is one of the most elusive and alarming trends we have seen. These shell companies have websites and often the individuals who set up these counterfeit companies trick Google into assigning locations to them. *Business Insider* first reported on this issue in 2015, not only confirming what we were already seeing in our industry, but also blowing the whistle on an organization that admits to creating hundreds of phony companies.

Don't underestimate how committed these fraudsters are; not only do they have staff members who answer phones to "verify" employment, but for an additional fee, they will provide positive references from "past supervisors."

However, even if a suspicious-seeming company turns out to be real, hiring organizations should be diligent with background checks and reference checks, which should always be verbal. I am finding more and more companies fail to conduct thorough reference and background checks, when these should go well beyond looking just for criminal history and employment verification. Often, the operations managers waiting for new hires don't know these important steps are being skipped or sidestepped, perhaps because there's a cap on what the organization will spend on such efforts (more about this below). This can result in a bad hire even though someone looked really good on paper.

How to Determine if a Company is Real

It is easier to confirm that a company is real than to prove it isn't. Here are some specific steps you can follow to provide insight into a company's validity.

Check State Registries

As a rule, if you have never heard of a company, you should search for its registration. If a company has legitimately been organized, it will be listed on the appropriate state's registry. But…realize that companies do not always have to register their business where the business resides. For example, our company headquarters is in Florida, therefore our business is registered

with the state of Florida and can be found on the Florida's Division of Corporations site. But we were once registered in Georgia and would also be qualified to register in the state of Delaware.

So, while you want to start with the state where the company's headquarters is located, you may have to broaden your search if you want to prove fraudulence.

Other Resources for Your Sleuthing

If searching the Secretary of State or Divisions of Corporation site for the state where the company resides doesn't yield results, consider using Manta Business Directory. Manta scrapes each state's corporation database and allows companies to register with them directly. While not as reliable as the Secretary of State listings, it can be a good source if you are unsure which state a company may be registered with.

One of my personal favorite corporation resources to use is OpenCorporates. Their database consists of filed corporations across the globe and it is extremely accurate. However, if you use this source often, you will be required to pay a membership fee. But if you hire CRAs or deal with fraudulent candidates, the fee is worth it.

What isn't Likely to be Found

Fictitious names and trade names can be difficult to trace. For example, while you can easily find our corporate name on Florida's corporation site, you won't be able to find our trade name. While trade names are required to be registered, they aren't easily searchable like corporation names are. Much like single-member LLCs, they can be difficult to track down and even more difficult to prove fraudulent.

What Happens if You Can't Verify the Company is Real?

If you are unable to verify the legitimacy of a company through a corporation search, you can certainly research their activity online.

Start with a LinkedIn presence. While not all valid companies have LinkedIn, if the company does have a LinkedIn presence you will be able to gain insight into its validity. Start by assessing

how fleshed out the company's profile is. Then take a look at the individuals who are connected to it along with their titles, etc. You should know that anyone can build a fake LinkedIn company page and have many people connected to it, but real people will be posting as well as sharing information about company milestones. LinkedIn companies also include an Insights tab that will show a history of employees connected to it.

And if the company is a sponsor claiming to conduct trials in the U.S., you can also check out ClinicalTrials.gov. Just be aware that not all studies are required to be on this government site. You can also search for press releases and check out other resources such as Crunchbase.

We also keep a history of companies we can't verify and, suffice it to say, trends will start to reveal themselves if you just track the history long enough.

Even if the Company is Real, be Diligent in Background and Reference Checks

I am finding more and more companies fail to conduct thorough reference and background checks. And often the operations managers don't know these important steps are being skipped or sidestepped.

If you are an operations manager, find out what the background and reference check processes are. We provide some important items to consider in a different article, but here are a few important things to confirm.

See if There is a Financial Threshold for Background Checks

I spoke recently with someone who told me their human resources (HR) department had a cap on what it would pay for employment verification. Among other factors, this can be because some of our larger industry contract research organizations (CROs) and sponsors require a verbal employment verification, and background check companies will charge extra for the additional effort that takes.

In this particular instance, my friend told me that she had gut churns when interviewing a particular candidate and was counting on the employment verification to either confirm or deny her suspicions. She didn't know HR wouldn't conduct an employment verification if it required

an extra charge. Unfortunately, sidestepping this employment verification resulted in a bad hire. She later found out that the individual had never worked with the large CRO represented on his resume. Being thorough in the background check would have avoided the situation.

You should find out if there is a limitation on how much your company will spend on *any* aspect of the background check. Keep in mind that a thorough background check goes well beyond a criminal history and employment verification analysis. If there is a threshold set for any portion of the background check, either obtain permission to exceed that threshold or speak to your leadership about alternative methods of obtaining a thorough result.

Always Do Both

Often companies will skip reference checks, but as noted above, background checks aren't always effective. Because of our experience with fake job applicants, we actually put more stock in reference checks—if they are done correctly—especially when it comes to confirming the experience of contractors.

Just know that background checks aren't going to be effective in some instances and reference checks aren't effective in others. Do both and you will increase your chances of confirming the candidate's qualifications.

Reference Checks Should Always be Verbal

Why? For two reasons. First, references can be easily falsified. Fake job applicants will go to great lengths to represent someone as a past clinical operations manager when they are really a sister, a wife, a friend, a colleague, or someone from their "fake company" arrangement.

Business e-mails can be spoofed, so even if the candidate is using an e-mail from a well-known company domain, don't assume it is valid. Create a reference template that includes open-ended questions that cover hard and soft skills. Then verbally speak to each reference. Verify the candidate's title, the dates they worked together, and the company where they worked together—and then dig into the reference questions. Be sure to listen with your ears *and* with your gut. Pay attention to what they are saying as well as their pauses while also tuning into energy shifts. If you are "using your gut" during these calls, you will be able to feel it if something is amiss.

Which brings me to the second reason why you want to verbally check references. People are more likely to be forthcoming with the truth when in a verbal discussion versus responding to a questionnaire through e-mail. When you ask a direct question, honest people will want to answer it. They may still pause, but they will be more honest with their answers. And of course, you are looking for references who will answer your direct questions about the candidate's hard and soft skills.

Was the Company in Operation When the Candidate "Worked" There?

I recently had an applicant whose resume showed she was employed by a company two years before it was formed. We also consistently see where folks state they worked for a company after it was no longer in business. Always make sure the candidate's employment dates align to when the companies were active, so that you can catch fake job applicants who represent they worked for a company before or after the company actually existed.

We have also seen a strong trend of candidates listing multiple companies on their resume which did exist, but which have been acquired or gone out of business. This act alone doesn't necessarily mean fraudulence, but digging deeper to verify employment can be a challenge. And in some instances, impossible.

In Conclusion

Currently, approximately 60% of the candidates applying to our open positions are proven to be fake job applicants. It takes time to identify those candidates who are valid…and unfortunately, it isn't always possible to prove that a candidate is fake (until it is too late). But if you don't try your best to implement the advice above, you'll have no one to blame but yourself when what you thought was a golden, new hire turns out to be a tin-plated fake.

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SITES & SPONSORS

Converting Meetings Data into Valuable Metrics and Insights for Study Sites and Sponsors

Chris Bryant

Recently, an industry driven by metrics admitted it's probably not making the most of its data. This conclusion—noted in the marketing sector—offers both a warning and sound advice for the pharmaceutical industry, which collects data from its investigator meetings, speaker trainings, and ad boards, but often doesn't have all necessary resources to convert this information into meaningful metrics and actionable insights that can impact business strategy.

More than 500 business-to-consumer marketing, media, and advertising executives were surveyed about challenges to measuring their return on ad spend (ROAS), an important indicator of their return on investment (ROI). Wakefield Research, in partnership with LiveRamp, conducted the survey and released the resultant report, "Looking to Improve ROAS, Organizations Shift Focus from Data Collection to Measurement Optimization in 2024."

Among the findings, it was stated that 97% of executives in marketing, advertising, and brand management had challenges using data to measure impact. In fact, 90% admitted they invested heavily in data collection, but "not enough in the measurement and analytics capabilities they need to use the data to its full potential." More than three-quarters of them, then, are making improving their measurement rationale and analytics interpretation capabilities a priority this year.

Making Better Use of Existing Data

Pharmaceutical companies have always collected data in some format from their investigator meetings, speaker trainings, and ad boards. Many use the information for compliance purposes as well as to assess the ROI or educational impacts of the meeting itself. As meeting technology has become more sophisticated, more and different types of meeting data have become accessible.

While the intention is to gather more actionable insights, often the result is that organizers are either overwhelmed by raw data they don't have time to correlate, or simply hand-pick the same few datasets they've used for years. This is understandable but also a huge, missed opportunity. Data used correctly can yield a story about the meeting that is easy to understand and easier to act upon by both sponsors and trial leads.

The focus needs to switch from collection to purposeful metrics optimization to make converting data to insights more seamless. This is not as daunting as it seems; the right technology partner should be able to help.

Bridging the Gaps

Ultimately, you need to bridge the gaps between study teams, life science stakeholders, and technology providers. The first step, then, is to work with your technology partner in the meeting planning stage to identify data that would help you answer important questions, test theories and preconceptions, and provide context for insights the stakeholder could easily act on. Your partner should be able to develop a plan for how to acquire those data as part of the meeting using their technology (or engineer engagement)—ideally, by working directly with study teams on their goals and obtaining buy-in for metrics optimization.

The goal is to gather demographic information that will provide context when correlated with all other meeting metrics. Correlating demographics with pre- and post-test data that show the level of knowledge on the topic could, for example, highlight differences in understanding of patient profiles or enrollment procedures among different sites. If your technology partner can provide you with content engagement insights at the site level, post-investigator meeting follow-up can be more targeted and, ultimately, yield faster results.

Going Above and Beyond

To really make the most of measurements and analytics though, you need to go beyond the demographic, contextual information and develop datasets around information that can impact your business.

Consider the information you've never received from a meeting before, but which would impact how you develop or market a drug, or even just improve future meetings. Collect the same data across a series of meetings on the same topic (multiple regional investigator meetings for a global clinical trial, for example). Then measure and analyze those data to see what patterns emerge in the meetings themselves or in the attendees' understanding or behavior. Benchmarking across all meetings and events enables you to look at meeting performance for ways to improve programming to meet your goals in the future.

In many cases, pharmaceutical companies and their meeting partners don't have the extensive databases, data warehousing, and analytics tools in-house to make sense of the raw data in this way. To some extent, this is a challenge the marketing industry shares (compounded by the fact marketers have data coming in from multiple sources for one ad campaign).

The right technology partner should be able to help you with transforming data into insights so you don't need to build out that infrastructure. As the level of insights you can obtain from data collected during life science meetings continues to increase dramatically, lean on your technology partner to make sure your data are used to their fullest potential.

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PRESCRIPTIONS FOR BUSINESS

Taking Quadruple Aim: Improving Clinical Research Access, Affordability, Quality, and Experience

Sam Srivastava

One of the biggest challenges facing the clinical research industry now is lack of stakeholder engagement. Trials are increasingly complex: taking longer, costing more, and requiring more technology and data than ever. It took an average of 7.1 years to develop a new drug (from starting clinical trials to approval) in 2022 (up from 6.9 years in 2021) at an average cost of $2.3 billion, according to the Deloitte Centre for Health Solutions.{1} A clinical investigator at a hospital or in a doctor's office trying to manage a trial now uses more than 12 pieces of technology, on average.{2}

For people who want to participate in a clinical trial, the barriers are high. They must first overcome the fact that only 3% of physicians globally participate in clinical trials, so their doctor probably isn't involved.{3} Then, if they do find a pertinent clinical trial, 70% of people must drive an average of more than two hours to participate.{4} Furthermore, they must change their pattern of care to go to the clinical research site. It's very burdensome, and just one of the reasons contributing to the fact that more than 30% of participants in a trial drop out over time.{5}

Personal Perspective

Unfortunately, my father had amyotrophic lateral sclerosis (ALS) and passed away from the disease. I spent much of my time working with payers, providers, social workers, and employers trying to get a better system of care for my father. Now, I'm fortunate to be in a position of helping sponsors determine how to cure ALS, working in an organization involved in everything

from trial design, start-up, and partnering with sites to recruiting patients, gathering clinical endpoints, and completing a trial.

However, as I took on this job, I quickly discovered that the clinical research delivery model is even more antiquated than the care delivery system. For the past 10 years, the care delivery system has been aligning around value-based access, affordability, quality, and experience. Clinical research has a terrific opportunity to rally around that same quadruple aim.

Improving Access and Affordability

We need to make it easier for people to participate in clinical research. The strategies employed to connect patients with clinical research sites also need to vary by geography. There are distinct differences between urban, suburban, and rural communities. Successful outreach requires cultural competency, knowledge of how care is delivered, and attention paid to how research is understood in local markets. It's not just the language that information is written in, but also the cultural sensitivities that are critically important.

We have an elegant process for capturing data and identifying participants who might be eligible for a trial, running their information against inclusion and exclusion criteria, understanding the sites and their ability to perform, and figuring out which ones might be suitable for a trial. The bigger challenge is reaching out to those potential participants—enabling them, and sometimes their family members, to better understand the trial. This would help them enroll, while ensuring they have transportation to and from the research site will help them to stay enrolled.

We talk about social determinants of care as barriers to care delivery, but there are also social determinants to clinical research. On average, 75% of the U.S. participants in clinical trials are white Caucasians. That does not reflect the United States, where approximately 40% of the population is multiethnic and diverse.{6}

We tend to conduct clinical research where participants have means and awareness, so they're typically white, affluent, educated, and in urban settings. From an ethical perspective, we need to do better at reaching into communities and personalizing clinical trials so that the social determinants of clinical research are effectively addressed.

Improving Quality and Experience

The data required for a clinical trial, and the evidence that's generated and collected, is three times greater than 10 years ago.{7} As an industry, we have a great opportunity to improve the quality and efficiency of data collection and use now.

One step in the right direction is for organizations to host external advisory committees—ideally composed of leading industry experts from all stakeholder groups—so that new perspectives can help organizational leaders be ready for the challenges on the horizon relevant to the interaction of care and trials, in terms of patient centricity and transparency, among other concerns. Underscoring the importance of this type of engagement, research conducted by the Tufts Center for the Study of Drug Development showed that protocols which were developed with a patient advisory board had a 30% reduction in clinical endpoints, 20% fewer inclusion/exclusion criteria, and a 50% reduction in the amount of data collected, significantly simplifying the trials.{8}

Innovation is central to the ability to accelerate clinical research, which is why more organizations should also host "innovation studios" to allow scientists, managers, clinicians, and product and technology leaders to come together to focus on big, bold technology and product innovations. Such studios allow organizations to take an idea, develop it, test it, and have a viable product or service that is delivered to the market at warp speed. For example, in one organizational setting, an innovation studio-inspired approach to streamlining operational processes has allowed institutional review board services that used to take 45 days to conduct to be reduced to an average of four or five days.{9}

Industry Call to Action

As an industry, we have not been able to bring care delivery into alignment with clinical research; however, we have a powerful opportunity to see this through now with the confluence of data and technology, backed by a drive to make clinical trials more diverse and personalized.

Let's bring the quadruple aim in care delivery to clinical research. Let's start with the patient and make clinical research more accessible, more affordable, higher quality, and a better experience.

Let's make the system better for everybody—not incrementally or in just a few small ways, but by rapidly and fundamentally reinventing it.

Next Steps

We can start by building coalitions of all the stakeholders—sites, sponsors, contract research organizations, regulators, vendors, and more—and publicizing collaborations that have produced great outcomes by sharing best practices and tools that are leveraged as a group.

Second, we can work with leaders at global forums to make this agenda item number one.

Third, we need to get grassroots, community-based organizations and regulatory authorities involved.

Overall, we need to demonstrate proof of concept and the will and support around it to move from quality issues toward this call to action wrapped around access, affordability, quality, and experience.

Finding ways to break down barriers, drive interoperability, and increase connectivity will enable fresh thinking and collaborative approaches that will help to make the quadruple aim a reality for clinical research.

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TRIALS & TECHNOLOGY

The Power of AI in Pharma to Achieve Regulatory-Ready Studies

Daniel R. Drozd, MD, MSc

Observational studies are instrumental in learning about the natural history of diseases and the impact of treatments on patients in real-world settings. These studies are more impactful and generalizable when they incorporate: 1) deep clinical phenotypic and outcome data, not just administrative-coded data; 2) a diverse group of participants, not just patients at a small number of academic sites; and 3) comprehensive data from across the patient journey not limited to a single clinic, hospital, or healthcare system.

In 2016, the U.S. Congress passed the 21st Century Cures Act,{1} which provided the U.S. Food and Drug Administration (FDA) with additional ability to leverage real-world evidence (RWE) in regulatory submissions. In the intervening eight years, numerous additional guidance documents and frameworks have been released.{2–5} Key to these guidance documents is the notion of assessing if data are fit-for-purpose, that is whether the data are reliable and relevant to answer a specific regulatory question.

Today, researchers still face challenges in accessing deep, diverse, longitudinal, fit-for-purpose real-world data (RWD). Recent technological advancements like purpose-built large language models (LLMs) can help with these challenges. When paired with novel patient-mediated approaches to data collection and generation, they are finally helping to unlock the full potential of medical data to drive better research and improve healthcare.

In this article, I'll help demystify how LLMs can be used in fit-for-purpose observational research and offer key questions to consider when assessing their use.

The Growing Use of LLMs in Biopharmaceutical Research

LLMs are proving valuable for a variety of real-world applications and can be further fine-tuned in specific domains to improve their accuracy. Biopharma companies are now using LLMs to analyze large volumes of clinical data to identify novel patterns, optimize clinical trial design, and assist in regulatory compliance. These powerful new technologies can enable researchers to track disease progression and uncover insights faster than is possible when using only manual approaches.

The most recent FDA guidance about the use of RWE in regulatory submissions{5} is a positive step toward clarifying use of this data for regulatory purposes, but specific recommendations for the use of artificial intelligence (AI) are missing from current guidance, despite many sponsors already using various AI techniques, including LLMs.

While specific guidance is needed, ultimately, by applying existing fit-for-purpose frameworks and focusing on data relevance and reliability in a specific clinical context, we can understand how purpose-built LLMs can help companies generate RWD that meet regulatory standards.

LLMs and Data Reliability

Data can be considered reliable when it accurately reflects the underlying medical concept of interest. Reliability includes whether the data are: 1) *plausible* (e.g., a patient's weight is within a believable range); 2) *consistent* (e.g., variability in a patient's weight in a given period of time is biologically possible); 3) *complete* (e.g., the incidence of missing data is minimized and understood).

Traditional RWD studies have either relied on secondary uses of existing structured data, often administrative claims, intended to support billing or labor-intensive and time-consuming manual chart reviews and data abstraction. The latter was often necessary because, for many studies, claims data lack enough detail to accurately phenotype patients or capture key covariates and outcomes.

LLMs provide a robust and novel approach to radically simplifying this previously manual data abstraction process, because of their ability to abstract and structure key clinical data from the unstructured portions of providers notes at scale. They can contribute to data completeness by finding references to additional providers and visits within records, and by facilitating processes to retrieve those records, when appropriate.

Still, even the best LLMs are not without their own limitations, chiefly that they can, at times, "hallucinate" or generate spurious results. One key to minimizing this is to ensure that the LLM being used has been trained on relevant records and data—a generalized model is often not good enough and too prone to error and hallucination, but one trained and tuned specifically on relevant medical record data can dramatically increase data quality.

While LLMs can quickly accomplish tasks that were previously labor-intensive and time-consuming, incorporating human review is still crucial to ensure transparency, validate data quality, and meet regulatory evidentiary requirements. An LLM-driven, human-in-the-loop approach can balance the benefits of AI with safeguards against potential risks.

When evaluating the ability of an LLM-based structuring approach to produce reliable data, consider asking:

- What quality control processes are in place to minimize the risk of hallucinations and spurious data?
- Are human data abstractors involved, and how are they trained? Are there rigorous protocols and processes in place?
- How frequently and how is the quality of the LLM assessed?

LLMs and Data Relevance

Data are considered relevant when they reflect the population of interest and capture important exposures, outcomes, and covariates.

LLMs can contribute to generating relevant data in two primary ways. First, an LLM trained on heterogeneous medical records from a diverse population of patients can minimize potential

biases related to treatment patterns, race, ethnicity, or socioeconomic factors that may be present if models were trained on only data from specific regions, health systems, or electronic medical record providers.

Second, by facilitating data abstraction from a broader range of records, LLMs may enable abstraction of essential exposures, outcomes, and covariates that were either too labor intensive or difficult to abstract using traditional methods.

When assessing the ability to use LLMs to produce relevant data, consider asking:

- Do the relevant variables exist within the data the models were trained on?
- What data were the model trained on? Are these data relevant to my population of patients and my research questions?
- What is the timespan covered by the longitudinal patient records used to train the model? Do the data used to train the model cover a time period contemporary to my research questions?

Moving Forward with AI in Observational Research

The impact of advanced techniques like purpose-built LLMs have the potential to dramatically change the clinical research landscape.

For biopharma companies, there is potential to drive faster, more efficient studies and to incorporate a far more holistic view of the patient journey and experience.

For patients, LLMs can help facilitate inclusion of a more diverse set of patients in research, allow insights from that research to be shared more quickly, and ultimately speed the availability of novel life-altering treatments.

Advanced LLMs trained on relevant clinical data can speed the generation of normalized, validated RWD from messy records. When built into the study design from the beginning, this technology can be leveraged in ways that generate fit-for-purpose, regulatory-ready data.

However, realizing this new future will require thoughtful implementation of AI with continued human oversight and review to maintain high data quality and reliability.

As we rapidly enter a new era of AI-powered observational research, the industry can meet the growing demands for evidence generation and regulatory requirements with greater data completeness, accuracy, and traceability at an unprecedented scale and pace.

This shift will not only transform how research is conducted, but also accelerate the entire process of bringing treatments to market and improving health outcomes for patients worldwide.

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GOOD MANAGEMENT PRACTICE

The Path to Clinical, Regulatory, and Commercial Success in Rare Disease Studies

Christian K Schneider, MD

Research within the rare diseases space brings its own set of challenges associated with clinical care, regulatory compliance, and commercial activities within the clinical trials environment. Managing each of these realms requires a deep knowledge of the disease state, the development space, and what data and evidence the regulatory authorities and payers will demand.

During a recent panel discussion, experts in innovative trial design, regulatory strategy, market access and reimbursement, and commercialization explored the clinical, regulatory, and commercial pathways to success. The panelists delved into the interdependencies of these areas to unravel some of the challenges and considerations when undertaking a development program for a rare disease treatment.

Panelists included the author of this column, Christian K Schneider, MD, Chief Medical Officer, Strategic Product Development Consulting; Dennis Earle, Senior Director–Development Consulting and Scientific Affairs; Dr. Brad Carlin, Senior Advisor, Data Science and Statistics; and Erika Wissinger, PhD, Senior Director within Market Access and Healthcare Consulting, all of Cencora.

Alternative Evidence Pathways

Increasingly, regulators understand that in rare diseases, randomized controlled trials with a diversity of patients are not feasible.

“A lot of regulators are looking not just at the primary endpoint in isolation, but also other evidence—pharmacodynamics, plausibility of effects, maybe even some exploratory endpoints, and so on,” Schneider said. “There is also growing flexibility to employ novel statistical approaches.”

An area of growing importance with rare diseases is non-interventional or observational studies—both natural history and patient registry studies. One question that arises with these is how to adjust for bias in the data.

As Carlin noted, there are ways to adjust for the possibility of bias in an observational database. “There are statistical tools, such as propensity score matching, that attempt to correct for bias and not having a randomized design,” he said. “There’s reason to believe that carefully applied versions of those methods will be enough to satisfy regulators and other interested parties in rare disease settings.”

There are already clear examples of regulatory flexibility when it comes to natural history and patient registry data.

“Sometimes patients have been enrolled in a patient registry for a long time and a new treatment becomes available,” Carlin said. “If we then give this treatment to a subset of the patients, each can act as their own control just by looking at what happens before and after the intervention. Statisticians call that a crossover study. Normally, we would randomize the order in which the subject receives treatments: some would get treatment and then get placebo, while others would get placebo and then get treatment. In the rare disease space, we don’t have that luxury. Everybody’s starting on ‘placebo’ (their own natural history) and then switching to treatment. That’s an example where regulators have been flexible and have allowed us to get the approvals and information we need on an orphan drug without a randomized design.”

An important consideration with non-interventional studies is whether the data are sufficient to support the statistical objectives.

“In my experience, there’s a wide degree of variability there,” Earle said. “Some disease registries have data approximating clinical trial data in terms of rigor, and others are a lot looser.”

Data rigor is key not only from a regulatory perspective, but also when it comes to reimbursement.

“Any data that can supplement the full value story for the asset in addition to clinical trial data, and that support the messaging around clinical benefit for the patient will be helpful in making a convincing story for the payer,” Wissinger said.

Europe as a Target Market

There has been a lot more discussion of late about whether Europe is still an attractive market for rare disease products, and there are signs of decreased competitiveness in the orphan drug space.{1}

Schneider, however, noted that Europe is a highly developed market, with a lot of experience in handling products such as advanced therapy medicinal products (ATMPs), and with programs for how to work with the agencies. “A key intention of the European Commission is to facilitate innovation and provide incentives by not over-regulating the industry,” he said.

Wissinger added that while Asia is an attractive market from a commercial perspective, Europe also is a large market and one that nearly all manufacturers are still interested in entering. She also noted that, from a health technology assessment perspective, while it is challenging, a lot is changing in Europe with the Joint Clinical Assessment (JCA) coming into effect in January 2025. Under the JCA, European Union members will work collaboratively to evaluate the clinical evidence of new treatments. The JCA will be mandatory for new oncology drugs and ATMPs as of 2025.{2}

"The hope is that it will make the process smoother for the individual pricing negotiations because the clinical efficacy and potentially comparative efficacy [of the new treatment] against standard of care has already been addressed in the JCA," Wissinger said. "There is cautious optimism at the moment."

Defining Substantial Improvement for Expedited Approval

Determining acceptable benchmarks for rare disease therapies may not always be about extending survival, but instead might be improving quality of life (QoL). In such a scenario, therapy innovators would need to include an endpoint of patient relevant outcome.{3}

"We all know of examples where an orphan drug does not necessarily produce a better survival outcome for the patient, but does have an advantage," Schneider said. "An extreme example would be if the current treatment is given intravenously at hospital in the intensive care unit every day, whereas the new treatment is one pill every other month; that's an obvious improvement in QoL. That's why it's important to talk to the regulators so this claim can be considered meaningful for the development program, as it's something you will need to know early on when you plan the clinical study."

The payer strategy also should be considered early on because the QoL factor is very important for payer reimbursement in a number of markets, Wissinger said. "It's the holistic view of the overall benefit to the patient, to the caregiver, and, in some cases, the overall societal benefit—for example, ability to return to the workforce" she explained. "It's really that specific value message around the benefit for the individual asset."

Earle highlighted a 2014 recommendation from the American Society of Clinical Oncology that an improvement of overall survival of 20% would be considered generally clinically meaningful. "On occasion, there may be more specific guidance that you can use to guide your clinical development," he said.

From his experience with clinical studies where there is both a clinical and QoL endpoint, the debate can be whether it's necessary to show improvement on both of these endpoints, Carlin said. "Sometimes going with the QoL endpoint is worrisome because the QoL concern wasn't

there 10 years ago, so we haven't really thought hard about this. Moreover, while QoL may be very important to patients, drug developers may worry that doctors won't prescribe their new therapy if its only significant benefit over the current standard of care is improved QoL. So, while this endpoint is increasingly important, it is on a case-by-case basis."

Attitudes to Innovative Trial Design

There is often an assumption that regulatory authorities and payers are slow to adapt to alternative methodologies, but in many cases they are open to innovative trial design. For example, the U.S. Food and Drug Administration (FDA) established the Complex Innovative Trial Design (CID) Meeting Program, which offers sponsors using complex adaptive, Bayesian, and other novel designs more meetings with the agency.{4}

"Those meetings are a chance to negotiate the nature of the design, review the existing historical data, and really dig in a little bit more than you would normally within the regulating environment," Carlin said. "The exchange for this is that FDA is allowed to publish the results on their website, instead of maintaining the developer's confidentiality until approval. The CID program is just one example of FDA's recent encouragement to use Bayesian method, causal inference tools, and other novel methods to try to bridge some of the gaps that arise when you can't do traditional randomized trials."

The European Medicines Agency (EMA) has published a reflection paper on the use of single armed trials in the rare and other disease spaces,{5} which, again, is where Bayesian methodologies might be leveraged to address gaps in data, Carlin added.

Some of the larger health technology assessments also have clarified their positions on issues such as surrogate endpoints and single-arm studies.

"Germany's IQWiG (Institute for Quality and Efficiency in Health Care) has specific guidance around what needs to be proven to demonstrate the quality of the relationship between a surrogate endpoint and a hard clinical endpoint," Wissinger said. "That's why it's important that early on, when you're considering the regulatory strategy, you make sure the evidence also will resonate with payers."

The benefit of a Bayesian approach is that it encourages a thought process of questioning and making sure everything has been considered before progressing, Carlin added.

Regulatory science is now well established within the health authorities and is considered integral to keeping pace with scientific and technological advances. For example, the EMA's "Regulatory Science to 2025" strategy seeks to build a more adaptive regulatory system to respond to innovative and more complex therapies.{6} The FDA's CID program is similarly focused on innovation, and the United Kingdom's Medicines and Healthcare products Regulatory Agency has its own Innovation Accelerator, which supports developers of innovative products across the regulatory journey.{7}

"What is often clear when dealing with the intersection of clinical medicine and regulatory science is the need to establish that surrogate endpoints are definitively associated with improved clinical outcomes," Earle said. "And those instruments need to be validated. That is a big clinical regulatory development challenge—and one that remains constant despite the fact that there's huge unmet medical need in a lot of these rare diseases."

Getting Innovative Medicines to Patients

From an access perspective, Wissinger pointed to the importance of patient engagement to truly understand what the patient pathway looks like.

"What is the symptom burden and actual impact of burden of the disease?" she asked. "That leads to quantifying the unmet need, which is important for payers, particularly with a new treatment for which there is no real standard of care other than maybe symptomatic treatment. Patient advocacy can also contribute to the generation of real-world evidence, which can be factored into the total package of evidence that's put in front of payers. There may even be some healthcare provider education necessary; for example, if a treatment will fundamentally change the care pathway for those patients, you want to get some advocacy from the healthcare provider."

Wissinger added, "Once you've passed that health technology assessment hurdle, you also need to think about patient support and patient access schemes. There are logistical aspects to the

commercialization, such as managing cold chain supply for patients outside of the main centers. There are a lot of steps that need to be considered as early as possible to make sure that you get the product to the patient."

Optimizing the Trial with the Patient at the Center

While there is often talk about patient centricity when referring to rare diseases, more needs to be done to bring the trial to the patient, for example, through telemedicine, as much as possible.

"There are a number of clinical evaluations, including limited history, adverse event assessments, and drug administration, that can be done by remote nursing staff to reduce the burden on the patient," Earle said. "So, keeping it generally focused on patient centricity, supplementing that with specific clinical operations initiatives, and integrating that with some Bayesian methodologies really gives you an optimal chance of having a timely, well-executed, rare disease development program."

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GLOBAL PERSPECTIVE

The Politics of Health: How Elections Will Impact the Life Sciences

Ivor Campbell

The global landscape for medical technology, biotechnology, and life sciences is on the cusp of seismic change.

The confluence of geopolitical tensions, economic uncertainty, and evolving social values has created a complex web of challenges and opportunities for these sectors around the world.

The broad life science industry too is in the midst of a period of significant transition. While the shadow of the pandemic recedes, its effects linger in the form of a market correction and an evolving healthcare landscape.

This, coupled with looming patent expirations, the impact of new drug pricing regulations, and tighter universal regulation of medical devices, presents a complex environment for both large and small life science companies.

Amidst these challenges lies an undercurrent of excitement fueled by groundbreaking innovations in advanced therapeutics, artificial intelligence (AI), and digital engagement strategies.

Successfully navigating this new reality will depend significantly on the policy decisions of governments in the most advanced economies.

With elections this year in the United States, the United Kingdom, and India—all major players in the life sciences industry—what changes and benefits can we expect to see for companies and their investors, for healthcare providers, and for patients?

The Looming Shadow of Economic Uncertainty

A key concern for businesses is economic stability. The U.K., under a new Labour government, will likely see increased public investment in healthcare infrastructure, potentially boosting domestic medical technology and life sciences industries.

Last February, the Labour Party published its “Prescription for Growth”—an official plan for the reinvestment and revitalization of the National Health Service (NHS) alongside the country’s life science industry.

The strategy is aimed at keeping the sector competitive in a country that has recently been struggling to maintain relevance in the global medical device and clinical trials scenes. At the same time, Labour has promised to end the rolling NHS junior doctor, nurse, and senior consultant strikes that have crippled the NHS amid sluggishly rising rates of pay for staff and international competition to identify and hire the most highly skilled medical staff.

Presented by new Secretary of State for Health, Wes Streeting, the plan set the tone for the new government’s determination to make good on promises to an industry on edge.

As part of that plan, Labour has pledged to strengthen the Office for Life Sciences while creating a more certain funding environment and a more streamlined funding process.

The implementation of new, 10-year budgets for key research and development institutions to attract long-term investment is aimed at ending what Labour saw as the short-termism of its Conservative predecessor in government.

The 2024 U.S. Election: Pharma in the Crosshairs

In the U.S., both main parties are pledging to reform the pharma industry and, while their approaches may differ, both Donald Trump and now Kamala Harris are expected to focus on drug pricing and market competition, signaling potential upheaval for the industry, whoever wins.

The Democrats' Inflation Reduction Act (IRA)—particularly its Medicare drug price negotiation provision—is being touted as a win against "Big Pharma's price gouging."

While the industry has criticized this as "price control," the election of the incumbent vice-president would signal consolidation of the IRA, putting further pressure on drug prices.

Despite criticizing the IRA in the past, Trump is also prioritizing a reduction in drug costs. His previous "most favored nation" executive order—later withdrawn—aimed to leverage international prices to lower U.S. drug costs.

While drug pricing isn't as central to Trump's current campaign, his stance suggests a potential willingness to implement similar measures to the Democrats, if elected.

One area where the candidates disagree sharply is market competition. Harris supports "march-in rights" to allow public access to patented drugs at lower prices, a stance vehemently opposed by the industry which fears it will stifle innovation.

Conversely, Trump champions free market competition and biosimilars. His 2018 law bolstering the U.S. Federal Trade Commission's oversight of biosimilar deals, aimed to increase competition for expensive biologics. While this has benefited some companies with robust biosimilar pipelines, others, like AbbVie, have faced market share erosion for blockbuster drugs like Humira.

In India, the recent re-election of Narendra Modi as Prime Minister for a third, consecutive term, will fast-track his stated determination to make the country the world's third largest economy, up from fifth.

The medical technology, biotechnology, and pharmaceutical sectors will all be affected by Modi's "made in India" policy, which aims to supercharge the country's manufacturing base to help boost growth and create more jobs.

Projected revenues in India's medical technology market this year are expected to top US$8.71 billion. With an anticipated annual growth rate of 7.61%, they are predicted to reach US$12.57 billion by 2029.

Despite this rapid growth—a result of increased government investments in healthcare infrastructure and rising demand for advanced healthcare solutions—India's performance is dwarfed by the U.S., whose medical technology sector is expected to generate US$210 billion this year.

Other Economic, Scientific, and Ethical Factors

Biopharma companies on both sides of the Atlantic, meanwhile, are prepared for a protracted recessionary environment in the coming 12 months.

While venture capital funding remains above pre-pandemic levels, securing financing now requires stronger clinical data and longer negotiation periods.

Private equity firms, increasingly partnering with venture capitalists, offer an alternative source of funding, as seen in KKR's recent investment in Catalio Capital Management.

AI—both in terms of machine learning and generative AI—is revolutionizing the industry, with companies like InSilico Medicine and Relay Therapeutics leading the charge, accelerating the drug development process. AI promises to drive incremental but significant efficiency gains across operations, including clinical trial design, patient recruitment, manufacturing, supply chain management, competitive intelligence, and sales and marketing.

Meanwhile, new cell therapies are showing promise in oncology. Allogeneic therapies are gaining traction, and the application of CAR-T in autoimmune diseases is expanding. However, manufacturing bottlenecks and safety concerns, such as secondary T-cell malignancies, need to be addressed.

Across all areas, success will depend on companies being able to navigate market uncertainties, adapt to evolving regulations, harness the power of AI, and embrace innovative engagement strategies. Those which can effectively leverage these trends will be better positioned to unlock the next stage of value creation and shape the future of healthcare.

Beyond economic considerations, governments will grapple with increasingly complex ethical dilemmas that directly impact the trajectory of these industries. For example, advancements in

areas like gene editing, reproductive technologies, and AI raise profound questions about their application and potential consequences.

Shifting Demographics and the Prioritization of Healthcare Spending

Globally, governments face the dual challenge of aging populations and declining birth rates. This demographic shift will force difficult choices regarding healthcare spending priorities.

Will governments prioritize geriatric care and technologies aimed at managing age-related diseases, or will they focus on preventative care and technologies promoting the health and well-being of younger generations?

The potential for a government-led initiative to incentivize childbirth through improved maternal healthcare and childcare support underlines this critical dilemma. The outcome of this debate will have significant implications for the types of technologies and research that receive government support and funding.

The Potential of Emerging Markets

While established markets grapple with these challenges, emerging economies, particularly in South-East Asia and South America, present a compelling alternative.

These regions often boast rapidly growing populations, increasing healthcare expenditure, and a burgeoning middle class with rising healthcare demands.

Governments in these regions are actively seeking to attract foreign investment and develop their domestic healthcare industries. Companies willing to navigate the complexities of these markets, including regulatory hurdles and infrastructure limitations, could find significant growth opportunities.

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