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Precision Cuts Both Ways: Focusing Self-Reflection, Empathy, and Communication on Clinical Research's Technologically Demanding Landscape

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Association of Clinical Research Professionals

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

Director, Advertising & Exhibition Sales
Tammy B. Myers, CEM
tammy.myers@acrpnet.org
(703) 254-8112

Media Kit
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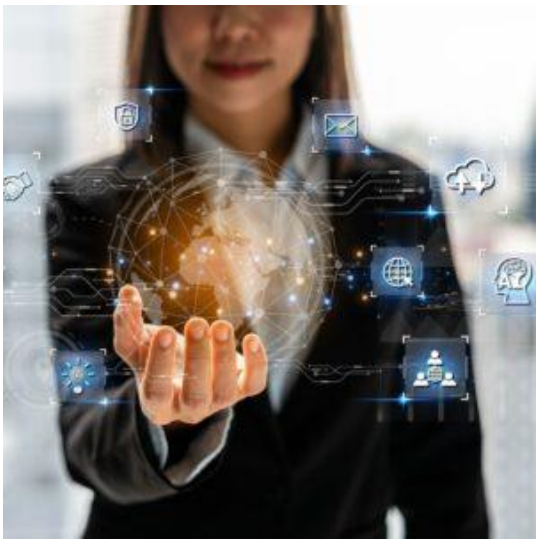
Embracing the Future: Opportunities and Challenges of AI Integration in Healthcare

Shriya Das, MS, MSc



The rapid evolution of artificial intelligence (AI) in healthcare promises transformative impacts across various medical domains. Notably, AI excels in harnessing vast amounts of data for a variety of purposes, and this article emphasizes the significant potential of AI in achieving "precision medicine" among those purposes. However, the surge in AI technologies comes with notable challenges, including concerns over patient data privacy, the unpredictability of AI in clinical scenarios, and potential breaches linked with extensive data sharing. The future integration of AI demands a multifaceted approach—from regulating data management and ensuring transparency to reshaping medical education to better incorporate technology understanding. In this context, stakeholder perspectives and prioritizing human-led decisions stand out as pivotal. To truly harness the benefits of AI in medicine, there's an imperative to navigate these challenges and embrace a holistic, informed approach.

Background

AI in healthcare is advancing rapidly with numerous applications across medical domains. Studies highlight AI's role in interpreting radiographs, detecting cancers from mammograms to skin lesions, analyzing CT scans, identifying brain tumors, and predicting Alzheimer's disease from PET scans. AI assists in areas like pathology, retinal imaging, arrhythmia detection, hyperkalaemia identification from ECGs, colonoscopy polyp detection, genomics, facial genetic condition identification, and optimizing *in vitro* fertilization success. Using vast electronic health record (EHR) data, AI extracts critical clinical information, predicts patient risks, improves diagnostic evaluations, anticipates health deteriorations, enhances decision-making, and streamlines clinical workflows. This includes tasks like analyzing doctor-patient interactions and predicting hospital appointment attendance.{1}

Clinical care is multifaceted, necessitating a strategic use of AI to elevate care quality and benefit both patients and providers. Operationally, AI in clinical management should address challenges in care logistics, data handling, and algorithm oversight. Broader societal efforts are essential for crafting ethical, regulatory, and payment structures. A holistic, informed approach to AI will foster a dynamic environment for its integration into clinical practice.{2}

Meanwhile, the future of AI in medicine hinges on the ability to protect the privacy and security of health data. With the rising concerns about hacking and data leaks, there's a pressing demand for algorithms that safeguard a patient's medical information.{3}

AI is the Future

AI excels in gathering and merging vast and diverse data to individualize medicine and constantly evolve from it. Big data also has a role to play. Complementary technologies such as "smart wearables" have the potential to increase the power of medical AI through the provision of large volumes of diverse health-relevant data, collected directly from the user. The combined impact of these technologies will help us to move closer towards achieving precision medicine, an emerging approach to disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle.{4}

In terms of using AI for pre-screening potential subjects for a clinical trial at site level, numerous studies indicate that EHRs contribute significantly to administrative strain and the rising burnout among both trainee and practicing doctors. AI can make this process of potential participant identification via database search and collecting their medical histories for review faster.

While natural language processing (NLP) can aid in streamlining medical record-keeping, ambient clinical intelligence (ACI) provides an interactive digital backdrop for both doctors and patients. This environment can potentially interpret patient-doctor interactions and automatically update EHRs. This can also help site staff to identify a potential participant in real time, if the correct parameters are fed to the AI tools being used. AI can also be used at study start-up stage where AI tools can give real-time information on potential sites that have reliable patient populations and regulatory approval timelines at the country and site levels, among other considerations.

Numerous initiatives aim to harness ACI, marking a pivotal AI application in medicine to address contemporary challenges faced by medical professionals. One major obstacle in embracing AI-driven medical technologies is the concern over medicine becoming impersonal. This is often linked to the expanding administrative tasks placed on doctors. Yet, innovations like ACI and NLP promise to alleviate such administrative pressures, allowing medical professionals to center their attention on patient care.{5}

Quality and Regulatory Compliance Risk

Machine learning and deep learning need vast datasets, often larger than those from clinical trials. While specialties like ophthalmology have thrived due to abundant, curated imaging datasets, this also poses risks. While the principle of "do no harm" guides healthcare, breaches in patient privacy can result in significant damage, affecting areas like employment or insurance and risking identity theft. Completely anonymizing data

is challenging, and there's always a risk of re-identification. For instance, facial recognition can be applied to CT scans, and machine learning can discern age, gender, and health factors from various images. Over time, even non-image datasets may be able to perform brisk identification by linking with other accumulated patient information. This hinges on handling patient data, intertwining with concerns of patient privacy.{6}

When utilizing AI in various stages of clinical research such as the development of protocols, execution of clinical trials, and manuscript creation, copyright issues can inadvertently arise. AI often sources information from a multitude of databases and publications to generate content or make decisions. There's a risk that the AI might use copyrighted material, unbeknownst to the user, leading to legal complications and questions regarding the originality and authenticity of the research output. Ensuring that AI systems are designed to recognize and avoid the use of copyrighted material is essential to maintain the integrity of the research process.

AI's data privacy challenges arise from the need for specialized expertise and resource-intensive computing, especially for rare diseases which require data pooling from multiple institutions. This inter-institutional sharing can elevate data breach risks. Partnerships with large pharmaceutical and tech corporations heighten concerns, given the recent emphasis on data monetization, likening it to "data being the new oil." The increasing intersection of healthcare businesses and academic data can intensify threats to privacy. Exclusive deals that limit clinical data sharing may contradict the Belmont principle of justice.{7}

Owing to AI's inherent complexity in terms of transparency, close collaboration with the firms that design and uphold this tech becomes crucial. The U.S. Food and Drug Administration has shifted its focus to accrediting the entities behind AI development, acknowledging the ever-evolving nature of AI. The European Commission has introduced laws setting standardized AI guidelines, emphasizing privacy and data management similar to the European General Data Protection Regulation. Meanwhile, countries like Canada are still in the process of defining AI-specific regulations.{8}

Although AI systems might be trained on extensive datasets, they can come across unfamiliar data and situations in a clinical environment. This unpredictability might reduce their accuracy and reliability, potentially compromising patient safety. Several challenges impede AI's full acceptance in the medical field. These range from the absence of clinical studies proving its superior reliability compared to conventional methods, to

concerns about assigning blame for medical mistakes. Particularly, the application of data protection rules to this context warrants thorough consideration. Properly governing this technology via legal measures is vital to prevent potential loss of human touch.{9}

Potential Enhancements of AI Tools in Clinical Research

Grasping the perspectives of stakeholders is pivotal when crafting policies for AI in clinical settings. It's imperative for AI developers to prioritize learning, foster dialogue, and team up to address differences in opinions among stakeholders. Tools that aid in visual data interpretation and data aggregation are more welcomed by healthcare professionals compared to ones that directly shape clinical verdicts, or that might jeopardize the clinician-patient bond or the independence of clinicians. Routine digital data tasks, like interpreting radiological or dermatological images, are perceived as more suitable for AI than hands-on or dialogue-based tasks, such as surgical procedures or consultations.

Privacy concerns are paramount, especially when AI is applied in clinical trials involving sensitive patient data. Different applications of AI, whether in protocol development, trial execution, or manuscript creation, come with varying levels of privacy concerns. For instance, when AI is used in the execution of clinical trials, it may have access to sensitive patient information, raising concerns about data security and patient confidentiality. Ensuring that AI systems adhere to stringent data protection regulations and ethical guidelines is essential to safeguard participant privacy and maintain the trust and integrity of the research process. Clinicians express concerns about potential privacy violations and the challenges in comprehending or directing AI tools. Meanwhile, patients fear the diminished role of clinicians and a lack of inclusive decision-making. A shared sentiment emphasizes the importance of human-led decisions and maintaining compassionate, personalized communication during clinical interactions. Observational studies indicate that patients lean toward human counselors who can understand their individual situations, envisioning AI as a supportive tool rather than a replacement for clinical guidance.{10}

Further, accuracy is very important in clinical research. The reliability of AI in developing protocols, executing clinical trials, and creating manuscripts heavily relies on the quality of the datasets it utilizes. AI systems are only as accurate and reliable as the data they are trained on. Inaccurate, outdated, or biased data can lead to misleading or erroneous outcomes, which can compromise the validity of the research. It's crucial to ensure that AI systems have access to comprehensive, up-to-date, and accurate datasets to enhance the reliability and validity of their contributions to clinical research.

Finally, there might be concerns about the originality and innovation of the AI-generated protocols. In the execution of clinical trials, issues might revolve around the AI system's decision-making process, its adaptability, and its ability to handle unexpected scenarios. In manuscript creation, concerns might focus on the authenticity and credibility of the AI-generated content. Tailoring strategies and safeguards specific to each application of AI is crucial to address these unique challenges effectively.

Conclusion

Medical training needs to integrate modern technology more effectively. Current curriculums offer limited exposure to technologies that healthcare professionals will encounter. For AI systems to be properly integrated into clinical care, specialized training on these technologies, which might independently perform tasks like diagnosis and surgery, is essential. As clinician roles transform, the focus should shift toward handling intricate health situations and to mastering the skills necessary for interpreting and conveying diverse data relevant to specific medical cases. To prepare future doctors for these challenges, a more comprehensive educational approach that encompasses an understanding of technology and its outcomes is vital.

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Shriya Das, MS, MSc, (shriyadas513@gmail.com) is an Independent Researcher based in Flower Mound, Texas.

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PEER REVIEWED

Utilizing Cultural Humility as a Tool to Support Diversity in Clinical Research

Jessica Fritter, MACPR, ACRP-CP; Bashar Shihabuddin, MD, MS

As applied to the clinical research enterprise, "cultural humility" is a continuous process of self-orientation toward caring for others based on self-reflection and assessment, appreciation of others' experiences, and expertise on the social and cultural context of their lives, with an openness to establishing strong relationships within the research team and with study subjects. Applying cultural humility training to a clinical research infrastructure provides open awareness of biases, privileges, and the limitations of one's own knowledge. These insights may enhance one's approaches to interactions with potential subjects during recruitment and with actual subjects during study conduct while complementing existing cultural competency training and, in turn, supporting diversity among team members and research subjects.

Background

Diversity training predates the concept of cultural competency and humility. Workplace diversity training was launched in the 1960s prompted by legislation related to discrimination.{1} In many instances, these training sessions evolved into employee questionnaires with little feedback, as well as hiring tests with the only product being a list of "do" and "don't" recommendations.

The term "cultural competence" was first introduced in 1989 in a report titled: "Towards a culturally competent system of care."{2} the authors of which concluded that cultural differences could lead to inequitable care when medical organizations and staff are not culturally competent. Since that time, cultural competency training has become ubiquitous in healthcare settings, various businesses, and academic institutions, with the belief that more knowledge about another's culture results in more competent practice.

However, cultural competency training often assumes that learning about some aspects of someone else's culture or experiences results in a competent person, suggesting that once one attains this knowledge through

training, they are culturally competent. This design treats culture as rigid not fluid, while in fact culture is a concept affected by various structural, systematic, and personal elements. Furthermore, cultural competency training may become tedious and leave no lasting impact, and some participants may harbor animosity toward the training or its elements, resulting in more harmful attitudes. It has been suggested that cultural competency training does not impact any aspect of teamwork nor client relations.{3}

Cultural Competency vs. Cultural Humility

Cultural humility builds on cultural competence. Cultural competence provides a foundation of knowledge and awareness of various backgrounds, attributes, and historical events. Cultural humility translates that knowledge and awareness into the process of accountability aimed at personal and systematic change.{4}

The Cultural Humility Process

Cultural humility is a lifelong process of learning from others and self-reflection focusing on mitigating power imbalances and creating accountability at various levels: personal, team, institution, etc. This is achieved by encouraging reflection on one's own beliefs, values, and biases—both explicit and implicit. In turn, the impact of one's own culture on research team interactions and subject recruitment can be assessed using a person-centered stance, open to and respectful of others' views. This continuous fluid dialogue and process orientation promotes real partnerships internal to the team and external to the community where subject recruitment occurs.{5}

Achieving partnerships by being culturally humble allows engagement with people who are different on a personal and experiential level, with a curiosity and empathy about others lived experiences that are different from one's own. This could range from a simple endeavor, for example learning to pronounce names, to more complex ones, for example talking about experiences with racism, sexism, and classism. It is important to approach all these endeavors with the beginner's mind and to listen nondefensively, particularly when in a leadership position. This will allow one to show appreciation and respect for other cultures.{6}

Cultural Humility and Team Cohesiveness

It is important to know and understand one's own cultural background and how it influences perceptions and potential biases. The process of cultural humility in a team setting starts with leadership and the ability to be vulnerable, which leads to team cohesion.

Cooks-Campbell showed five ways a team can practice cultural humility in terms of team bonding, coaching, conversing, using what you learn, and understanding limitations.{7} Team bonding is a time for the team members to get to know one

another better and through common activities. A way to practice cultural team bonding may be eating different cuisines or learning about other languages. Coaching is helpful in identifying self-awareness and challenging expectations. When in conversation, it is essential to allow others to lead the conversation and share their experiences. Using what you learn means when you identify something of concern within your institution, you hold all partners involved accountable and advocate for change. Understanding limitations means recognizing the fact that culture is evolving, and people are going to change.{7}

Cultural humility is just as important in leadership. Leading by example and modeling learning and self-reflection demonstrate empathy and respect to the team. Engaging in difficult and critical conversations allows for open dialogue and facing assumptions head on. Practicing inclusive leadership and advocating for diversity and staff development are key components to practicing cultural humility as a leader.{8}

So how do you practice cultural humility within your clinical research team? Let's think about how this works when talking about subject recruitment. As a team, you can discuss each member's experiences with subjects of varying cultures. What were their experiences as patients and subjects in research studies? What setbacks did they experience and how did they overcome any obstacles? What was successful and allowed them to be present and engaged with the subject and family?

A recent study of clinical research coordinators (CRCs) in a large collaborative pediatric emergency medicine research network found that most felt that their various races and ethnicities, as well as their ability to speak languages other than English, made them more successful overall in study recruitment. However, some CRCs felt that their gender hindered their sense of belonging in the research team.{9} This study highlights how cultural humility can lead to discussions revealing not only diversity among research teams, but also supporting team members who may be struggling due to personal factors or characteristics.

In turn, cultural humility may improve community engagement, increase a community's knowledge of research studies, and support the design of clinical research projects with a focus on the subjects, not just the science.{5} In one examination of the topic, authors provided critical information on how research does have local spillover into the community, and how it is important for research to mirror its community. They discovered that, on average, every additional publication can reduce local mortality from a disease by 0.35%.{10}

Conclusion

Cultural competence provides knowledge and an opportunity for self-awareness while cultural humility emphasizes accountability and change. Cultural humility is a continuous process of learning and self-reflection. Applying cultural humility to your teams allows for vulnerability, accountability, growth, and learning. It is

important to have open communication to discuss cultures and reflect on those interactions. Moving forward, it is imperative to understand and practice cultural humility in your research setting.

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Jessica Fritter, MACPR, ACRP-CP, (fritter.5@osu.edu**)** is Associated Faculty of Clinical Practice at The Ohio State University College of Nursing, works as a partner in BJE Consultants, and serves as the ACRP Content Committee Vice Chair for 2023 as well as Chapter President for the Ohio Chapter of ACRP. She also works in workforce development for The Ohio State University Center for Clinical Translational Science.

Bashar Shihabuddin, MD, MS, (bashar.shihabuddin@nationwidechildrens.org) teaches and practices in the Pediatrics and Emergency Medicine areas of Nationwide Children's Hospital in Columbus, Ohio, and is an Assistant Professor at The Ohio State University College of Medicine.

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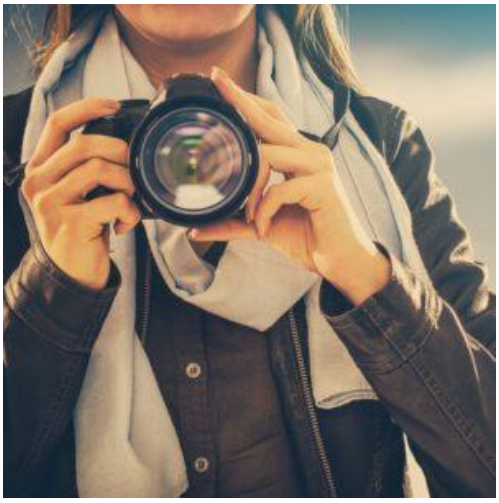
SPECIAL FEATURE

Looking at Clinical Trial Technology Through a Site Lens

Elisa Cascade, MBA; James Wurdeman



Adoption of technology by clinical trial sites has increased significantly over the past decade, especially amongst organizations that perform more than five research studies annually. Technology systems considered core to a clinical research site's operations include:

- Clinical trial management system (CTMS): A CTMS is responsible for managing all operational aspects of a clinical trial from study start-up to closeout. Critical features include, but are not limited to, study milestone tracking, review/sign-off workflows, calculation of subject visit schedules, financial billing/tracking, billing compliance, and task management.
- eRegulatory management (eReg) system: An eReg system contains the electronic final copy of site-level essential documents related to study startup and amendments, training documentation, delegation of authority log, and other items needed for audit or inspection. The system also manages subject-level documents such as screening/enrollment log, list of subject identification codes, and signed consent forms. Other items include, but are not limited to, protocol deviations/exceptions, safety (adverse events/serious adverse events) log, as well as correspondence with the sponsor, contract research organization (CRO), or monitor.
- eSource/electronic data capture (EDC): eSource and EDC systems capture source data in an electronic format. While there are many similarities between eSource and EDC, eSource will capture every piece of information potentially needed from a standard of care, research, and workflow perspective. Another important aspect is remote monitoring functionality, as this is the dataset generally monitored during source data verification (SDV). EDC is often a subset of eSource because it does not collect protected health information (PHI).

The primary goal of these systems is to facilitate the research process at the clinical trial site, regardless of funding source—industry-sponsored trials, research grants, or investigator-initiated studies. Through use of technology, in combination with development of standard processes and associated training, research sites are able to address many of the common U.S. Food and Drug Administration (FDA) inspection findings, such as protocol compliance, source documentation, and regulatory documentation for activities including adverse events and informed consent.{1} Also important are integrations with site systems such as those to support staff resource planning (e.g., human resource systems) or to drive efficiency (e.g., labor to generate and record invoices).

Sponsors and CROs looking for process automation, higher quality study delivery, and transparency into study status are also investing in technology related to such activities and features as essential document collection, learning management systems (LMSs), eConsent, patient recruitment tracking, and many more. Thus, it is not surprising that in the 2023 Advarra Study Start-up Survey,{2} sites reported that setup and training on sponsor technology is the most burdensome start-up activity, with 55% rating this activity as very or extremely burdensome. Further, the situation is worsening, as 67% of sites reported that the burden associated with sponsor technology has grown over the past five years.

In this paper, we provide a summary of the technology needs of different types of sites (i.e., not all sites are created equal) and highlight barriers to implementing sponsor/CRO technology from the perspective of sites that currently have technology.

Variance of Technology Needs by Type of Clinical Trial Site (i.e., Not All Sites are the Same)

Site technologies such as CTMSs, eRegulatory management systems, and eSource/EDC systems are used by a variety of clinical research sites. As mentioned above, because the needs of each type of site organization differ slightly, it is unlikely that a “one size fits all” technology solution will work. A high-level overview of types of clinical research organizations and requirements for clinical research technology follows.

Academic medical centers (AMCs)

AMCs typically manage between 500 and 2,000 studies per year—inclusive of industry-funded studies, research grants, and investigator-initiated trials. These institutions often have a central research office that coordinates technology system purchase, implementation, and reporting.

A CTMS is critical for these AMCs to coordinate all aspects of study delivery including, but not limited to, patient visit scheduling across various departments (e.g., clinic visits, diagnostic imaging) in compliance with

the protocol schedule of events, billing clinical research vs. standard patient care, and facilitating the workflow for ethics submission in cases where the AMC requires review by a local institutional review board (IRB). The CTMS also allows for tracking of key performance indicators (e.g., patient enrollment and retention), both for progress monitoring dashboards and a historical record of operational metrics. Integrations are common between the CTMS system and a median of six specific hospital systems (e.g., electronic medical/health records [EMRs/EHRs], Human Resources, Finance),{3} and a primary reason why clinical research sites can't just use a CTMS provided by the sponsor/CRO, a question often asked by sponsors/CROs who lack familiarity with site systems.

For the 72 organizations that meet the standards for research of cancer prevention, diagnosis, and treatment from the U.S. National Cancer Institute (NCI),{4} a CTMS is also critical for application to and review of Nationally Designated Cancer Center status.{5}

Having invested in CTMS, these AMCs are next likely to purchase an eRegulatory system to collect documents associated with each clinical study. While the volume of studies varies across type of clinical research site, the institution-specific requirements for eRegulatory binder systems are similar and integration with a site's CTMS is desirable for pre-population of standard study information and personnel across systems.

Finally, AMCs may also choose to invest in an EDC system to capture information on single-site studies (e.g., grants, investigator-initiated studies). For industry-sponsored studies, the sponsor/CRO will typically provide an EDC to the site for use on that study, so site-specific EDC is used outside of industry-funded studies. eSource use by AMCs is less common, because their own institutional EMR/EHR system is typically source for the clinical study.

Non-academic hospitals/health systems/clinics

Like AMCs, non-academic hospitals/health systems/clinics typically provide clinical research services in addition to patient care, and thus have their own EMRs/EHRs that serve as source for a clinical study. Another similarity with AMCs is the need for a CTMS to organize all aspects of study delivery across approximately 200 to 800 clinical studies per year. However, the non-academic site's needs tend to be simpler than the AMC's because these sites typically do not have a local IRB process to coordinate, nor do they participate in as much research grant or investigator-initiated studies. Performance tracking dashboards and access to historical operational metrics are of value to the non-academic centers, particularly in larger institutions that conduct research across departments.

Due to the high volume of studies per year, these non-academic hospitals/health systems/clinics may also invest in an eRegulatory system. As mentioned above, requirements are somewhat standard across sites with a desire for pre-population of study information from CTMS. Because they have their own EMR/EHR and participate primarily in industry-sponsored studies, use of eSource and EDC is not common.

Standalone clinical trial sites and networks

Many of these stand-alone clinical trial sites and networks are dedicated to clinical research, and thus lack the practice management system and/or EMR/EHR systems seen at AMCs or non-academic hospitals/health systems/clinics that also provide patient care. Large clinical trial sites may perform as many as 40 studies per year, and site networks may oversee an aggregate of 200 to 500 studies across regional—and increasingly multinational—clinical trial sites.

Similar to other types of sites, a CTMS is often the first technology system purchased by independent sites, and this is particularly important in the case of site networks that have a central office that monitors study progress (e.g., performance metrics) and provides centralized services for individual sites (e.g., business development, feasibility, billing/invoicing, patient payments). In the case of site networks, technology is typically purchased by the central office to facilitate cross-site and cross-study project management, as well as to capitalize on technology purchasing power. In addition to a CTMS, sites/site networks will next typically invest in an eRegulatory management system, and eSource may be purchased by the site network as a third supporting technology, particularly in cases where no EMR/EHR system is available.

Implementing Sponsor/CRO Technology in Technology-Enabled Sites

Barriers to adoption of sponsor/CRO technology by clinical research sites are well documented and include, but are not limited to, too many systems with different login credentials, duplication of training, systems require too much time and/or detract from patient care, and the systems are not easy or intuitive to use.{6}

Technology-enabled sites experience these barriers, but have additional challenges to using their own technology in combination with sponsor/CRO provided technology, as described below.

<u>Duplicate activities:</u>

- Issue: Sites choosing to invest in CTMS and eRegulatory management systems already automate many clinical trial activities covered by sponsor/CRO technology, such as sending participant visit reminders (CTMS), collecting/storing documents needed for study start-up (eRegulatory), and/or capturing electronic

participant signature in informed consent (eRegulatory). When sponsors/CROs provide these types of tools to sites in the context of a single study, technology-enabled sites either don't use the functionality (resulting in incomplete data/lack of transparency for sponsors/CROs) or, in cases where use of the tool is mandatory for study participation, sites require added work to perform the activity in two unconnected systems.

- Potential solutions: Integration across site and sponsor technology to form a connected ecosystem is one way to overcome this barrier. In a 2023 survey by Advarra, more than 70% of sites rated integration of their eReg system with sponsor tech as extremely or very valuable. Selecting technology providers that have already established integrations with site technology is one way that sponsors and CROs can ease site burden. Another action that sponsors/CROs should consider is selecting technologies that enable navigation with single sign-on between site and sponsor technology using the site's own credentials. Using the site's own credentials to access sponsor technology was rated as extremely or very valuable by more than 80% of sites.{2}

Unified site reports/dashboards:

- Issue: As mentioned above, one of the primary drivers in an organization's decision to invest in site technology is the need for transparency across all ongoing studies. While this is helpful to all sites, unified reporting/dashboards are critical to operations for some types of sites. One example is AMCs that are not only working on studies across sponsors/CROs, but also working on non-industry–funded studies. National Cancer Institute–designated cancer centers are another example of where reporting is critical to attaining and maintaining certification. Unified reports and dashboards are also extremely important for site organizations with a central office that requires transparency to deliver central activities (e.g., recruitment support) and/or provide clinical trial oversight/management. Examples include a central office across all sites in a site network, or a central office across all research departments in an AMC.
- Potential solutions: Support the site's use of its own tools and associated reporting/dashboard functionality to deliver centralized activities and track important study and participant milestones across all studies. This can be facilitated through point-to-point integration with each technology, or even better, for a more modern technology configuration with near real-time data sharing from the central data warehouse. Many of the larger sites (especially AMCs) and site networks have sufficient internal information technology capabilities to support data amalgamation for unified dashboards/task lists, a tool rated as very or extremely useful by 77% of sites in Advarra's 2023 survey.

Site processes/standard operating procedures (SOPs):

- Issue: To facilitate new employee onboarding and deliver high-quality, regulatory-compliant research, sites have developed SOPs, work instructions, and other process maps that incorporate use of site technology. Having a scalable way to manage onboarding and oversight of clinical research site staff has been critical to maintaining study operations in recent years, with site networks having experienced double the usual staff turnover rate (increase from 10% to 37% pre-COVID-19 to 35% to 61% after).{7} Introducing new technologies often requires deviation from and/or modifications to standard site process and associated change management activities (e.g., staff training, job aids). This may impact both staff efficiency and study delivery quality.
- Potential solutions: Selecting technologies with streamlined user experiences is paramount to minimizing site burden. Discussions with sites, sponsors, and CROs suggest wide variance in the ease of use across sponsor technology vendors. For example, one sponsor that recently switched start-up technology vendors reported a decrease in site support calls from 150 to three over the same timeframe due to ease of use. For sponsors or CROs selecting to adopt the same technology across their entire portfolio, there is an opportunity to partner with very large sites to offer change management support prior to start-up.

Conclusion

In speaking with study sponsors and CROs, there appears to be a disconnect as to why sites need their own technology and can't use the technology provided to them by a sponsor/CRO for a particular study. As described in this paper, the unique features required by sites to operate a study combined with the need for integrations to other systems in the organization pose serious challenges to sites using the same technology as a sponsor or CRO. Further, for CTMS in particular, finding a single system that can meet the needs of all site customer types—AMCs, other health systems and clinics, and sites/site networks—adds even greater complexity.

Understanding that sites will continue to use their own technology, sponsors, CROs, and technology providers all need to strive to minimize site burden when adding sponsor/CRO technology for a study. While some of these challenges are universal to all sites, others are specific to technology-enabled sites, including the real potential for duplicate work, compliance risk due to process change, and the need to preserve unified data tracking and reporting. Sponsors and CROs can help by considering the site technology experience when selecting the portfolio of technology systems used within a study. Integration for data and document flow, navigation with login using the site's credentials, data access for consolidated reporting, and a simple, intuitive user experience are all important factors for consideration for our sites.

Press releases, websites, and participation of sponsors and CROs in clinical trial workforce associations such as the Association of Clinical Research Professionals all point to a strong desire to decrease site burden, but there's not always a clear, actionable path for sponsors and CROs to address the problem. Sponsors and CROs that are truly site centric will be looking for ways to reduce friction so that technology isn't just an additional challenge to a workforce that is already suffering from a widening gap between the supply of and demand for trained staff.{8} Recognizing that experienced sites are already struggling to achieve workforce levels to keep pace with industry clinical trial volume, anything sponsors and CROs can do to decrease burden will have a positive impact on the clinical trial industry—within and beyond an individual trial.

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Elisa Cascade, MBA, is Chief Product Officer at Advarra and the 2024 Chair of the Association Board of Trustees for ACRP.

James Wurdeman is Senior Vice President for Technology Strategy and Innovation at Advarra.

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SPECIAL FEATURE

Deconstructing the Biosimilar Promise: Can Industry Deliver on Access *and* Affordability?

Dr. Christian K Schneider

It is widely accepted that biosimilars hold the potential to improve patient access to life-changing therapies. However, questions remain about what will be needed to deliver on the promise of greater biosimilar access and affordability.

In a recent panel discussion that I moderated, industry experts weighed in on the state of the biosimilar market, today's regulatory climate, and what will be required to realize their potential. Participants included Leah Christl, PhD, Executive Director, Head of Global Biosimilars Regulatory Affairs and Regulatory and R&D Policy, Amgen, and previously Associate Director for Therapeutic Biologics and Director, Therapeutic Biologics & Biosimilars Staff, at the U.S. Food and Drug Administration (FDA); Martin Schiestl, Global Head Regulatory Affairs Policy of Sandoz Biopharmaceuticals; and Elena Wolff-Holz, Global Head Clinical Development, Biocon Biologics, and previously chair of the European Medicines Agency's (EMA's) Biosimilar Medicinal Products Working Party (BMWP).

The experts provided a global perspective on where they see the biosimilar industry headed, as well as steps to support and influence efficient biosimilar development methods to take cost out of the process.

State of the Industry

Biosimilars have been on the world stage for almost two decades, with the European Union approving its first biosimilar in 2006—Omnitrope (somatropin)—and the United States establishing patent requirements for its first competitor biologic in 2015. The logic behind the promise of biosimilars is that they should be easier to produce, since they require less upfront investment in research and development (R&D) than the reference products that they mimic.

While uptake and savings did not initially meet expectations, more recently biosimilars have produced tangible savings. According to the *U.S. Generic & Biosimilar Medicines Report*, the U.S. healthcare industry has saved approximately $23.6 billion since the first biosimilar was introduced in 2015.{1} The number of new products also continues to grow. In Europe, the number of biosimilars has nearly doubled from 2016 to 2022, with a significant increase in competition.{2}

With an ever-increasing prevalence of chronic disorders feeding a steady stream of global demand, we have seen far greater acceptance of biosimilars by physicians and patients. For example, 15 years ago we talked about biosimilar monoclonal antibodies as being totally impossible, but these are now fairly mainstream.

To realize the promise of biosimilars, there is a need for more industry-regulator collaboration, particularly on updating and aligning the guidance to create more efficiencies based on historical learnings and product maturity.

“I’m concerned that we may be closing regulatory pathways in the future,” Christl said. “We must continue to have conversations about the science and the regulatory pathways—among manufacturers and with the regulators.”

With the development of the next European Regulatory Network Strategy coming in 2025, Wolff-Holz noted that one question looms large: Will the current guidance documents take precedence, or will they change?{3} If the latter, biosimilar companies could be forced to omit certain programs. “There are major differences in what the FDA requires and what EMA requires, for example, and this may lead to these tough decisions,” she said.

Influencing the Pathways Forward

One key issue is the inclusion of comparative efficacy studies. While traditionalists may support clinical trials that arrive at a validated endpoint on efficacy and safety, others lean toward pharmacokinetic and pharmacodynamic (PK/PD) studies that look at the totality of evidence.{4} PK/PD studies look at biomarkers on the mechanistic pathway to support biosimilarity, and such studies are both shorter and less costly.{5}

“When I was at the FDA, we talked about the totality of the evidence, not just the stepwise approach. For years, the FDA didn’t have any product-specific guidance, and part of that was to allow the space to remain as flexible as possible,” Christl said. Now in industry, she commented that starting the process using comparative analytics is the only way to fit into development timelines.

PD markers are proving themselves with less complex products. “Historically speaking, we’ve seen clear PD markers, which correlated with efficacy and are broadly acceptable,” Wolff-Holz explained. “The question is, ‘What about the more complex drugs like monoclonal antibodies?’ The problem there is that we do not have many PD markers that we trust.”

However, she noted that “there are a few examples,” with one fully approved in Europe. The challenge, she noted, is to develop a sensitive enough marker, which “can be a solution for some drugs, but it’s not the savior of the entire conundrum.”

Christl agreed, adding: “For pharmacodynamic markers, the FDA’s approach doesn’t need to be a validated surrogate endpoint.” While she noted that there was “a push to look at pharmacodynamic endpoints and markers on the mechanistic pathway,” it is just a part of the process to collect other data as a part of the study. This is where the FDA has gone, she added, starting with a biosimilars action plan and continuing with the latest iteration of the biosimilars user fee program and a formal regulatory science program.

Christl added that one of the projects under the regulatory science program involves increasing the efficiency of biosimilar development and includes research into pharmacodynamic markers. She noted that the FDA continues to work in this area through a grant program.

Industry or academia could conduct work in this area, asking questions such as: “Are those markers on the mechanistic pathway that are tied to the analytics for that biological function? Can they be tracked alongside other data that we’re collecting?,” and “Can they be informative about biosimilarity?”

The Impact of Competition

Lack of competition remains an issue since the high cost of development can make it difficult to make the case for a biosimilar when the market isn’t big enough to support return on investment.

In some cases, a biosimilar may also be considered for add-on therapy. “We try to design a study to show the add-on effect in the efficacy endpoint,” Schiestl said, noting that if the add-on effect is small but requires large clinical trials, it isn’t sustainable. With a growing trend to adopt combination therapies, the best, most effective solution would be to push for efficient requirements for biosimilar approval, Schiestl added, which means rethinking the scientific question and then determining the most appropriate study to answer it.

The shift to rare diseases also presents funding considerations. “When you are talking about a rare disease, you have a very limited patient population,” Christl said. “This makes it difficult to do even pharmacokinetic similarity studies. How can you work within the regulatory system to get the data necessary to scientifically support the right assessment? Not every product is going to look the same in terms of development. There are some things that we need to think through to get the data that we need.”

Educating Stakeholders on Reduced Clinical Trials

To gain buy-in for new biosimilar testing protocols, Christl explained that it is essential to educate stakeholders as the industry moves into new therapeutic areas. “Discussing the power of comparative analytics with clinicians is difficult,” she said.

She recalled an experience at a therapeutic conference where she received significant backlash on new testing approaches. “We were talking about the analytical similarity assessment and mentioned comparability,” she said. “It had the exact opposite effect that we expected. Clinicians

came up to me afterward and basically said, 'I don't want to use the reference product anymore. I feel that the FDA has been keeping information from us that it's not the same product over its lifetime.' I think as we look at these data packages, and continue to look for efficiencies in these programs, the regulators, manufacturers, patient advocacy organizations, and therapeutic organizations all need to work together and dig into the education around that."

Christl added, "It's not so much getting into what's in the data package and the specific analyses that were done. It's talking more broadly about the pathway, the science around it, and having confidence in the regulators. That's what matters."

As Schiestl noted, "History tells us that once prescribers understand the science behind it, they support it. There is still a lot of misinformation out there about biosimilars. In the end, I think education is important, especially focused on separate regulatory requirements needed for regulatory decision-making. We should not do clinical studies for comfort reasons, which otherwise don't contribute to the regulatory decision-making process."

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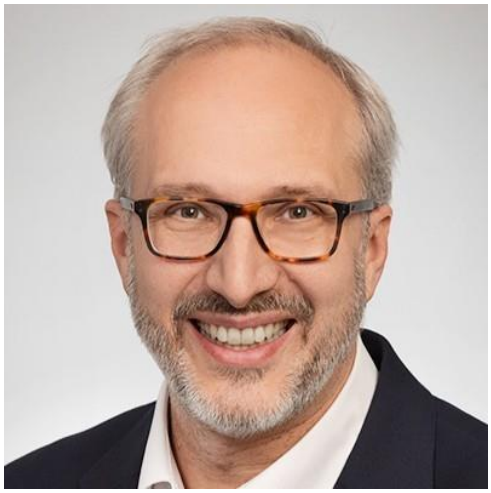

Dr. Christian K Schneider is a leading authority on biosimilars and Head of Biopharma Excellence and Chief Medical Officer for Strategic Product Development Consulting at PharmaLex (now Cencora PharmaLex). He has broad global regulatory authority experience having served as chair of the European Medicines Agency's (EMA) Biosimilar Medicinal Products Working Party (BMWP) for nine years and was one of the key architects of the agency's advanced therapies and biosimilars framework.

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PRESCRIPTIONS FOR BUSINESS

Empowering Precision Medicine: Transforming Clinical Trials with Precision-Based Solutions

Mark Melton, MSc

Precision medicine has emerged as a game-changer, revolutionizing the landscape of clinical trials and offering new hope for advancement of critical medicines. However, the intricate nature of precision medicine requires precision-based solutions for trial sponsors, clinical research organizations (CROs), labs, and research sites. The existing clinical trial management approaches no longer suffice, as they fail to serve the best interests of all stakeholders involved as the complexity of trials increases. Manual processes within the trial system often lead to operational challenges that also create data silos which cause mistakes carrying hefty consequences for patients, including the denial of entry into potentially life-saving trials when protocols are not followed. A lack of focus on effective communications and global data compliance can also prove to be costly in the long run.

To address these pressing issues, trial sponsors and research sites must pivot toward precision-based solutions. This transformation involves leaning into automation; prioritizing effective communication between sponsors, sites, and all vendors; and ensuring biospecimen protocol

adherence. Having a game plan in place for global data compliance and implementing these strategies will surely promise substantial, long-term benefits.

Harness the Power of Automation

Leveraging technology is paramount for streamlining and automating processes, and for improving the traceability of lab kits, patient samples, and the data that result from testing those samples. Traditional manual processes no longer work for the complexity of precision medicine. These targeted clinical trials designs increase complex collections, biomarker assay designs, number of lab vendors utilized, and ultimately more complex data. It's time to lean into automation to not only expedite trial progress, but also to safeguard the integrity of collected data.

One of the biggest problems I see right now is that the data that facilitate patient sample tracking and reconciliation come from many different sources, including trial sites, central labs, and third-party testing labs. These data sources have different databases, reporting capabilities, and business objectives. Sponsors, or their CROs, are often left to find ways to integrate, harmonize, and report out data from multiple systems. It's a no-brainer that technology should be able to automate this process, and the best way to do so is to control both data input and output. This means controlling sample collections and data generated at the birth of a sample, and how those data are transmitted to lab vendors and reported out to ensure proper data integrity and sample processing. But the reality is that current technological solutions are fragmented, with some solutions managing input of data and others managing output. True automation should manage the entirety of the process from start to finish.

The potential impact that manual processes can have on patient care can be seen in the collection of samples for companion diagnostic (CDx) testing. These samples can gate the ability for a patient to be eligible for a trial, as they are used to show the existence of a specific biomarker a drug used on the trial is targeting. I was once part of a team that was running more than 40 trials, many of which involved CDx testing. There were thousands of patients being enrolled per month and tens of thousands of samples being collected across the globe. We were trying to manage all of this manually and had a big team to do the work, but the inability to get insights from clinical trial sites around these CDx sample collections, combined with delayed lab reporting, ended up

causing several patients to screen fail. That means they couldn't get potentially life-extending or life-saving treatments. This isn't as rare as you would hope, and serves as an example that should inspire everyone to leverage technology for the sake of patient care.

Prioritize Effective Communication

Effective communication serves as the linchpin of any trial, but especially for precision medicine–based clinical trials. Implementing strategies to cultivate improved collaboration between trial sponsors, CROs, lab vendors, and research sites is pivotal for enhancing the efficiency and success of clinical trials.

A significant challenge lies in the differing perspectives held by sites and sponsors, as well as the complex role of CROs. Sites often feel undervalued, unheard, and burdened with the weight of trial responsibilities, while sponsors see themselves as industry experts with limited visibility into innovative trends. Complicating matters is the common involvement of CROs, positioned in the middle and promoting their own solutions amid high staff turnover. In addition, at times communication to the sites from the CROs doesn't align with what the sponsor had intended, causing further confusion. This dynamic impedes the efficient, unbiased communication that is in the best interest of the patients.

For the most effective communication strategy, we need a multi-pronged solution that acknowledges the diversity of valid opinions. Site networks and site management organizations can do their part by helping sites simplify and harmonize processes while advocating for better compensation. This, in turn, provides sponsors with increased predictability compared to working with independent sites. It also empowers sites to negotiate better contracts and influence decisions made in the sponsor and CRO sectors of the industry.

Sponsors, if possible, should exert more influence over site selection and engagement, ensuring that transparent processes are being implemented. When leveraging CROs, sponsors must ensure messaging aligns with their intentions and remains consistent across all sites. It is also critical to ensure fair and timely compensation for sites. This not only demonstrates acknowledgment and appreciation, but also equips sites with the necessary resources, promoting enhanced communication and, ultimately, better patient recruitment.

Finally, it is also essential to institute rigorous site surveillance and implement metrics to measure performance. This approach helps gauge what is effective, identifies areas that need improvement, and facilitates informed discussions with sites about their standing relative to others involved in trials.

Ensure Global Data Compliance

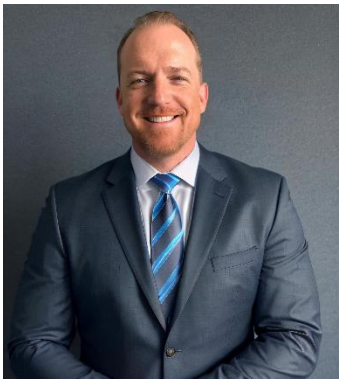
In the realm of precision medicine, adopting a global perspective is a must. Sponsors and CROs should prioritize cross-border adherence to regulations, as establishing a framework for worldwide data compliance is a critical necessity for the success of precision medicine initiatives.

Data regulations, much like laws and cultural customs, vary depending on geographic locations. For instance, within the European Union, the interpretation of the General Data Protection Regulation varies among member countries, adding complexity to compliance efforts. Additionally, variations exist among broader regulatory bodies such as the U.K.'s Medicines and Healthcare products Regulatory Agency, the U.S. Food and Drug Administration, and the European Medicines Agency. Diverse guidelines, laws, and recommendations can all go on to impact restrictions on sample collection, permitted tests, duration of sample and data retention, and geographical constraints on these activities. A failure to comply with these different guidelines could result in financial penalties and impediments to utilizing collected samples and data for testing and analysis.

There are two ways to address the challenges of running cross-border trials. First, maintaining rigorous control over informed consent forms (ICFs) and securing language approval are critical. The ICF delineates, among other things, permissible actions with samples and data. Second, engage legal and compliance experts in different regions to push back on divergent interpretations of the relevant regulations. This helps to ensure meticulous oversight of how data are processed, managed, stored, and ultimately disposed of, in compliance with regulatory requirements. Together, these measures establish a robust framework for navigating the intricacies of global data compliance in precision medicine clinical trials.

Conclusion

The paradigm shift toward precision medicine within clinical trials demands a strategic integration of precision-based solutions, including automation, effective communication strategies, and global data compliance. Automation is key to optimizing processes, ensuring data integrity, and protecting the interests of patients. Establishing transparent communication strategies is crucial for fostering optimal collaboration between trial sponsors and research sites. Finally, when trials cross borders, having a plan in place to ensure global data compliance becomes a must-have. Precision medicine demands precision-based solutions, and integrating these three key elements holds substantial long-term benefits for the advancement of critical medicines.



Mark Melton, MSc, is Vice President of Scientific Operations and Development for Slope.

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NEW E-R-A IN PROJECT MANAGEMENT

Harmony of Mind, Body, and Spirit: Fostering Clinical Project Managers' Spiritual Growth and Well-Being

Zoran M. Pavlovic, MD

Clinical project managers face a range of well-being issues that are unique to their field. These challenges stem from the high-pressure nature of the pharmaceutical and clinical research industry, where the stakes are often very high, and the work can be both demanding and complex.

Here are some of the well-being issues that these managers commonly face:

- High-Stress Levels: The pressure to adhere to regulatory requirements, manage tight project timelines, and ensure the successful development and launch of new drugs while meeting the expectations of disparate stakeholders, including investors, company executives, research and development teams, regulatory bodies, marketing departments, and the public, can result in significant stress.
- Work-Life Imbalance: Long hours and the demanding nature of project deadlines often mean that work can encroach on personal time, leading to an imbalance that can affect family life, social relationships, and overall life satisfaction.

- Mental Health Challenges: The high-stress environment can contribute to mental health issues such as anxiety and depression. The responsibility for the success of critical projects, combined with the fear of failure, can take a toll on mental well-being.
- Physical Health Concerns: Continuous stress can manifest in physical health problems, including headaches, fatigue, and cardiovascular issues. The demands of the job may also lead to neglect of physical health, such as inadequate exercise and poor dietary habits.
- Coping with Rapid Industry Changes: The pharmaceutical industry is subject to rapid changes due to new scientific discoveries, regulatory changes, and market dynamics. Keeping up with these changes requires constant learning and adaptability, which can be stressful and overwhelming.
- Isolation and Team Dynamics: Clinical project managers may often work in siloed environments, particularly in large organizations or when managing remote or international teams. This can lead to feelings of isolation and challenges in team dynamics, affecting morale and mental well-being.
- Uncertainty and Risk Management: The inherent uncertainty in drug development, from clinical trials to regulatory approval, creates a high-risk environment. Managing these risks and dealing with the associated uncertainties can be a source of constant anxiety.
- Resource Constraints: Limited resources, whether in terms of budget, workforce, or time, can add to the pressure, as cinical project managers are expected to deliver successful outcomes within these constraints.
- Career Progression Anxiety: In a highly competitive field like pharmaceuticals, there is often pressure to advance and succeed in one's career. This can lead to anxiety about job performance, promotions, and maintaining relevance in an ever-evolving industry.
- Impact of Technological Advancements: Rapid technological advancements in the pharmaceutical industry can be both a boon and a bane. While they offer new opportunities for innovation, they also require project managers to continuously update their skills and knowledge, adding to the pressure of staying current in the field.

7 Whys

Spiritual growth offers a path to balance and well-being, bringing together the mind, body, and spirit. Here are seven profound benefits of spiritual growth that can lead to a more harmonious and fulfilling life.

1. Enhanced Self-Awareness

Spiritual practices like meditation and mindfulness increase self-awareness, helping individuals understand their thoughts, emotions, and behaviors more deeply. This heightened awareness can lead to more thoughtful decisions, better stress management, and improved emotional regulation.

2. Reduced Stress and Anxiety

Regular spiritual practices are proven to reduce stress and anxiety levels, promoting a sense of calm and tranquility (Goyal, et al., 2014). This reduction in stress and anxiety can improve physical health, enhance mental clarity, and foster a more peaceful life.

3. Improved Physical Health

Spiritual well-being is linked to better physical health, including lower blood pressure and improved immune function (Seeman, et al., 2003). This connection emphasizes the interplay between spiritual practices and physical well-being, leading to a healthier lifestyle.

4. Greater Resilience

Spirituality often provides a framework for coping with life's challenges, enhancing personal resilience (Pargament, 2013). This resilience is crucial in navigating life's ups and downs, promoting a sense of strength and perseverance.

5. Improved Relationships

Spiritual growth fosters qualities like empathy, compassion, and patience, which are vital for healthy relationships (Masters and Spielmans, 2007). These improved interpersonal skills can lead to deeper connections and more fulfilling relationships.

6. A Sense of Purpose and Direction

Engaging in spiritual practices can help individuals discover a greater sense of purpose and direction in life (Ryff, 2021). This sense of purpose can guide life choices and foster a feeling of fulfillment and satisfaction.

7. Enhanced Connection and Community

Many spiritual practices are communal, providing a sense of belonging and connection to others (Pargament, 2013). This community aspect can alleviate feelings of isolation and promote a sense of unity and support.

7 Hows

1. Meditation and Mindfulness

Regular meditation and mindfulness can reduce stress, improve concentration, and enhance overall emotional well-being (Goyal, et al., 2014). You may start with short, daily sessions using apps or online videos. Practice mindfulness in everyday activities.

2. Yoga

Yoga has been shown to improve physical flexibility, reduce stress, and promote mental clarity (Ross and Thomas, 2010). You could start by joining beginner classes or following online tutorials. Start with basic poses and gradually explore more advanced practices.

3. Journaling

Journaling can provide emotional release, foster self-awareness, and aid in problem-solving (Pennebaker and Smyth, 2016). You can start by dedicating a few minutes each day to writing in a journal, focusing on your thoughts and spiritual reflections.

4. Spending Time in Nature

Spending time in nature has been linked to reduced stress, improved mood, and increased cognitive function (Bratman, et al., 2015). You can begin by spending more time outdoors, whether it is walking, gardening, or simply sitting in a natural setting.

5. Reading Various Publications on Spirituality

This practice enhances understanding, inspires, and can lead to a more profound sense of purpose and connection (Veling, 2007). You may start by selecting books or articles on spirituality and dedicate time each day for reading and reflection.

6. Prayer or Chanting

These practices can enhance feelings of hope, provide comfort during times of stress, and foster a sense of community (Masters and Spielmans, 2007). You may begin with prayers or chants from your religious tradition or explore mantras that resonate with your beliefs.

7. Attending Spiritual Gatherings or Workshops

Group practices can offer a sense of belonging, increase social support, and provide opportunities for learning and growth (Pargament, 2013). You may start this practice by seeking out local or online groups, workshops, or gatherings that align with your spiritual interests.

Conclusion

The journey of spiritual growth offers numerous ways to harmonize the mind, body, and spirit. By engaging in spiritual practices, you can cultivate a balanced, healthy, and fulfilling life marked by resilience, purpose, and deeper connections.

If you are interested in finding out how to achieve your professional and private goals and improve your quality of life, you are invited to schedule a 30-minute complimentary discovery session with the author. For more resources on well-being, mental health, stress management, burnout prevention, soft skills development, and other methods for refining your leadership skills and enhancing your self-care, visit here to learn about the Institute of Coaching and here to view the author's monthly "*Leading Minds*" newsletter on LinkedIn, which is part of a movement valuing balanced, impactful, and empathetic leadership.

Resources

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Zoran M. Pavlovic, MD, (heruka.innovations@gmail.com) is a psychiatrist, psychotherapist, and executive coach for life science leaders on agile, entrepreneurial, and mindful leadership with Heruka Lifescience and Health Innovations. He is also a creator of 4-H SWELL (States of Wellness) Leader ® Well-Being executive coaching approach and training.

BY THE NUMBERS

Peaks, Valleys, and Mild Fluctuations in the Clinical Research Statosphere

Curated by Gary W. Cramer, Managing Editor for ACRP

3.75 billion The total amount of National Cancer Institute and nonprofit organization funding in U.S. dollars for breast cancer research and advocacy from 2015 to 2018, according to Cleveland Clinic researchers, which was the highest level of support among 12 types of cancer examined. Coming in second at $1.99 billion was leukemia and, in last place, endometrial cancer with $94 million in support.

Source: https://ascopubs.org/doi/10.1200/OP.23.00126 (*ASCO Publications*)

250+ The number of clinical trials completed from 1990 to 2021 for Alzheimer's disease and related dementias that were examined by University of Illinois Urbana-Champaign researchers, who found that caregivers' responsibilities to study participants were specified in information filed for less than half of the studies.

Source: https://www.newswise.com/articles/ahs-researchers-give-adrd-caregivers-more-information-in-clinical-trials (*Newswise*)

71 The percentage of participants who, in a recent pilot study from Medable Inc. and Duke University, said that enhanced electronic informed consent was more informative than text-only informed consent, and who indicated that the digital elements were personable and made them feel more informed, engaged, comfortable, and prepared to participate in clinical research.

Source: https://pilotfeasibilitystudies.biomedcentral.com/articles/10.1186/s40814-023-01432-w (*BMC*)

26 The percentage of average total turnover for clinical monitoring roles found in the U.S. in 2022 as part of an annual survey by BDO, down from 28% in 2021. Outside the U.S., average total turnover in these roles decreased from 29% in 2021 to 22% in 2022.

Source: https://www.bdo.com/insights/tax/2023-2024-clinical-research-organization-compensation-turnover-insights-report (*2023/2024 Clinical Research Organization Compensation & Turnover Insights Report*)

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