Clinical Researcher

The Authority in Ethical, Responsible Clinical Research

February 2023 (Volume 37, Issue 1)

Revolutions Within Our Reach

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Clinical Researcher

Association of Clinical Research Professionals

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Clinical Researcher is published on a bimonthly schedule. As of 2022, each Home Study test based on journal articles grants 3 Continuing Education Credits. The test based on this issue should be available for purchase online in March 2023.

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Large and small companies are keen to move new in vitro diagnostic devices (IVDs) to market and will tap into contract research organizations (CROs) and clinical sites to support the clinical validations required for IVD regulatory submissions. IVDs are regulated as medical devices in the United States, but the obligations to demonstrate diagnostic test reliability involve some unique study designs and study implementation technicalities worth reviewing. For example, a safe IVD product will have minimal risks associated with false test results; and an effective IVD will yield meaningful information useful for clinicians to manage patient care and treatment decisions. This limited review highlights compliance obligations and operational logistics associated with IVD clinical performance studies that may prompt sites, sponsors, and CROs to explore talent, update standard operating procedures (SOPs), or edit templates and tools to include the unique aspects of IVD products, study designs, and tactical implementations of IVD clinical trials.

Background

Often, the most exciting studies to offer patients are those that present innovative treatments or technology as an option for disease management. These are the studies most interesting to investigator champions who want access to novel drugs and devices; and the most successful for recruitment when the research offers hope for patients who may otherwise be running out of options. Admittedly, IVD studies may not have the same attraction because, in most cases, the subjects agree to provide a biospecimen for the study, but the information generated by donating a specimen is rarely shared with investigator/clinicians or subjects.
However, the safety and efficacy of IVDs is important. Laboratories and device manufacturers develop diagnostic assays to aid clinicians in diagnosis and management of health conditions and diseases. It requires various sample types—blood, urine, sputum, and swabs. The tests could claim to detect cancer cells, pathogens, analytes, and biomarkers of disease risk, and are used to monitor treatment or make ongoing clinical decisions.

When the rapid spread of COVID-19 led to a pandemic, IVD products became the rising star of clinical studies. In response to the national emergency, government agencies, laboratories, device manufacturers, and consumers took an interest in the availability of diagnostic testing to track disease prevalence and manage public health. With the current spotlight on IVD clinical trials, it is a good time to consider similarities and differences between medical devices and IVD medical devices and ways to demonstrate safety and effectiveness.

**IVD Product Development and Regulatory Strategy**

The U.S. Food and Drug Administration (FDA) regulates IVDs as medical devices subject to 21 CFR § 812 in the *Code of Federal Regulations*, the Investigational Device Exemption (IDE) regulation that sets the boundaries around how to introduce an investigational device into interstate commerce for the purposes of research. This IDE regulation identifies when an exemption is required from the FDA before distributing a medical device for a clinical study. In addition to FDA regulations, International Council for Harmonization (ICH) E6 Principals of Good Clinical Practice (GCP) are recognized by European countries, the U.S., and Japan as a standard for how to conduct human subjects research. This standard describes how best to protect patients and preserve the integrity of the data.\(^1\) FDA also recognizes ISO 14155 from the International Organization for Standardization as applicable to clinical investigations of medical devices and ISO 20916, as it is specific to IVD clinical performance studies.

An IVD includes reagents, instruments, and systems used to collect, prepare, and examine specimens from the body intending to diagnose or aid in the diagnosis, screening, or monitoring of disease or physiological status.\(^2\) IVD clinical performance studies need to demonstrate the safety and reliability of the test and the test results.
FDA classifies a medical device by risk, with a Class I device having the lowest risk and being exempt from the IDE regulation. These products must comply with all Good Manufacturing Practices (GMPs) (see 21 CFR 820) and a manufacturer can “register” the product and sell it without clinical performance evidence.

Class 2 devices are low to moderate risk, and they are “cleared” through the 510(k)/de novo pathway. Medical device 510k submissions identify a predicate device that is most similar to a proposed product’s intended use and technology characteristics to demonstrate “substantial equivalence” of the investigational product to the commercially available predicate device.

Class 3 devices are the highest risk devices, such as typical implantable medical devices or, in the case of an IVD, an HIV test that could cause significant harm to patients if the test result is inaccurate. ICH E6 and the ISO standards are good guidance for conducting studies to gather appropriate device safety and performance data.

**IVD Risks and Pivotal Study Design**

ISO 20916 acknowledges study designs incorporating a reference measurement procedure that allows an assessment of “percent agreement” of the investigational test to the reference measurement that may or may not be the “predicate device.” When an assay claims to identify a specific target or analyte, a pivotal study of clinical performance may include testing a specimen on the investigational assay and comparing the results to testing on a comparator assay. The comparator may be an appropriate predicate technology, or may even be a different cleared or approved technology that measures the same target with even greater sensitivity.

When an assay claims to identify a biomarker that may aid in the diagnosis of cancer, the pivotal study for this product may require a comparison of the assay performance to a gold standard in cancer diagnosis—most likely a biopsy. In this case, the technology must also have a predicate device to pursue a 510(k) regulatory pathway, identify as a novel de novo product with a Class 2 risk, or follow a Class 3 premarket application (PMA) for FDA approval.

There are two risk indicators to consider in the clinical performance evaluation of IVD products. The first is the risk of a false or inaccurate test result to patients that would cause the FDA to
consider the IVD as high risk. An example might be a companion diagnostic used to make a treatment decision (start or stop a therapeutic) or to monitor the effects of the therapeutic or adjust or titrate its dosing. This means there is a risk that if the assay result is incorrect, a patient may receive inadequate or toxic doses of the therapeutic or no therapeutic at all.

The second is the risk of the clinical performance study itself. Recall that institutional review boards (IRBs) overseeing safety and ethics at study sites serve as the FDA surrogate in device risk determinations. As noted earlier, non-significant risk (NSR) device studies do not require an IDE application; however, significant risk (SR) devices intended for research must have an IDE from the FDA before distribution.[4]

A device’s intended use and indications for use drive the risk classification of the device. If the risk of an incorrect test result is potentially harmful to subjects, the IRB/FDA may consider the device SR. For example, if a false negative test means a subject does not appropriately triage to a next step that prevents, treats, or mitigates disease or disease risk, the IRB/FDA may consider that high risk. Likewise, if a false positive test means a subject triages to a next step that is potentially invasive or high risk, the IRB/FDA may consider that high risk as well. The study may be NSR (noninvasive sample collection, clinical care at the clinician’s discretion, test results are not used to direct or manage patient care), but the intended use of the commercialized product may still be Class 3 risk requiring a full PMA submission to the FDA.

IRB members should know that IVD research is exempt from the IDE regulations if the device meets certain criteria, including a non-invasive sampling procedure and a test result that is not considered “diagnostic” without confirmation of the diagnosis by another medically established product or procedure. If the IRB deems the research study SR because inaccurate IVD results could lead to misdiagnosis and/or treatment error, an approved IDE is required to conduct the study.[4]

If there is an intent to disclose the investigational test result to the clinician and/or the subject, the protocol and informed consent should include an explanation of how a potentially false result will impact the subjects. The IRB will consider this risk to subjects in the determination of a NSR vs. SR study that would require an IDE. Sponsors may make an initial NSR determination
based on the potential low risk of harm to the subject from participation in the study, including the risks associated with the use of the device. If the IRB disagrees and determines by a risk/benefit assessment that the research is SR, the sponsor must notify the FDA of the IRB determination within five working days and submit an IDE application before commencing the study. SR research reviewed by the IRB should include evidence of an IDE number from the FDA prior to approval to ensure agency awareness and appropriate regulatory oversight.

The IRB should be informed of, and especially consider, a risk/benefit determination for subject safety and welfare when any laboratory testing involves the analysis of human DNA, RNA, chromosomes, and proteins or metabolites that detect genotypes, mutations, or chromosomal changes and is therefore by definition genetic testing.\(^5\) IRB submission information should include a description of the genetic testing and impact of potential results; a plan to manage significant genetic test results; an informed consent disclosure to subjects if the genetic testing could misidentify parentage or disclose a hereditary disease or genetic mutation associated with increased risk of disease; and details on the availability of subject and family genetic counseling and any plans to bank specimens for genetic testing.

ISO 20916 defines an “interventional study” as a study in which the investigational test result is disclosed to the clinician and/or the subject and used to manage the patient care during the study. Key regulatory points regarding disclosure of investigational IVD test results in an assay study include the following:

- The U.S. Department of Health and Human Services (HHS) and FDA regulations (45 CFR § 46 and 21 CFR §§ 50 and 56, respectively) are silent regarding the return of individual investigational laboratory test results to research subjects; however, using investigational test results to manage clinical care would seem to be increased risk if the test is not yet proven safe and effective.
- FDA may require IDEs for a broader set of clinical investigations, and it is unclear under such IDEs whether IVD research test results may be communicated to subjects.
- Clinical Laboratory Improvement Amendments (CLIA) regulations prohibit research labs from providing test results to patients generated by non-CLIA-certified labs when those
results are provided for treatment purposes. Only CLIA-certified laboratories can release data to subjects and the data must be from validated tests.

- The Centers for Medicare and Medicaid Services (CMS) forbids any communication of test results to patients from non-CLIA-certified labs. Laboratories that perform testing for clinical research studies may not be CLIA-certified and often use unvalidated tests.
- The Health Insurance Portability and Accountability Act (HIPAA) requires patient access to results that are part of their designated record set (clinical researchers must release research data to study participants); however, the Office of Civil Rights within HHS has not provided guidance on how to interpret the term “designated record set” in the context of return of results from non-CLIA research labs.\(^6\)

Some understanding of CLIA regulations helps put these points into perspective. Laboratories in the U.S. that perform testing on human specimens for diagnosis are regulated by CLIA. Three federal agencies—FDA (test risk categorization), CMS (clinical laboratory oversight), and the Centers for Disease Control and Prevention (scientific consultation)—support CLIA quality standards for laboratory testing to ensure accurate and reliable test results.

CLIA categorizes tests according to technical complexity and risks associated with false test results. The categories from lowest to highest are waived tests, moderate to high complexity, and high complexity tests. Prior to human specimen testing for clinical use, testing facilities must apply for a CLIA certificate corresponding to the category of testing the facility will perform.\(^7\)

The reference to non-CLIA labs differentiates research labs that perform laboratory testing from clinical laboratories that perform testing on human specimens and report results to clinicians to use to manage clinical care. It makes sense then that agencies would prohibit disclosure of investigational test results to patients if those test results are generated by a non-CLIA-certified laboratory. It is, however, permissible to run an FDA pivotal clinical performance study in a non-CLIA-certified laboratory, so long as the assay development is compliant with GMP design controls and the test results will not be disclosed to subjects or clinicians for clinical care.
Securing Biospecimens

The most obvious approach to acquiring specimens might be a prospective sample collection by obtaining informed consent from the target population and then collecting the specimen (e.g., swabs, stool, fluids, blood, etc.). In this case, the sample collection supplies are also accessory medical devices subject to risk assessment, device classification, and investigational use only (IUO) labeling.

FDA and ISO 20916 address the risks of sample collection and any potential harm associated with the sampling procedure as part of the device risk classification and the study risk determination by the IRB. ISO 20916 also considers the safety of the assay in the hands of the intended user while using it in the intended use environment on the intended use population as an element of risk assessment.

Typically, a study design mirrors the commercial testing scenario. For example, if an investigational test will be commercialized as an over the counter (OTC) product for lay users to purchase and test themselves, the study would enroll lay users who perform the test using only the quick reference guide (QRG) in a “simulated” home setting.

Depending on disease prevalence, there may not be enough of a target population (e.g., very small numbers of carriers of an infectious disease) to achieve the numbers of test results required to support the product claim. In this case, it may be an option to enrich a population for positives by using residual samples from known positives, buying banked samples from a broker, and/or using spiked samples.

A study is not considered human subjects research so long as the specimens are transferred with no direct patient identifiers and there is no interaction with human subjects when samples are left over from routine care collections, acquired from banked sources who obtained the samples with the appropriate permissions, or obtained through some other contrived means.

Other related factors to be aware of on this topic include:
• In the U.S., such studies do not require IRB oversight or informed consent from subjects; however, it would be appropriate to request a central IRB exempt determination only for the purposes of due diligence and documentation.[8]

• In the U.S., an individual responsible for treatment, payment, or clinical operations is permitted to remove identifiers to create samples and annotated clinical data defined as a limited dataset under the HIPAA regulation.

• In this case, it is permissible to use a Material Transfer Agreement with Data Use terms (HIPAA transfer method) that permit transfer of the material and use and disclosure of a limited dataset without HIPAA authorization along with the transfer of the samples.
  ○ Alternatively, at the time of IRB request for an exempt determination, a waiver of HIPAA authorization request may be granted if:
    ▪ Use and disclosure of HIPAA-defined Protected Health Information (PHI) involves no more than minimal risk to individuals and their privacy (there is an adequate plan to protect identifiers from improper use or disclosure, plan to destroy identifiers at the earliest opportunity, and adequate assurances the PHI will not be reused).
    ▪ The research cannot be practicably completed with the waiver.
    ▪ The research cannot be practicably completed without data—in this case, likely dates of service (i.e., date of sample collection, date of a testing result).
    ▪ Privacy risks are reasonable in relation to the anticipated benefits.[9]

• ISO 20916 permits the use of leftover samples for research without subject consent so long as there is no other interaction with the subjects and the test result is not being used to manage patient care.

Managing IVD Clinical Performance Studies

Site Qualification and Study Start Up

An IVD Clinical Performance Study may require a qualified laboratory for different kinds of testing. Some case examples follow:
An investigational assay (a moderate- to high-complexity lab instrument) is deployed to a lab environment for trained laboratory operators to run a candidate test for results. This lab may be a qualified “research” lab, but so long as the study is not interventional and the test results will not be released to the clinician or subjects for clinical care, this lab is NOT required to have CLIA Certification. This lab however, must “qualify” to perform the testing according to the investigational assay’s instructions for use (IFU) and must be qualified for research activity (i.e., qualified test operators and GCP training). This lab is responsible for the investigational product, reagents, sample preparation, etc. and testing according to the study protocol. This makes this lab “engaged” in the research and requires that this lab be considered a “site” that the IRB must approve for participation. This laboratory “site” requires all standard essential documents required for activation. Key areas of query for laboratory qualifications should include:

- Appropriate certifications for the assay type
- Laboratory Director with principal investigator (PI) qualifications
- Laboratory capability and qualifications to manage and track investigational product and specimens (traceability—parent/child sample chain of custody) and perform the specific testing (manual cytology, microscopy, pathology, etc.)
- Ability to generate collection kits and labels correlating all specimens and aliquots or “child” samples to a single clinical subject*
- Equipment and supplies required by the investigational assay IFU (freezers, refrigerators, centrifuge, laminar flow hood, reagents, antibodies, vortex mixer, cell sorter, 240-volt outlet, etc.)*
- Laboratory information system conforms to 21 CFR § 11 requirements for electronic signatures (individual accounts, log in credentials, auto log off, prompted password changes, limited log on attempts; at least two distinct components to eSignature, loss management for ID/passwords; user roles and permissions matrix, data quality checks, interface capability, internal testing; date and time stamp, virus protection, system controls to prevent external access)*
- Audit trail and export capabilities that preserve data integrity and security
- Written SOPs for clinical studies
A clinical performance study may require “comparator” testing on an instrument already cleared or approved for testing or detection of the target analyte. Laboratories that perform commercially available testing to provide test results as comparator data in alignment with all of the following conditions are not engaged in human subjects research, because:

- the services performed do not merit professional recognition or publication privileges;
- the services performed are typically performed by those institutions for non-research purposes; and
- the institution’s employees or agents do not administer any study intervention being tested or evaluated under the protocol. {10}

Further, an IRB requirement for oversight is limited to human subjects research and, in this case example, the lab is not engaged in human subjects research, because:

- the lab is performing services as a vendor;
- the services the lab performs are services typically performed for non-research purposes; and
- the lab is not interacting with subjects and is not receiving any personal data about subjects.

It is recommended that the study documents/trial master file (TMF) include an IRB exempt determination for this laboratory citing the salient factors (marked *) from above. When the IRB determines the reference lab is exempt from oversight, it also means lab personnel are not required to meet the experience and training obligations otherwise applicable to those who are engaged in research (i.e., GCP training). The TMF should include an executed vendor agreement between the lab and the sponsor, the appropriate CLIA certification (the laboratory is qualified to perform the services they typically provide for non-research purposes), and the IRB letter indicating the reference lab is exempt from IRB oversight.
• An investigational assay may be a point of care (POC), OTC, or direct to consumer (DTC) test that requires the clinical performance study to evaluate the test performance in the hands of the user in the intended use environment. For these kinds of investigational assays, be aware that:

  o a POC test intended use environment may require a CLIA Certificate of Waiver (for simple testing done for example in a doctor’s office)
  o an OTC or DTC test may require a simulated home use environment (not subject to CLIA regulations)

**Investigational Product Accountability**

In addition to traditional medical device accountability, ISO 20916 requires the same accountability tracking for all investigational reagents and accessories. These ancillary supplies are considered part of the investigational assay and should be labeled as Investigational Use Only (IUO).

Beyond device tracking, ISO 20916 requires accountability for specimens. These could be prospectively collected solely for research, might otherwise be banked/archived or contrived samples, or could be leftover clinical samples. Most sample tracking logs include variables critical to how the specimen performance is affected by any “excursions” from controls such as temperature, sample preparation, or specific technological processing steps to run the assay.

Some assays require special processing SOPs and/or require processing within conditions or a time window in which the samples are still considered “fresh.” Some samples are limited to a certain number of freeze/thaw cycles. Likewise, ISO 20916 addresses specimen chain of custody so that all of the specimen (which can turn into multiple child samples from the parent specimen) acquired from the subject or for the study is accounted for, including leftover samples when testing for the study is completed.
Data Management and Monitoring

Data collection for an IVD study is more about the relationship of multiple specimens to a single clinical subject compared to medical device data collection involving one subject, an index procedure or event, and then multiple longitudinal outcome measurements. A single IVD study subject may provide multiple specimens. These could include the same sample type but more than one sample, to allow for investigational assay testing as well as comparator assay testing. There might also be different sample types to allow performance evaluation of a test using, for example, a swab compared to urine.

An electronic data capture (EDC) configuration must connect a single subject and relative clinical data (demographics, disease history, symptoms, etc.) to potentially many samples (sample type, date/time of collection, storage, shipping, freeze/thaw, aliquot volumes, residual disposition, etc.) and test results (instrument, cartridge, reagents, quality control findings, date/time of testing, etc.). User comprehension, user experience, and observer surveys are common data collection events for assay testing for POC, OTC, and DTC use products and environments.

Managing data integrity often calls for a combination of data review and monitoring. Data review is the act of assessing data to identify blank fields, data outside boundary edits, missing data, and data trends. Data review is often facilitated by system-generated queries triggered by electronic edit checks built into the database.

Data review of instrument data, which is most often considered “original source,” is important to track samples, testing, and test results, which can be akin to tracking “enrollment” when the study does not include prospective specimen collection. Monitoring is the act of assessing data for verification to source documents. Data monitoring is performed by individuals qualified by appropriate training. Monitoring for IVD study data may be a combination of standard source data verification for clinical data, ensuring direct data capture on specimen and testing logs is complete, verification of accurate transcription into an EDC, and data review of instrument output.
Monitoring IVD studies includes all of the standard accountability for human subject protection, GCP, protocol training and compliance, maintaining adequate records and regulatory documents, and tracking site performance metrics. Specimen accountability has already been noted and should be addressed in the monitoring plan.

Adverse events (AEs) affecting the health and safety of subjects are uncommon in IVD studies, given most sampling procedures are not invasive and studies involving leftover or archived samples do not involve human subjects. AEs related to the use of an IVD medical device (adverse device effect) include “any AE resulting from insufficient or inadequate instructions for use…malfunction of the IVD (and) any event resulting from use error or intentional misuse of the IVD…. False negative or false positive results are not considered AEs unless seen in an interventional study where inappropriate patient management decisions are made based on those false results” (ISO 20916).

**Conclusion**

It is a simple and true statement that the U.S. FDA regulates IVDs as medical devices. IVDs are the same but different, a phrase and concept that recognizes both similarities and differences. The application of laws and regulations are the same for IVDs, but the lens for risk assessment, for example, is a different focus on accurate test results and how a false test result might cause harm to patients instead of bodily harm associated with implanted devices. Likewise, the same GCPs apply to medical devices and IVDs; however, with the latter, study implementation is “different enough” to have a separate ISO 20916 guideline.

There is a reported “bolus of companies in the diagnostics and genomics tools market” reporting hot products and business objectives at the 2023 JP Morgan Conference.{11} Words like liquid biopsy, cancer screening, cancer risk scores, multiplex respiratory panels, targets, biomarkers, and antigens highlight the investment in rising star diagnostics especially in oncology and infectious diseases. Large and small companies are keen to move new IVD products to market and will tap into CROs and clinical sites to support the clinical validations required for regulatory submissions.
With this limited review, perhaps there is new awareness of compliance obligations and operational logistics associated with IVD clinical performance studies. It might be time to explore talent, update SOPs, or edit templates and tools to add attention to the unique aspects of IVD products, study designs, and tactical implementation of IVD clinical trials.

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As decentralized clinical trials (DCTs) become more prevalent, particularly in the wake of the pandemic, their lower burden approach can make participation more attractive for some. Yet the vexing issue of retaining participants throughout the course of a trial will continue to be problematic without a thoughtful approach to keep them engaged. A three-phase model of engagement, based on proven science and intelligently informed by utilizing data, can make important inroads into solving this long-standing challenge.

Background

While concerns about how to successfully increase access and the pace of enrollment for clinical trials have often kept principal investigators and sponsors up at night, retaining enrolled participants is also critically important to consider. Poor retention rates can lead to increased costs and a loss of useful data for regulatory submission. According to Forte Research, the average dropout rate across all clinical trials is 30% and the average cost to recruit just one participant is $6,533. Retention throughout each phase of a clinical trial plays an important role in a study’s success, both from an economic and scientific point of view.

Despite the enormous impact that poor retention can make, a comprehensive study of more than 5,500 clinical trial participants, conducted by the Center for Information and Study on Clinical Research Participation (CISCRP) in 2019 and again in 2021, concluded that nearly one-quarter of all participants who enroll in clinical trials do not complete them, thus threatening the quality of the data and the integrity of a vast number of studies. [1]
The CISCRP survey results shed some interesting light onto why retention is such a challenge. The data seem to indicate that the burdens that many traditional clinical trial participants face have become more onerous in recent years. For example, in the 2021 survey, 44% of study participants indicated that traveling to a study clinic was “somewhat” or “very burdensome,” up 15% from just two years earlier. Additionally, the length of study visits was cited as “somewhat” or “very burdensome” by 40% of those who were surveyed in 2021, nearly double what respondents indicated in 2019.

These stark shifts in attitude over such a brief period can likely be traced to the repercussions of the pandemic. Participants seem to have appreciated the pivot that clinical trials made to online and digital methods due to COVID. A full one-half of the respondents who were surveyed in 2021 said that they wanted to see telemedicine and virtual clinic visits continue for clinical trials, even after the pandemic. These numbers are even more pronounced for Hispanic and Black respondents, with more than 60% of Hispanic and 56% of Black respondents favoring the digital shift.

The Case for Decentralized Trials, and the Challenges They Must Overcome

This growing discontent among prospective participants at the disruptive nature of traditional clinical trials presents a clear opportunity to do things differently. As the data from the CISCRP survey indicate, prospective clinical trial participants have a clear preference for studies that are more convenient and less demanding on their time. Decentralized trials (which invariably require less travel, less time spent in clinical settings, and incorporate more convenient methods of communication) clearly fit the bill.

Would a shift to participant-preferred DCTs automatically reduce the challenges of retention? First, it is important to recognize that the issue of compliance in healthcare (which for clinical trials is often manifested as dropping out of a study) are as old as medicine itself. Healthcare practitioners have struggled since the beginning of time, with varying degrees of success, to ensure that their patients adhere to their recommendations.

Clinical trials, of course, are not immune to these same challenges. There are countless reasons why noncompliance and poor retention occur in healthcare settings. Even when a participant has
every intention of completing a study, there are a myriad of reasons why they might lose their motivation and drop out. Yet, this outcome can be greatly improved through thoughtful and intentional engagement.

Dr. John P. Docherty, adjunct professor of psychiatry at Weill Cornell Medicine in New York City, notes that while digital health applications can be easier and more convenient to use, such benefits alone are not enough to create and sustain the level of engagement required for successful clinical study participants, particularly if they do not feel valued or have confidence using the technology. “Many things can interfere with engagement,” he says. “It requires a much deeper understanding in order for engagement to truly be effective.”

So how can study sponsors traverse these challenges and properly engage their DCT participants in ways that will help them stay enrolled in a study? “As the writer H. L. Mencken famously said, ‘For every complex problem there is an answer that is clear, simple, and wrong,’” Dr. Docherty says. “And this same logic holds true when it comes to healthcare compliance.”

There are no simple solutions. However, a lot can be learned from the extensive body of work across the behavioral, cognitive, and psychosocial sciences. Moreover, understanding how the most successful digital platforms engage their users can also provide some valuable insight.

The process begins by understanding what engagement means. When digital health applications first came to market, the understanding of user engagement was relatively simple. Analysis focused primarily on limited data such as how often users logged into the application or how much time they spent with it. Over time, the understanding of user engagement has become more sophisticated and nuanced. “We are thinking about engagement in a much more subjective way now,” says Dr. Docherty. “And to make a digital health application work, we know now that it has to be an enriched experience that draws on all of the aspects that cause people to be engaged with any activity.”

More advanced and thoughtful analysis of user data is particularly important when it comes to digital healthcare applications because healthcare settings, including those of clinical trials, exist outside most people’s comfort zones and typically increase anxiety. Add to this the fact that, while the digital environment of DCTs can mitigate some challenges, the experience of engaging
with the health application will invariably fall short of scrolling through Instagram or TikTok, where the algorithms are carefully designed to serve you more of what you already like. Further, the lack of frequent, in-person engagement with patients in a decentralized trial—while helping to reduce travel and time burdens—can also create a scenario where there is less opportunity to engage in a meaningful way.

**A New Solution: The Three-Phase Model of Engagement for DCTs**

A framework structured around the three phases of the engagement process (initiation, strengthening, and the maintenance of engagement) can provide a scaffolding that will enable sponsors to better understand how they can leverage technology to their advantage when interacting with trial participants. This three-phase framework enables trials to incorporate an extensive body of knowledge from across the psychosocial, behavioral, and cognitive sciences, and translate it all effectively to the digital health environment. Noteworthy here is that, while it’s not an easy fix, baking proven engagement strategies into decentralized trial platform technology offers a sustainable way to both improve participant access as well as retention throughout the duration of the study.

*Phase 1 – Initiation*

Initiating engagement is what starts prospective participants on the path toward trial completion. There are several factors that can help facilitate a participant’s initial engagement, starting with thoughtful technology design. An effective user interface is essential to induce participation and reduce early friction and anxiety that can impede participation.

Another initiation component is reflected in the Transtheoretical Model, or Stages of Change,\(^2\) which lays out the process that individuals go through while thinking about making a behavioral change. In addition, Motivational Interviewing,\(^3\) a goal-oriented style of communication, as well as Patient Activation Measure,\(^4\) which can help to measure a prospective subject’s engagement, should be employed. These tested strategies have been used for decades across various specialties with great success, and they can be effectively incorporated into the engagement algorithms used in digital applications to encourage and support engagement.
Ultimately, participants must feel competent and confident about their ability to use the technology in a decentralized trial. It isn’t good enough to simply assume that the application is user friendly. Additionally, health applications have the added layer of requiring users to have a relatively good level of health literacy. They need to understand the information that the application provides and be able to respond accurately and completely. Gently assessing participants for these criteria and providing them with the education necessary to make them comfortable is essential.

*Phase 2 – Strengthening Engagement*

Next, teams must work to strengthen that initial engagement, which is a central component for achieving what is referred to as “adherence” in the healthcare community. The often-used quote attributed to former U.S. Surgeon General C. Everett Coop, “drugs don't work in patients who don't take them,” indicates just how endemic the issue of adherence has been across healthcare over the years. However, digital health applications might offer a unique solution.

“Adherence is a complex and dynamic problem in healthcare delivery that we have never been able to effectively address before because it's too challenging to do in a face-to-face setting," says Dr. Docherty.

People’s feelings about healthcare and even their ability to access that care for logistical or financial reasons can change quickly, making it impossible for providers to understand what a patient or subject might be thinking at any given moment. Because of this, it is virtually impossible for providers to react properly to or anticipate how someone’s views or access will evolve over time. “Yet now, thanks to digital applications, we are capable of dealing with this ever-changing variable effectively, in real time, because we can see the participant’s behavior reflected in the data,” explains Dr. Docherty.

Boredom, fatigue, stress, and other demands can create a drag on a participant’s desire and ability to continue with a study. To prevent such attrition, engagement can be strengthened by establishing a collaborative relationship and “therapeutic alliance.”{5} Building a sense of trust and helping participants recognize that you and they are working together toward a collective goal is key. Key to this is to explicitly agree on required tasks and inform the patient about the
importance of each task to the study. This signals a collaborative relationship from the start, and when this engagement happens within a digital application, it can be more easily reinforced in an organic, burden-free way.

**Phase 3 – Maintaining Engagement**

The hard work doesn’t stop after the enrollment. In addition to continuing with tailored, subject-specific communications informed by adherence management data, the Nudge Theory{6} can be deployed. Platform providers should provide systems that guide trial participants to make good choices and stay on task. For instance, some applications might make lifestyle recommendations and send medication reminders as well as include motivational messaging. “If you start to notice from the digital data that a participant’s behavior is changing suddenly, technology makes it easy to adjust certain aspects of how you are engaging to maintain participation motivation,” Dr. Docherty says.

An advantage of a digital application for the maintenance phase is how often these data-driven prompts and changes can be made without having to ask the participant directly. This intuitive responsiveness can often yield better results than one-on-one, in-person questioning that may feel intrusive.

**Holistic Patient Engagement in DCTs**

A carefully designed framework can help guide the process of combining time-tested theories from the psychosocial, behavioral, and cognitive sciences with the exceptional analytical and intuitive technologies of digital applications. However, in all cases—whether a decentralized trial or hybrid or traditional onsite trial—engagement can only be improved if it is addressed holistically. At each stage of trial participation, changing circumstances, attitudes, and emotions must be considered, as well as those of the participant’s caregivers. Get this right, and the industry will see a real breakthrough in improving the systemic challenge of retention, thereby improving the speed, quality, and integrity of the trial and the generated data.

NOTE: The Interactive Journal of Medical Research published a peer-reviewed study of these considerations – see it [here](#).
References


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Despite the huge advances we have witnessed in recent years, one of the biggest barriers to technology-driven decentralized clinical trial (DCT) adoption remains a lack of agreed standards for compliance and ethics. Without definitive guidance, sponsors can find it challenging to be sure all the providers they enlist to conduct a study are collecting, managing, and sharing data ethically. However, a laser focus on joined-up, patient-centric, highest-standard processes could help organizations navigate the complex landscape and unlock the transformative power of digital data collection.

A Burgeoning Sector

DCTs, in which site visits are either replaced or augmented with remote data collection, are fast becoming the new normal. In 2022, an estimated 1,300 trials had a virtual component, representing a 28% increase from the previous year. [1]

It is a model that is streamlining research and making it more efficient, more patient-centered, and more inclusive. Furthermore, it is all being made possible by advances in digital health technologies, from remote data collection to patient support platforms.
Yet while the medical community is embracing this new way of working, barriers to adoption remain. One of the most pressing is a lack of a standardized regulatory framework.

DCTs widen access to studies by tearing down geographical barriers. When data collection happens remotely, participants do not need to live within travelling distance of a site. Yet just as DCTs are making research ever more international, cross-border variations in compliance guidelines are threatening to cancel this advantage out.

**Evolving Regulatory Landscape**

Until relatively recently, regulatory change had not kept pace with the rapid digital transformation of clinical research. The two sectors, after all, move at vastly different speeds. However, regulators are pushing forward.

In the United States, for example, the Food and Drug Administration (FDA) has published a suite of guidelines on the use of digital health technologies in clinical trials over the last few years. In Europe, the Accelerating Clinical Trials in the EU (ACT EU) initiative, part of the wider “modernization” of the region’s clinical trial regulation, places a clear focus on the effective remote collection of data during DCTs. Furthermore, the European Medicines Agency set out recommendations for the use of DCTs, with the intent to aid the use of DCT elements in clinical trials in Europe. Meanwhile in the United Kingdom, the Digital Technology Assessment Criteria (DTAC) sets minimum clinical safety, data protection, technical security, interoperability, and usability and accessibility standards for solutions to be used within the country’s National Health Service.

Such progress has been widely praised. Yet the region-by-region development of standards and guidelines creates a complex landscape for drug and technology developers to navigate. There is, for example, still much ambiguity around data capture, sharing, storing, and monitoring guidelines.
Transcending Regional Differences

During a DCT, data on everything from bank details to home addresses, regular blood pressure readings, and adverse events will be collected, stored, and monitored. It may even be shared between various third parties involved in delivering that trial, whether they be mobile health providers, travel systems, or expense reimbursement platforms. People need to feel confident that their most private personal data are being looked after.

The European Union General Data Protection Regulation (EU GDPR) is among the strictest set of data protection rules in the world.\(^6\) That makes it a good benchmark for any digital platform or solution, no matter where it operates.

As well as providing prescriptive data security guidelines, GDPR sets out the principles of processing with a call for careful consideration on what kinds of personal data are collected, how they are used, and how they are stored and maintained.

When digital health technologies are built around this clarity of purpose from the outset, it demonstrates a solid understanding of the value of following gold-standard data processes. It also acts as a “badge of honor” that gives trial participants and investigators confidence in how their information is used.

Mind the Data Gap

Sponsors setting out on the DCT journey, though, often find themselves in the position of selecting multiple partners and vendors, all providing their own individual technology and data protection policies.

Many of these providers may need to share data in order to fulfil their function. Mobile health teams need home addresses and access to clinical data, for example, whereas reimbursement platforms will need bank details and appointment dates, while travel systems require passport information.

With so many moving parts, it can be challenging to maintain appropriate oversight to ensure that each provider has access only to what they need and has the relevant protections in place—
but failure is not an option. As we have already seen in the evolution of digital health technologies to date, trust is hard won, but very easily lost.

Successive high-profile scandals, such as London Royal Free’s failure to comply with the Data Protection Act when granting Google’s DeepMind access to 1.6 million patients’ data in 2016,\(^7\) dented public faith in the approach.

That tide, however, is turning. More than 4.7 million people, for example, registered with the ZOE COVID app for regularly submitting their own health data and watching the research it facilitated change the course of the pandemic.\(^8\)

Maintaining this level of trust is mandatory if DCTs are to fulfil their potential, and sponsors are acutely aware that any breach of security could send the quest for more efficient clinical research back to square one.

One possible solution involves seeking out partners who provide seamless, integrated DCT services, all built to the highest possible standards of data protection. Consolidating siloed services reduces the likelihood of data protections “falling through the cracks” between disparate providers and eliminates the risk of sharing data with multiple separate businesses.

**The Road Ahead**

While regulatory bodies are making progress on digital health technologies and DCT guidelines, there is still much work to be done. Due in part to the unease around data security, many areas are still not keeping pace with change.

Specific considerations, such as the compliance of sharing data to enable investigational products to be sent directly from a warehouse to a patient’s home, rather than via a pharmacy, for example, remain unanswered. Getting to the bottom of questions such as these will greatly help make research more efficient for sponsors and more convenient for patients.

In the meantime, it is up to the research community to build the best possible protections for the invaluable data we collect, by focusing on trust and transparency, and setting ourselves the highest possible standards.
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The U.S. Food and Drug Administration (FDA) is getting serious about requiring diversity plans for clinical trials, as evidenced by this year’s omnibus spending bill signed by President Biden. Sponsors need to prepare for these new requirements now. A key focus in these diversity plans should be participant payments and reimbursement.

Appropriate payment to research participants is a critical aspect of diversifying clinical research participation.\(^1\)

Think of what it takes for you to get to a doctor’s appointment. If you are a parent, you must find childcare. If you work, you need to take time off. If you work in an hourly job or are self-employed, you may not have any paid time off, so you will need to factor in reduced income as well. If you have a disability that affects your mobility, those hurdles are magnified, and you may need to take a caregiver with you. Research studies often involve frequent appointments, and without appropriate compensation, many potential participants will be left out.

**IRB Perspective**

Institutional review boards (IRBs) are often seen as a barrier to paying participants in clinical research. While that may have been true in the past, thinking on this topic has evolved significantly during the past few years, informed in part by recognition of the importance of research participants as partners rather than as research “subjects.”\(^2\)
IRBs are tasked with ensuring that research recruiting and consenting processes do not exert undue influence on participants, and high payments may be seen by IRB members as unduly influential. Their concern is that payments could incentivize someone to participate in activities they would otherwise choose not to pursue—particularly people with low incomes. However, when an IRB insists on lower payments, participants who have less free time, less available income, or more burdensome lives are less likely to participate, and the study ends up with a participant population that does not match society because only those people who can bear the financial burdens of research participation will enroll.

**Current Thinking**

The clinical research enterprise now recognizes that payments can incentivize participants without being unduly influential. While there is a perception that IRBs will not approve high payments for participants, that is changing. During the past 24 months, out of approximately 10,000 IRB reviews conducted by WCG IRB, only 13 reviews resulted in the IRB specifically requiring modifications to the participant payment plan (see figure below for the reasons behind these decisions), and no records included a request to decrease the proposed payments to participants.

![Reasons Why IRB Required Modifications to Participant Payment Plans in 2022](image)
Should IRBs consider requiring higher payments? The majority of studies reviewed by the IRB do not include any payment to participants other than reimbursement for expenses. Often, even reimbursement is incomplete or capped, requiring participants to pay upfront for ride-shares, taxis, airfare, meals, and hotel stays. IRB discussions rarely focus on this disincentive to participate. Out of the 10,000 records reviewed, not a single one required that payments to participants be increased.

IRB members reflect the values and norms of their communities, and the events of the past few years have led to increased awareness of the importance, both scientifically and ethically, of having diverse representation in clinical trials. However, for improvements in participant diversity to occur, there must be greater support for higher payments to research participants and a reliance on mechanisms other than limiting payments to ensure participants are recruited ethically. This support cannot start at the level of IRB review.

Conclusion

The time has come for sponsors and clinical research organizations to accurately assess the costs to individuals tied to their research participation and provide them with just compensation for their service. These conversations need to be initiated by sponsors during the planning and budgeting process for trials. Ideally, sponsors will work with participant advocacy groups and other community stakeholders to understand the financial challenges faced by a given participant population before developing a budget for recruitment. Appropriate compensation should be considered in the context of the overall goal of improving diversity in clinical trials.

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In a little more than two decades, the volume of clinical research studies has grown exponentially with little sign of slowing down. As medicine progresses, researchers have expanded the breadth of treatments to address a wider range of health problems.

While this growth is certainly good (the clinical research market is expected to reach $8.8 billion over the next five years), it comes with its share of challenges. Clinical research sites lack the human talent to conduct the bureaucratic work of clinical research, greatly restricting the potential of many clinical study sponsors in the field.

A BDO report published in 2023 found that clinical research associates (CRAs) experience a turnover rate of 32% of in the United States. Overall, the industry has seen nearly a 10% decrease in staffing levels, creating first a manpower crisis and secondly, a training challenge to keep staff qualified for participation in clinical trials.

**Managing Design Complexity**

As medical treatments become more specialized, clinical trials also rise in design complexity. Combine complex design with staffing shortages, and site leaders will definitely find themselves with trial delays either from long start-up timelines or extended deadlines that further delay clinical studies.

Clinical trial design has advanced faster than some technology solutions available to site personnel. As a result, clinical sites often rely on legacy systems, both internally and provided by
trial sponsors. In addition to the scientific complexity in today’s protocols, they must often sort through complex technical requirements for each study. This results in a time-consuming and arduous process that often overtaxes those completing the work. The increased likelihood of human error can lead to inaccurate data requiring multiple systems edits to clean the data throughout the study and especially before the study ends.

The challenges contribute to an industry at a crossroads. There is ample opportunity for those who can overcome staffing issues and employee burnout to take advantage of the countless new studies waiting for clinical research sites that are adequately prepared to handle them.

**The Need for New Solutions**

Next-generation technology for randomization and trial supply management (RTSM) has emerged as a solution, replacing legacy systems commonly referred to as the old interactive voice response systems (IVRS). RTSM empowers sponsors to design complex clinical trials while keeping the site’s user experience simple, allowing for more time tending to test subjects and not handling data entry or interpreting technical requirements.

Clinical sponsors have typically leveraged either waterfall or agile software methodologies in their RTSM design. Waterfall has served as the traditional method for developing systems. Similar to coding, waterfall methodology collects all customer requirements at the beginning of a project and then builds a system to meet those requirements.

However, today’s waterfall methodology can no longer keep up with complexity demands as it lacks the agility and speed necessary to make changes as the study protocol and treatment options evolve. It fails to address changes quickly and ultimately presents research teams with an increased workload thanks to lengthy change orders. Risk management was not a typical element of waterfall development; therefore, changes introduced to a live system often took significant time and resources to implement, and often included focusing on elements that were not high priority to the study. With legacy systems, this is even more difficult since it may require specialized resources and lengthy testing and validation cycles.
Modern RTSM systems use an iterative process that enables user-friendly, early, and continuous delivery of the configured solution. Agile design methodology incorporates feedback and multiple design reviews during the requirements-gathering process to nimbly adjust designs as the system is built. An iterative build process also highlights high-risk areas of the design early, allowing teams time to discuss design options and mitigate risk by streamlining the design. Risk management and flexible, yet managed, change control systems are essential for this model to be successful. Even more significantly, there are seldom design changes during the testing and overall validation process in iterative development models. Multiple design reviews early on mean no surprises later, so testing can be laser-focused on verifying that results match requirements.

Once the system is in the hands of clinical sites, the continuous feedback loop of agile design ensures an intuitive experience for sites that can alleviate a CRA’s workload and burnout. This facilitates the randomization side of RTSM, ensuring that sites can randomize with confidence. The trial supply management is equally important and a modern RTSM will pre-emptively order materials before they run out to keep the supply chain turning smoothly. Single sign-on capabilities in most RTSM systems makes it simple for site staff to log into just one system and access all of the trials that they might be working on.

RTSM can help minimize waste, as well as time, while leveraging computer processing to alleviate human input for data entry and other manual tasks. Clinicians spend more time doing research work and avoid the burdensome tasks that lead many to leave their current positions or the industry altogether.

**The Path Forward**

The clinical research field finds itself at an exciting point. The growth of clinical research and the demand for research services provide an ample business opportunity. For those in the field, this growth leads to new career opportunities and research programs that can spark their intellectual curiosity.
To manage this growth, clinical researchers must rethink how they operate. Manual processes and extended timelines do not meet modern needs. Clinical organizations need agility and resilience to manage this onslaught in work, and that means using agile and resilient tools.

As clinical trial sponsors look at their operations, they should look for efficiencies in each process. For many, that includes leveraging RTSM technologies, supply chain management best practices, and new ways of easing the burdens on clinical sites.

Take the steps now to prepare your organization for this imminent future. Today’s efforts can provide immense dividends with increased capability and a happy and engaged clinical staff. The worker shortage will continue until employees feel heard and are happy in an environment that fits their needs. Leverage RTSM to improve operations and employees at your clinical sites will likely stay more engaged.

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Efforts to improve the regulatory review process through standardization, harmonization, and digitalization have gathered steam in recent years with regulators and industry alike pushing forward with data-driven initiatives. Guest contributors from PharmaLex discuss what these mean for 2023 and beyond.

For the past several years, and particularly since COVID-19, regulators and industry have been on a mission to streamline regulatory reviews, remove redundancy in the submission process, and ultimately bring products to market faster while not compromising on safety.

These objectives have led to several prominent projects and collaborations aimed at leveraging digitalization and data-driven processes to assist both submitters and reviewers. In the year ahead, these initiatives are expected to gain even greater traction as all stakeholders seek to tap into more sources of data, standardize and harmonize regulatory and business processes, and take advantage of new technologies such as automation and artificial intelligence (AI) to make the entire drug development and approval process better, faster, and safer.

There are several prominent global programs overseen by regulatory authorities as well as a number of industry-led initiatives that seek to digitalize and streamline different parts of the product lifecycle—from research and development (R&D) to regulatory submission to manufacturing and beyond.

The FDA and KASA

The first of these efforts is the U.S. Food and Drug Administration’s (FDA’s) pharmaceutical quality initiative dubbed the Knowledge-Aided Assessment and Structured Application (KASA),
which was announced in 2019 as part of broader work by the regulatory authority to modernize its regulatory assessments.

KASA “captures and manages information about inherent risk and control approaches for product design, manufacturing, and facilities, in a structured format.”{1} The objective is to take the chemistry, manufacturing, and controls (CMC) information that is included in submission documents and communicate that information to the authorities in the form of structured data. A structured assessment, aided by analytical tools to minimize text-based narratives, gives regulators a better understanding of the entire process and lets them make quality-based assessments in a more efficient, consistent, and objective way. The agency can also make use of KASA to tap into its broad repertoire of historical data to support decision-making.

The KASA review program is already under way, starting with abbreviated new drug applications (ANDAs) for solid oral dosage forms. The agency noted after the November 2022 meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee its intention to seek input on the vision to expand KASA to include all drug substances, new drug and biologic applications, and post-approval changes over the next five years. The agency also is seeking input on stepping up digitalization in KASA through data standardization and utilizing data from cloud-based servers.{2}

A related project is the FDA’s effort to develop structured data standards for pharmaceutical quality (PQ)/CMC information and a structured exchange standard for submitting those data to the agency.{3}

**EMA and DADI (PLM Portal)/IDMP**

Digitalization is also a high priority for the European Medicines Agency (EMA), which is replacing its PDF electronic application forms (eAFs) for regulatory submissions with digital submissions through its Digital Application Dataset Integration (DADI) project. Now referred to as the Product Lifecycle Management (PLM) Portal, the objective is to have sponsors submit information about their products in a structured fashion.
The portal will enable the EMA to build a large database of product details, all using the same terminology, to match up safety trends and spot signals that might have been missed with unstructured information. The agency has launched the web-based Human Variation eAF for centrally authorized products on the PLM portal and the development team is working on the data and functionalities needed to support decentralized procedure, mutual recognition, and national procedure variation applications. The goal is to introduce these to the eAF during Q2 2023, and to bring in further capabilities to support the transition to variation eAFs during Q2 and Q3. [4]

DADI is aligned with Identification of Medicinal Products (IDMP), since the portal will draw on elements of the SPOR (Substance, Product, Organization, and Referential) data. DADI and IDMP also offer drug and device companies a detailed framework to accelerate their digitalization initiatives. Since the new eAF will include a subset of IDMP data and offer the Fast Healthcare Interoperability Resources (FHIR) data standard, which will in time become mandatory, preparing for DADI is a key step toward IDMP readiness. [5]

**Regulatory Consortia**

There have also been stronger efforts by regulatory authorities to harmonize processes through several key collaborations, among them the Access Consortium, whose members include Australia (Therapeutic Goods Administration – TGA), Canada (Health Canada), Singapore (Health Sciences Authority – HSA), Switzerland (Swissmedic), and the United Kingdom (Medicines and Healthcare products Regulatory Authority – MHRA).

The health authorities from these countries collaborate to promote greater regulatory alignment, promote international cooperation, reduce duplicative efforts, and improve each agency’s capacity to review and approve products. Stated objectives for 2021 to 2024 include expanding work-sharing initiatives and sharing best practices, as well as finding ways to collaborate throughout a product’s lifecycle. One key area of focus is using real-world data and real-world evidence to inform clinical trial design, craft regulatory approaches, and support early access to emergency products, such as for COVID-19. [6]
Another regulatory consortium is Project Orbis, which brings together the FDA, the TGA, Brazil's National Health Surveillance Agency (ANVISA), Health Canada, Israel Ministry of Health (IMOH) Pharmaceutical Administration, the HSA, Swissmedic, and the MHRA. Project Orbis was established by the FDA’s Oncology Center of Excellence to support collaborative review of new cancer treatments to speed up access for patients in need.

**Industry-Based Collaborations**

Several prominent industry collaborations have formed in recent years to improve the product application process, address common industry problems, and establish best practices.

Accumulus Synergy is a nonprofit organization that is working with health authorities globally to come up with a central global mechanism for submitting application information through a multi-tenant, cloud-based environment accessible by all regulatory bodies. The objective is to achieve a single product, process, dataset, and submission platform. To date, 12 pharmaceutical companies are members of Accumulus. The organization will be rolling out pilots through 2023 and plans to have the platform broadly available in 2024. One of the first pilots will involve Project Orbis, initially testing submissions of synthetic data and carrying out full data pilots over the next year to 18 months.[7]

Another industry-led, nonprofit organization is the Pistoia Alliance, which has more than 200 life sciences members, including 18 of the top 20 pharmaceutical companies. The organization has more than 25 projects under way, aimed at addressing common industry barriers to innovation, including working with regulators to adopt new standards and supporting the implementation of AI. One key Pistoia Alliance project is an Identification of Medicinal Product (IDMP) Common Core Ontology to help bridge “regional and functional perspectives on common substance-related data objects and global and scientifically objective representations by a semantically defined integration layer of the IDMP standard.”[8] The goal is to ensure data usability across organizational boundaries and regulatory jurisdictions and counter any inconsistencies in interpretation of the standards.

In a similar vein, the DIA RIM Working Group proposed the Regulatory Information Management (RIM) Reference Model to address the problem of a divergent understanding of the
scope, terminology, processes, and data requirements of RIM. It is hoped that the RIM Reference Model will become a globally accepted standard, just as the trial master file (TMF) model has. This too started out as a DIA-led program and has since become integrated into Clinical Data Interchange Standards Consortium (CDISC) standards.

**Streamlining R&D and Regulatory Processes**

These different programs all come at a time when data have indeed become the new currency for the industry. Companies are seeking to tap into the vast amount of data they have and the ability to use data analytics to support their R&D and business goals—whether using real-world data to support clinical trials or gaining insights for a line extension or to analyze their marketing channels.

In 2023 and beyond, we are likely to see more companies make use of tools and technologies to assist them with processes such as intelligent automation, including natural language processing/generation as well as structured content management and authoring. Indeed, companies have already seen success in applying robotic process automation (RPA) to clinical and regulatory realms. In the near future, they are likely to look for further efficiencies by leveraging these tools to mine data and make decisions based on broader sources of information, as well as to tools such as natural language process to streamline authoring.

Other areas that will likely gain traction in the year ahead include the Internet of Things and RPA in manufacturing and packaging, for example, intelligent blister packs for clinical study supplies or post-market to monitor compliance with treatment protocols—innovations some leading companies are already trialling. With the trend toward decentralized clinical trials, wearables are likely to be more widely used during studies to monitor patients, and potentially even predict a safety signal.

In the area of CMC where manufacturing changes take place throughout the lifecycle of a product, companies often have to deal with different requirements globally. Here AI and other tools could prove helpful to allow companies to bundle submissions across multiple countries to optimize processes and limit redundancies.
Many of these digital innovations came to the fore during the COVID-19 pandemic as companies and regulators turned to digitalization to prevent too much disruption. They have proved that many processes can be handled better, faster, and more safely than seen from the use of previous methods. As an example, in the past, oversight of the TMF was a very manual process that involved site check-in and document collection. With more trials becoming decentralized, site visits have become unnecessary and all the information that previously was collected in-person can be accessed remotely.

The next step will be for companies to figure out how to govern these digital processes and technologies without stifling innovation to speed time to market. Already, the clinical realm has made huge leaps forward with digitalization. In 2023, we’re likely to see more digital advances to improve quality and drive greater efficiencies across organizations.

Certainly, regulatory requirements from the likes of EMA and FDA are driving change. Equally, however, companies are looking for opportunities to break down some of the functional data silos that have long plagued the industry. They’re looking to optimize their processes and streamline the handoffs between clinical and regulatory teams as well between manufacturing and quality functions.

**Meeting the Challenges Ahead**

While the move to digitalization and data-driven processes creates many synergies, there are obstacles for companies to overcome. For example, companies with multiple national registrations in the European Union will need to manage thousands of entries to the PLM Portal and will also need to find a way to maintain connectivity between their internal stores of data and what ends up at the health authority.

Managing these processes will mean some internal juggling as well as putting pressure on the health authorities that are implementing digital solutions that don’t enable direct machine-to-machine information transfer, as is the case with the PLM Portal. The best way forward will be to get involved in some of the consortia that are working to bring about greater harmonization, such as the Pistoia Alliance and Accumulus Synergy.
Change management will also become more important in order to help employees adopt new processes, such as structured content management. The business will need to invest more heavily in training efforts to help people adopt new technologies. Also, as with any change, it’s likely that the early adopters will lead the charge and, as their successes become apparent, others will follow suit.

From the regulatory authority side, there will need to be consistency and follow-through. Companies have invested time and money in preparing for IDMP only to see the EMA announce a change of plan and instead adopt the PLM Portal, at least for the time being. Having spent millions on new systems and processes, master data management, and new terminologies and ontologies, companies rightfully felt the rug had been pulled from under their feet. These sudden changes of direction will dissuade industry from investing time and money in any new regulatory initiative until it becomes mandatory.

With concerns over national or global recessions or downturns persisting, companies will likely want proof that an investment will provide clear business benefit—as many automation and AI innovations undoubtedly do provide—or certainty from the health authorities.

Nevertheless, 2023 will bring more investment in digital innovations that will help to move the needle for companies—whether in R&D, regulatory submissions, manufacturing, or commercial.

References


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**Cary Smithson** is Director of Regulatory Solutions at Phlexglobal, drawing on more than 30 years of experience in life sciences focused on leading strategic initiatives to drive increased business productivity, enhance regulatory compliance, and simplify information management and the use of technology.
Central to the discussion of assuring access to safe and effective therapeutics and devices is the recruitment of study participants who represent those destined to use these products. Historical gaps in the inclusion of women and racial minorities in clinical trials prompted policy as early as 1993, with the National Institutes of Health (NIH) Revitalization Act mandating the inclusion of these groups in trials conducted by those receiving NIH funding. However, requirements for reporting on racial and gender demographics in these trials are all too often still met with missing or incomplete data.

A study published last month (January 2023) in the open access journal Scientific Reports offers a detailed review and meta-analysis of gender, racial, and ethnic demographics in nearly 3,000 studies conducted in the U.S. between 2008 and 2019. The authors compared study demographics with U.S. Census data, and while there were some differences in the demographic percentages from year to year and for various subcategories, the results show that women remain slightly underrepresented in Phase II but accurately represented in Phase III trials.

Demographic representation according to race showed “underrepresentation” compared to their population percentage estimates for Hispanics, American Indians and Alaskan Natives, Asians, Whites, and multiracial study participants. At the same time, Native Hawaiians, Pacific Islanders, and Blacks were “overrepresented.” Black or African Americans represented 17% overall for all trials reviewed but 12.3% of the U.S. population based on the 2010 U.S. Census data.
The authors report that their findings “should be considered in the context of several limitations,” given the challenges with reporting race/ethnicity in trial databases. Nevertheless, the results show a mixed picture of successes and the need for continued efforts. This retrospective review comparing U.S. demographic data on race and gender to actual enrollment is helpful; still, the purpose of including a diverse study population is to ensure the results regarding safety and efficacy apply to all user groups.

U.S. Food and Drug Administration draft guidance on diversity plans issued in April 2022 encourages sponsors to submit a plan “as soon as is practicable during medical product development.” Sponsors should identify the influence of gender, race, and ethnicity on the safety and effectiveness of those most likely to be affected by the disease under study. As noted in the draft guidance, diversity in study enrollment goes beyond race and ethnicity since other demographic populations are underrepresented in trials. These include “gender identity, age, socioeconomic status, disability, pregnancy status, lactation status, and co-morbidity.”

Sponsor challenges to creating a plan to identify groups may include the rapidly changing demographics of race in the U.S. Compared to 2010, the 2020 U.S. Census revealed that the population is much more diverse, with a decline in the white population by 8.6% and a 276% increase in those who identify as multiracial (two or more races) from 9 million to 33.8 million. During the lifecycle of a drug, significant demographic changes will reinforce the need for continued safety monitoring but may require additional information on therapeutic benefits.

There are many scholarly articles on how to increase diversity in clinical trials. Approaches to increasing participation will likely be as diverse as the groups identified. Efforts to understand and define the most effective methods should begin with accurate and complete reporting of our study population group and sub-group characteristics. Lastly, central to any diversity initiative’s success is the public’s trust in the research process itself.

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It is no secret that employees are the heart of any business. It is, therefore, important that they remain engaged so that they can continuously provide high-quality work. Even though this is true in any business sector, it is particularly important for companies in the life sciences industry, where personnel must deal with many complex processes in a highly regulated environment to ensure both product and operations are compliant.

But what must life sciences company leaders do to make sure their staff are engaged? While there are many aspects to be considered, one that takes this goal a long way is having an effective training program. This cannot be just any training program, rather one that is linked to the goals of your organization.

There are several reasons why effective training programs are key. First, every organization in a regulated industry must train its employees, as is required by all major regulatory bodies around the world. Second, training helps with developing or refining the knowledge and skills of the personnel so that they can safely, effectively, and consistently perform their jobs. This, in turn, is proven to boost their engagement levels while attaining a quality culture throughout your organization.

Moreover, enhancing the knowledge and skills of employees naturally increases their abilities for future delivery. Consequently, establishing a training program linked to the organization goals will provide you with well-trained, proficient, and engaged employees who will be able to speak knowledgeably about the industry, and will greatly contribute to increasing customer satisfaction levels.
What is Employee Training?

At its core, training is teaching, or developing any skills and knowledge that relate to specific competencies. Employee training provides workers with education and skills related to their jobs and areas of expertise to assist them in staying up to date with the skills that are needed and in demand from the job market they belong to.

When dealing with a regulated environment such as that found in the life sciences industry, the expectations from regulatory bodies such as the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and Health Canada are clear. Regulations from these agencies set out requirements for education and training, as well as the number of personnel needed to perform required tasks and duties. Some common expectations outlined in regulations are:

- “Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions.”[1]
- Tasks, roles, and responsibilities are defined in job descriptions and organization charts.
- Personnel are trained and/or otherwise qualified in the procedures and methods they use and the tasks they perform.
- Key personnel—including consultants and contractors—have the professional, educational, and experiential credentials required.
- Supervisors and management have training that is appropriate to their functions.

The takeaways here are simple but critical: regulatory investigators are looking for assurance that personnel have the qualifications and skill sets required to perform tasks and fulfill their duties. Given these expectations, every individual must be educated and qualified (and re-trained or re-qualified, as needed) to perform the specific tasks they are assigned.
Developing an Employee Training Program Linked to the Organization’s Goals

There are some valuable steps that organizational leaders can take to ensure their employees are not just trained to the requirements, but also to the goals and objectives of the organization:

1. **Identify Your Needs and Establish Goals**

   Be clear from the outset what the organization is trying to achieve (goals, objectives, and mission statements). This is important for a very practical reason: you want to invest your money wisely. This first analysis will identify job-related tasks that must be learned, next steps, and strategies to achieve the goals, competencies, and skills required to perform the job. It will also identify the employees who need training. For example, you might identify the need to strengthen the technical side (products/processes) of your sales team, so they can add new elements into their sales pitches. This step should help with that determination.

2. **Turn Internal Subject Matter Experts into Training Partners**

   These resources are critical as they are the content experts. They can contribute to the design of the training program by ensuring the course content is focused on the learner’s needs. They will also help ensure that courses are effective and meet business objectives.

3. **Assess the Current State of Training**

   The assessment should cover:
   
   - Organizational skills: Do the people in your organization have the knowledge and abilities required to achieve your organization’s strategic objectives?
   - Occupational skills: Do employees possess the knowledge, skills, and abilities required to do their day-to-day jobs?
   - Individual assessment: How is each employee performing? What are their required training needs?
4. **Identify Strengths and Gaps**

The assessment should identify who needs training and the type of training needed to bridge gaps and enhance company performance. The following questions may be used as a starting point:

- What is the organization trying to accomplish?
- What skills are needed for organizational success?
- What is the current skill level of each employee?

5. **Track, Analyze, and Improve**

Once started, the training must be executed continuously to achieve full benefits. Training should not be a one-off event, otherwise, the benefits may be short-lived. You need to also keep in mind that everybody learns differently, and what works for some individuals may not work for others. Therefore, it is extremely important to track and measure the results and strive for an individualized approach (or focus) when needed.

Another important aspect is being able to deliver training at the right time. If there is a training need or the need to improve the knowledge or skill set of a team from a particular area, it is important to address it with the right training at the right time. One example would be the onboarding training that every new employee is expected to receive. It must be done immediately to equip the new employees with the required tools to execute appropriately right away.

Having a competent, professional workforce is essential to meeting the dual goals of business requirements and regulatory expectations. With an effective training program that is linked to your organization’s goals, you can efficiently accomplish both, and increase employee’s engagement levels as a result.
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Clinical Researcher—February 2023 (Volume 37, Issue 1)

NEW E-R-A IN PROJECT MANAGEMENT

Leading Intelligently with Heart (Part 2): Enhancing Project Managers’ Emotional Intelligence Through Mindfulness

Zoran M. Pavlovic, MD

Following up on some of the emotional intelligence (EI)-driven leadership topics I began addressing in my column for the August 2022 issue, the concept of mindfulness is rooted “in the ancient wisdom tradition of Buddhism.”[1] Still, it can also be linked to and religions Hinduism and other spiritual-based traditions.[2] Although mindfulness practices began thousands of years ago, present-day mindfulness therapies are credited to Dr. Jon Kabat-Zinn, an American professor of psychology at the University of Massachusetts in Boston who developed a stress-reduction program in the late 1970s.[3]

While theories of mindfulness have evolved over the years, its objective remains the same: to achieve a state of profound insight.[3] Rynes, et al.[4] define mindfulness as “enhanced attention to and a receptive awareness of current experiences.”[5] Such heightened awareness “involves rigorous mental practice to develop focus, awareness and living in the moment.”[6]

Broadening the definition and the scope of mindfulness, Dr. Kabat-Zinn also explains that the word for mind and heart in Asian languages are the same and that mindfulness and compassion are interconnected.[7] This interconnectedness demonstrates that mindfulness contains an emotional component. When considering Mayer, Salovey, and Caruso’s[8] definition of EI—that is, being able to “perceive accurately, appraise, and express emotion…access and/or generate feelings when they facilitate thought…understand emotion and emotional
knowledge…[and] regulate emotions to promote emotional and intellectual growth”{9}—connections between EI and mindfulness become even clearer.

First, mindfulness enables heightened awareness,{10} and EI emphasizes the importance of perception{8}; essentially, it can be rather difficult to understand the various interpretations of perception without heightened awareness. Second, mindfulness corresponds to living in the moment,{10} while EI emphasizes the need to accurately understand emotions{8}; given that emotions occur at the moment, assessing them accurately as they occur is an important aspect of mindfulness. Third, the pursuit of emotional and intellectual growth is at the center of EI,{8} while mindfulness emphasizes the importance of continuous and rigorous mental practice.{5}

Frizzell, et al.{1} identified a positive correlation between individuals who practice mindful meditation and their ability to establish effective relationships—a key determinant of strong social skills. Han and Zhang{11} found that “employees who are not operating in a mindful state of awareness tend to act without thinking, may not notice when new information is available…and are not aware of or open to looking at alternate ways of accomplishing a certain task.”{6} These individuals tend to relate with others in what is called “automatic pilot”—that is, they may not always reflect before acting and therefore rely on previously held beliefs to make decisions.

Further, better stress management and coping abilities have been noted in those professionals who have undergone mindfulness training. This increase in resilience can help project managers (PMs) lessen the negative impacts of their demanding jobs, reducing emotional exhaustion, increasing their commitment to their work, and improving their performance when facing challenges in their workplace. Mindfulness has also been identified as a protective factor against the stress caused by emotional labor (i.e., when handling emotionally difficult situations).

**Practicing Emotional Intelligence**

Offered here are some excerpts from the book *Poised for Excellence*’s chapter on “Emotional Intelligence Drives Leadership Success,” by Karima Mariama-Arthur,{12} who writes, “The strategies outlined in the following sections offer guidance for cultivating the skill and insight required of an emotionally intelligent leader. They are distilled from the lessons I have learned from exceptional leaders across various industries.”
Increase the Range of Your Emotions

Challenging yourself to identify and experience a more diverse range of emotions daily can increase self-awareness. You can escalate this process simply by being more sensitive to your emotions. When they arise, identify them individually by name and think about why you are experiencing them. …Over time, you will discover key distinctions that will help you expand and take control of your emotional wheelhouse.

Exercise Greater Control Over Thinking and Behavior

Learning to control thinking and behavior takes work, but it is doable with discipline and consistent effort. Instead of habitually reacting to stimuli, decide to respond on your terms. In other words, be proactive rather than reactive. When faced with a decision, consider the possible options and their consequences. …By focusing on producing the best outcomes through clarity of thought and intentional behavior, you can completely transform your state of mind and achieve positive results.

Thoughtfully Engage Others to Develop Empathy

Developing empathy is vital to improving every interaction, and it requires intentional engagement with others. Embracing perspectives other than yours, being less judgmental, and giving others the benefit of doubt are ways to cultivate empathy through thoughtful engagement. …These strategies enhance the ability to establish rapport and understanding, which are the basis for trust, high-quality interactions, and long-term relationships.

Ramp Up Intrinsic Motivation

If you are serious about making progress in any area of life, start by determining whether you are driven by the carrot or the stick. Do you find the promise of reward more motivating or the fear of punishment? …Adopt whichever mindset is more compelling and then formulate a strategy broken down into individual tasks. This will move your goals forward and decrease the anxiety of tackling them all together.
Increase Social Competence

Because we are social beings, it is nearly impossible to avoid human contact. Therefore, it makes sense to embrace relationships and make them work to your advantage. Learning social competence is a multifaceted process that involves basic conversation, complex communication, networking, collaborating, social etiquette, and conflict resolution. …To get started, move out of your comfort zone and practice active listening, engaging in meaningful conversations, collaborating, negotiating, and exercising common courtesies whenever possible.

For Your Consideration…

Below are some additional tips that have proven to be very helpful for my coachees when setting their goals in an emotionally intelligent way:

- Do your best to align future objectives, visions, or plans with your current beliefs. If they aren’t, you risk striving toward an end that won't be beneficial to you.
- Everything begins with your feelings. Compare and contrast your goals to your feelings and thoughts.
- Always connect emotionally with your goals.
- Take note of and practice the behaviors and habits that will assist you in reaching your goals.
- Develop strong positive attitudes and beliefs that will support your values and contribute to your success.
- Increase your self-awareness to recognize when your goals don’t align with your values.
- Remember that, depending on their congruence, beliefs, attitudes, and behaviors support and strengthen each other, whether negatively or positively.
- Structure your goals following your values, attitudes, and the likelihood of success, and never forget to set a clear deadline.
- Finally, continuously monitor and measure your progress toward achieving your goals.

References


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Another revolution around the sun has not only brought us all into 2023, but has also brought me to a head-on collision with my 17th anniversary of working for ACRP on the same day as this issue of Clinical Researcher goes online. As Wallace Shawn’s character from The Princess Bride would say, I find this to be “Inconceivable!” Like a stranger in a strange land, I am boldly going into an undiscovered country, along with all the other sci-fi and fantasy references I can carry with me. You see, I’ve never worked this long for a single employer before (my previous record was 15 years and four months, to be precise, but somehow hitting my 16th year devoted to clinical research last year didn’t affect me as much as this year’s new notch in the belt); where do I go from here?

Well, I came onboard just in time for ACRP’s 30th anniversary in 2006 and was a seasoned pro at living the membership association lifestyle by the 40th in 2016, so typing away for another few years to see what the 50th anniversary celebration will look like shouldn’t be too much of an ask. In the meantime, revolutions of the “way things are” vs. “the way things should be” sort are happening everywhere you look and reach in the clinical research enterprise—in trial designs and technologies, in workforce training and development, in regulatory compliance, in data management, in patient recruitment and retention… the list goes on—as can be appreciated from the contents of this issue. Here are hints of some more revolutions you may wish to explore, brewing out there among organizations of note (no endorsements implied) in their various kingdoms and fiefdoms. Have fun storming the castle!…

**Reaping Retention from Robust Employee Rewards**

Employee turnover continues to plague the global market for talent in contract (or clinical, if you prefer) research organizations (CROs). The companies that will be successful in not only retaining top talent but also in recruiting will employ innovative approaches to their reward strategies, according to the latest Insights Report based on results from the recently published “BDO CRO Industry Global Compensation & Turnover Survey.” This Insights Report discusses
how now, more than ever, companies are digging deep to find ways to make sure employees stay, which is stirring the buzz term “The Great Retention.”

Looking at compensation levels, plan design, and employee turnover, the annual survey collected data for 268 positions in the U.S. and 55 countries outside the U.S. to help clinical research outsourcing companies develop confidence in their pay levels by providing data necessary to gain insight into their compensation practices relative to the market.

**AI and Big Data Impacts on Pharma Expected to Live Large in 2023**

Artificial intelligence (AI) and Big Data will be the two most impactful technologies for the pharmaceutical industry for the fourth year in a row in 2023, according to a survey by GlobalData. The data and analytics company notes that 39% of healthcare industry professionals in the survey believed that AI would be the emerging technology bringing the greatest impact on the pharmaceutical industry in 2023, followed by Big Data with 27% of the selection.

The “State of the Biopharmaceutical Industry 2023” survey results reveal that AI and Big Data were trending as the two most disruptive emerging technologies since 2020, with a significant margin from the third choice in all four years (see figure below).
“It might take some time for AI and Big Data to display their true power, but the two technologies together are expected to play an important role in the industry, in terms of optimizing the entire pharmaceutical value chain,” said Elton Kwok, market research manager in Pharma at GlobalData. “This powerful duo can be applied to optimize a wide range of processes, from drug design to end-user reach.”

**U.K. Independent Trial Sites Continue to Prosper Despite Decline of NHS Sites**

The independent site management organizations (SMOs) which run clinical trials on behalf of the pharmaceutical industry continue to expand not only the number of trials being brought to the United Kingdom, but also the number of patients enrolled. While the Association of the British Pharmaceutical Industry reported that there was a substantial decline in patient numbers at National Health Service (NHS) sites in the U.K., independent SMOs are doing well.

According to Chris Dodd, chief commercial officer of Panthera Biopartners, “The SMOs which recruit tens of thousands of patients each year to clinical trial sites across the U.K. not only continued to run trials during the pandemic—including many of the major vaccine studies—but also rapidly recovered from COVID and are providing global pharmaceutical companies with access to more and more U.K. patients. However, the U.K. NHS sites have not only been closed to clinical trials for years, but are also very slow in moving from discussion to enrollment.”

**Partnership Aims to Bolster Clinical Trials for Natural Products**

United Natural Products Alliance (UNPA), an international trade association for natural products, and Radicle Science, a proof-as-a-service company offering a path for non-pharmaceutical products to clinically prove their true effects beyond placebo, have announced the launch of a partnership enabling UNPA members priority access to join in Radicle’s clinical trials as participants, furthering their synergistic missions. Collectively, they expect to generate important new findings to prove the effectiveness of natural products while illustrating the power of large-scale clinical data.

“For far too long, only patented pharmaceuticals could afford clinical trials, traditionally costing millions and taking years,” shared Dr. Jeff Chen, MD, cofounder and CEO of Radicle Science. “We’ve democratized access to clinical trials to close the proof gap between natural
supplements and pharmaceuticals. As the UNPA has played such a monumental role in the legislative history of supplements, it’s fitting that UNPA members will help make history by personally participating” in the company’s clinical trials.

UNPA represents 100 natural products, dietary supplement, functional food, and scientific and technology and related service companies. Meanwhile, at the end of each Radicle study, volunteers are unblinded immediately and provided with personalized health reports so they can understand their product usage and the outcomes on their unique body.

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