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The Authority in Ethical, Responsible Clinical Research

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Clearing the Path to Tomorrow's Impactful Trials

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Association of Clinical Research Professionals

Managing Editor
Gary W. Cramer
gcramer@acrpnet.org
(703) 258-3504

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EXECUTIVE DIRECTOR'S MESSAGE

Looking Back, Moving Forward

Susan P. Landis, Executive Director of ACRP

As 2024 draws to a close, I, along with the ACRP staff, wish all of you—our members, volunteers, collaborators, and partners—a truly joyful holiday season.

Amidst the last-minute shopping and shipping, the must-dos and go-tos, I am taking my eyes off my to-do lists (yes, plural) to reflect briefly on the year in the rearview mirror and to take a glimpse at what's ahead. With your support, ACRP is on an historic path of progress for advocating for your professional accomplishments and development as we continue in service to our mission to ensure excellence in clinical research. Here are some examples of what was accomplished this past year:

- This year ACRP passed an historic milestone of 17,000 members, signaling a trajectory of growth for your professional organization not seen at this pace in many years.
- ACRP now has certified more than 42,000 clinical research professionals across our six certifications, and this year saw welcome growth in clinical research professionals signing up for their initial certification designation.
- 23,000 clinical research professionals accessed ACRP's training and continuing education programs, and we climbed to more than 40 Organization Members.
- Today, more than 50 clinical research professionals are designated as ACRP Fellows, a mark of distinction that recognizes individuals who have made substantial contributions to the Association and the clinical research industry.
- This year also showed continued—and exciting—growth in our fundraising efforts in support of ACRP Scholarships and Grants through the Ride4DEI. This year alone, ACRP's volunteer cyclists raised $84,265, and in total together we have raised nearly $250,000 since 2021 in support of access and advancement in clinical research careers.

Progress is propelling us forward. As we enter the New Year, we recommit to our strategic imperatives that guide the development of our programs and benefits for our members. These include:

- Learning: We will lead in the development of training and education programs that ensure the quality of conduct in clinical research.
- Credentialing: We will continue to usher in certification, certificate, and badging programs that recognize your professional growth and, importantly, your contributions to clinical research.
- Career Growth: We will continue to provide clinical research professionals with resources to support career advancement.
- Workforce Development: We will lead efforts to shape the story of how your profession influences and impacts individuals and communities around the world, and we will advocate in every way possible for recognition and reward for your contributions to better health outcomes for all.

We have important work to do ahead, and we are grateful to do it with you—and for everyone who chooses this remarkable career. We are excited about the discoveries and advancements that await us in 2025, and look forward to engaging with you in another year of making critical progress while facing the challenges and opportunities ahead.

—ACRP—

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PEER REVIEWED

Best Practices for Handling Informed Consent in Emergency Medical Cases

Muhammad Waseem, MBBS, MS, FAAP, FACEP, FAHA, FSSH, CPI

Informed consent, a cornerstone of ethical research involving human subjects, presents a unique challenge in emergency medical cases. The Nuremberg Code, a pivotal document that originally defined informed consent, and the Declaration of Helsinki, which underscores the ethical dilemma and provides regulations for exceptions to informed consent, are not just crucial but carry significant weight in understanding the complexities of clinical investigation for potentially life-threatening interventions in emergent conditions. These documents emphasize that specific reasons must exist to justify the inclusion of research subjects with a condition that renders them unable to provide informed consent, particularly in emergencies with a significant threat to the patient's well-being or life.

Research without permission can be done when enrollment decisions must be made immediately and the patient's wishes are unknown because of the situation. This reiteration of the importance of informed consent in emergency medical cases reinforces the ethical considerations in such situations.{1}

Emergency research often necessitates Exemption from Informed Consent, a regulatory mechanism that allows research to be conducted without the explicit consent of the research subjects (see Table 1). This exemption, as outlined in the 1996 release of 21 CFR Part 50.24 of the *Code of Federal Regulations* by the U.S. Food and Drug Administration (FDA) for human subject research, is pivotal. The FDA and the U.S. Department of Health and Human Services are crucial in providing the regulatory oversight to allow "emergency research" without informed

consent. Their diligent oversight ensures that emergency research is conducted ethically and with the subjects' best interests in mind, thereby reassuring the medical community and the public.{2}

Utilizing exceptions to obtaining informed consent in emergency research offers significant benefits. It provides the potential for broader subject recruitment and ensures the possibility of obtaining informed consent later. This approach can enhance the feasibility and effectiveness of emergency research, ultimately benefiting the patients involved. Emergency research can be conducted without consent through community disclosure or consultation, followed by notification and obtaining permission from the subject or their family for continued participation after the intervention is applied. The community's involvement in the research process through disclosure and consultation is crucial and significant to the success of emergency research.

Prospective Consent

Prospective consent, a method for ensuring informed consent from research subjects, holds promise in addressing the challenges of obtaining informed consent in emergency medical cases. It involves identifying an at-risk population and acquiring consent from as many of them as possible before an emergency arises. This approach provides a framework for ethical research in such situations. A "consent in advance" model already exists for specific conditions, such as organ donation, and its potential in emergency cases is worth exploring, offering a hopeful solution to the challenges of emergency research.

The critical challenge, however, is recruiting an adequate number of individuals in at-risk groups to ensure enough will present with the emergency condition of interest. This approach raises the following question: Given the unlikelihood of any individual developing the emergency condition of interest, can their consent be truly informed? Will the identified potential subject pool consider all the risks of participation? Might individuals be convinced to volunteer when they would not have otherwise?

Because the chance of participating in the trial is so low, many will likely give little thought to the potential consequences. For example, if a new medication was in clinical trials to be provided within a three-hour window to patients who come to the Emergency Department having had a

mini stroke, all patients being followed in the hospital with prior transient ischemic attacks could be asked for prospective consent should they present with the condition again.

There must also be a robust mechanism for differentiating those who have consented from those who have either refused or have not been approached. Another issue to be considered is the Hawthorne Effect, which states that a person's behavior may be influenced purely by observing their behavior. In the research context, this effect could lead to subjects altering their behavior or responses because they know they are being followed, potentially skewing the results. This effect is essential to consider when designing and conducting research, as it can impact the validity of the results and the ethicality of the research process. For instance, if subjects are aware that their behavior is being observed, they may alter their behavior to conform to what they believe the researchers want to see, thereby compromising the accuracy of the data collected.

Deferred or "Delayed" Consent

In this case, subjects are recruited without consent using the deferred consent approach, and consent is obtained later. Deferred consent is a process where subjects are enrolled in a study without their initial consent, but consent is sought at a later, more appropriate time. If implemented correctly, this approach can ensure that consent is only for the patient's continued research participation. However, a key consideration is the impact on data analysis if consent is required for this review but not granted. If missing data are omitted from complete data, then the analysis may be susceptible to bias. Therefore, it's crucial to consider the implications of deferred consent on data analysis and the potential for bias in the results.{3}

Although it is plausible that using deferred consent may result in more scientifically rigorous research, several concerns remain. Subjects cannot refuse or consent to something that has already happened. This raises important ethical questions and requires further discussion. Would it be ethically permissible to enroll subjects in research without their consent? Are there times when researchers should forego consent? Also, several patients might need help to discuss their research participation. What should be done with the data collected from these subjects? Can it be included in the analysis? Many believe it should be considered as something other than a tactic to improve recruitment.{4}

Proxy Consent

This principle allows a proxy to act on behalf of another individual who cannot decide. A proxy can provide authorization for care and research participation. However, this approach also has its inherent challenges. For example, could a proxy accurately represent the wishes of another individual? If they can do this, they must decide what decision they believe the subject would make. The difficulty lies in ensuring that the health proxy represents the subject's wishes and not the proxy's.

Addressing Ethical Concerns

Research quality depends on ethics, a well-designed protocol that addresses patient safety, and appropriate data collection tools**.** Research is only valid if it is conducted ethically. Various approaches can be used to address ethical issues; however, it's important to note that public disclosure and community consultation requirements may be specific to people's cultural values in the United States.{5} Medical professionals, researchers, and institutional review board (IRB) members play a crucial role in ensuring that research is conducted ethically, that participation in studies empowers patients, and that researchers are held accountable for the validity and ethical conduct of the study.

Community Consultation

Addressing the ethical concerns intrinsic to the emergency research context is vital when considering exceptions to informed consent. Requiring community consultation could be a significant step in this direction. Emergency research with a waiver of consent requires trust between research professionals and society. This consultation should include two-way communication, in which the communities are educated on the content of the research study and the meaning of and need for consent exceptions.{6} The purpose of community consultation is not to provide community consent or disapproval but to foster a sense of shared responsibility and understanding, thus highlighting the ethical considerations in emergency medical research and making the audience feel trusted and part of a collective effort.

Public Disclosure

This is a viable and inexpensive way to inform a large target population about emergency medical research. Furthermore, reporting clinical trial results to the appropriate registries could strengthen research transparency.{7} The availability of results in the public domain helps inform medical judgment and advance medical science.{8}

IRB Practices and Intensive Oversight

A diligent IRB review of study proposals is a vital protection for research subjects. Mechanisms exist to safeguard the rights of prospective medical research subjects and promote their protections for particularly vulnerable participants and specific circumstances. Although the minimum frequency of continued review is no less than once per year, the degree of risk involved in research procedures should determine the frequency of continued review. Also, studies that are greater than minimal risk require full committee review.

IRBs should choose the most appropriate method for obtaining informed consent under challenging situations.{9} There may be variations in the interpretation of waiver of informed consent regulations among the IRBs.{10} However, the extent of protection should depend upon the risk of harm and the likelihood of benefit to the subjects. It is essential to recognize that the judgment that any individual lacks autonomy should be periodically reevaluated.

Sponsor Role and Responsibilities

The sponsor is responsible for a clinical investigation and is generally responsible for ensuring informed consent is obtained before enrolling participants in research studies. Sponsors are required to take extra steps to protect human subjects. They must monitor the progress of all research involving an exception from informed consent.

FDA Guidance

On December 21, 2023, the FDA expanded informed consent exceptions with a final rule permitting the IRB to waive or alter elements for specific FDA-regulated minimal-risk clinical investigations (see Table 2). This document provides an exception from the requirement to obtain

informed consent when a clinical investigation poses no more than minimal risk to the human subject and includes appropriate safeguards to protect the rights, safety, and welfare of human subjects. This clarified the FDA's guidance and reduced confusion about when emergency research can proceed without obtaining an individual subject's informed consent.

However, this is a narrow exception to the requirement for obtaining and documenting informed consent. This applies to a limited class of research activities involving human subjects who need emergency medical intervention but who cannot give informed consent because of their life-threatening medical condition. The exceptions involve critical situations such as emergencies or public health crises.

Conclusions

Informed consent is not always feasible in emergency research, and a waiver of informed consent gives directions for engaging effectively in emergency medical research. Such consent waivers are only permitted under highly restricted and specific circumstances, and the intent of waiving the requirement for prospective, voluntary consent should be in the interests of the patient's safety and rights and that of the public.

When obtaining consent is not feasible, the research should pose no more than the minimum risk. Regulatory exceptions where any procedures conducted to save the subject's life are available and require prompt reporting to IRB for review. Hence, the protection of the rights and welfare of individuals involved in the research process should be adequate. Researchers should commit to developing context-appropriate strategies and flexible approaches to ensure they are conducting ethical research in such situations.

Table 1: Informed Consent Exception Requirements for Emergency Research {11}

- A life-threatening condition or situation exists
    - Available treatments are either not tested or unproven or unsatisfactory
    - Need exists for research to evaluate the safety and efficacy of treatment
- Obtaining informed consent is not feasible
    - The subject is unable to consent because of a medical condition
    - There is no time to contact a subject's legally authorized representative
- Possibility must exist that the subject will benefit from treatment
- The research could not practically be carried out without the waiver

Table 2: Common Rule Criteria to Permit a Waiver or Alteration of the Informed Consent

- The research is designed to ensure that subjects are exposed to no more than minimal risk, providing a high level of safety and reassurance.
- The requested waiver or alteration is a necessary and justified step, without which the research could not practically be carried out.
- If research involves identifiable private information or identifiable biospecimens, it could not practicably be carried out without using such information or biospecimens in an identifiable format.
- The waiver or alteration ensures that subject rights and welfare are not adversely affected, demonstrating commitment to ethical research.
- Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

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Muhammad Waseem, MBBS, MS, FAAP, FACEP, FAHA, FSSH, CPI, is a Professor at Weill Cornell Medicine and an Attending Physician and Research Director for Emergency Medicine at Lincoln Medical & Mental Health Center, where he is also Vice Chair of the Institutional Review Board. Among other organizations, he is active with the Society for Simulation in Healthcare, Public Responsibility in Medicine and Research, the American College of Emergency Physicians, American Academy of Pediatrics, and the American Heart Association.

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PEER REVIEWED

Microgravity-Enabled Oncology Research Programs

Deepika Khedekar, MPharm

This article highlights the urgent need to explore solutions that enhance the robustness and efficiency of cancer clinical trials and research programs. It delves into the role of the microgravity environment in advancing cancer research, focusing on novel experiments that have enabled us to accelerate cancer cell growth in microgravity, shorten drug testing timelines, develop 3D tumor spheroids with much higher resolution in space, and crystallize the KRAS protein with five times the signal-to-noise ratio observed on Earth. These developments hold the potential to expedite clinical research on Earth by providing detailed insights into cancer cell development, driving drug development, and helping clinical trial researchers better understand how drug-target pairs might behave in trials. The article also examines the challenges and risks that clinical research programs may face in the future as they integrate microgravity experiments into their research.

In response to these challenges, the article proposes a holistic framework with a two-fold approach. The first part of the framework aims to summarize the findings from all space-based cancer research experiments conducted so far, and the second part offers a comprehensive blueprint for incorporating this novel microgravity environment into cancer clinical research programs, with a hope to make them more robust and efficient.

Global Landscape of Cancer Research

Approximately 10 million people die each year due to cancer.{1} Five-year survival rates for certain types of cancers, like lung cancer, are alarmingly low, at around 20%.{2} Moreover, 40% of lung cancers are diagnosed at a late stage.{3} Despite more than 7,459 cancer trials being registered online, 95% of these investigational drugs probably will never see the light of the day.{4,5} Abnormally high mortality rates, late-stage diagnoses, high failure rates of cancer trials, surging demand for oncology services, and staff shortages are some of the key symptoms of a broader issue that needs urgent attention. There’s a pressing need to elevate the resilience and efficiency of cancer research programs. While researchers around the world are trying to address this problem through diverse lenses, it turns out that the outer space or microgravity environment might offer us fertile ground to address these challenges.

Microgravity Environment and Early Experiments

On Earth, gravitational force keeps us anchored as we walk or drive, enhancing our operational efficiency "physically." However, astronauts don't have this luxury. As one travels away from Earth this gravitational force greatly subsides, reducing to a mere fraction of what it is on Earth. This is why astronauts are often tethered to their spacecraft with a harness when working outside, to compensate for the near absence of gravity. Hence, this outer space environment where the gravitational force is barely existent is known as the microgravity environment.

To date, numerous experiments have been conducted in this microgravity environment to understand its effects on the human body. Notably, NASA's Twin Study, which involved two twins—with one remaining on Earth and the other spending 340 days in space—was spearheaded by NASA's Human Research Program.{6} This study conducted on two genetically similar individuals helped scientists understand the effect of the space environment on the human body and served as the foundation model to expand medical research in space.

Over the past few years, cancer research teams around the world have conducted multiple experiments in this microgravity environment of space to decode its impacts on cancer cells and the results have been astounding.

Tumor Spheroids in Microgravity Environment

Scientists have observed that, in the microgravity environment of space (where gravity is almost non-existent), cancer cells can grow into tumor spheroids that closely resemble those found in the human body on Earth. Replicating this phenomenon in laboratories on Earth, outside the human body, presents a considerable challenge, making it difficult to study these tumor structures in detail. The unique conditions of space allow scientists to overcome this obstacle, as cancer cells in space naturally form three-dimensional structures that can be studied more thoroughly. This discovery has the potential to increase the precision of our oncology research programs here on Earth.

For instance, a research study aboard the International Space Station (ISS) is underway to investigate the pathogenesis of diffuse midline glioma (DMG).{7} This malignancy, emerging from the glial cells within the central nervous system, predominantly manifests in the pons area of the brainstem and primarily targets young children aged 5 to 7. With an alarming 150 to 300 new diagnoses annually and a survival rate of less than 10% two years after diagnosis, the urgency to find better treatments is palpable.{8} This space-based study of DMG cancer cells aims to shed light on their unique properties, leveraging the microgravity environment of the ISS to uncover details about their structure and behavior that could lead to more robust and effective treatments. Beyond DMG, microgravity also plays a crucial role in advancing protein crystallization within oncology research.

KRAS Protein Crystallization in Microgravity

Some 30 to 40% of all cancers originate due to mutations in the KRAS gene. This gene produces proteins involved in the growth and death of cells.{9} Due to mutation in the KRAS gene, the corresponding protein generated by this gene remains in a perpetually active state and doesn't switch to inactive state periodically as it would if the gene was not mutated. This results in it continuously sending signals that correspond to cell growth, leading to different types of cancers. This phenomenon makes it important for researchers to study the KRAS proteins generated due to mutated KRAS genes so they can develop drugs to block this protein's action and treat these types of cancer cells.

The challenge is that we cannot fully stabilize the structure of this protein on Earth in the labs, and hence researchers often have a hard time to fully understand the molecular structure and develop corresponding drug-target pairs. This is the problem that the Frederick National Lab for Cancer Research addressed by sending these protein molecules to space with the help of the ISS team.{9} After a predefined interval of time, when a capsule carrying these protein molecules that were crystallized in space returned to Earth, these researchers found that the corresponding crystals formed in space were much more refined, exhibited 50% more orderliness, and the signal-to-noise ratio in them was five times more than similar molecules that were crystallized on Earth. Thus, experiments like this can help us explore the structure of such vital proteins in detail and ensure the next generation of drug-target pairs we develop in oncology are more robust.

Decoding the structure of cancer cells is not the only way microgravity can accelerate the cancer research program on Earth; it can also accelerate their growth and shorten our drug testing cycles.

Accelerated Growth of Cancer Cells in Space

Researchers have observed that cells proliferate at a much faster rate in space than on Earth. A team at Sanford Stem Cell Institute of University of California San Diego observed that when full-blown cancer cells were sent to space in the form of tumor spheroids, their size tripled in just 10 days.{10} This acceleration is attributed to the reduced gravitational forces in space, essentially microgravity. This is astounding because this phenomenon presents an opportunity to test investigational oncology drugs at a pace much faster in a microgravity environment than it might be ever possible here on Earth. This team proved this hypothesis by sending a triple-negative breast cancer tumor organoid to space with an anti-cancer drug. The team concluded that the growth of cancer cells can be reduced at pace much faster in space compared to that on Earth. That brings us to this question: What if we could simulate a microgravity environment here on Earth? Would that yield similar results?

Effect of Simulated Microgravity Environment on Cancer Cells

While there is a need to conduct more experiments in the simulated microgravity environment here on Earth, initial experiments conducted by researchers in Australia seem promising. A research team at University of Technology, Sydney took four different types of cancer cells from different parts of the body—breast, ovary, lungs, and nose—and put them in a simulated microgravity environment here on Earth. What the team found was that in 24 hours, 80% to 90% of these cancer cells died.{11}

While these experiments conducted by cancer research organizations across the world have opened up new avenues to make our cancer research programs more robust and efficient by leveraging the microgravity environment, there is need to develop a standardized framework to address the challenges and risks inherent in this novel approach and to maximize the application of these novel experiments to oncology research programs around the world.

Challenges and Risks

Whether we continue to conduct biomedical oncology research experiments in space or expand our initiatives to include full-fledged cancer clinical trials in space, there are challenges and risks that are yet to be addressed. Transporting cells and equipment to space is not only an extremely capital-intensive endeavor, but also demands intricate planning for each mission. The effect of prolonged exposure to microgravity on our health, DNA, and most importantly immune system is not yet fully clear and needs more research work. These hurdles are further compounded by the limited capacity of the ISS for research activities, the difficulties in managing and transmitting clinical data between Earth and space, and the lack of a standardized framework and governance oversight for translating the findings from oncology experiments in space to Earth. These challenges are summarized below (see Table 1), and will need to be addressed if we are to fully explore the potential of microgravity to advance cancer research here on Earth.

Table 1: Challenges for Conducting Cancer Research Experiments in Space

Challenge	Overview
Financial Constraints	High costs of transporting research equipment and cancer cells to space significantly impact budgeting for oncology experiments.
Experiment Design and Logistical Challenges	Designing oncology research experiments that can be conducted in the space environment requires detailed planning that should factor in an array of prerequisites: payload limitations, crew readiness, communication challenges, limitations related to real-time reporting of adverse events, and more.
Radiation	Assessing the effects of space radiation on human health is crucial for the safety

Exposure Risks	and integrity of oncology trials and research experiments conducted in space.
Adaptation of Research Protocols	Space-based research may require significant adaptation of Earth-based oncology research protocols to suit the unique conditions of microgravity and radiation exposure. The microgravity environment and spaceflight can result in significant physiological stress and can have significant impacts on cellular and molecular processes.
ISS Research Capacity	Limited research capacity on the space station restricts the extent and variety of oncology experiments that can be conducted.
Microgravity Health Impacts	The effects of prolonged microgravity on the human body, crucial for understanding cancer progression and treatment efficacy in space, remain largely unknown.
Space-Earth Data Communication and Management	Ensuring the efficient management and real-time transmission of clinical data from space to Earth is essential for timely monitoring and responses in research experiments and clinical trials.
Trial Design Complexity	Designing oncology trials that can be effectively conducted in the constrained environment of space or that leverage the findings from space requires holistic collaboration of multiple stakeholders from both the oncology and space research community.
Participant Recruitment	The feasibility of recruiting suitable participants for space-based oncology trials poses unique challenges, including redefining acceptable health criteria and consent under unusual conditions.
Ethical Considerations	Ethical issues are magnified in space research due to increased risks and unknowns, necessitating rigorous review processes and contingency planning for participant safety.
Absence of Regulatory Framework	The absence of established frameworks for space-based oncology research has severe impacts on governance, ethical considerations, and procedural standardization.
Research Findings Translation	Developing protocols to translate discoveries from space into actionable oncology treatments on Earth is essential for leveraging space research benefits globally.

Acknowledging the array of challenges and risks inherent in space-based oncology research, the SPACE-ONCO model has been established. This initiative is designed to centralize the results of oncology experiments conducted in space and ensure their widespread dissemination within the global oncology community. These pivotal results are summarized in Table 2 below. Additionally, this aims to provide a structured approach for overcoming unique challenges that oncology research organizations across the world might encounter as they pivot toward leveraging the microgravity environment to advance cancer treatments on Earth. This framework is elaborated in Table 3.

Table 2: Findings from Space-Based Oncology Research Experiments Conducted to Date

Scope	Findings
Tumor Spheroids in Space{7}	● Microgravity exposure for up to 14 days in space results in the formation of detailed tumor spheroids that mimic the natural growth of cancer cells in the human body on Earth. ● Microgravity in this case serves as an unprecedented platform to study cancer cell interactions, development, dissemination, and response to various treatment modalities.
KRAS Protein Crystalliza-tion in Space{9}	● Some 30% to 40% of cancers result from mutation in KRAS gene. ● The KRAS gene produces proteins that control the growth and death of cells and mutation in this gene can result in these proteins continuously sending signals of growth to cells which makes them cancerous. ● It's vital that we have a detailed understanding of the molecular structure of this protein, but on Earth in the labs, it's hard to stabilize these molecules. ● This same protein molecule in the microgravity environment of space stabilizes much better and resultant crystallizes are more refined, bigger, and offer a signal to noise ratio that is five times better than in those crystallized on Earth. ● This makes it easier for research groups to study this protein in detail, develop drug-target pairs that are more robust and effective, and thus accelerate our ability to develop effective cancer drugs here on Earth.
Accelerated Growth of Cancer Cells in Space{10}	● Normal stem cells present in our blood switch between "sleep" and "active" states and remain in "sleep" state for 80% of the time. ● If they remain in an active state for a longer time, the stem cells age faster and lose their ability to clone and make blood. This happens often when our body is under stress. ● It is observed that stem cells age faster in microgravity than on Earth. ● Similarly, cancer cell tumor spheroids, when introduced in the microgravity environment, triple in size in just 10 days. ● When these same triple-negative breast cancer tumor spheroids were sent to space with anti-cancer drug, their growth was reduced at pace faster than on Earth.
Effect of Simulated Micrograv-ity Environ-ment on Cancer Cells{11}	● Researchers took cancer cells from different parts of the body—breast, ovary, lungs, and nose—and put them in a simulated microgravity environment here on Earth. ● They found that in 24 hours, 80% to 90% of these cells were dead. ● There is more research work needed on this front, but the initial results suggest new avenues to conduct oncology research experiments in simulated microgravity environments on Earth.

SPACE-ONCO Framework: Holistic and Responsible Integration of Microgravity Environment in Cancer Clinical Research Programs

This framework (see Figure 1 and Table 3) is meticulously designed to navigate the unique challenges and opportunities presented by conducting oncology research in space, aiming directly at the needs and interests of oncologists and the clinical research community. It outlines a series of structured steps, each accompanied by actionable items, intended to facilitate the translation of space-based research findings into practical, Earth-bound clinical applications.

By establishing collaborations with regulatory bodies, securing essential funding, adapting research protocols for the space environment, and ensuring the ethical recruitment and safety of participants, this framework provides a comprehensive roadmap for pioneering oncology experiments beyond our planet.

The focus on mitigating radiation exposure, leveraging the ISS's research capacity, and understanding microgravity's impact on health highlights the framework's commitment to pushing the boundaries of current cancer treatment modalities and knowledge.

Moreover, the framework emphasizes the importance of effective data management between Earth and space, innovative trial design, and the translation of research findings to enhance clinical oncology practice. By advocating for a collaborative approach that involves key partnerships with space agencies, aerospace engineers, and the broader oncology research network, the framework aims to harness the unique aspects of the space environment to advance cancer treatments.

For oncologists and clinical researchers, this represents an exciting frontier of exploration that promises to yield new insights into cancer biology, potentially leading to breakthroughs in therapy and patient care.

Through dedicated communication channels, training in space-specific data management systems, and a focus on the practical application of research findings, the framework seeks to integrate space-based research into the fabric of oncology, enriching the field with novel perspectives and tools to combat cancer.

Figure 1: SPACE-ONCO Framework—Microgravity-Enabled Cancer Clinical Research Program

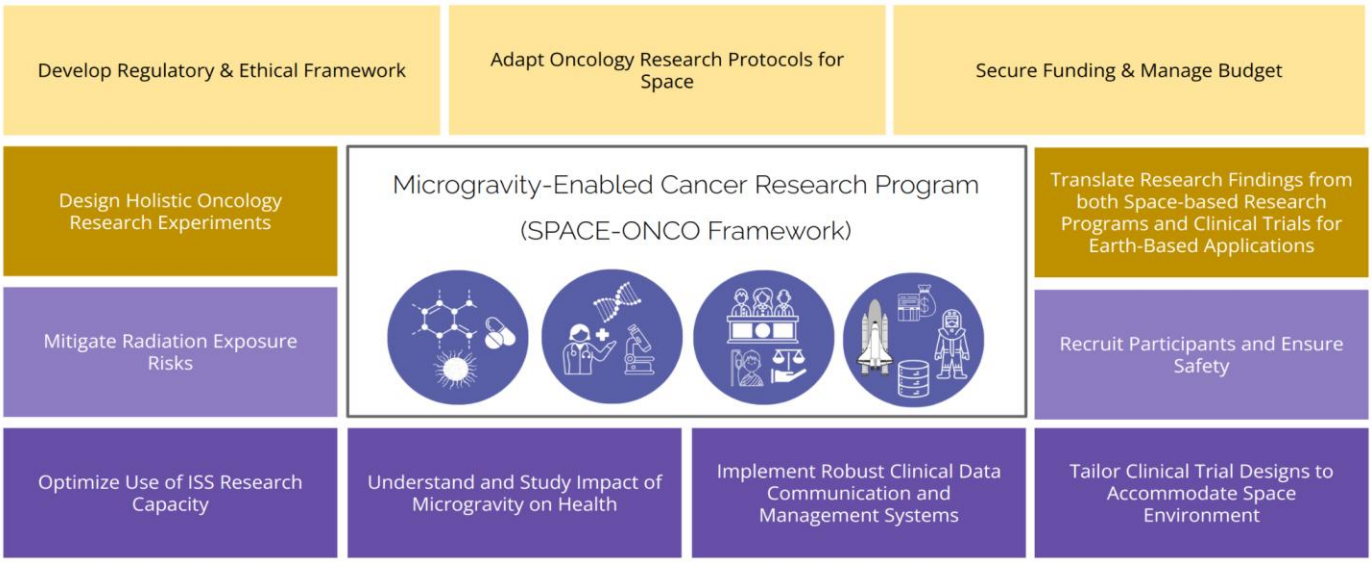

Table 3: SPACE-ONCO Framework for Responsible and Holistic Integration of Microgravity Environment in Cancer Clinical Research Programs

Pillar	**Overview**
Develop Regulatory and Ethical Framework	• Engage with space and health regulatory bodies to ensure compliance with both space research and clinical trial regulations. • Formulate ethical guidelines that specifically address patient consent and safety within the unique confines of space research. • Create a multidisciplinary oversight board including oncologists and space scientists, to review and adapt regulations and guidelines as space-based oncology research evolves.
Secure Funding and Manage Budget	• Seek collaborative funding opportunities with organizations interested in the intersection of space research and oncology, including cancer research foundations and space agencies. • Propose joint funding applications with aerospace companies focusing on health research in space, highlighting the potential for groundbreaking discoveries in oncology. • Organize a consortium of oncology research institutions to pool resources and share the financial burden of space-based research projects. • Ensure this consortium provides equitable access to space-based research programs and resources for countries across the world irrespective of their demographics, economic strength, or capabilities.
Adapt Oncology Research	• Define clinical research protocols that address the unique aspects of microgravity and radiation on cancer biology.

Protocols for Space	● Initiate pilot studies on Earth that simulate aspects of the space environment, such as radiation and microgravity, to refine protocols before space implementation. ● Establish a task force of oncologists and space scientists to continuously review and update research protocols based on the latest scientific discoveries.
Design Holistic Oncology Research Experiments	● Design oncology experiments that are not only feasible in space, but which also yield results with clear implications for Earth-based clinical practice. ● Work closely with aerospace engineers to ensure experiment hardware is optimized for space conditions while meeting clinical research standards. ● Develop a comprehensive logistics plan that includes contingencies for experiment adaptation based on real-time data and findings. ● Explore the integration of robotics and automation to streamline the challenges associated with transporting samples to and from space research labs.
Mitigate Radiation Exposure Risks	● Conduct joint research with radiation oncologists and physicists to develop innovative radiation shielding techniques relevant to both space and terrestrial oncology settings. ● Integrate advanced biomonitoring systems into research protocols to assess the real-time impact of space radiation on cellular and molecular processes. ● Share findings with the wider oncology community to enhance understanding of radiation's effects on cancer and normal tissues, potentially informing radiotherapy approaches.
Optimize Use of ISS Research Capacity	● Advocate for dedicated oncology research slots on the ISS through collaborations with space agencies, emphasizing the potential for significant advancements in cancer treatment. ● Foster partnerships with existing ISS research projects to explore synergies and shared use of equipment and facilities, maximizing the impact of each experiment. ● Organize a space oncology research network to streamline proposals, share results, and coordinate access to the ISS and other space research platforms.
Understand and Study Impact of Microgravity on Health	● Prioritize the study of microgravity's effects on tumor growth and metastasis, involving collaborations between space biologists and clinical oncologists. ● Share microgravity research findings at oncology conferences and in clinical journals, highlighting their relevance to understanding cancer progression and treatment resistance. ● Utilize Earth-based microgravity analogs (i.e., complementary studies to replicate space study results, validating their applicability to clinical oncology).

Implement Robust Clinical Data Communication and Management Systems	● Develop secure, efficient data management systems that allow for seamless integration of space-based research data into Earth-based clinical databases. ● Train research teams in the utilization of these systems to ensure high-quality data collection, analysis, and real-time decision-making. ● Share best practices and systems architecture with the broader oncology research community to facilitate the adoption of space-based oncology research methodologies.
Tailor Clinical Trial Designs to Accommodate Space Environment	● Leverage the unique environment of space to conduct cancer clinical trials that could benefit from microgravity conditions, such as novel drug delivery systems. ● Collaborate with clinical trial specialists to design space-compatible trials that can yield results directly translatable to terrestrial setups. ● Share trial designs and outcomes with the oncology community through dedicated workshops and publications focused on space research's clinical applications.
Recruit Participants and Ensure Safety	● Create clear, comprehensive recruitment and informed consent processes that address the unique aspects and risks of space-based research, ensuring participants are well-informed. ● Implement strict safety protocols, closely monitored by a dedicated team of oncologists and space medicine experts, to oversee participant well-being. ● Develop an international registry of space research participants to monitor long-term health outcomes and contribute to a broader understanding of space's impact on human health.
Translate Research Findings from Both Space-Based Research Programs and Clinical Trials for Earth-Based Applications	● Establish a dedicated translation committee and protocol to evaluate space-based research findings for their direct applicability to clinical oncology, focusing on rapid implementation. ● Ensure this protocol and committee factor the physiological stress and other impacts induced due to space-based research on cellular and molecular processes into these translations. ● Implement post-treatment health evaluation programs to study recurrence of oncology symptoms or condition (if any) and optimize the oncology research protocol developed for microgravity environment to address this challenge and minimize the recurrence of cancer in such patients. ● Foster collaborations between research institutions, hospitals, and the pharmaceutical industry to expedite the development of treatments based on space research discoveries. ● Organize annual forums that bring together space researchers and the oncology community to discuss the latest findings and their implications for cancer treatment.

By focusing on these core areas, providing a structured approach, and promoting interdisciplinary collaboration, this framework aims to make space-based oncology research a key component of future cancer clinical research programs, ensuring resilience, efficiency, and patient-centered ouctomes.

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Deepika Khedekar, MPharm, (deepika.khedekar@gmail.com) is a Centralized Clinical Lead with IQVIA Inc., Mumbai, India.

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SPECIAL FEATURE

Social Media Marketing and its Vital Role in Improving Clinical Trial Recruitment

Alen Hadzic, MIE; Justin Scott Brathwaite, MBA; Milan Sheth, MS;
Viswakanth Makutam, PharmD, MS; Sandra Warne, BS

Why is marketing and advertising often overlooked in clinical research? Patient recruitment and retention in clinical research frequently encounter obstacles, resulting in delays and increased expenses. While marketing and advertising have the potential to address these issues, they are frequently underutilized in clinical trials due to ethical concerns, regulatory constraints, and misconceptions about their role. Researchers often express concern that incorporating marketing strategies might compromise the trial's scientific integrity or conflict with regulatory standards that emphasize patient protection over promotional activities.{1} Additionally, a common misconception is that marketing pertains only to commercial products, not medical research.{2} As a result, these tools are often not seen as integral to the clinical trial process.

However, the absence of effective marketing can have real consequences. Lack of targeted outreach can hinder studies from recruiting and retaining diverse patient populations, potentially resulting in biased outcomes and limited generalizability.{3} Incorporating marketing techniques—such as digital recruitment strategies, predictive enrollment timelines, and community engagement—can improve patient diversity, streamline recruitment processes, and ultimately help researchers meet their enrollment goals.{4} Thus, to enhance the effectiveness of clinical trials, it is crucial to draw upon expertise from business strategy, management, marketing, and sales, rather than relying solely on traditional clinical practices.{5}

This article explores how marketing, when applied strategically, can bridge business strategies with clinical objectives to improve patient engagement, enhance recruitment, and ensure more timely clinical trial outcomes.

The Power of Predictive Timelines in Digital Recruitment

Clinical trial sponsors often overlook the value of digital marketing, social media, and other outreach methods in connecting with potential participants. Conventional recruitment techniques like flyers, physician referrals, and cold calls often prove to be slow, inefficient, and unreliable–which contribute to delays that adversely impact timelines and study budgets.{6} However, digital platforms like Facebook and Instagram offer social media targeting that presents a solution for any recruitment campaign.{6} Such platforms also provide a data-driven approach to calculate enrollment fulfillment timelines with quantifiable and actualized precision, thus allowing for real-time adjustments in targeting and strategy.

Social media targeting can streamline recruitment and allow for precise estimation of timelines for enrollment. Facebook and Instagram offer unparalleled targeting options that make traditional methods obsolete. Utilizing these platforms enables clinical trial recruitment teams to focus on potential participants based on demographics such as age, sex, and proximity to research site through radial targeting.

There are numerous ways to engage potential participants, allowing for multiple targeting strategies that can be tested simultaneously. Real-time metrics provide essential information on the effectiveness of various strategies in engaging the intended audience and optimizing cost-per-interest. This flexibility enables adjustments to be made in real time, allowing for budget optimization and strategic reallocation based on the relevance, cost, and overall performance of each targeted interest.

A lead-generation strategy is one of the simplest and most cost-effective targeting methods. By creating an advertisement that directs potential participants to a questionnaire tailored to the study protocol, this approach ensures only qualified individuals proceed. The questionnaire uses conditional formatting to filter and register only those who meet the criteria as potential leads.

This strategy effectively identifies interested and qualified patients residing within a defined radius of the clinical site, enhancing the recruitment process.{7}

Once a targeted digital campaign is live, it becomes possible to estimate the timeline for enrollment fulfillment by leveraging data from ad performance and pre-screening processes. Social media platforms provide real-time metrics that reveal how many individuals are clicking on ads, completing pre-screening questionnaires, registering as leads, and expressing interest in the study. As more leads are registered within a campaign, the cost per lead conversion generally decreases, and the overall performance becomes more efficient. This unique aspect of online advertising ensures that, for successful campaigns, costs typically decrease the longer the campaign runs.

When leads begin registering, native advertising algorithms optimize by targeting similar profiles to those already qualified, resulting in an increasingly refined “cost per lead.” This cost often decreases over time as the algorithm gains insights into the ideal patient profile. Evaluating these data points allows for the prediction of potential participants entering the recruitment funnel and estimation of both the timeline and necessary costs to generate a specified number of prescreened leads. Once there are data available on how leads transition from the digital ad stage to pre-screening calls, it becomes possible to develop an enrollment conversion model for more precise projections.

For instance, if it is known that 80% of the pre-screened leads generated through social media result in successful pre-screening calls, 60% of these leads book appointments to visit the research site, 70% of those actually attend the appointment, and 60% of attendees ultimately enroll in the study, you can accurately determine how many pre-screened leads are needed to enroll 50 patients. Based on these conversion rates, to achieve 50 enrolled patients, you would need approximately 248 prescreened leads.

$$\text{Number of Pre-screened Leads Required} = \frac{\text{Target Number of Enrolled Patients}}{\text{Conversion Rate 1} \times \text{Conversion Rate 2} \times \text{Conversion Rate 3} \times \text{Conversion Rate 4}}$$

Target Number of Enrolled Patients: The number of patients you want to enroll.

Conversion Rate 1: The percentage of pre-screened leads resulting in successful pre-screening calls.

Conversion Rate 2: The percentage of leads who book appointments.

Conversion Rate 3: The percentage of booked appointments that actually attend.

Conversion Rate 4: The percentage of attendees who ultimately enroll.

Additionally, if the cost per lead is $50, the total cost to generate these 248 leads would be $12,400. With this investment, the 50 required patients can be enrolled, resulting in a cost per enrolled patient of $248. By knowing these key conversion metrics and costs, one can precisely predict how many leads are necessary, the total budget required, and the cost per patient for enrollment, allowing for better planning and allocation of resources in clinical trial recruitment.

Digital advertising also allows for continuous optimization throughout the recruitment process, which is critical for staying on track with enrollment goals. Two key re-optimization points can help refine the process.

Re-Optimization Point #1: Prescreening Adjustments

After initial calls, if it is found that many participants are disqualified due to missing medical history or incorrect criteria, you can adjust your questionnaires or messaging to attract more suitable candidates. This prevents wasted time and money on advertising for unqualified leads and helps keep the recruitment timeline on track. You simply need to turn the advertisement off, edit it, and turn on the new one. This process is live and immediate, with no need to wait.

Re-Optimization Point #2: Onsite Screening Adjustments

If participants are frequently disqualified during onsite screenings, feedback from the clinical team can help refine your targeting. For instance, adjusting geographic targeting or including additional medical history questions in the digital ads can help reduce disqualifications, ensuring that only qualified candidates move forward.

One of the most powerful aspects of social media targeting in clinical trial recruitment is the ability to predict the diversity profile of your participant population with remarkable accuracy. This is relevant because diversifying clinical trial participants is one of the industry's biggest challenges that requires a multifaceted approach, including marketing and advertising.{8}

By understanding the demographics of the disease, user base of platforms like Facebook and Instagram, and those of the targeted geographic, you can forecast the diversity profile of your enrolled participants. No other method offers this level of precision.

$$E_r = T_p \times D_c \times D_d \times U_p$$

Explanation of Terms:

- E_r: Expected number of participants of a certain race or ethnicity in the target population.
- T_p: Total population size for the specific geographic region (e.g., total population of Houston).
- D_c: Demographic percentage of the target race or ethnicity within the city (e.g., percentage of Hispanic or Latino individuals in Houston).
- D_d: Disease-specific demographic percentage for the targeted race or ethnicity (e.g., the proportion of Hispanic individuals affected by the disease in question).
- U_p: Proportion of users of the targeted race or ethnicity on the advertising platform being used (e.g., percentage of Hispanic individuals using Facebook or Instagram).

For example, if you're recruiting for a diabetes trial, you already know that certain populations are disproportionately affected by the disease. In the U.S., studies show higher prevalence rates among Hispanic, African American, and Native American communities.{9} Urban areas with diverse populations, for instance, allow you to adjust your ad radius and messaging to ensure that clinical teams not only reach a broad spectrum of participants, but also recruit from a demographic pool that reflects the diversity necessary for real-world trial outcomes. The interaction between the advertisement and the diversity of the population within the set radial target cannot be replicated by any other method to the authors' knowledge.

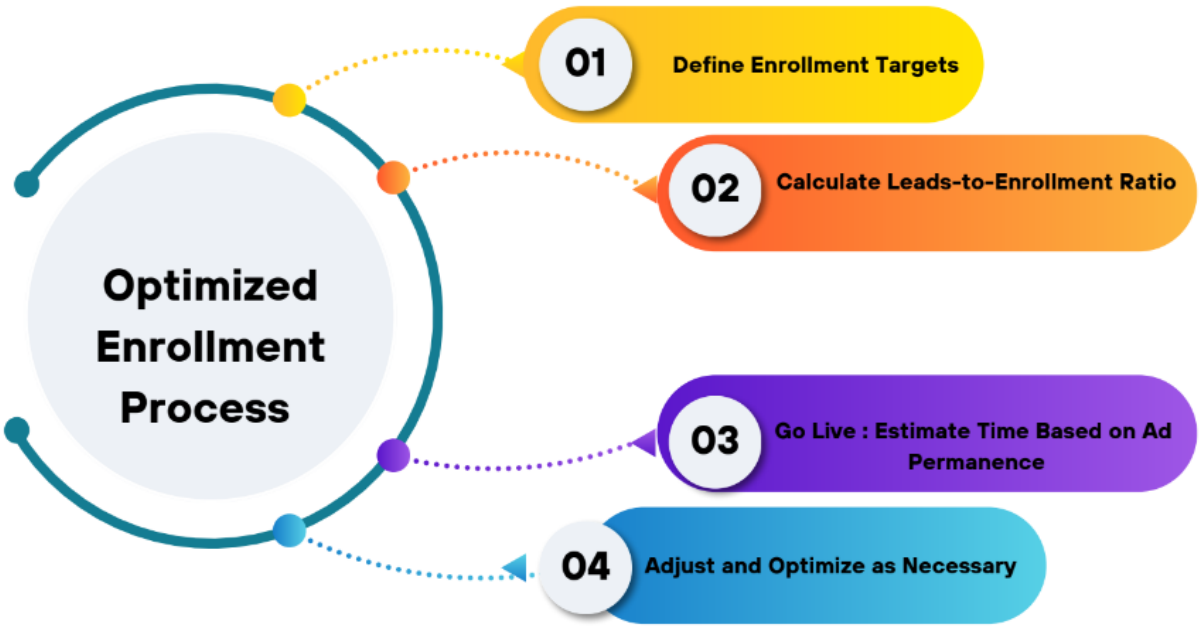
In addition, geographic limitations present significant barriers to the enrollment of diverse and underrepresented populations in clinical trials, as these groups may not have easy access to trial

sites.{10} However, targeted marketing and advertising strategies offer a possible solution by reaching and engaging individuals from specific backgrounds who live near the trial locations.

Thus, by combining disease state demographics, social media platform user data, and regional demographic information, you can predict and achieve a representative participant pool. This level of control over your diversity profile is unique to digital recruitment methods and cannot be replicated with traditional approaches.

Crafting Predictive Enrollment in Four Steps

Once you've collected data on your conversion rates, lead generation rates, and disqualification rates, you can build a predictive timeline for enrollment fulfillment in four steps.



Step 1: Define Enrollment Targets

Start by determining how many enrolled participants are needed to complete the study. Let's take the previous case of 50 enrolled patients.

Step 2: Calculate Lead-to-Enrollment Ratio

Next, use historical data to calculate how many leads are required for each enrollment. Based on the previous example, 80% of pre-screened leads result in successful pre-screening calls, 60% of those book appointments, 70% of those attend the appointment, and 60% of attendees enroll. With these conversion rates, you would need approximately 248 pre-screened leads to enroll 50 patients.

Step 3: Go Live

Here, you estimate time based on ad performance. Review the ad campaign's daily performance to determine how quickly these 248 leads can be generated. If the ad campaign generates 10 leads per day, it would take about 25 days to gather the 248 required leads to meet the enrollment goal.

Step 4: Adjust and Optimize as Necessary

Finally, account for potential delays in the process, such as the need to re-optimize the campaign or adjust prescreening questions based on real-time feedback. This could add a few extra days to the initial timeline, but these adjustments will improve participant quality and ensure higher enrollment rates. Conversely, by optimizing the ads, a few days may even be removed from your timeline. Factoring in these delays and incorporating important feedback will give a more accurate and optimized timeline for achieving recruitment goals.

By following these steps, one can more effectively plan and execute clinical trial recruitment, ensuring that enrollment targets are met within a realistic timeframe and budget.

Concluding Remarks

In summary, social media targeting and data-driven recruitment have revolutionized the way clinical trials are conducted, offering precision, inclusivity, and efficiency that traditional methods simply cannot provide. Leveraging real-time feedback loops and continuously refining the recruitment process can allow for greater accuracy when predicting enrollment fulfillment timelines, helping to ensure that a study stays on track.

Credits

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Alen Hadzic, MIE, is CEO of Clinical Trial Scan.

Justin Scott Brathwaite, MBA, is a Site Readiness and Regulatory Senior Specialist.

Milan Sheth, MS, is a Clinical Research Coordinator.

Viswakanth Makutam, PharmD, MS, is a Clinical Research Quality Associate.

Sandra Warne, BS, is a Clinical Project Manager.

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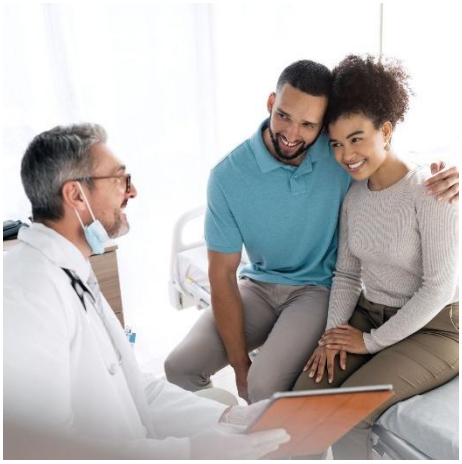
RECRUITMENT & RETENTION

From Participants to Partners: An Urgent Call to Transform Patient Engagement in Clinical Research

Jena Daniels



Engaging patients in clinical research has long been seen as important, yet it has been slow to evolve. For years, clinical research has largely been designed with the assumption that participants should conform to rigid protocols, often neglecting the voices of the very people who will be impacted most by the outcomes. A 2018 study, published in *Research Involvement and Engagement*, estimated that far less than 1% of clinical trials meaningfully and actively engage patients in any part of the research process.

While too many clinical trials are centered around the convenience of researchers and sponsors rather than patients' needs and preferences, this paradigm is shifting—thanks, in part, to the U.S. Food and Drug Administration's (FDA's) June 2024 draft guidance on submitting Diversity Action Plans, which requires sponsors of certain clinical studies to submit plans that detail the steps sponsors will take to include underrepresented populations in their trials, addressing factors such as race, ethnicity, age, and sex. The FDA also highlighted the importance of early patient engagement in trial design and planning, illuminating the significant value of patient advisory boards.

Additionally, patient advocacy networks are growing and getting louder, incorporating the voices of patients into clinical trials and developing unique ways to improve patient participation and adherence.

Karen Utley, whose daughter Samantha was born with a rare neurodevelopmental condition called CDKL5 Deficiency Disorder, speaks directly to the benefits such networks offer to trial participants: “Both mine and my daughter’s experiences were carefully considered during the decentralized trial she participated in,” said Utley. “And these learnings were incorporated to enhance processes and technologies to improve the trial experience for both my daughter and me as her caregiver. I found the experience to be immensely rewarding—a genuine gift of personal experience for the benefit of others.”

Beyond just their participation, patients are a valuable resource for researchers. Now, thanks to such efforts, their voices are being heard more clearly.

“Patients love to get involved in research and have their stories heard,” said Wes Michael, founder and CEO of Rare Patient Voice, an organization that helps to amplify the voices of patients and caregivers. “Patients have valuable feedback to offer so sponsors need to get them involved early and often and not just pay lip service to them.”

Amplifying Patient Voices

Patient advocacy networks, as well as the rising prevalence of decentralized trials and remote patient monitoring technologies, are providing patients with more flexibility and convenience. These developments are reducing some of the logistical burdens that have historically made participation in clinical trials difficult. It’s a step in the right direction, but more work must be done to create a genuinely patient-centric research environment.

The integration of patient perspectives earlier in the clinical trial process—well before recruitment—is key. One way to do this is by utilizing upfront study simulations that involve patients, caregivers, and research staff in mock trials to work through protocols as if the study is already underway. This allows participants to identify issues they might face in a real trial, such as challenges with recruitment materials, consent forms, and logistical aspects including travel and compensation. By proactively involving patients early, sponsors can refine the trial design and reduce the likelihood of patient dropouts or delays due to unforeseen obstacles downstream. The extra time up front can save time and money in the long run, as well as result in better outcomes.

This approach can also provide patients with a better understanding of the tools and technologies they are being asked to use, leading to better adherence. For example, in a recent cancer trial, patients were asked to use a wearable device with a single-size armband and provide feedback. Since these patients were going through chemotherapy, they experienced extreme weight fluctuation, suggesting an adjustable armband was more appropriate. The patients also reported that the device wasn't easy to clean, its battery life was insufficient, and it looked too much like a medical device. While these patients fully understood the value of the device, they were less likely to adhere to the protocol if these issues went unaddressed. Once this information was shared with the sponsor, it found a better solution that undoubtably led to better adherence. This kind of real-world feedback early in a trial when adjustments can still be made can only come from patients who are actively participating from the start.

Finally, the clinical research enterprise must continue to take a broader view of patient populations when designing trials. Rare diseases, chronic conditions, and diverse demographics often face unique challenges in accessing research. These challenges require nuanced approaches that acknowledge the lived experiences of people. By embracing diversity and including a wide range of individuals in the design of trials, researchers can ensure that clinical studies reflect the varied needs of those they aim to serve.

Overcoming the Remaining Hurdles

Despite the clear benefits of a patient-centric approach, significant hurdles remain. Building and sustaining a robust patient engagement initiative not only requires commitment but also resources. Collecting patient feedback through surveys, focus groups, or simulations takes time and money, and many trial sponsors are hesitant to allocate those resources upfront. Further, with the increasing complexity of trials and the diversity of therapeutic areas, the convenience of a one-size-fits-all solution for patient engagement is rare.

While wearables and remote monitoring technologies can enhance patient adherence and participation in some studies, they are not universally applicable. Certain patient populations, such as the elderly or those with limited access to technology, may struggle to engage with digital tools. Moreover, studies involving complex drug regimens or invasive procedures might

not easily lend themselves to decentralized formats. These disparities between trials require a flexible, adaptable approach to patient engagement, which can be difficult to scale.

Additionally, the regulatory framework governing clinical trials presents a significant challenge. While the FDA and other agencies have made strides in embracing innovation, headwinds persist around the approval and standardization of new engagement tools and methodologies. Flexibility and collaboration between sponsors, regulators, and patient groups will be essential for overcoming these barriers.

Collaboration is Key

One of the most powerful drivers of change in clinical research is the collaboration between stakeholders: research sponsors, trial sites, technology companies, patient advocacy groups, and regulatory bodies. Each has a unique role to play in advancing patient engagement. However, these groups often operate in silos. To break down these silos and achieve meaningful change, there must be a shift toward collaborative partnerships.

The inclusion of research sites in this conversation is key—and too often, the missing piece to this puzzle. Sites are on the front lines of patient recruitment and retention and are uniquely positioned to provide practical feedback about the realities of implementing patient engagement strategies. Sites can highlight issues such as staff training, protocol complexity, and patient preferences that might otherwise be overlooked by sponsors or technology developers. Incorporating the site's perspective into early-stage planning will lead to smoother trial operations and better patient experiences.

Similarly, patient advocacy groups play an important role in educating patients about clinical trials, addressing concerns, and providing support throughout the process. These groups are often the best advocates for ensuring that trials are designed with the patient's needs in mind, rather than just research tools. Involving patient advocates from the earliest stages of study design will allow researchers to identify potential barriers to participation, address misconceptions, and ensure that the trial is responsive to patient concerns.

Prioritizing Patient Engagement

To truly transform patient engagement in clinical research it must be integrated into every phase of trial design and implementation. Too often the industry treats patient engagement as an afterthought—a vague notion that can be "tacked on" at the end of protocol development or implemented sporadically through post-trial surveys. However, as Michael at Rare Patient Voice pointed out, this is no longer acceptable if we want to improve both the experience and the outcomes for patients.

"Patient participation should be part of a trial's standard procedure up front," Michael said. "You don't want to have to go backwards, so patients need to be involved from the beginning, before a trial goes too far. Today with modern technology and expanding regulatory frameworks for patient participation, it's easier than ever to engage patients if you make the effort."

Patients are experts in their own experiences, and their insights can be instrumental in shaping successful trial protocols, study design, and operational strategies. By embedding patient engagement into every stage of the trial, researchers and sponsors will ensure that patient needs are met from the very first step to the final follow-up.

Open-ended questions should replace simple yes-or-no surveys to better understand the complexities of the patient experience. These dialogues invite patients to share concerns, preferences, and ideas for improvement that may not be captured through basic quantitative measures. Asking questions like "What would make participation in this trial easier for you?" will foster meaningful feedback that can inform trial adjustments.

Upfront study simulations—where patients, caregivers, and trial staff work through study protocols together—are a crucial tool for gathering this feedback. These simulations allow researchers to anticipate challenges and mitigate them before the trial is underway, saving time and resources in the long run. With patient engagement built into the trial's design phase, sponsors can avoid costly delays, dropout rates, and dissatisfaction that can arise from an inadequate understanding of patient needs.

The Future is Now

Patient engagement is no longer a "nice-to-have." It is a necessity for achieving meaningful, reproducible outcomes in clinical research. By actively collaborating with patients, sites, advocacy groups, and regulators, we can create trials that not only meet scientific goals but also respect the lives of those participating in them. Much work needs to be done, but by embracing collaboration and committing to patient-centered practices, stakeholders can create a clinical research environment that prioritizes not just the success of the trial but the experience of the people who make that success possible.

"People understand that clinical trials are important, and they want to participate in them, but they also can't turn their lives upside down to do so," Michael concluded. "People have to find a way to work the trial into their lives, and sponsors need to meet them where they are to help make that happen."

Jena Daniels (jena@medable.com) is a manager with 12 years of experience in enabling digital solutions within academic and industry-sponsored clinical trials. As a 2021 *PharmaVoice* 100 recipient, Best Decentralized Clinical Trial Businesswoman of 2022, and Top 50 Women Leaders of San Francisco for 2023, she is most known for establishing Medable's Patient Caregiver Network, which seeks to engage and empower expert patient and caregiver advocates to assist product development, refine study workflows, and tailor the overall trial experience. She has coauthored more than 30 peer-reviewed publications focusing on how to leverage machine learning, artificial intelligence, and remote patient monitoring to triage, diagnose, and provide early intervention for children with autism spectrum disorder.

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SITES & SPONSORS

Complex Science vs. Trial Efficiency: Do Clinical Leaders Have to Choose?

Manny Vazquez, CCDM

Every year, clinical trials reach new levels of innovation. From the explosion of biomarker use in precision medicine, such as Genomics England's 100,000 Genomes Project that supports patients affected by rare diseases and cancer,{1} to the expanded use of real-world and digital device data.{2} The industry continues to evolve and increase in complexity.

A large-scale analysis of protocols and other data sources from more than 16,000 studies found that clinical trials across all the indications evaluated are becoming more complex.{3} Complex science often undermines operational efficiency. Over the past seven years, the average number of amendments per protocol increased by 60%, while the typical time to implement an amendment has almost tripled.{4}

Applying simple adjustments to a gene therapy trial, such as expanding the number of participants, can make or break a study by causing costs to escalate sharply. Over-hyped technologies (like decentralized clinical trial solutions) haven't delivered on their potential, leading to lower operational efficiency rather than sought-after improvements. To avoid a tug-of-war between scientific rigor and operational efficiency, we must prioritize the user and data journeys of sites, patients, and sponsors. Simpler everyday experiences and connected data are the basis for delivering the trials we need rather than what the technology allows.

Unblocking Barriers for Sites

Sites have been voicing their concerns for years about the growing technology burden. Common pain points include navigating more than 15 portals per study, organizing password changes every six to eight weeks, and accommodating each sponsor's unique definitions, standards, and database setups. Not only do disconnected tools take site staff away from patient care and absorb their time in training, but they also undermine data quality by forcing repeated data entry. Viviënne van de Walle, medical director and founder of PT&R, likens the site experience to being stuck "in a really bad escape room."

Thankfully, we are turning the corner as an industry on delivering better site support. The aspiration of fewer systems will reduce the site administrative burden and positively affect patient recruitment and engagement. Hopefully, a better patient experience would widen access to life-enhancing treatments, particularly in rare diseases.

Reflecting on her experiences and needs as a rare disease patient, Helen Shaw, co-founder of the virtual site VCTC, observes: "I see how hard it is to take part in a clinical trial. But patients do want that opportunity to be offered—something that they wouldn't get in their standard care—whether additional MRIs or new medicines."

New Dialogue Needed

Simplifying at a time when science is becoming more complex can feel counterintuitive. However, when sites and sponsors shed the legacy systems holding them back, they can finally determine which processes they need to run the trials they want.

Sponsors and contract research organizations increasingly focus on alleviating sites' concerns when introducing new systems, even when those systems are ultimately designed to simplify processes. This involves aligning on shared objectives and working together closely.

All sites are unique, bringing varying levels of technological experience. A "one-size-fits-all" interaction style is one of the most cited challenges sites face in their partnerships with sponsors.{5} One clinical trial management software leader notes the impact of this mindset on

sites: “Every site can have a different starting point or place of comfort when it comes to implementing technology. The ideal is to remove some administrative burden, but sites can have mixed feelings about new technology.”

They add, “Simplifying is a big win. It shows that we’re moving to a mindset of fixing problems instead of just adding more functionality.”

Connected Data as the Pillar for Smart Automation

With cell and gene therapies accounting for a more significant share of the drug development pipeline,{6} we can expect a changing research profile: more studies with relatively small patient populations and rolling regulatory approvals, leading (hopefully) to compressed timelines. Yet, paradoxically, even a study of 30 to 40 patients can still ingest and generate huge volumes of relevant data (e.g., DNA-related, molecular information), because each person is treated as an individual rather than a study average. These data are then used to develop highly personalized and effective treatments.

As we transition into a non-electronic data capture-centric world, we will need more flexible data management so that sponsors can drive science forward while delivering complex studies efficiently. Rather than a one-size-fits-all approach, systems and technology must be able to support many protocols with enough flexibility for niche trial requirements.

Artificial intelligence (AI) and machine learning (ML) will have an essential role in transforming raw data so that they are clean and usable: Andy Cooper, CEO of CluePoints, a risk tracking and analytics provider, observes that ML is already taking the noise out of edit checks, for example.

AI and ML are not yet ready to solve all our data challenges. In the meantime, automation can generate value at multiple points during clinical data management. Commenting on its impact within their organization, a senior data science leader at a top global healthcare company says: “The growing number and complexity of trials means that we should be working at scale, not just in production and facilities but also in our clinical setup. These functions must be able to work together and to scale.”

Once all study data are connected, advances in clinical trial efficiency become feasible. For instance, automation is one of the main four pillars that the author's healthcare company is optimizing for growth. Its data science leader explains the importance of another pillar—a strong data foundation—to their team's success: "It's common for data infrastructure set up to be horribly patchworked. You can't introduce meaningful end-to-end automation on poor data and without seamless processes. We need to get rid of the patchwork."

Complexity Meets Efficiency

The time is right to interrogate and leave behind old habits, including excessive data collecting, cleaning, and querying. Too much time, money, and effort are spent today on the latest technology, generating surplus data—all in the name of "innovation." A pragmatic, no-nonsense approach focuses on the value first to innovate sustainably. Regulators are already moving in the right direction by encouraging us to apply a risk-based approach to trial design and focus on the data and processes that safeguard trial quality.{7}

If we aim to bring all data together with the right processes and trained people, clinical teams can focus on the science, while data management can help systematically find patterns within (and across) studies. The benefits of a centralized approach go beyond operational efficiency and, over time, could change the economics of clinical trials. Having medical, investigators, and site coordinators on one connected platform will make it easier to meet ambitious patient recruitment timelines and tackle emerging drug development challenges sooner.

We must end the tug-of-war between scientific rigor and trial efficiency. By prioritizing simpler everyday experiences for sites, clean and connected data, and a pragmatic approach to innovation, we will advance science together.

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Manny Vazquez, CCDM, Veeva Clinical Data Strategy, has spent almost 20 years in clinical data management, starting in a small oncology biotech before moving to the CRO space for 10 years. In early 2022, he joined Veeva Systems to support strategy for the Clinical Data suite of applications. He can be reached at manny.vazquez@veeva.com.

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PRESCRIPTIONS FOR BUSINESS

Quality Management Insights from Contract Manufacturing Organizations

Londa Ritchey

The pharmaceutical industry and the creation of new drugs is expected to continue growing at a steady rate over the next decade.{1} To keep up with this growth, many companies are turning to contract manufacturing organizations (CMOs) to assist with product manufacturing. A key benefit CMOs provide is to maintain a manufacturing footprint, and the skilled talent needed to support product manufacturing. This reduces the need for the product owners to carry these costs or delay progress of their drug development until these resources are directly available. Often CMOs can also assist in bringing products to market more quickly by providing assistance on process and analytical development aspects. However, as with most things, the benefits of CMO use also come with some risks.

A CMO can be an important party in the product supply channel. The product sponsor is expected to ensure the CMO is part of a robust supply channel that minimizes the risk to patient safety and product supply.{2} To meet this requirement, the product sponsor establishes and maintains a diligent quality management strategy for oversight of the CMO. Outsourcing the manufacturing activity does not alleviate the product sponsor from responsibility for the quality and safety of the drug product. This holds true for product manufacturing whenever the product is intended to be consumed by a patient and involves clinical trials and post-market approval expectations. As outsourcing has become a more common practice, regulatory authorities have evolved their expectations for contract manufacturing oversight.

Regulatory Expectations

Regulatory authorities worldwide understand the need for use of contract manufacturers. This is evident in the guidelines and directives that directly address the expectations for quality oversight of a CMO. For example, the European Commission devotes the entire Good Manufacturing Practice (GMP) Chapter 7 to Outsourced Activities and outlines the activities of Contract Giver (Product Sponsor) and Contract Acceptor (CMO).{3} The International Council for Harmonization's ICH Q10 contains expectations for oversight of outsourced activities.{4} Additionally, the ICH Q9(R1) updates include the expectation for integrating quality risk management (QRM) activities into industry operations. That includes the application of QRM to oversight of outsourced activities.{5}

The regulatory authorities have also reiterated that outsourcing does not mean the product sponsor can outsource responsibility for the quality and safety of the drug. Here are two examples of statements the U.S. Food and Drug Administration (FDA) has made in Warning Letters related to use of contract manufacturing and responsibilities:

- **"Responsibilities as a Contractor**
  FDA is aware that many drug manufacturers use independent contractors such as production facilities, …FDA regards contractors as extensions of the manufacturer. You are responsible for the quality of drugs you produce as a contract facility regardless of agreements in place with product owners."{2}
- **"Use of Contract Manufacturers**
  FDA is aware that many drug manufacturers use independent contractors such as production facilities, …FDA regards contractors as extensions of the manufacturer. You are responsible for the quality of your drugs regardless of agreements in place with your contract facilities."{6}

More recently, a Warning Letter was issued to a sponsor company utilizing a CMO which had itself received a Warning Letter. The company continued to distribute drug products from their CMO after the CMO received the warning Letter. Specifically, the Warning Letter captures the following points:

- "You also failed to have adequate supplier qualification procedures to ensure that the drug products received … were manufactured in compliance with CGMP prior to being distributed."{7}
- "You received and delivered into interstate commerce … products that were found to be adulterated ..."{7}

These statements represent the current thinking of regulators as regards the responsibility for ensuring the quality of the drug products manufactured at CMOs on behalf of product sponsors. It is clear that this is a shared responsibility and both parties are responsible for ensuring drug products are produced under current GMP (cGMP). Both parties must have a focus on patient safety.

Importance of Proper Qualification and Oversight

The key to avoiding negative regulatory actions when utilizing a CMO is in the initial qualification activities and ongoing quality management engagement with the CMO. Here are some recommendations based on best practices encountered over years of personal experience:

- The CMO should be qualified through an onsite audit to ensure the facility and staff are capable of manufacturing, testing, storing, and distributing product in a manner consistent with cGMP. This initial qualification should also consider the capabilities of the CMO to control contamination, including cross-contamination from the other products being manufactured in this the same facility. The initial qualification activity completed prior to agreements to initiate work with the CMO.
- The initial qualification audit is based on a sample of activities available for review during the agreed time. This may not allow enough time to capture all aspects of the controls needed for ongoing compliance. Therefore, it is also important to have ongoing quality management engagement with the CMO. The expectations for quality performance, responsibilities, and communications should be captured in a quality agreement between the CMO and product sponsor. It is essential that each party conduct a comprehensive review to ensure the agreement captures the specifics needed for the product under consideration. Once the agreement is in place, ongoing engagement with

the CMO is needed to ensure the product sponsor's requirements are fulfilled as expected. The expected communication plan and governance should be outlined and agreed in the quality agreement.

It is common for commercial product sponsors to have formal qualification and quality oversight plans with CMOs already in place prior to commercialization. It is less common for those product sponsors entering clinical trials. According to FDA's guideline for cGMP for Phase I investigational drugs and European Commissions GMP Annex 13 covering investigational drugs, even at the clinical Phase I stage these products must be produced under a state of control that ensures these products meet the safety, purity, and identity requirements needed for use in patients.{8,9}

Even in the early phases of clinical trials, it is important that product sponsors must have quality and maintain quality oversight engagement with the CMO. Unfortunately, failure in this area could result in the product application not being approved due to the CMO site failing the GMP inspection.{10}

This is not something to be learned at the application stage. Starting early with qualification of any facilities performing manufacturing on behalf of the product sponsor is essential along with continued oversight to stay on track.

Disclaimer

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Londa Ritchey is Quality Director at PharmaLex (a Cencora Company).

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TRIALS & TECHNOLOGY

Spotlight on Artificial Intelligence's Impact on Healthcare

Dev Nag

Artificial intelligence (AI) is transforming healthcare, promising improved patient outcomes, streamlined drug development, and enhanced diagnostics. Its applications in personalized medicine, medical image analysis, and remote patient monitoring are particularly noteworthy. Beyond these advancements, AI is revolutionizing clinical trials and medical device development—areas that clinical research professionals may not yet fully appreciate.

While much of the public discourse around AI focuses on its theoretical risks or future potential, the technology already has a tangible, measurable impact on healthcare today. From identifying new drug candidates in record time to interpreting medical images with improving accuracy, AI is reshaping how healthcare providers approach treatment, diagnosis, and patient management. This real-time integration of AI into clinical settings isn't just improving care—it's fundamentally changing how we understand and practice medicine.

Personalized Medicine: Tailoring Treatments to Individual Needs

AI's capacity to analyze extensive patient data enables the creation of highly personalized treatment plans. By examining genetic profiles, medical histories, and lifestyle factors, AI could recommend therapies tailored to individual patients, moving beyond the "one size fits all" approach. For example, AI-driven models have been used to predict patient responses to various cancer treatments, enhancing the effectiveness of therapies.

Moreover, AI's integrative analysis allows for the continuous refinement of treatment strategies as patients' conditions evolve, ensuring care remains responsive and individualized. This approach has shown promise in managing chronic diseases, where personalized interventions can significantly improve patient outcomes.

Speeding Up Drug Discovery

Traditional drug discovery is a lengthy and costly endeavor. AI expedites this process by efficiently analyzing molecular structures and predicting potential drug candidates. Machine learning algorithms can process vast datasets to identify promising compounds, reducing both time and expense in drug development. Notably, AI has been instrumental in identifying potential drug candidates for diseases such as COVID-19, showcasing its capability to accelerate therapeutic discoveries during critical times.

The integration of AI has also led to the development of novel small molecule therapeutics, with startups leveraging AI to advance drug discovery pipelines. AI-driven platforms allow researchers to explore chemical spaces that were previously too vast to analyze manually, including simulating how small molecules interact with biological targets, predicting their therapeutic potential, and identifying any likely side effects. This significantly accelerates the identification of promising drug candidates, particularly in areas like oncology and rare diseases, where traditional methods may have failed.

Startups such as Insilico Medicine and Atomwise are at the forefront of this revolution, using AI to predict the efficacy of compounds before they even reach the lab for physical testing. Doing so reduces the time and cost of drug development, which traditionally could take a decade and millions of dollars. The ability to quickly generate and test hypotheses about molecular interactions has led to breakthroughs in the discovery of small molecules that can target previously "undruggable" proteins, opening up new possibilities for treating diseases that were once deemed untreatable.

Remote Patient Monitoring: A Proactive Approach to Healthcare

AI-powered devices enable real-time monitoring of patients' vital signs, facilitating early detection of potential health issues. Wearable technologies, for example, can continuously monitor heart rhythms to detect irregularities, allowing for timely medical interventions and reducing hospital visits. Studies have demonstrated that remote monitoring can significantly decrease hospitalization rates and healthcare costs, highlighting AI's role in proactive patient care.

Furthermore, AI's predictive analytics can forecast health trends, enabling adjustments in care plans before issues escalate, thus enhancing patient outcomes and optimizing resource utilization. Predictive analytics is particularly valuable in managing chronic diseases like diabetes, heart disease, and COPD, where small changes in a patient's vital signs or behavior can indicate a need for intervention.

For example, AI-powered tools can analyze daily glucose readings in diabetic patients to forecast potential spikes, allowing healthcare providers to adjust insulin dosages before critical levels are reached. This not only prevents emergencies but also enhances patients' quality of life by keeping their conditions under better control. Additionally, AI-driven forecasting helps healthcare systems allocate resources more efficiently, ensuring that the right level of care is provided at the right time, reducing unnecessary hospital stays, and optimizing the use of medical personnel and equipment.

AI in Clinical Trials: An Overlooked Revolution

AI's potential to transform clinical trials is substantial yet often underappreciated. By analyzing genetic, social, and environmental factors, AI can identify suitable patient populations for trials, predict participant responses to treatments, and thereby enhance studies' efficiency and success rates. Pharmaceutical companies are increasingly adopting AI to design and optimize clinical trials, leading to more effective and targeted therapies.

Moreover, AI's data analysis capabilities streamline the collection and interpretation of trial data, reducing errors and providing real-time insights. This facilitates more adaptive clinical trials, allowing for protocol adjustments as new data emerges, ultimately improving outcomes.

Next Steps for AI in Healthcare

The integration of AI into healthcare is poised to expand, further influencing personalized medicine, diagnostics, and patient monitoring. The life-changing potential of AI in redesigning clinical trials and expediting the development of new treatments is particularly exciting.

To stay at the forefront, clinical research professionals must embrace AI's evolving role in trial design and medical device development. Leveraging AI will lead to more accurate, efficient, and transparent clinical trials, setting new standards for innovation in healthcare.

Dev Nag is Founder and CEO of QueryPal and was previously CTO/Founder at Wavefront and a Senior Engineer at Google. He previously served as the Manager of Business Operations Strategy at PayPal and launched eBay's private-label credit line in association with GE Financial. He also previously co-founded and was CTO of Xiket, an online healthcare portal for caretakers to manage the product and service needs of their dependents.

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