

Clinical Researcher

The Authority in Ethical, Responsible Clinical Research

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Everything Must Change

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Clinical Researcher

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EXECUTIVE DIRECTOR'S MESSAGE

A Preview of 'Overcoming Obstacles to Decentralized Clinical Trials'

Susan P. Landis, Executive Director of ACRP



Perhaps you are familiar with the old saying about how “life is what happens when you’re busy making other plans.” In our field, the corollary could be that “decentralized clinical trials (DCTs) are what happen while the industry is busy clarifying guidance for them.”

In the “necessity is the mother of invention” atmosphere of the pandemic’s early days, DCTs rapidly went from being a “nice to have” type of arrow in one’s clinical trials

quiver to a “need to have” one. Regulators appreciated that sponsors and trial sites were scrambling to adjust to the new normal of hybrid and fully decentralized trials and were generally flexible and encouraging about allowing professionals to manage those studies in the most expedient and safe manners possible under the circumstances. Now that the health crisis has calmed down considerably, these same regulators are nailing down guidance for how DCTs should be implemented—while industry simultaneously demands that sites and study teams incorporate them.

The lived experience in the clinical research enterprise is that DCTs, as they are widely being used today, fall somewhere between the hope and the hype that surrounded them back in early 2020. They morphed from being a framework for study conduct (not so dissimilar from the adoption of “pragmatic trials”) that was already using some decentralized components, however infrequently, to one that matured so rapidly, it outraced the ability of regulators to keep up.

To steal from another wise adage—the one about “the train has already left the station”—if you are going to clarify regulatory guidance for DCTs while they are being conducted, then you better ask the conductors (in this case, the sites and clinical research professionals actually implementing the decentralized components) about what needs to be clarified for the benefit of accelerating adoption and, thus, greater access for everyone to potentially life-changing clinical research trials. Which is to say (in an opinion I know is shared by others who have the subject matter expertise to be taken seriously on the topic) that trial sites themselves need to have the loudest voice and the most input on how DCTs can and should continue to be improved upon and executed.

Simply put, I know this to be true: the burden of the adoption of DCTs falls to the sites. That means that we have to listen to site leaders and their study teams about their experiences in order to get it right. That’s what ACRP has been doing.

Among other activities, your Association has striven to stay on top of the evolving situation by publishing blogs with timely commentary and offering webinars from subject matter experts on the DCT topic going back at least to early 2020, publishing [a white paper](#) with perspectives on DCTS for our profession in early 2022, launching [an introductory course on DCTS](#) last month, [commenting](#) on U.S. Food and Drug Administration draft guidance on DCTs earlier this month, and, soon, publishing a new white paper on “*Overcoming Obstacles to Decentralized Clinical Trials: Unique Perspectives from Research Sites and Clinical Research Professionals.*”

It was my happy privilege to be part of the writing team for this upcoming white paper, along with Mohammed Ali, Chief Domain Expert, Decentralized Clinical Care, Medable; Caroline Redeker, Senior Vice President, Corporate Development, Advanced Clinical; Sarah Gillespie, Associate Director, DCTs, Syneos Health; and C. Jill Dawson, Consultant to the Association of Clinical Research Professionals.

What follows is just a taste of the full white paper. I welcome your feedback on what it has to say, because learning from one another is one of the things that makes this industry great.

Introduction to the White Paper

Use of decentralized clinical trial (DCT) elements accelerated sharply during the COVID-19 pandemic, enabling many trials to continue when they would otherwise have been impossible. This experience has confirmed that DCT technologies can enable sponsors, sites, and principal investigators (PIs) to meet their obligations to protect patient safety and deliver high-quality data. DCT and hybrid trials support a patient-centered approach by reducing barriers to study participation such as transportation, logistics, and geographical location, helping to improve access for diverse and underrepresented populations. { 1 } However, despite this significant progress, barriers remain. The result is that many sites do not yet use DCT elements, and those who do seem to find them burdensome, including the inconveniences of multiple technology platforms, passwords, and sign-in procedures. Furthermore, there are concerns that the momentum gained may be lost without deliberate action by stakeholders to commit to using decentralized and hybrid trial components.

A think tank was convened by ACRP to discuss progress to date and document barriers to adopting DCT and hybrid components in clinical trials from the perspectives of sites and clinical research professionals. Titled “*From Trepidation to Trust: Documenting the Realities of Hybrid and Decentralized Clinical Trials Adoption*,” the think tank involved 42 participants from trial stakeholder groups. Discussions at the think tank helped crystallize the viewpoints from a full range of clinical research professionals about strategies and solutions to overcome barriers and accelerate adoption of DCTs. This paper presents these viewpoints and proposed solutions.

For the purposes of the think tank, DCTs were defined as “studies executed through telemedicine and mobile/local healthcare providers, direct-to-patient shipments, and using processes and technologies differing from the traditional clinical trial model only at the site.”

Barriers to Success

Based on an online poll, participants identified the top barriers to implementation of DCT elements as:

- The need for clarity from regulatory bodies, including addressing the role of PI oversight
- The importance of addressing budget issues
- The need to define responsibilities and accountability for managing third-party vendors
- The necessity to allow time and budget to train site staff on process and change management

Potential solutions to these barriers are discussed in the full white paper.

Stay Tuned

We conclude that DCT technologies—especially as part of a hybrid approach—can improve the patient experience, reduce the burden of trial participation, and enable remote interactions and data-gathering. They offer increased access to varied and underserved populations, helping boost the diversity of trial participants. Much recent progress has been made, including from a regulatory perspective, and in the emergence of vendors with groundbreaking new DCT technologies.

However, the multitude of challenges discussed at the think tank account for the fact that today, rather than saving time or money at site level, DCTs in fact increase the site burden. This happens in part because the use of trial-related technologies is complex and because, despite positive experiences during the pandemic, concerns remain about the rigor, reliability, and reproducibility of findings from DCTs compared to traditional, site-based trials. Without additional training, the clinical research workforce may not be sufficiently familiar with DCTs to handle their novel data flows, designs, and possibly statistical analyses. Further, fully validating the DCT model will require overcoming challenges related to sharing data across the industry.

Foundational to the future of DCTs will be regulatory clarity and solid evidence that these trials truly make a difference. With these in hand, trial stakeholders can look forward to improvements in the widely shared goals of improved diversity, engagement, and retention.

Intrigued? Keep watching the ACRP announcements on our website and in our e-newsletter and social media for word about when this valuable resource will be available for download.

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PEER REVIEWED

Perspectives from Principal Investigators on Improving Diversity Among Clinical Research Participants

Nadine H. Spring, PhD, CCRC; Jeanne Connors, PhD; Michael Schwab, PhD;
David O. Anderson, PhD



Clinical trials play a crucial role in making new medical treatments and devices available. However, historically, these trials have lacked diversity in participant representation, posing challenges in determining the safety and efficacy of treatments for specific populations. This qualitative phenomenological study explored the experiences of clinical research principal investigators (PIs) in addressing diversity in clinical trials. The PI respondents, recruited through social media and professional networks, shared their insights through interviews. Thematic analysis revealed several emergent themes, including passion for clinical trials, increased awareness of the importance of diversity in clinical trials over time, frustration with eligibility criteria, recognition of the need for diversity among staff, awareness of barriers to diversity, concerns about the lack of formal training, and optimism for future strategies and solutions. The study's findings have implications for social change by guiding efforts to attract underrepresented minorities to participate in clinical trials, ultimately promoting diversity, reducing health disparities, and improving health equity.

Background

According to the U.S. Food and Drug Administration (FDA), a clinical research study is an investigation or research that involves one or more human subjects that is undertaken to assess or evaluate the safety or effectiveness of a medical device.

Clinical research studies are conducted to test the safety and efficacy of promising, novel treatments and diagnostic tests. The findings from clinical research studies fill knowledge gaps by providing new information about ways to treat, prevent, and diagnose diseases. Studies are needed to advance medicine and healthcare as well as to optimize outcomes. (Umscheid, et al., 2011)

Volunteers join these studies and contribute to the data. In many of these studies, the diversity of the participants is not representative of the general population. (Selker, et al., 2018) Some populations, such as African Americans and Hispanics, are disproportionately underrepresented in medical research studies. (Occa, et al., 2017) Evidence has indicated that outcomes, such as adverse reactions and efficacy, can differ by certain patient characteristics, such as gender and ethnicity. (Stronks, et al., 2013) Clinical research studies need to consider diversity when the goal is to improve care and outcomes for all patients.

There is a gap in research where the volunteer patients evaluated in the clinical trials and the target patient populations differ. In the real world, outside trials, this creates an issue where the data about the general population are lacking. This difference in the knowledge about treatment effects in diverse patient populations is widespread in medical practice and occurs with some of the most prescribed medications. (Selker, et al., 2018)

According to Kennedy-Martin, et al. (2015), when the external validity of randomized control trials in the fields of cardiology, mental health, and oncology were examined, it was found that more than 70% of the patient participants included in these trials were not representative of the patients encountered in routine clinical practice.

Racial and ethnic minority groups are routinely disproportionately affected by health conditions such as Type II diabetes mellitus, cardiovascular disease, stroke, HIV/AIDS, and many types of cancer. (Noonan, et al., 2016) Many studies of diseases, such as different forms of cancers, neurologic diseases, and cardiovascular disease, have revealed that the study populations are not representative of the racial and ethnic make-up of those who are most affected by these diseases. (Amorrortu, et al., 2018) The population difference between the trials and real-world practice could significantly impact the external validity of randomized clinical trial findings. (Kennedy-Martin, et al., 2015) The lack of a diverse patient participant pool and a shortage of publicly

available data means that healthcare providers and patients often cannot discern which medications and devices are safe and effective for specific demographics. (Fox-Rawlings, et al., 2018)

Methodology

The methodology of this study involved conducting semi-structured interviews with PIs in clinical research. The population for this study included PIs with at least two years of experience conducting clinical trials in the United States. These PIs had experience in academia, industry, or government agencies with medicines and devices. Experience in any of the four phases of clinical trials was considered. Respondents were screened for eligibility based on their experience in conducting clinical trials in the United States (see Table 1 for demographics).

Recruitment was done through social media platforms by posting recruitment flyers. Purposeful sampling was employed to identify potential respondents. A demographic questionnaire and interview guide were used during the study, providing baseline information, and focusing on research questions.

The interviews were conducted from June 2022 to October 2022. Respondents provided informed consent and received a \$25 Amazon gift card after each interview. Interviews were audio-recorded, transcribed, and reviewed for accuracy. Data analysis was conducted using NVivo Qualitative Research Software, Version 12. Saturation was reached when no new data, themes, or codes emerged from the interviews. The interviews ceased when saturation was achieved, which occurred at 15 respondents.

Results

The preliminary coding of the 15 transcripts yielded 86 nodes. The next step was categorizing these nodes into 12 major categories and subcategories by grouping. Sorting was completed based on concepts that emerged that were the same or similar. Some nodes were merged or deleted because they were repetitive.

The last phase of the data analysis process involved reviewing the categories in NVivo and manually producing themes based on recurrences in the data from the transcripts of the 15 respondents. The result was seven primary themes and several subthemes that revealed the lived experiences of the PIs when addressing diversity in clinical research studies (see Tables 2 and 3).

Table 1: Demographic Information for Respondents

Respondent Number	Gender	Race	Ethnicity	Experience (years)	Specialty	Type of practice
001	Female	Asian	Non-Hispanic	2	Optometry	Private medical practice
002	Female	Asian	Non-Hispanic	8	Pulmonology	Academic medical center
003	Female	Other	Hispanic	10	Rheumatology	Academic medical center
004	Female	White	Non-Hispanic	2	Endocrinology	Academic medical center
005	Female	Other	Unknown	11	Family medicine	Clinical research center
006	Male	White	Non-Hispanic	25	Internal medicine	Clinical research center
007	Female	Asian	Non-Hispanic	2	Internal medicine	Clinical research center
008	Female	Asian	Non-Hispanic	15	Emergency medicine	Industry
009	Female	White	Non-Hispanic	36	Internal medicine	Clinical research center
010	Female	Black or African American	Non-Hispanic	3	Rheumatology	Academic medical center
011	Female	Other	Hispanic	4	Rheumatology	Academic medical center
012	Male	Asian	Non-Hispanic	2	Neurology	Academic medical center
013	Female	Other	Non-Hispanic	5	Rheumatology	Academic medical center
014	Female	Black or African American	Non-Hispanic	12	Rheumatology	Academic medical center
015	Female	Asian	Non-Hispanic	2	Rheumatology	Academic medical center

Table 2: Themes for RQ1—What are the lived experiences of clinical research PIs regarding diversity in clinical research?

Theme	Number of respondents	Percent (%)
Theme 1: Passionate about working in clinical trials	9	60
Theme 2: Increased awareness over time	10	67
Theme 3: Frustration with stringent eligibility criteria	9	60
Subtheme: Perceived belief that sponsors can do more		
Subtheme: Link diversity goals to funding		
Subtheme: Partner with patients		
Theme 4: Perception that increased diversity among staff is needed	7	47

Table 3: Themes for RQ2—What do clinical research PIs identify as concerns for diverse participants in clinical trials?

Theme	Number of respondents	Percent (%)
Theme 5: Knowledge and awareness that there are multifaceted barriers to having diverse participants in clinical research	14	93
Subtheme: Meet the needs of underrepresented populations		
Subtheme: The role that race and mistrust plays		
Theme 6: Concerns that no formal training exists	14	93
Theme 7: Optimism for the future with strategies and solutions	15	100

Respondents were prompted to share what attracted them to serve as a PI on clinical research studies. Serving as a PI can be a challenging role; respondents shared that they enjoyed the innovative components and the medical aspects of being involved in clinical research studies. They enjoyed being a part of the process of helping their patients and bringing new therapies to the market.

The PIs who participated in this study have an average of nine years of experience, and over the course of their career they have seen some changes as it relates to diversity in clinical research. There is more awareness about the need to have representation in clinical trials. There are now recommendations from government entities urging pharmaceutical companies to address this. Respondent 010 indicated that the COVID-19 pandemic has helped to shape some of the conversations around this “since the pandemic has started and since...people’s eyes have been open[ed] to social justice issues in this country.”

The respondents seemed frustrated that study criteria often don’t match those of the average patient in their practice with the condition of interest. The eligibility criteria for some clinical trials can be so strict that it is difficult to get the average patient with the condition into the study. Study Respondent 003 stated “...although I see primarily Hispanics and African Americans, sometimes these patients do not meet criteria for some of my studies.”

The PIs indicated that the field of clinical research itself isn’t diverse or representative of the population served. Respondent 001 suggested a potential solution would be to have more diversity amongst PIs, and that “just having more doctors of diversity...as your [PI] would be, I think, a huge thing. Because...when you see someone who looks like you, it does make an impact.” Respondent 003 stated, “Change the makeup of the workforce.”

In their answers to the prompt “In your experience, tell me about challenges towards recruiting diverse populations into clinical research studies,” the respondents reported there are countless barriers faced and experienced by PIs as related to increasing diversity in clinical research studies. These barriers include difficulty in reaching these patients due to difficulty in accessing diverse patient populations. There are concerns with care responsibilities for dependents of the study participants, barriers tied to time commitment, concerns with improper consent, language barriers, cultural differences, an absence of diversity among the research staff, mistrust of the medical research process, and a fear of being used as a “guinea pig.”

Race and mistrust emerged as a subtheme to the knowledge of the barriers to having diverse participants in clinical research studies. Many respondents alluded to what happened with the Tuskegee Syphilis studies as well as to present-day atrocities such as injustices in the judicial system, educational system, and healthcare. These include “It is difficult to get these groups into clinical research studies when they do not trust the system.”

Study respondents expressed the urgency of improving diversity in clinical research studies. The push came from their employers, pharmaceutical companies, and from government entities such as the FDA and National Institutes of Health. However, they expressed frustration at being unable to find and attend formal training on this topic. The respondents expressed that they received numerous trainings to become a PI, but nothing on recruiting underrepresented populations. To become PIs, respondents expressed that they received training and certifications and, in some instances, research mentorship.

While all the respondents expressed that they enroll underrepresented populations into their research studies, none have had any formal training on how to successfully enroll these populations into clinical research studies. For example, Respondent 001 stated, “I will have to be honest with you, I got zero training in that.”

The PIs in this study were optimistic and hopeful that we are heading in the right direction. They expanded on strategies that could help to address increasing diversity in clinical research studies. Study Respondent 013 indicated this can be approached by tackling language barriers and improving the research infrastructure.

Discussion

There were notable findings from interviews with 15 PIs in clinical research. Due to time constraints and funding, many medical schools do not routinely prepare students and physicians for clinical research. (Adams, et al., 2017) The fact that these PIs pursued additional training exemplifies their level of commitment and dedication to the clinical research process.

These investigators expressed awareness of the importance of diversity in clinical trials, driven by existing mandates and new recommendations from government agencies. They are optimistic

about achieving diversity and have already implemented solutions at their research sites. They expect pharmaceutical companies to do more and desire training on approaching ethnic and underrepresented populations for trial participation.

The passion of the investigators for their work and the positive impact on patients' lives stood out. They acknowledged the challenges but expressed dedication and commitment to the research process. Over time, they have become more aware of the need for diversity and have implemented strategies to attract underrepresented groups.

Frustration was expressed regarding eligibility criteria that often exclude the average person with the condition under study and the reliance on laboratory test results developed based on European American norms. The investigators emphasized the need for diversity in the clinical research staff to effectively serve and enroll underrepresented populations. The findings align with those of previous studies, highlighting the importance of establishing advisory panels and increasing recruitment from underserved groups in the research field. (Bodicoat, et al., 2021)

Further Considerations

Further considerations for this study include conducting a larger, mixed-methods exploration of PIs' efforts to address underrepresentation in clinical research. This would involve a more diverse group of participants from various practice settings. The study revealed a need for formal training on attracting and retaining underrepresented populations, indicating the potential for future research and the development of training programs in this area. Exploring effective patient partnerships and expectations from pharmaceutical companies are additional areas for future study. Recommendations include expanding the participant population, exploring different practice settings, and examining the pharmaceutical industry's role.

Public health practitioners can utilize the study findings to develop targeted, culturally congruent programs addressing health equity and disparities in underrepresented populations in clinical trials. The study's insights offer potential solutions and strategies for addressing the needs of underrepresented populations in clinical research.

Limitations

This study faced several limitations. The small sample size of 15 respondents constrained the generalizability of the findings. The strict eligibility criteria further restricted the findings to a specific group of U.S.-based, English-speaking researchers. The demographics of the respondents, with only two males and a predominant Asian representation, may have introduced biases. The use of purposeful sampling resulted in self-selection bias. Recruitment through social media excluded PIs not on social media, potentially affecting the representativeness of the sample. The COVID-19 pandemic affected participation. The study design, being qualitative, focused on the experiences of PIs and did not seek statistical significance or a large sample size. Finally, this study was developed as an academic thesis by the lead author, and her personal biases may have influenced data collection and analysis, although steps were taken to minimize bias.

Conclusions

This study has implications for positive social change and advancing care for underrepresented populations. The recommendations for creating training programs could contribute to designing programs and training that are relevant and culturally appropriate for increasing diversity in clinical research studies. This implementation alone could result in more representation in the research studies, having more data and safety and efficacy profiles of many therapies for ethnic minority groups, improving health equity, and reducing health disparities. Furthermore, this study's respondents revealed innovative recommendations for future researchers and public health practitioners to promote positive outcomes.

Finally, this situation of underrepresentation in clinical trials is critical. Diversity in clinical trials is needed and it's needed now—the advancement of care, medicine, and science for underrepresented groups depend on it. Now, imagine a world where certain groups are not disproportionately affected by certain conditions. Imagine a world where there are no health disparities. Imagine a world where there is health equity. This study has shown us that we still have so much to do, and that there are so many layers to address. It won't happen overnight, but achieving representation in clinical trials can help to get us to that world.

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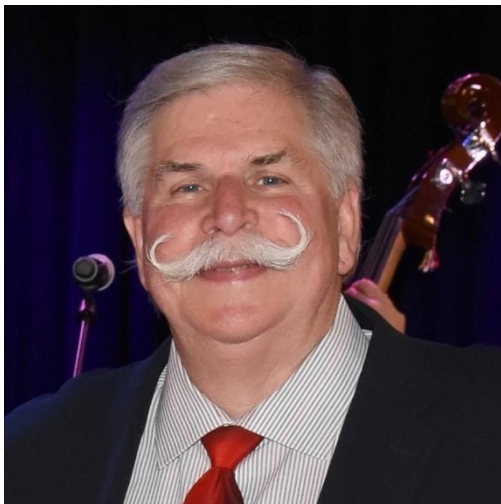
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Nadine H. Spring, PhD, CCRC, (nadine@springwell360.com) is Director of Operations at SpringWell360 LLC. The full version of this study, “Clinical Research Principal Investigators’ Perspectives of Improving the Diversity of Clinical Research Participants,” serves as her doctoral dissertation at Walden University and will be available online on ProQuest in late April 2024.

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PEER REVIEWED

Possibilities and Challenges for Digital Medicine in Oncology Clinical Trials

Sherajum Monira, MS; Martha Toral



Digital medicine, often referred to as mobile health, is a rapidly emerging field that relies on evidence-based, state-of-the-art technologies in contrast to traditional medicine to transform the way healthcare is delivered.^{1} Powered by high-quality hardware and software, this ground-breaking technology collects and tracks health data that can be used to manage critical

health conditions. It facilitates sophisticated and accessible tools for patients and healthcare practitioners to address a wide range of illnesses through high-quality, safe, and effective measures and data-driven interventions.

Measurement, intervention, and combination goods are the three primary categories of digital medicine products, as shown in Table 1.^{1} Numerous digital medicine products can be used in healthcare—for example, smart insulin pens that monitor insulin levels, pills with cameras built in for detecting colon cancer, blood sugar monitoring wearable sensors, artificial intelligence (AI) that can look for suspected cancer indications during a colonoscopy, smartwatch sensors that can record heart rhythm, and early detection of cancer.^{2,3}

Table 1: Distinction Between Digital Health, Digital Medicine, and Digital Therapeutics

Digital Health	Digital Medicine	Digital Therapy
Electronic Medical Record	Measurement Products	Rehabilitation Exercise VR
Digital Medicine	Intervention Products	Medication AI Devices
Telemedicine	Combination Products	Patient Education Apps

Digital medicine represents a paradigm change in oncology research by harnessing technological breakthroughs to address the constraints of traditional clinical trial procedures. Researchers may collect huge amounts of patient-generated health data by adding digital tools into the clinical trial process, providing for a more comprehensive assessment of illness development, treatment response, and potential adverse events. Furthermore, digital medicine allows for continuous remote monitoring, removing geographic obstacles, improving patient convenience and accessibility, and fostering medical research and innovation.

This article navigates into the recent development and background of digital medicine in the field of oncology trials and explores its future potential and advantages. Further, it depicts the key challenges such as privacy, security, and technical instructions which need to be addressed to unlock its true potential.

Background

In 2020, an estimated 19.3 million new cancer cases and 10 million cancer deaths were reported worldwide. Further, in 2040, there are expected to be 28.4 million new cancers, almost a 50% rise from 2020.^{4} This trend is extremely concerning and highlights the growing global burden of cancer. Cancer care faces major hurdles due to a lack of medical resources and an uneven

distribution of medical care levels. The encouraging aspect is that digital medicine includes a wide range of cutting-edge technology and applications like machine learning, AI, and cloud computing to provide promising solutions to cancer patients.

Although digital medicine is still in its early stages, it has the potential to transform cancer care in a variety of ways, such as identifying diseases early, providing more effective treatments, and enhancing patient outcomes by enabling more precise, personalized, and data-driven approaches. Healthcare workers may improve patient outcomes and minimize the burden of cancer on individuals and healthcare systems by leveraging the ground-breaking power of digital technologies.

The Merits of Digital Medicine

The use of digital medicine in oncology clinical trials has brought many benefits to studies, including applicability, improved cost-effectiveness, patient benefits, increased accuracy of real-time data collection, and personalized and adaptive treatment plans. {1} The encouraging applicability and flexibility of digital medicine are allowing this technology to be integrated into oncology studies.

Another aspect of digital medicine that is attractive to researchers is the potential to decrease healthcare costs as well as the time a patient spends accessing healthcare. {1} One example of individuals spending less time receiving medical care is through teledermoscopy. In Australia, a study showed the use of teledermoscopy in the diagnosis or treatment of skin cancer resulted in a decreased clinical resolution by 26 days. However, the cost was \$54.64 more than the use of non-digital medicine. {5} In this particular case, one can argue that, although the cost of

treatment may be higher, the significant time reduction in resolution may also be cost-effective if other factors are reviewed. For instance, the increased lag time in treatment for a patient with difficulties traveling to the clinic could increase costs for an individual not receiving the proper care in a timely manner.

Digital medicine can be utilized to not only lower cost, decrease time, and increase accessibility to those in rural areas or individuals facing challenges traveling to the clinic, but also to increase recruitment and help close the equity gap in healthcare. Digital medicine also has the potential to improve the quality of care for a patient and increase the efficiency of patient enrollment in oncology trials.^{6}

Technological devices containing sensors to monitor a patient's physiological activities can improve the treatment and early diagnosis of a disease.^{1} This real-time information occurs while the patient is at home or conducting their daily activities, and can be used to further monitor oncology clinical trial patients while receiving treatment. The additional and abundant amount of information can result in valuable data for a researcher, potentially increasing the safety profile and improving quality control.^{1}

Other ways oncology clinical trials have been able to take advantage of digital medicine is through the use of AI and natural language processing.^{1} These digital medicines were shown to have equal or superior capabilities when compared to manual screening in patient enrollment in cancer clinical trials.^{6} A meta-data analysis of information from articles that identified using AI for patient enrollment in oncology trials had promising findings. The analysis revealed that out of the 19 datasets used, 18 had an 80% or better accuracy, sensitivity, and specificity than manual screening for patient enrollment in oncology trials.^{6}

If digital medicine is able to facilitate the screening and enrollment process in cancer clinical trials, this can move clinical trials at a faster pace, ensuring adequate and eligible patients are enrolled. This technology can also be used at a wider scale by including information from patients in numerous hospitals and other facilities across the United States or globally to identify clinical trials a patient would qualify for. This capability would drastically increase enrollment and improve the dire enrollment rates that currently exist in oncology trials, where the enrollment of cancer patients is less than 5% and almost 20% of oncology trials end early due to enrollment issues.^{6}

The many advantages offered by the variety of digital medicines currently being developed and those currently used bring a bright prospective future to the advancement of research, diagnosis, and treatment of cancer.

Applications of Digital Medicine in Oncology Trials

Cancer prevention, screening, therapy management, and follow-up can all benefit from the use of digital medicine. The collected data can also be used for scientific study, clinical quality control, and other objectives, which will aid in the resolution of current tumor-related medical issues.

Cancer Prevention

Cancer prevention can benefit tremendously from digital medicine. A plethora of digital medicine resources, such as sun protective behaviors and tumor prevention via mobile phone applications, have been developed and applied to encourage health behavior change. Recently, the relationship between wearing an ultraviolet (UV) radiation monitoring device and UV

exposure discovered that parental and child outdoor activity and sunscreen use time varied considerably after wearing the monitoring device, which is crucial for skin cancer prevention.{7}

Numerous research efforts reveal that obesity plays a significant role in most common cancers such as breast cancer, colorectal cancer, endometrial cancer, renal cell cancer, and esophageal cancer. Thanks to digital medicine, recent mobile apps can facilitate the shaping of individuals' approaches to cancer prevention. Patients are presently adopting mobile health modalities for managing cancer caused by obesity, since they offer tracking and monitoring, give dietary and exercise recommendations, provide encouragement for medication adherence, allow for distant treatment, and supply individualized treatment.{8} Weight loss and a decline in body mass index were found to be strongly correlated in a recent meta-analysis looking at the impact of mobile app interventions.{9}

Cancer Screening

Digital medicine has potential for improving tumor screening and diagnosis by utilizing big data technology and machine learning algorithms to detect cancer at an earlier stage. A study using a web-based chatbot, for example, found that women's cancer risk may be predicted in advance using collected information about a patient's family history of cancer and following recognized guidelines.{10} This scalable solution can successfully assess cancer risk, detect adverse events or recurrence earlier, engage patients in educational material, and pave the way for preventive genetic testing, which could lead to better patient outcomes and more efficient cancer therapy.

By identifying high-risk patients ahead of time, medical practitioners can provide tailored and focused care during visits to them. The chatbot assessed one-quarter of the subjects who met the

USA National Comprehensive Cancer Network genetic testing criteria. Furthermore, digital biomarkers can be generated by digital medicine products for early-stage cancer detection. Sensors detect or algorithms infer digital biomarkers. A noninvasive sensor will be able to monitor specific tumor targets in the future.

Cancer Treatment

The use of smartphone mobile games for chemotherapy self-management in patients with breast cancer is an intriguing and promising breakthrough in cancer care. A related study's findings are positive, indicating that web-based self-management mobile games, when compared to traditional education approaches, have the potential to increase patient education, drug compliance, psychological status, and quality of life, and to lessen physical side effects.{11}

Meanwhile, clinical decision support systems (CDSS) are computer-based technologies that can assist healthcare providers in making efficient and educated cancer treatment decisions based on patient data. For example, based on a patient's cancer type, stage, and genomic profile, CDSS can recommend the best chemotherapy plan. Recent findings suggest that higher level CDSSs that employ automated clinical guidelines, AI, data mining, and statistical approaches can result in considerable improvements in process outcomes and guideline adherence.{12}

Privacy and Security Challenges

Privacy and security issues are major concerns in digital medicine when considering data sharing and the use of data-sharing platforms. Although the sharing of de-identified data of a patient is an important tool for researchers, the National Institutes of Health (NIH) requires some researchers to make their data available to other researchers through an NIH database, and this

can create privacy and security issues.{ 13 } The risk of re-identification is present as identifiable markers in a dataset can be used. The use of digital medicine and the transfer of subject information at a faster pace, and at times in real-time, would increase these risks and certain provisions would need to be added to decrease these dangers.

When considering databases such as the Personal Genome Project (PGP), which is a significant scientific achievement, one must consider their potential threats to privacy. The profiles in the PGP database were connected to names and contact information by using the database's demographics and comparing them to information found in public records.{ 13 } Another example is the Project Data Sphere platform, which is an open-access data-sharing database entirely built on oncology clinical trial data.{ 14 } Currently, the database contains raw deidentified late-phase oncology clinical trial information from 120,000 patients including more than 20 tumor types.{ 14 }

While the benefits of such databases are significant, one must wonder if they outweigh the risks. A large benefit to these data-sharing platforms comes from the potential to collaborate with numerous researchers nationally and internationally. Another advantage is that a researcher has the ability to answer research questions in a short time, increasing their efficiency. Additionally, these data can serve as surrogate endpoints and assist with the selection of subgroups in clinical trials investigating new oncology therapies.{ 15 }

As another example, since it is a tool that is seen as highly advantageous, there isn't much scrutiny given to those who request access to Data Share. This platform prides itself on its open-access model for the reasons mentioned above, even though it provides the least amount of

scrutiny for its users. Once an individual is given access, they have full access to the copious amounts of late-phase oncology information, which can result in potential misuse of these data.

Although the capability exists through these databases to further cancer research and bring forth novel therapies in a more efficient way, for example, by informing researchers on the dose adjustments for chemotherapy patients or leading to changes in national guidelines, { 15 } the patient's safety, including aspects related to their privacy and confidentiality, should come before any potential benefit. To limit these risks, one would need to perform a well-developed balancing act by restricting specific information yet providing accurate data.

Innovation of Future Treatment

The future of digital medicine holds a lot of potential for cancer treatment. Using cutting-edge digital technologies, doctors and researchers can develop more efficient, personalized, and patient-centered cancer treatments that improve patient outcomes and quality of life. Here are some potential digital medical advancements for future cancer treatment.

Artificial Intelligence

Scientists supported by the National Cancer Institute are already using AI to improve cancer detection in cervical and prostate cancer. They have also developed AI applications for improving cancer screening, diagnosis accuracy, and cancer surveillance.

AI algorithms can swiftly assess massive volumes of patient data and assist clinicians in making correct clinical and therapy decisions. Others use it to evaluate imaging data and electronic health records to personalize radiation doses for patients. The U.S. Food and Drug

Administration (FDA) has approved the first AI-based software to analyze images quickly and help radiologists detect breast cancer in screening mammography. {16}

These are merely illustrative examples. AI could truly improve cancer care in the future by developing novel cancer medicines or forecasting a patient's risk.

Advancing Smart Technology

Wearable technology is revolutionizing cancer treatment with the aid of real-world and real-time data from patients. Wearables have the potential to significantly improve cancer patients' ability to control their condition. Patients, for example, frequently feel nausea and other common side effects because of chemotherapy treatments and the illness itself; this condition is easily cured with a simple workout plan. Wearables linked to smartphone apps for data logging can easily track this. Also, wearable sensors and smartphone apps can be used to collect digital biomarkers.

iPhones are also low-cost and user-friendly medical tools for tumor detection. For instance, the FDA recently approved the Butterfly network's novel ultrasound-based imaging system, which links to an iPhone. {17} This AI-based app is capable of scanning the full body from head to toe, and works in tandem with hardware to help experts evaluate diagnoses and deliver improved treatments.

Conclusion

Oncology clinical trials are being transformed by digital medicine, which uses technology to enhance patient interaction, monitoring, and treatment plans. We can hasten the development of

novel medicines, improve patient care, and eventually make major progress in the fight against cancer by embracing digital technologies and data-driven methodologies.

The key aspects of cancer treatment are early detection and personalized care, and they have never seemed more feasible than they do now, thanks to breakthroughs showing promise in oncology clinical trials made possible by wearable devices, smartphone apps, AI, and machine learning algorithms. Data from oncology clinical trials are proving the potential for digital medicine technology to offer more inexpensive and less intrusive cancer management solutions, and the development of a comprehensive and successful cancer-fighting strategy more likely by the day in the digital era.

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SPECIAL FEATURE

Career Navigation in Contract Research Organizations: A Vignette

Meghan Francis, MPH; Andrew Pucker, OD, MS, PhD



[Editor’s Note: The following presents a fictionalized scenario and details to illustrate career options worth considering in certain clinical research settings.]

Irene works at a large university as a research assistant in a multiple sclerosis laboratory, and she is finishing her Master’s in Public Health (MPH) degree. She has recently started looking for potential jobs as she nears graduation.

Taking advantage of the university’s courses with the hope of bridging research and health outcomes, Irene is completing a six-month seminar series aimed at better understanding clinical and translational sciences. In this course, she learns about a position during a presentation on clinical research, called a clinical research coordinator (CRC), which sounds interesting to her because it merges patient interaction with clinical research. This position is also often called a study coordinator.

Irene has been focusing on biomedical research and epidemiology during her MPH coursework, and she is intrigued enough by what she hears during this lecture to reach out to the presenter, Dr. James, who is the Director of Clinical Trials at her university. Dr. James later offered Irene a CRC position in her research clinic. This simple inquiry about clinical research jump-started Irene’s career, and she has not looked back.

Turning Barriers to Bridges in CROs

Irene, like many others, lacked awareness of clinical research as a career opportunity. This specific issue is highlighted in a call to action from the Association of Clinical Research Professionals (ACRP) in its “Barriers to Bridges” white paper.^{1} This paper likewise highlights the current battles contract research organizations (CROs) are facing. A CRO is a multi-service company that is contracted by a sponsor (a company managing or financing the clinical trial for drug or device development) to perform services needed for a clinical trial, such as clinical operations, data management, clinical site monitoring, biostatistics, and medical writing, amongst other potential services.

CROs ensure clinical trials are conducted using Good Clinical Practice (GCP), which is an international standard for conducting clinical research with human subjects, and CROs ensure that trials are performed efficiently while protecting patient safety while testing product efficacy. CROs also serve as a liaison between clinical trial sites (e.g., private practices, hospitals, and universities where clinical trials are performed), the sponsor, and trial vendors who supplement the capabilities of the CRO and sponsor (e.g., biological sample testing at laboratories, image analysis at independent reading centers, and pharmacovigilance [safety reporting]).

One of the most difficult hurdles with employee recruitment for CROs and clinical trial sites is that qualified candidates do not realize positions in clinical research are a potential option when searching for careers. More awareness of positions in clinical research to younger candidates interested in science, technology, engineering, and math careers is needed to make it accessible and appealing.^{1} Potential candidates may be those who received a degree in health sciences but did or did not choose to go onto graduate school. Successful candidates display meticulous organization, proactivity, and effective communication with others. Persistence is also needed as candidates may need to apply to multiple job openings.

Clinical research is a highly specialized field in which, historically, candidates need at least two years of experience in clinical research before someone is willing to offer them

an entry-level position. Thus, even if potential applicants are aware of the field, they may not fully understand how to obtain a position. Some CROs have developed comprehensive training programs to provide candidates with immersive “mock” training experience, such as a clinical research associate (CRA) training program for those who wish to monitor clinical trials as direct employees of sponsors, under contract as independent consultants, or as a CRO employee.

Bilodeau notes how CROs may invest in the training of less experienced staff to become CRAs through extensive workshops, mock simulations with constructive criticism and confidence building, in-field training, mentoring, and modules to develop soft skills, and that this contributes to bridging the gap of the need for experienced CRAs.{2}

Making the Leap

More often than not, the CRA position is not a starting point for a clinical research career, but there are a multitude of backgrounds that can result in a successful career as a CRA. Even as someone with a master’s degree and onsite research experience as a CRC, Irene found it extremely difficult to break into the specialized CRA role, which she learned about while working as a CRC in 2017, due to companies only wanting to hire CRAs with at least two years of experience in that direct role.

The pandemic has since forced many companies to reassess the way they are hiring CRAs and has spurred the above-mentioned training programs, yet the need for new CRAs has dramatically increased, possibly because employees are less interested in traveling in the most recent climate.{3} This is a particular issue with the CRA position, because many CRAs travel more than 50% of the time. Furthermore, sites are also facing staffing and retention challenges. This issue is highlighted in an Open Letter from the Society of Clinical Research Sites, which states clinical sites are facing 35% to 61% turnover rates for patient-facing staff. Further, sites report that it costs approximately six months of pay to train new clinical staff, who are often less-experienced than their predecessors, so it takes longer before they can independently function in their new role.{4}

As a new CRC working in ophthalmology with Dr. James, who is providing hands-on mentorship in the therapeutic area, Irene gains valuable experience learning how to properly perform informed consent, process lab samples, submit ethics documents to the institutional review board, follow protocol procedures, administer questionnaires, collect and file regulatory documents, resolve monitoring visit findings, report adverse events and protocol deviations, and enter data in source (typically the original paper recording form) and the electronic data capture system. Irene enjoys her work because she has patient interaction and is involved downstream in bringing cutting-edge ophthalmology technology safely to the market.

After a two years, Irene has worked on a multitude of studies in different phases and therapeutic indications and is interested in expanding her career; one of the CRAs assigned to her site encourages her to apply for a CRA position at an ophthalmology CRO with a CRA training program. Intrigued by the idea of traveling the country and enhancing site relationships, Irene interviews and accepts a CRA position, and enters the CRA training program. By the time she has completed the program, she has learned how to perform different types of trial visits (e.g., pre-study, site initiation, interim monitoring, and closeout), review data via source data verification with medical records and source, issue and resolve queries, perform investigational product accountability, and complete simulated monitoring visits and associated reports to document significant findings as well as action items.

Upon completion of the training program, Irene is assigned to monitoring duties on two sponsored studies—one related to dry eye and the other to contact lenses—and communication with site staff, the clinical study managers, and project directors is an integral part of her new job. The CRA also ensures site staff have proper training and credentials as well as ensuring up-to-date equipment and lab certifications.

Since ophthalmology is a niche therapeutic area, Irene's previous experience as a CRC helps acclimate her to the position, as she is familiar with looking at medical records and source for unique ophthalmology assessments. The dry eye trial uses a Central Reading Center to certify photographers and assess image quality, and Irene's background in

ophthalmology allows her to successfully train sites on the specific processes for the imaging protocol and its image certification requirements. Irene excels as a CRA because she is empathetic, self-motivated, accountable, and punctual with meeting deadlines.

Career Growth at a CRO Post-Pandemic

A few years (any many hotel stays and flights) later, Irene seeks a position with less travel and the ability to work fully remote from home, reflecting a trend which can benefit both employees and employers. The Council for Disability Awareness reports that careers without remote work options experienced a 50% increase in the usage of sick time during the pandemic, but remote work options “experienced lower than average increases,” which may help companies decrease costs related to employee absence.{5} Imani Dunbar from LinkedIn reported that before the pandemic, 2% of jobs listings on LinkedIn were remote, but it is currently at 15%, and the flexibility is intriguing to candidates.{6} Rumanance reports that remote work allows for more flexibility from CROs when hiring talent because geography is no longer a limiting factor.{7}

Looking for a permanently remote and work-from-home position, Irene successfully transitions to a clinical study manager role (sometimes called a clinical trial manager) at an ophthalmology CRO. Study managers largely focus on customer service deliverability to the sponsor, and ensure that trials run smoothly by identifying, resolving, or escalating issues involving trial timelines and deliverables. Study managers display critical thinking and creativity while following the protocol and GCP. In trial start-up, they are responsible for overseeing feasibility, site selection, and site start-up, including managing contracts, budgets, and developing trial documents (plans, logs, manuals, etc.). Study managers can often leverage their site relationships to try to identify the potential first-subject-in (first subject enrolled), and the strong relationship may assist with boosting subject enrollment at a site.

Study managers must be strong communicators because they are interfacing with the sponsor, trial team members, site leaders, and vendors. The background requirements for the role include at least five years of clinical research experience and a bachelor’s degree

in a health-related field, besides which, CRA experience is preferred along with a strong foundation for GCP, regulatory, and clinical operations procedures.

Study managers also work directly with project directors who provide high-level oversight of the trial, including scope of work, deliverables, and related activities. Project directors often collaborate with other departments to improve inter-departmental functions, oversee trial budgets, review project health, and strive for customer satisfaction while also being the point of escalation for clients. They have typically at least seven years of clinical research experience and a bachelor's degree in a related field. Irene hopes to one day become a successful project director, and strives to continue to hone her project management skills.

Conclusion

While this article mainly focuses on career progression in clinical operations at a CRO, there are many other entry-level positions to be considered in clinical research, such as in the areas of patient recruitment or navigation, medical writing, data management, biostatistics, reading centers, clinical photography, and regulatory compliance. We should also note that although bachelor's and master's degree programs in clinical research can be found at many institutions, there is no single, clear-cut path or set of skills required to begin a career in this growing field. Companies are furthermore beginning to train more employees from scratch to allow for lateral moves from other professional fields. Thus, it may be easier than ever to begin a career in clinical research at a CRO, and if CROs are investing in their employees, then it could be a welcoming and rewarding career path for new prospects to the field.

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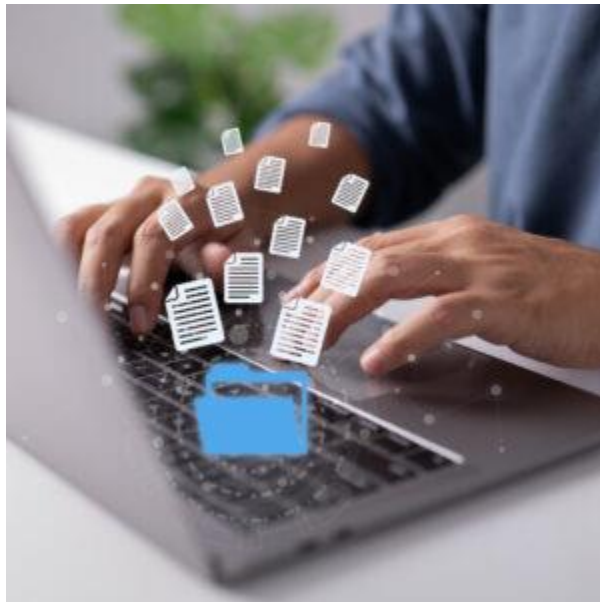
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CULTIVATING QUALITY

Data Integrity in Pharmaceuticals: Empowering Trustworthy Decisions from Source to Success via Registration Dossier

Olena Chervonenko, MS



Part 1: Data-Driven Decision Making—The Power of Trustworthy Data

In the pharmaceutical sector, data and Data Integrity are subjects of extensive study, research, and publication. Amidst discussions regarding quality control and software, it is crucial to remember the ultimate objective of this effort: the creation of a Registration Dossier ensuring that the data generated during the different stages of the lifecycle of the product are accurate, complete, and reliable.

When purchasing a dossier, one is essentially acquiring a treasure trove of invaluable data. This includes comprehensive information on a pharmaceutical product's pharmaceutical development, preclinical data, and crucial clinical trials data. Additionally, the dossier contains vital data about the product's quality—a testament to its efficacy and safety. The assurance of quality lies firmly in the robustness of these data, making it an indispensable asset for any discerning buyer.

The Registration Dossier serves three pivotal purposes, each essential to the success of a pharmaceutical product:

Proving Product Quality: The Registration Dossier acts as a comprehensive testament to the quality of the product. It meticulously documents every aspect of pharmaceutical development, preclinical and clinical data, and quality assurance measures. By presenting a dossier backed by

robust data, pharmaceutical companies assert the high quality and efficacy of their products, inspiring trust among stakeholders, regulators, and end-users alike.

Gaining Marketing Authorization: A well-prepared Registration Dossier is a prerequisite for gaining Marketing Authorization from regulatory agencies. By adhering to Data Integrity principles and providing a comprehensive, transparent, and scientifically sound dossier, pharmaceutical companies establish the credibility of their product, the product's quality, safety and efficacy, and its compliance with regulatory requirements. This paves the way for agencies to grant the necessary permissions, allowing the product to enter the market and benefit patients.

Facilitating Technology Transfer: Beyond regulatory approval, the Registration Dossier serves as a valuable asset for companies that are potentially interested in acquiring the product for further technology transfer. In the complex world of pharmaceuticals, seamless technology transfer relies on the availability of accurate and reliable data. A carefully compiled dossier enables a smooth handover of technology to other pharmaceutical companies, fostering collaborations and expanding the product's reach.

The creation of a Registration Dossier is not merely a procedural task; it is a strategic endeavor with far-reaching implications. By upholding Data Integrity and providing a robust dossier, pharmaceutical companies unlock new avenues for technology transfer, fostering growth and innovation in the pharmaceutical industry.

Part 2: Understanding Data Integrity and its Relevance

Data Integrity, as defined by ISO/IEC 2382:2015, pertains to maintaining accuracy and consistency regardless of changes made.^{1} For pharmaceutical companies, Data Integrity is of utmost importance, driving crucial aspects such as drug development, clinical trials, manufacturing, and regulatory compliance. Uncompromised Data Integrity instills trust in the quality, efficacy, and safety of medicines.

Understanding the “Data Lifecycle” from its origin to the final report is paramount in today's landscape. The integrity of data, from how they were captured to how they are reported, holds the key to informed decision-making. Data serve as the foundation for critical choices, and data

imbued with integrity empower these choices with precision and reliability. Embracing digital data and their governance offers advantages that drive faster and more accurate decisions. Adherence to robust principles such as ALCOA+ and compliance to regulatory requirements such as the U.S. Food and Drug Administration's (FDA's) 21 CFR 11 from the *Code of Federal Regulations* and the European Medicine Agency's (EMA's) EudraLex Annex 11, backed by thorough validation, ensure that Data Integrity remains at the core of the entire data lifecycle.

ALCOA+ stands as the gold standard for Data Integrity in the medicinal products realm. Its attributes are hailed as the epitome of data reliability not just within this sector, but also in various other industries. Upholding the principles of ALCOA+ ensures that data remain trustworthy and accurate throughout their lifecycle, instilling confidence in decision-making processes across diverse domains.

ALCOA+ is the acronym for Attributable, Legible, Contemporaneous, Original, and Accurate, and encompasses the following quality attributes for data{2,3}:

Attributable: Tracing data to individuals and measurement systems for accountability.

Legible and Permanent: Ensuring data remain readable and accessible throughout their lifecycle.

Contemporaneous: Capturing data in real-time for accurate and timely records.

Original Record or "True Copy": Preserving the authenticity of data from their sources to subsequent modifications.

Accurate: Defining processes for precise data capture, including source verification and format documentation.

The "+" expands beyond ALCOA to encompass the attributes of Complete, Consistent, Enduring, and Available:

Complete: Ensuring data include relevant metadata for comprehensive documentation.

Consistent: Maintaining the correct chronological order of data to preserve consistency and sequence.

Enduring: Safeguarding the longevity and integrity of data throughout storage and use.

Available: Enabling easy accessibility and verification by authorized personnel.

It is important to note that the ALCOA+ principle applies to electronic data, paper records, and hybrid systems, encompassing various types of data management. {4}

The comprehensive requirements set by regulators for the Pharmaceutical Quality System (PQS) today include the following main documents:

- FDA 21 CFR Part 11
- FDA Guidance for Industry Data Integrity Compliance with Drug current Good Manufacturing Practice (cGMP)
- EMA GMP guidance to ensure Data Integrity
- Medicines and Healthcare products Regulatory Authority (MHRA) GxP Data Integrity Guidance and Definitions {5}
- World Health Organization (WHO) Guideline on Data Integrity, Annex 4 {6}
- PIC/S Good Practices for Data Management and Integrity in Regulated GMP/Good Documentation Practice (GDP) Environments {7}
- GAMP Records and Data Integrity Guide—ISPE/GAMP, March 2017 {8}
- European Union Good Manufacturing Practice, Volume 4, Annex 11 {9}

Part 3: Proving Product Quality

Within the realm of pharmaceutical development, a cornerstone principle to follow, as per the International Council for Harmonization guideline Q8(R2), {10} is Quality by Design (QbD). The objectives of QbD include achieving meaningful product quality specifications, increasing process capabilities and reducing product variability, and increasing product development and manufacturing efficiencies, {11–13} ultimately, designing a manufacturing process that is able to manufacture a product that consistently meets the set quality requirements. This rigorous

approach to pharmaceutical development not only serves as a critical component of the Registration Dossier, it also lays the groundwork for when future changes such as upscaling or transferring a process are planned.

The Registration Dossier is a comprehensive compilation of data, evidence, and scientific understanding that showcases the quality, safety, and efficacy of the product. At its core, the dossier is built upon robust data, carefully documented, and upheld with unwavering belief in the principles of Data Integrity.

Data Integrity is the bedrock on which the Registration Dossier stands tall, providing confidence to stakeholders, regulators, and end-users. A thorough approach to data collection, analysis, and documentation ensures that every facet of the product's development is transparent, traceable, and credible. As the dossier traverses the regulatory pathway, the assurance of Data Integrity empowers pharmaceutical companies to gain Marketing Authorization and pave the way for future technological advancements.

With Data Integrity at the helm, the Registration Dossier becomes a catalyst for continuous improvement. Data-driven insights gleaned from pharmaceutical development studies and manufacturing experience form the basis for informed decision-making. These insights provide the scientific understanding necessary to support the establishment of the design space, specifications, and manufacturing controls.

Furthermore, as processes evolve and new equipment is introduced, Data Integrity acts as a safeguard against potential pitfalls. It enables companies to assess the impact of changes with confidence, ensuring that the quality, safety, and efficacy of the product remains uncompromised. By building Data Integrity into the fabric of pharmaceutical development, companies create a culture of excellence and accountability that extends far beyond the initial dossier submission.

The dossier, fueled by irrefutable data and a commitment to Data Integrity, not only proves the quality and safety of the product but also emboldens the industry to achieve new heights of excellence. As the pharmaceutical landscape continues to evolve, the role of Data Integrity in

nurturing robust products and fostering a culture of continuous improvement becomes increasingly vital.

Implementing Data Integrity in pharmaceutical development requires a comprehensive approach that spans various instruments and methods. Here are some key instruments and ways to ensure Data Integrity throughout the pharmaceutical development process:

Data Governance and Standard Operating Procedures (SOPs): Develop clear and robust Data Governance policies and SOPs that outline the principles and procedures for data collection, management, and documentation. These SOPs should encompass all aspects of data handling, from raw data acquisition to data review, approval, and archiving.

Training and Education: Provide regular training and education to all personnel involved in pharmaceutical development on the importance of Data Integrity, best practices, and compliance with relevant guidelines and regulations. Ensure that personnel are aware of their responsibilities in maintaining Data Integrity.

Audit Trails and Data Logging: Implement electronic systems with audit trails that capture all actions taken on data, including data entry, modification, and deletion. Maintain data logs and audit trails and ensure these are readily accessible for audit purposes. A system should be in place describing the periodic review and audit requirements of audit trails and data logs.

Data Backups and Data Recovery: Establish robust data backup and recovery procedures to safeguard against data loss or corruption. Regularly back up data and validate the integrity of backups to ensure data availability and reliability.

Electronic Signatures and Authentication: Use electronic signatures for data entry and approvals, ensuring traceability and accountability. Implement secure user authentication measures to prevent unauthorized access to critical data. { 14 }

Validation and Qualification of Systems: Validate all computerized systems used in pharmaceutical development to ensure they meet Data Integrity requirements. Regularly assess and requalify systems to ensure their continued reliability.

Risk Assessments: Conduct risk assessments to identify potential vulnerabilities in data management processes and address them proactively. Assess the impact of identified risks on Data Integrity and implement appropriate mitigation measures.

Data Review and Oversight: Implement a robust review process for data to ensure accuracy, completeness, and consistency. Establish a clear oversight mechanism to monitor data-related activities and address any issues promptly.

Vendor Qualification: Perform thorough vendor qualification for outsourced services or software providers to ensure they adhere to Data Integrity principles and regulatory requirements.

Data Encryption and Security: Use encryption and other security measures to protect data during storage, transmission, and sharing. Implement access controls to restrict data access based on the principle of least privilege.

Continuous Improvement: Foster a culture of continuous improvement by regularly reviewing data management processes, identifying areas for enhancement, and implementing corrective actions as needed.

Documentation and Record-Keeping: Maintain comprehensive documentation and records of all data-related activities, including data collection, analysis, and decision-making processes.

Quality Risk Management: Integrate Quality Risk Management (QRM) practices into data-related processes to identify, evaluate, and mitigate risks to Data Integrity effectively.

Periodic Data Integrity Reviews: Conduct periodic Data Integrity reviews and audits to assess compliance with established procedures and identify opportunities for improvement.

By adopting these instruments and methods, pharmaceutical development organizations can establish a strong foundation of Data Integrity, ensuring the credibility, reliability, and compliance of data throughout the entire lifecycle of the pharmaceutical product.

Part 4: Gaining Marketing Authorization

Keeping all primary data and their associated documentation (such as chromatograms, spectra, calculations, validation data, clinical trial data, stability data, and quality control data) together with their backups is a critical aspect of ensuring Data Integrity in the pharmaceutical development and manufacturing process. This comprehensive data preservation is essential for successful GMP inspections. The agency responsible for conducting GMP inspections depends on the region and country where the Marketing Authorization application is submitted.

The GMP inspection is a crucial step in the regulatory approval process. For example, the FDA, TGA (Therapeutic Goods Administration of Australia), MHRA of the United Kingdom, Health Canada, and PMDA (Pharmaceuticals and Medical Devices Agency of Japan) conduct pre-authorization GMP inspections to ensure compliance with GMP regulations before issuing Marketing Authorization for medicinal products.

Regulatory inspectors will review the PQS during the inspection, together with all data generated during the development, manufacturing, and testing of the pharmaceutical product, to ensure data have been appropriately recorded, stored, and maintained.

The key aspects that regulatory inspectors will focus on during the GMP inspection regarding Data Integrity include:

Data Integrity Controls: The regulatory inspectors will examine the PQS to ensure that robust controls are in place to prevent data manipulation, loss, or unauthorized access. This includes implementing ALCOA+ principles for Data Integrity.

Data Management and Storage: The inspection will verify whether the PQS has the required procedures for data management and storage. This includes secure data storage, appropriate access controls, and regular backups to prevent data loss.

Audit Trail and Version Control: The regulatory inspectors will assess if there is a comprehensive audit trail system in place that records all changes to data and provides details on who made the changes, when the changes were made, and why these changes were made.

Version control for documents and data is essential to ensure traceability and prevent unauthorized alterations.

Data Accessibility: During the inspection, it is expected that data are easily accessible for review and verification. This includes having organized and well-maintained records that can be readily presented to the inspectors.

Training and Personnel Competency: The regulatory inspectors will assess the training, competency, and understanding of the importance of Data Integrity of personnel who are involved with data generation, recording, and management. Adequately trained personnel, with a good understanding of the principles of Data Integrity, are more likely to adhere to Data Integrity practices.

Validation and Documentation: The inspection will verify that all analytical methods, equipment, and processes used to generate data are properly validated or qualified and documented.

Data Review and Approval: The PQS should outline a clear process for data review and approval with definitions of roles and responsibilities, ensuring that data are thoroughly reviewed and approved by authorized personnel before their inclusion in the Registration Dossier.

The consequences of Data Integrity issues identified during a GMP inspection can be severe, putting the company under significant financial and reputational risk. A Warning Letter from regulatory authorities such as the FDA or a Non-Compliance Report from European regulatory bodies not only highlights potential shortcomings in Data Integrity practices, but also reflects on the overall quality and compliance of the company's operations.

Notably, between 2017 and 2022, the FDA issued more than 160 Warning Letters citing Data Integrity deficiencies, with 13 Warning Letters issued in 2022 alone. {15}

Approximately half (42, 49%) of the total 85 GMP Warning Letters issued by the FDA in 2018, for example, included a Data Integrity component. {16}

Such regulatory actions can lead to costly remediation efforts, possible product recalls, delays in product approvals, and even the suspension of manufacturing activities. Moreover, the damage to the company's reputation can erode trust among stakeholders, customers, and the public, impacting future business opportunities and market standing. Therefore, ensuring robust Data Integrity measures is paramount for safeguarding the company's financial stability and preserving its reputation within the pharmaceutical industry and regulatory bodies.

Part 5: The Final Milestone—Ensuring Success After Receiving Marketing Authorization

Receiving Marketing Authorization is a momentous achievement for any pharmaceutical company, marking the green light for commercialization. At this juncture, companies are presented with two pivotal paths: embarking on commercial manufacturing independently or exploring the possibility of selling the authorization and executing a site transfer to another manufacturer. The success of the first option rests entirely on the company's capabilities, while the latter demands a rigorous evaluation of Data Integrity through a thorough due diligence process.

During due diligence, potential buyers or partners thoroughly examine the data presented in the Registration Dossier to gain an in-depth understanding of the product's scientific foundation and technological intricacies. Key elements, such as the Quality Target Product Profile (QTPP), Critical Quality Attributes (CQAs), clinical/non-clinical data, risk assessments, design space, control strategy, and product lifecycle management, undergo rigorous scrutiny. The integrity and reliability of data become the focal points, serving as the bedrock of assessing the product's quality, safety, and efficacy, and the robustness of associated processes and potential risks.

Conducting due diligence is a comprehensive undertaking, involving a precise evaluation of all aspects of the product, including the data captured in the dossier. The comprehensiveness of the data is crucial, as potential buyers or partners, who might not be intimately familiar with the pharmaceutical product, seek transparency and clarity. This is particularly significant when contemplating technology transfer or divesting the Marketing Authorization to another manufacturer.

In addition, the due diligence process assesses the feasibility and practicality of the technology involved in the pharmaceutical product's manufacturing process. This entails evaluating the compatibility of the manufacturing equipment and facilities with the processes and specifications detailed in the dossier. The ability of the technology to scale up and adapt to the new manufacturing site becomes a pivotal consideration, and only concrete data can instill confidence in interested buyers.

Indeed, the due diligence process holds immense importance as it directly influences the chances of success of the chosen path. Thoroughly assessing Data Integrity and technological workability lays the groundwork for seamless technology transfer or fruitful collaborations with new partners. This rigorous evaluation ensures that the Marketing Authorization, accompanied by the reliable data and scientific understanding within the dossier, opens doors to a successful journey in the pharmaceutical market.

Part 6: To Sum Up

The unwavering commitment to Data Integrity, adhering to current requirements and expectations, stands at the core of the pharmaceutical industry. This foundational principle empowers every stage of a pharmaceutical product's development, from inception to the market's fruition. By upholding Data Integrity, pharmaceutical companies establish a strong reputation for excellence, inspiring confidence among stakeholders and regulatory bodies and fostering a culture of trust. Furthermore, this dedication to Data Integrity paves the way for transformative innovations that ultimately benefit patients and society as a whole. The significance of Data Integrity cannot be overstated, as it not only ensures compliance with regulations, but also elevates the pharmaceutical industry to new heights of integrity and reliability.

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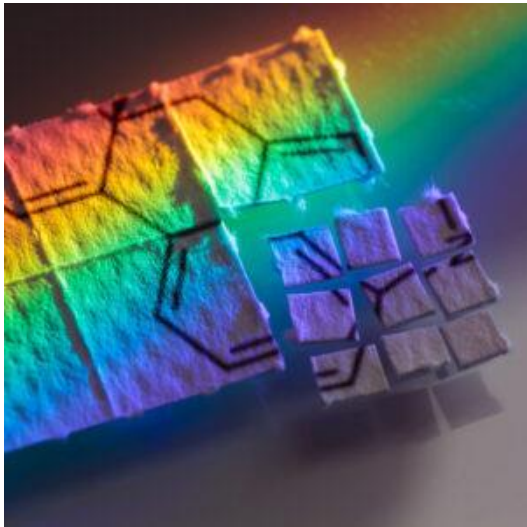


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ETHICS IN ACTION

Ethical Considerations for Clinical Trials of Psychedelics

Currien MacDonald, MD, CIP



Psychedelics, often associated with “magic” mushrooms, are gathering attention, and for good reason. Psychedelics’ potential treatment areas include major depressive disorder,{1} alcohol abuse,{2} tobacco and other addictions,{3} cancer-related anxiety disorder,{4} obsessive-compulsive disorder, post-traumatic stress disorder,{5} eating disorders,{6} Alzheimer’s disease,{7} and fibromyalgia.{8}

That is a long list of illnesses that currently have high disease burdens, and some without any good current treatment options when first-line treatments fail. It is not an exaggeration to describe their potential benefits in terms of being breakthroughs in treatment. It is tempting to join those who are all-in on the drug class, such as those projecting its economic growth to more than \$10 billion by 2027.{9} Unsurprisingly, some are calling this enthusiasm an unfounded hype bubble that is sure to pop.{10}

So, which is it? A revolution in treatment, or unsupported hype over the chance to legalize getting high?

Babies and Bathwater

First, it is important to understand that psychedelics are not a monolithic topic. Psychedelics are an unofficial name for a set of compounds that differ in mechanism of action and, therefore, in effects.{11} “Classic” psychedelics include psilocybin, the active

ingredient in “magic” mushrooms, and often include MDMA, also known as “Ecstasy.” However, there are other compounds lumped into that term, including those not typically thought of as psychedelics; for example, esketamine, which has been approved by the U.S. Food and Drug Administration (FDA) for treatment-resistant depression with an oral antidepressant. (Another is ketamine, a much less expensive drug currently approved for anesthesia and used off-label for depression treatment.{ 12}) The risks of esketamine, including dissociation and the potential for abuse and misuse of the drug, make it only available through a restricted distribution system and a specific risk evaluation and mitigation strategy (REMS). For drugs found to have a high abuse potential, that strict level of control makes sense.

At the same time, the well-known risks of classic psychedelics are reported in the context of the use of illicit substances of unknown potency in unsupervised, non-medical situations.{ 13} The risks of a pharmaceutical grade psychedelic in the context of a full-psychiatric treatment regimen may be much different. The consideration of the potential risks of psychedelics in these situations needs to include appreciation of the patient’s expectations, the setting of the therapy, and the clinician-therapeutic relationship.{ 13} That is not to say the risks are lower, but they are more complex, and would need an individual assessment instead of a blanket or over-attentive focus on reducing the risks of abuse.

Pharmaceutical companies are well-versed in taking a raw source and producing a purified medical product to maximize benefits while reducing risks. Treating medicinal psychedelics as if they all had the same risk profile as illegal, uncontrolled drugs would be short-sighted. Similarly, dumping controlled therapeutic use in the same bathtub as self-medication attempts by those with mental illness or situations of recreational use will exaggerate risks and rob society of potentially great benefits.

Careful evaluation of the abuse potential of these drugs puts many of them lower than would be expected. For example, when evaluated according to the eight factors of the Controlled Substances Act (CSA), psilocybin had an abuse potential appropriate for CSA scheduling if approved with one review, suggesting that placement in Schedule IV may be appropriate,{ 14} which is similar to many other approved drugs.

Paving the Road or Setting Up Roadblocks

With the potential for a classic psychedelic drug to be approved, FDA has issued timely guidance.^{15} The agency identified this class of drugs, including related drugs like MDMA, as having “unusual characteristics” that should be considered, and noted “there is limited experience as to the configuration of programs that may support approval of a psychedelic drug.” The guidance is described not as “specific recommendations on study design,” but instead as “foundational constructs” to consider. In a press release,^{15} the FDA specifically notes the potential for abuse of these drugs as a necessary consideration. The guidance points out several large considerations for study approach that are the same as for other drugs, but which, when applied to this drug class, may represent substantial issues for drug approval. These include:

- manufacturing steps for what may be considered a “botanical” product,
- a study intervention with effects so obvious that a control arm is difficult, and
- the fact that these drugs are often used in a psychotherapy program instead of just as daily pills.

There are also ethical issues with these trials. For example, psychotherapy’s main tenet is that all healing occurs in relationship with the therapist. A limitation of therapy, then, is the patient’s lack of allowance for the therapeutic relationship. Building trust, especially when you have a psychiatric illness, is difficult and arduous work. One of psychedelics’ main mechanisms is (easily but not completely accurately) described as inducing a psychologic flexibility. Long-held mental constructs are relaxed, potentially allowing for overcoming what was otherwise insurmountable mental disease.

At the same time, this psychologic flexibility can also be translated as increased suggestibility, potentially exposing patients to risks from others. FDA’s guidance states, “Subjects receiving active treatment with psychedelic drugs remain in a vulnerable state for as long as 12 hours.” The guidance follows with recommendations for monitoring by two monitors during the treatment session and consent disclosure of this risk during the treatment session.

With the potential for greater participant suggestibility comes a particular need for training regarding how and what specifically a participant is consenting to, what is being monitored by each monitor, and the likelihood of stronger and more complex emotional effects. The potential for either the patient or the therapist to form more than professional attachments is always a risk, and is especially heightened with psychedelic treatment. Use of touch, which can be powerfully therapeutic, can also be very damaging in psychedelic treatment. These issues, including touch, should be specifically addressed, as outlined in the Multidisciplinary Association for Psychedelic Studies Code of Ethics, {16} which was created to address issues arising in MDMA clinical trials.

However, let us not lose sight of the fact that it is this very risk which has the potential for effectiveness that has not been previously achieved. {17} It is not unusual in medicine to have a drug's powerful effect be inextricable from its potential for serious side effects.

The concept of vulnerability is not a new one for institutional review boards (IRBs); however, the temporary nature of the vulnerability makes the standard IRB methods such as exclusion of vulnerable participants or inclusion of a legally authorized representative problematic. In review of these trials, IRBs need to carefully consider what additional safeguards have been included in the study to protect the rights and welfare of these participants. These safeguards will be different in a “take home pill” study of anxiety compared to a study involving intensive psychotherapy sessions.

Other Roads Than the Highway

Additionally, FDA is considering the path to approval of a standardized medicinal product. With the compounds being illegal but readily available, FDA approval may not be the route all are considering, and studies “about” the drugs without requiring their use deserve attention.

For example, therapists working in these disease areas may well encounter people who are wanting to try or are already using psychedelics to self-treat. Caring and ethical therapists, committed to helping their patients, may struggle to navigate supporting a patient without

increasing their patient's or their own risk.{18} Carefully navigating the use of illegal substances in therapy other than working toward cessation is problematic. Supporting the use of an illegal substance puts a strain on therapists they may not know how to handle. The strain increases especially if the self-treatment appears promising, but really would do better with a trained clinician. A trial looking at data collection of illegal use vs. illegal use with a trained clinician may be very beneficial.

Illegal access is also an issue during review of clinical trials administering these drugs. We must carefully consider the ethics of psychedelics in research after the clinical trial ends. Starting a person on a treatment during the trial and then stopping when the trial is over is not unfamiliar, but it is unique in this case. A participant who was benefitting from a psychedelic trial faces a difficult choice when leaving the study, and the clinician treating them faces a different but similarly difficult one. The illegal versions of psychedelics are not difficult to obtain, and are often much cheaper than those versions available even through expanded access of experimental drug products.{19} The ethical obligations of the sponsor, clinician, and reviewing IRB will need careful attention.

True Measure of Any Society

Another societal issue is that certain mental health disorders have very limited options once initial treatment has failed. Moreover, some populations currently with challenges accessing healthcare are the ones with these illnesses and treatment-resistant diseases. Sadly, they are under-represented in clinical trials, but are the very populations for which psychedelic treatment may be especially effective. Paying attention to diversity in clinical trials will be especially important for these studies. When designing clinical trials with psychedelics, additional effort and emphasis on recruitment strategies, appropriate communication, multicultural competence, and flexible study designs are required.{20} When considering the REMS for approving psychedelics, similar considerations must also be made for these populations. A risk mitigation strategy that sets such a high barrier for use may functionally put a prescription version of these drugs out of reach of these populations. That could lead again to difficult decisions and rationalization for use of illegal and more risky versions.

Conclusion

We in the research field especially need to ensure that we do not lose sight of the potential benefits of these compounds while not under- or over-valuing the very complex risks from several perspectives. When conducting psychedelics research, including retrospective data collections, surveys, real-world evidence, post-approval studies, and comparative effectiveness research, we must be additionally attentive. We must not forget that the initial research temptingly hints that this class of drug may greatly help those we have so far failed, including populations who have significant additional burden. Extra attention is deserved to ensure neither unsupported enthusiasm nor unfounded fear rules the day.

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RECRUITMENT & RETENTION

Clinical Trials in Dravet Syndrome: Opportunities, Challenges, and Collaborative Solutions

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Dravet syndrome (DS) is a rare disease with immense medical need that presents as a severe neurodevelopmental disorder characterized by multiple types of medication-resistant seizures that begin in infancy. Termed a Developmental and Epileptic Encephalopathy, DS includes more than just difficult-to-treat seizures; as patients age, accumulating symptoms include developmental delays and cognitive impairments, behavioral challenges, sleep disruptions, and movement issues.

Patients also face a 15% to 20% premature mortality rate, most often due to Sudden Unexpected Death in Epilepsy.

DS is primarily caused by variants in a single gene, *SCN1A*, that cause a reduction in the number or function of sodium channels encoded by this gene.^{1} Due to this underlying reduction in sodium channel function in the brain in DS, use of sodium channel blockers, a common type of antiseizure medication, can actually worsen seizures and other symptoms for these patients.

DS is considered a rare disease, impacting about one in every 15,700 live births, or approximately 18,000 individuals in the United States.^{2} There are three antiseizure medications for DS approved by the U.S. Food and Drug Administration (FDA): pharmaceutical-grade cannabidiol (Epidiolex), stiripentol (Diacomit), and fenfluramine (Fintepla), as well as clear treatment guidelines that outline top-line treatment recommendations from experts.^{3}

Despite the concomitant use of multiple therapies, the majority of patients experience breakthrough seizures and significant symptom burden.

Unique Opportunities for Novel Clinical Interventions

Identification of the genetic cause of DS in 2001 expedited research through the ability to establish animal and cell models, as well as to develop treatments that more directly treat the underlying cause of the disease. For example, the potential of the serotonin pathway as a therapeutic target was underlined by zebrafish drug screens{4} and the subsequent success of human clinical trials for Fintepla.{5,6} Now there are four additional clinical studies exploring the ability of serotonin modulating drugs to reduce seizures in DS and related epilepsies. Additionally, new targeted genetic therapies are in development that have shown efficacy beyond seizure control in animal models of DS.

While the size of *SCN1A* creates a challenge to traditional gene-replacement approaches, researchers have uncovered other mechanisms of genetic regulation of *SCN1A* that can be targeted to increase expression of the healthy copy of the gene. In 2020, the first patients in a Phase I/II study received STK-001, an RNA-based therapy called an antisense oligonucleotide developed by Stoke Therapeutics that aims to increase expression of the healthy copy of *SCN1A* by targeting alternative splicing events. Several other approaches are in various stages of preclinical pipelines to similarly address DS at the genetic level.

As scientific understanding of DS continues to advance rapidly, there has also been a steady increase in access to free or low-cost genetic testing in the clinic. This has reduced the time from symptom onset to diagnosis for patients as well as helped to identify previously undiagnosed patients. Timely and accurate diagnosis can greatly guide clinical care for patients with DS, particularly alerting providers to the contraindication of sodium channel blockers. Moreover, accurate diagnosis allows the DS patient community the opportunity to organize and advocate.

Clinical Studies for Rare Diseases Require Unique Considerations

Trial participation for a patient with a rare disease that has significant medical needs can be challenging and adds to the already overwhelming caregiver burden on parents. Families often

live a significant distance from trial locations, requiring long-distance travel by car or by air. For a patient with uncontrolled and unpredictable seizures, travel can be difficult and there are often last-minute changes or cancellations to the travel itinerary and clinic visit. The required time to travel and participate can result in financial barriers from missed work, as well as the care of other siblings in the household while the patient and parents are away. Associated comorbidities in DS add to the travel burden, with medical equipment such as adaptive strollers, incontinence products, special dietary products, and seizure monitoring devices needed at the destination.

The recent focus on decentralized clinical trials could help to reduce some of the barriers to participation for rare disease patients. Utilizing telehealth visits and wearable devices can help to cut down on the number of in-person visits and ease participation burden, allowing more opportunities for access and diversity in trial participation.

Patient Advocacy Groups Can Accelerate Research and Clinical Studies

A clear benefit of patient community organizations is the support and connection that can improve the quality of life of rare disease patients and their families. However, there can be surprisingly far-reaching impacts of patient advocacy groups on research and clinical trials for rare diseases. An organized, informed, and connected patient community can ease some of the challenges for clinical studies in rare disease populations.

In 2009, the [Dravet Syndrome Foundation](#) (DSF) was founded to unite the patient community around advancing research for DS. In pursuit of this mission, DSF has directed more than \$6.7 million to early-stage academic research and has worked hard to establish an engaged clinical trial-ready community. The success of this is exemplified in part by the pivotal clinical studies in patients with DS that led to the approval of Epidiolex in 2018^{7} and Fintepla in 2020.^{5,6}

Clinical trials can be particularly challenging for rare diseases where the medical burden is high and patient populations are spread out geographically. Patient advocacy organizations like DSF can connect sponsors and clinical research organizations to key opinion leaders in the clinical and research spaces, as well as to institutions where expert healthcare providers are treating larger portions of the patient population. For example, DSF maintains a listing of Comprehensive Care Centers where healthcare providers have expertise in the treatment of DS and experience

with clinical studies. These listings assist families in gathering information as they choose their primary care providers, and can be beneficial to consider when sponsors are planning study sites for interventional trials.

When trials are enrolling, patient groups can assist in raising awareness of participation opportunities among the relevant patient populations that are spread out geographically. The DS patient community remains tightly connected through in-person events and online forums organized by DSF. The DSF Family Network includes an informal contact registry and online support groups that allow DSF to notify families of opportunities to participate in clinical studies.

Patient advocacy groups can additionally provide access to the patient voice, such as assembling panels of patients or caregivers to help sponsors and investigators understand the patient community needs, select relevant outcome measures, determine the feasibility of trial participation, guide patient-facing educational materials, and establish appropriate support measures to ensure a successful trial. DSF actively engages in the creation and curation of robust educational materials that engage the community in understanding the importance of research, patient participation in studies, and general concepts surrounding clinical trials to maintain a clinical trial-ready patient community.

Lastly, patient advocacy organizations are playing an ever-increasing role in educating regulatory bodies on the real-life needs and impacts of rare diseases in ways that can inform decision-making around novel therapeutics by considering the true risk-benefit framework from the perspective of those living with rare disease. DSF worked with the patient community to hold an [Externally-led Patient Focused Drug Development \(EL-PFDD\) Meeting](#) and develop a subsequent *Voice of the Patient Report* that provides insight into the patient-family perspective on the burden of living with DS, experience with current treatments, and the unmet medical needs for those living with DS. The input from these meetings and reports can help to inform the FDA's decision-making process, ensuring the patient perspective is considered in the benefit-risk assessment.

Professional Resources for Learning More About DS

With an ever-increasing number of identified rare diseases, it can be difficult for professionals to stay up to date on the most recent and accurate information. In addition to providing educational materials for the patient community, DSF curates resources for medical and research professionals related to DS, including:

- [webinars](#) created by expert clinicians specifically for healthcare professionals,
- overviews and links to the most recent [diagnostic and treatment guidelines](#),
- the [Dravet syndrome EL-PFDD meeting](#) recording and *Voice of the Patient Report*, and
- a listing of [actively enrolling clinical trials](#) and an overview of the therapeutic pipeline for DS.

Conclusion

Given the growing scientific knowledge, robust therapeutic pipeline, and organized patient population, there is immense opportunity to develop successful treatments to address DS. As with any rare disease, there can be significant challenges to participation in clinical studies for patients and families navigating life with DS. However, collaboration and thoughtful study design that includes patients and patient organizations like DSF can ease the burden of trial participation and facilitate successful study completion.

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TRIALS & TECHNOLOGY

An Adoption and Change Management Guide for Sites Implementing New Study Technologies

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Clinical research is the foundation of evidence-based medicine. Prospective clinical trials are the gold standard by which clinicians, medical centers, and life science companies assess the safety and efficacy of new interventions and treatments, expand their body of knowledge, and improve healthcare for millions of people.

However, for academic health centers, private health systems, and community clinics, the infrastructure needed to participate in clinical research is far from trivial. Identifying eligible patients, obtaining consent, executing the study, capturing data, and complying with all reporting and regulatory obligations take time and vital resources away from other important responsibilities at the site.

That's where new clinical research technology comes in. It has the potential to radically simplify the way clinical trials are run, automate data collection, improve data accuracy and completeness, and facilitate essential monitoring functions. With the right processes, success measures, and feedback loops in place, technology can substantially reduce the operational burden associated with running a clinical trial.

As Dame Sally Davies, former Chief Medical Officer and Chief Scientific Adviser at the U.K. Department of Health, noted in a recent interview, “We’ve got to make sure that everyone around the world has access to the health benefits of data and digital technology.”{1}

To accelerate that transition, we propose an implementation framework based on years of hands-on experience that sites of all sizes can use to evaluate and integrate new clinical research technology into their workflows.

Why Now?

Selecting the right tech to assist and streamline operations is a top priority for busy clinical research sites, but it’s become more critical today for three key reasons:

Volume of Studies—The number of new clinical trials grows every year. ClinicalTrials.gov, the online database run by the National Institutes of Health (NIH) in the U.S., listed twice as many new studies in 2022 as it did 10 years earlier.{2} As of July 2023, it showed 60,000 trials in active recruitment (nearly 20,000 in oncology alone), more than a third of which were set in the U.S. To provide more therapeutic options to their patients, some sites today are participating in dozens, even hundreds of clinical trials at a time. Managing so many concurrent studies without the right technology is time consuming, costly, and prone to errors.

Increased Complexity—Not only are clinical trials growing in volume, they’re growing in complexity. According to the Tufts Center for the Study of Drug Development (CSDD), a typical late-stage trial involves more than 100 sites and the collection of 3.5 million datapoints—three times more than 10 years ago.{3} According to CSDD director Ken Getz, “What we’re seeing is the consequence of biopharma companies engaging in more ambitious and customized drug development activity that targets a growing number of rare diseases, stratifies participant subgroups using biomarker and genetic data, and relies on more structured and unstructured patient data from a larger number of sources.”

High Staff Turnover—The “Great Resignation” hasn’t spared the clinical research sector. Healthcare workers are quitting in record numbers—especially workers with clinical trial experience—and it can take a full year to get new staff up to speed.{4} Sites are forced to learn

new technologies while simultaneously trying to recruit and maintain qualified, high-performing talent. This is incredibly hard to do. In a recent WCG survey of 500 research sites, staff retention was cited as a top concern by 63% of respondents, well ahead of patient recruitment and enrollment (48%).{5}

These forces contribute to major inefficiencies in the site-sponsor relationship. Despite the widespread use of electronic data capture (EDC) systems, study data entry remains cumbersome and time-consuming. According to a recent survey of clinical operations professionals, 75% still wrestle with manual processes and 58% with speed, visibility, and study oversight.{6}

Technology can alleviate these problems, but sites today are often bombarded with pitches from multiple software providers, and the solutions they sometimes rush to install aren't always a good fit. In its 2022 State of Healthcare survey, HIMSS noted that a third of clinicians struggle with a lack of proper training and clear communication about the tools they're asked to use, and for 37% of them, those tools don't fit their existing clinical workflow.{7}

Criteria to Consider Before Adopting New Trial Technology

There's a shift in the industry toward empowering sites to make their own tech investment decisions. "It's time for [contract research organizations] and other sponsor organizations to stop imposing their view on the data and embrace technologies that are in sync with the way sites are generating data—whether it gets created in a device, a lab, or through manual entry," says Hugh Levaux, former CEO/co-founder of Protocol First and current vice president for clinical research at Flatiron Health.

That's good news for sites currently juggling with dozens of sponsor-specific applications, but now that they're in the driver's seat, how should they go about vetting the new tech options available to them?

We've identified five key areas that site leaders should focus on as they consider adopting a new tech solution (see Table 1). Each criterium comes with a set of questions for the technology provider or sponsor making the solution available at the site.

Table 1: Technology Adoption Criteria and Relevant Questions for Study Site Leaders

Technology Adoption Criteria	Relevant Questions
Performance	<p>What specific gains will the new solution unlock at our site?</p> <p>How does it compare to competitors' solutions, and how viable is the company offering it?</p> <p>Will it benefit one study or multiple studies? One or multiple sponsors?</p> <p>What's the solution's expected return on investment?</p> <p>What's the basis for that calculation?</p>
Reliability	<p>What's the solution's uptime, and how well does it scale?</p> <p>How well is it supported, how often is it updated, and what's involved in those updates?</p> <p>What data quality monitoring and validation options are offered?</p> <p>Does it involve data streams outside the site's control?</p> <p>How recent are those data, and how often are they refreshed?</p>
Compatibility	<p>How does the solution fit with our existing tech stack?</p> <p>How does it integrate with our existing workflow?</p> <p>Does it help our site connect with sponsors more efficiently?</p> <p>Does it produce data in Study Data Tabulation Model format?</p>
Compliance	<p>What are our remote monitoring obligations?</p> <p>Does the solution offer secure remote document exchange?</p> <p>Is it compliant with HIPAA, GDPR, Title 21 CFR Part 11, and other regulations?</p> <p>Are there other compliance risks involved, both in the U.S. and elsewhere?</p>
Training	<p>How easy is it to use the solution?</p> <p>What steps are involved in installing it?</p> <p>Who needs to be trained on the new technology?</p> <p>How long does the training take, and what ongoing support will we get from the vendor and sponsor?</p>

Asking the right questions up front can save a lot of aggravation down the road.

From Adoption to Implementation

Selecting the right technology is crucial, but it's only a portion of the battle. It still needs to be installed, endorsed by leadership, and embraced by users. Anyone who's ever lived through a corporate-mandated cloud migration will attest to how difficult change can be if it's not carefully orchestrated.

There are many different ways to accomplish change management effectively, from Kotter's 8-Steps to McKinsey's 7-S model. [ACMP](#) and [Prosci](#) are excellent resources for change management strategies and techniques in general, and [ACRP](#) offers great insights for clinical research coordinators (CRCs) and other research professionals looking for best practices in the clinical research sector.

In our experience at Flatiron Health, we've noticed that successful site implementations tend to excel in a variety of areas (see Table 2):

Table 2: Change Management Steps and Why They are Crucial

Change Management Step	Why it's Crucial	Example
Scope Definition	What specific functions is the new technology going to replace and/or impact? It's absolutely crucial to manage expectations, and that means sizing up the project and defining its boundaries first.	Let's take a hypothetical example: A practice is considering the deployment of a new electronic health record (EHR)-to-EDC connector to replace manual data entry for certain study data elements related to oncology studies at the site, starting in January 2024.
Disruption Assessment	How is the new tool going to affect existing workflows? You need to map the new workflow against the old to quantify the impact and identify potential workflow gaps.	The new tool will save time by facilitating capture of unstructured data via EHR-embedded study specific forms, but it will require changes to the existing workflow of adverse event

		entry for study patients at the point of care.
Benefits Communication	What breakthroughs are you expecting with the new tool? Communicate benefits early and in a language that all stakeholders can easily understand.	The site expects significant reductions in data entry time and 100% elimination of transcription errors thanks to automated EHR-to-EDC data transfer.
Staff Training and Support	What will it take to train the staff and get them to embrace the new tool? Develop a pathway that makes sense, with clear timelines and full support from internal and external power users.	Training, robust knowledge management content, and comprehensive onboarding support will be provided by the vendor to the site’s CRCs and designated power users for the first six months. Other staff training to take place on a rolling basis and by therapeutic specialty.
Tiered Deployment	What pilot study would best demonstrate the tool’s potential? Reach for small, quick victories to prove value and ease concerns.	The site will first implement the new EHR-to-EDC tool for half of subjects on one Phase I study.
Success Messaging	What are the results of the pilot study, and what will the next steps be? Broadcast your success early and often to secure continued internal funding and support for the next phase in the tool’s deployment.	The site reduced the number of queries and met all data entry deadlines without the need for staff overtime. The next phase over the next six months will be to deploy the tool across all possible studies and expand training to five partner sites.

Onward and Upward

Clinical research sites have relied on technology for years to deliver optimal care to their patients, including digital tools that have been instrumental to help them manage their clinical research programs. However, many site leaders find it difficult to balance the growing needs of

their clinical research operations with the disruptions associated with the introduction of new technology into their existing workflows.

We hope the implementation framework discussed in this article can guide clinical research teams and other stakeholders in their technology selection, adoption, and deployment processes in order to fully leverage the immense benefits offered by modern innovations.

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RULES & REGULATIONS

What the FDA’s Final Guidance on Covariates Means for Fighting the Placebo Response in RCTs

Arthur Ooghe, BAsC, MEng; Samuel Branders, MS, PhD



In May 2023, the U.S. Food & Drug Administration (FDA) released final guidance on “Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products.” One relatively minor difference from the draft version actually represents a major step forward in statistical analyses for randomized controlled trials (RCTs).

This article explains the history of the use of covariates, the importance of this nuanced final guidance from the FDA, and a case study for drug developers seeking to apply this method to their statistical analyses.

The Role and Prevalence of Covariates in RCTs

By nature, people are heterogeneous. From differences in age and gender to medical history and psychology, heterogeneity is an important concept for managers of clinical trials to consider. In fact, drugs are required to be evaluated in a diverse population of patients from a sample intended to represent the general population.

While necessary to ensure clinical trial results are translatable, heterogeneity also introduces challenges to clinical trial data. It often translates into the heterogeneity of response. Furthermore, certain patient characteristics influence disease progression but are not necessarily indicative of drug response.

An age-old example of this challenge is age itself. A clinical trial patient's age could influence his or her response to treatment. However, this doesn't mean the drug is ineffective. This factor induces noise in clinical trial data, making it more difficult to demonstrate statistically significant differences between treatment groups. Another example is the baseline severity of a disease. For example, in a chronic pain indication, someone who has higher pain at the start of a study may see a sharper reduction in pain throughout treatment. However, this doesn't indicate drug ineffectiveness for those who have less pain at the start of the study.

Noise from prognostic factors like these makes it so the study statistician can't "see" anything else in the results between the active and control arm of the trial. In RCTs, there also may be bias in the data because of unequal distribution of patients between groups from random sampling. What can statisticians do to minimize these differences and biases while still being able to prove efficacy and safety for a generalized population?

The answer is called a covariate adjustment: a technique that aims to isolate the effect of the treatment being studied while accounting for the potential impact of baseline characteristics (covariates) on the outcome.

The use of covariates is not new to RCTs. In fact, in a survey of RCTs published across four journals from 2009 to 2010, 84% reported using covariates.^{ 1 } Because they are so widely used, the FDA and the European Medicines Agency (EMA) have issued regulatory guidance on their practical utility. The EMA's "Guideline on adjustment for baseline covariates in clinical trials" went into effect as of September 2015, and the FDA put forth a first draft of "Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biologics with Continuous Outcomes: Guidance for Industry" in April 2019.

So, what the new final guidance on the subject from the FDA provide statisticians with that they didn't have before is a necessary framework for adjusted analyses to be more precise than ever.

The FDA’s Final Word

There are relatively few differences between the final version (dated 2023) and the last draft version (dated 2021). This signals that substantial reflection had taken place over the two years to underpin the concepts that RCTs have followed for years.

In summary, the FDA highlights several important recommendations about the technique as a whole and selecting covariates themselves{2}:

- An analysis of an efficacy endpoint can be conducted unadjusted, but an analysis adjusted for baseline covariates can lead to a reduction in the confidence interval of the treatment effect estimation, leading to more powerful hypothesis testing with a minimal impact on the Type I error rate (false positive).
- Covariates should be few in number relative to the sample size and measured at baseline before randomization and treatment start.
- Covariates can be prognostic indices derived from scientific literature or defined and constructed based on previous studies.

The last bullet point above is where things get interesting for RCTs looking to improve treatment effect size evaluation. “Prognostic indices” refers to the use of composite covariates: a variable that combines multiple individual covariates into a single measure to simplify analysis and reduce confounding risks.

In light of this new final guidance, composite covariates are considered as any other individual baseline covariate, so long as the analysis model complies with the guidance. The FDA’s final word intends to encourage the correct use of prognostic factors to improve estimation precision.

What This Means for RCTs

Covariates that statisticians typically measure include demographic variables that are easily collected (age and gender) and baseline values of primary outcomes. However, while covariate adjustment is a tried-and-true statistical method, RCTs still face a high rate of failure. In fact,

nine out of 10 drug candidates fail in Phase I, II, and III clinical trials,{3} with up to 50% of these failures attributed to a lack of clinical efficacy.{4}

Evidently, treatment effect estimation is still imprecise, but adding more covariates to chip away at those numbers is not the answer either. This is because too many covariates increase the risk of becoming confounding factors with the exact opposite intended effect.{5} So, statisticians have to select the fewest number of covariates that are most likely to have a strong association with the outcome. While the classical approach works for simple situations, it is not enough for more complex scenarios at play in RCTs. This is where the final FDA guidance is a big deal, as it introduces a solution with composite covariates.

Adjusting for Complexity: The Placebo Response

One such complex scenario present in RCTs is the placebo response. The placebo response is the measured improvement of a patient after receiving a sham treatment, which results from a combination of several different factors that may mimic drug response, including baseline disease intensity, regression to the mean, and the placebo effect (where multiple psychological factors are involved).

The placebo response is a significant, specific source of variability that has plagued drug development for decades, representing a major cause of clinical trial failure.{6} Here are just a few examples of its prevalence across indications:

- Fibromyalgia: an average of 60% of the treatment response can be attributed to placebo response across endpoints.{7}
- Osteoarthritis: an average of 75% of the treatment response for pain endpoints can be attributed to the placebo response.{8}
- Depression: 68% of the measured treatment response was attributable to the placebo response, which was highest for the primary outcome (depression) but also substantial for anxiety, general psychopathy, and quality of life.{9}

It is well understood that the placebo response is an innate characteristic to patients, and it is evident that it is responsible for a lot of noise in clinical trial data that leads to higher rates of

failure. This begs the question: Can this characteristic be used as a covariate in clinical analysis like age or baseline intensity of a disease?

Up until recent technological breakthroughs, the answer has been no.

Constructing a Placebo Responsiveness Composite Covariate

As discussed, a covariate must be measured at baseline. For years, placebo responsiveness could only be estimated at the end of the study and only for the patient receiving a placebo, which means it couldn't be used in a covariate adjustment.

Today, however, it is possible to construct a composite covariate for placebo responsiveness based on baseline data.^{10} First, this requires an understanding of individual patient psychology based on stable personality traits and expectations. This information, combined with other patient baseline data (age, intensity of disease, etc.), provides a clear picture of an individual's characteristics that may impact treatment estimation. This is where technology comes into play.

Machine learning is a subset of artificial intelligence (AI) that uses statistics to find patterns in massive amounts of data. This is exactly what clinical trials need to be able to do: Find patterns in historical patient psychology data to predict placebo response. In 2023, this technology is more mature than ever, and disease-specific predictive machine learning models exist that have been calibrated based on historical data. The assessment of individual patient psychology can be combined with this trained algorithm to calculate a relative placebo responsiveness score for each patient at the beginning of the trial. This score, which is a combination of multiple factors associated with placebo response, represents a composite covariate that can be used in the statistical analysis.

This method has already been successfully applied in RCTs testing areas like pain, osteoarthritis, and Parkinson's disease. In specific cases, it has improved assay sensitivity (the ability to distinguish placebo treatment from drug treatment) by nearly 40%^{11} and improved study power by 14%. Moreover, the approach can be implemented for about 1% to 3% of the total per-patient cost for the trial and can be applied to virtually any therapeutic area or indication.^{12}

The advent of AI-based methods{13} has allowed researchers to mitigate the negative consequences of high placebo response rates by way of a covariate adjustment. In doing so, researchers can reduce the number of covariates for adjustment and increase the expected association with the outcome—aligning perfectly with the FDA’s final guidance.

Conclusion

The FDA has published its final official opinion on the use of covariates as a recommendation to improve treatment effect size evaluation—and it presents significant opportunity for managers of RCTs who are struggling with treatment effectiveness estimation due to the placebo response.

Placebo responsiveness almost always impacts results and represents a leading cause of Phase II and III trial failures. With machine learning technology, the characteristic can be accurately predicted before the study, which means statisticians can use the covariate approach to manage this significant source of data variability.

It is important to think critically and follow proper guidance as it relates to selecting covariates. However, this is a breakthrough method for RCTs that, when supported by the FDA’s final guidance, will unlock an entirely new level of precision in statistical analyses.

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OVER THE TRANSOM

Everything Must Change

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In my youngest days as a fresh-out-of-college journalist, I did a lot more original writing than editing, especially for my first job on a daily newspaper. Back then, with a different story deadline looming practically every day on the job, learning to roll with the punches of having my sterling prose edited by others before it went to print was part of a valuable learning process. The main lesson was not to let myself think that my own ways of wording things were so precious that they could not stand some mending when necessary.

These days, I do a lot more editing than writing, and the chores range in complexity from minor tweaks to massive overhauls of manuscripts, and everything in between. Every contributor to this journal has his or her own preferences for phrasing, grammar, organization, and complexity. My job isn't so much to smooth it all out into a calm sea of sameness as it is to make sure the peaks and troughs experienced within and between one article/column and the next aren't too jarring.

One little step in this mission that many readers might never think about focuses on breaking up big blobs of text with helpful subheadings (or "subheads"). These give the reader a bit of a breather between major subjects in the manuscript, but not all of the contributors include them in their original submissions, so I take a first stab at supplying them where I think they are necessary. Some authors, of course, don't like the wording of my subhead suggestions as much as what they come up with on their own once they have been made to think about it, and learning to be flexible as an editor in these circumstances was also a valuable experience for me in my earliest days in this job.

I think I wanted to tell you all this because it helps make some sense of the theme for this issue—"Everything Must Change." I'm pretty sure that somewhere along the way in my editing of materials for this August's cornucopia of topics, I suggested that exact phrase as a subhead for one of the manuscripts, but the authors disagreed and inserted some other wording with which they were more comfortable. That's fine, of course, but I couldn't let the idea go that, when you

take them as a gestalt, in one way or another the pieces of this issue are all about not just the need for, but the inevitability of, ongoing change in the clinical research enterprise—not just change for the sake of change, but change for the better.

Here are excerpts from recent announcements of some more changes happening in our industry (no endorsements implied) that I hope you will find useful, or at least can enjoy as a breather between some of the bigger, more important things you mean to accomplish with your day...

Cost of Translating Consent Documents May Serve as Barrier to Participation for Some

Cancer research centers conducting clinical trials could enroll more patients from underrepresented racial and ethnic groups by placing greater emphasis on relieving investigators of the costs of translating consent documents into languages other than English, [according to](#) a UCLA Jonsson Comprehensive Cancer Center study.

Consent documents presented to potential clinical trial participants are required to be in a language understandable to the patient, and studies sponsored by pharmaceutical companies—about 70% of all randomized cancer clinical trials—typically have budgets that cover the costs of translating documents into languages appropriate for participants. In studies that are not sponsored by drug companies or device makers, investigators often operate on a fixed, per-patient budget provided by a grant, often from philanthropic organizations or governmental groups. As a result, an unexpected cost, such as the cost of consent document translation, often reduces the funds available for other potentially important aspects of the research.

The UCLA research team, which published its findings in [Nature](#), theorized that these additional costs could discourage investigators from recruiting patients for whom consent document translation would be required, contributing to the disproportionately low rates of participants from traditionally underrepresented groups in clinical trials. Researchers analyzed “consent events”—situations in which consent documents were signed—and compared those for industry-sponsored studies versus studies not sponsored by industry. Each “event” did not necessarily represent a single patient, because some participants signed consent documents for multiple trials.

The researchers evaluated potential differences in the two types of trials based on participant primary language and English proficiency, basing their findings on more than 12,000 consent events that included 9,213 participants in trials at the cancer center between January 2013 and December 2018. The differences were dramatic. The proportion of consent events for patients with limited English proficiency in studies not sponsored by industry was approximately half of that seen in industry-sponsored studies. When patients from this group signed consent documents, the proportion of consent documents translated into the patient's primary language in studies without industry sponsorship was approximately half of that seen in industry-sponsored studies.

Academic/Industry Partnership Launches AI Program for Clinical Trials

Texas Tech University Health Science Center (TTUHSC) and Deep 6 AI have [announced](#) a collaboration, joining forces to integrate artificial intelligence (AI) within TTUHSC's electronic medical record (EMR) system to improve patient access to clinical trials. TTUHSC will use Deep 6 AI to precision-match patients to their clinical trials in real time. This process will allow researchers to find the right patients for their trials in minutes, which will greatly reduce the workload on their staff. By using these AI tools, TTUHSC researchers will ultimately give more patients access to participate in clinical trials and will be able to use any resulting therapies to treat patients even faster. This partnership further expands the Deep 6 AI ecosystem, which consists of millions of unique patient records and thousands of trial sites accessible to sponsors for their research.

One of the most time-consuming components of clinical research is finding patients who match the specific criteria needed for the study. Deep 6 AI uses natural language processing to search through millions of structured and unstructured EMR datapoints, such as physician notes, lab reports, outpatient notes, radiology reports, genomics results, and pathology reports, to precision-match patients to the ideal clinical trials. This process simplifies patient recruitment and allows administrators to focus on patient care and managing the trials, which is increasingly important when staff time is at a premium.

Generative AI Now Predicting Clinical Trial Outcomes

Insilico Medicine, a clinical-stage end-to-end generative artificial intelligence (AI) drug discovery company, [has demonstrated](#) that it can predict the outcome of Phase II to Phase III clinical trial success using its proprietary transformer-based AI clinical trial prediction tool called inClinico with a high degree of accuracy. The research has been published [in *Clinical Pharmacology and Therapeutics*](#). The AI engines used in the study are integrated into Insilico's inClinico system, designed to predict the outcomes of clinical trials as a part of the Medicine42 clinical trials analysis and planning platform.

The research paper included three types of validation of AI engines trained to predict the probability of success of Phase II trials, including retrospective, quasi-prospective, and prospective validation. The AI of interest was trained on more than 55,600 unique Phase II clinical trials over the last seven years. The subsequent model for clinical trial probability of success developed by Insilico researchers demonstrated 79% accuracy on the outcomes of real-world trials in the prospective validation set where those outcomes were able to be measured. The findings indicate that target choice is much more likely to impact clinical trial outcome prediction than trial design, underscoring that lack of efficacy is the primary driver of clinical trial failures.

Project Gives Trial Patients a Platform to Share Their Experiences and Influence Change

Mural Health has launched a non-commercial initiative to share the stories of the people who make clinical research possible. The Portrait Project is a collection of stories detailing the personal experiences of trial participants, caregivers, and medical professionals. The accounts are uncensored and, often, brutally honest. Each story serves to educate by sharing our industry's victories, what is working, where we have fallen short, and opportunities to improve. In all cases, the Portrait Project aims to amplify the voices of patients and their loved ones. It can be found on Instagram, Facebook, LinkedIn, or by visiting <https://portraitproject.muralhealth.com/>.

The Portrait Project serves to share the often-overlooked narratives of trial participants and to increase awareness, dispel misconceptions, reduce stigmas, and create a community that collectively uses its voice to influence positive change throughout the clinical research

ecosystem. Stories from the Portrait Project cover the spectrum of experiences—from cancer survivors who want to alleviate fears of the newly diagnosed, to caregivers who emotionally recount journeys that end in the deaths of loved ones. Certain stories highlight how clinical research profoundly changes lives for the better. Other stories will be critical of the clinical research industry’s imperfections, recounting moments of sadness, loss, and personal devastation.

Quantifying the Impact of the Pandemic on Cancer Center Clinical Trial Operations

Leveraging its network of North American cancer centers, the Association of American Cancer Institutes (AACI) circulated surveys to more than 100 cancer center members to assess how clinical trial office operations were impacted by the COVID-19 pandemic. A report summarizing the results of the longitudinal series of surveys was published in the *Journal of the National Cancer Institute (JNCI) Cancer Spectrum*.

The lead authors of “[Quantifying the Impact of the COVID-19 Pandemic on Cancer Center Clinical Trial Operations](#)” come from the University of Florida Health Cancer Center, the University of Kansas Cancer Center, and the Huntsman Cancer Institute at the University of Utah. According to [a press release](#) about the study, data shared in the report show that AACI cancer centers were able to keep oncology trials available to patients while maintaining safety. Survey results demonstrated a sizeable decrease in interventional treatment trial accruals in both 2020 and 2021 compared to pre-pandemic figures. Though the pandemic significantly impacted the national clinical research infrastructure, cancer centers were resilient, as evidenced by improvements in efficiencies and patient-centered care delivery. The pandemic necessitated rapid adaptation of trial operations to new best practices, including remote monitoring, remote consenting, electronic research charts, and work-from-home strategies for staff.

