

Clinical Researcher

The Authority in Ethical, Responsible Clinical Research

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I Can See Clearly Now

(The Power of New Perspectives On the Clinical Research Workforce)

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Clinical Researcher

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Six issues of *Clinical Researcher* will be published on a bimonthly schedule in 2022. The Home Study tests will grant 3 Continuing Education Credits.

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EXECUTIVE DIRECTOR'S MESSAGE

What's Already Here and On the Horizon

Susan P. Landis, Executive Director of ACRP



After some freezing temperatures here in “the cradle of CROs” (aka Raleigh-Durham, N.C.), the thermometer hit 65 degrees in mid-February. The hint of warmth and sunshine make me long for spring, and spring makes me think of gardening, and gardening makes me envision new things breaking through.

That image makes me want to share everything that’s going on at ACRP in the coming weeks. We are thrilled to be creating, curating, and coordinating programs for you—all in support of our mission to ensure excellence in clinical research.

First, I want to introduce two new team members. Phillip Green has joined ACRP as our new Director of Finance. Kara Bastarache joins us as our Senior Manager of Educational Programs, leading our [Partners for the Advancement of the Clinical Research Workforce](#) and our [Diversity Advisory Council](#). Welcome, Phillip and Kara.

February marks the celebration of Black History Month. ACRP is recognizing achievements and contributions of African Americans in clinical research, while [highlighting voices](#) among our membership, including those of Danielle (Coe) Mitchell and R’Kes Starling.

Members also will be heard at ACRP’s upcoming Partners for the Advancement of the Clinical Research Workforce Think Tank, to be held in conjunction with [ACRP 2022](#), the Association’s annual conference. Our esteemed group of thought leaders will be tackling how to reduce barriers to entering the field of clinical research, specifically discussing how to build and advance a diverse, research-ready workforce and how to look beyond job requirements and address skill sets needed for early talent development.

ACRP 2022 is just on the horizon, to be held at the Hyatt Regency Orlando April 22–25. Our theme is Celebrating YOU, and we look forward to reuniting to discuss strategies, best practices, and creative solutions for improving clinical trial quality and advancing your career. You can register [here](#) and read [here](#) about our plans and policies for ensuring the safety of our attendees at the conference. I hope to see you there!

Looking ahead to May, ACRP has kicked off [fund raising](#) for the second annual [Ride for Diversity](#) in conjunction with Clinical Trials Day. This *road trip for a reason* is being led by members Sergio Armani of Advarra (also ACRP Board member and Treasurer) and Rick Fisher of Velocity. Word has it that some of us will be riding in spirit on our stationary bikes—#ACRPeloton!

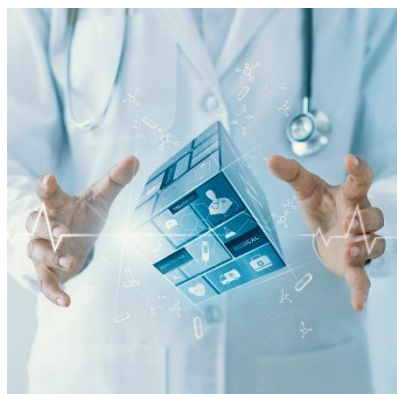
Wherever you are, I hope you also are experiencing a few warmer days and that the sunshine is helping you look forward to brighter days ahead.



PEER REVIEWED

The Clinical Research Investigator: Clarifying the Misconceptions

Steven Eric Ceh, DPM



The terms “investigator,” “co-investigator,” “clinical investigator,” “principal investigator,” “co-principal investigator,” “study principal investigator,” and “sub-investigator” are often used loosely. This article clarifies the roles and responsibilities for each term according to U.S. regulations and international guidance, with the following factors in mind:

- The terms investigator, principal investigator, and clinical investigator are interrelated but not necessarily synonymous.
- Sub-investigators are individual members of the research team and are not equivalent to investigators.
- Co-investigator and co-principal investigator are uncommon, misunderstood terms.
- Clinical investigator, as described in 21 CFR Part 54 in the *Code of Federal Regulations*, {1} differs from the term used in 21 CFR Parts 312 and 812, which is a cause for confusion.

Detailed information and discussion follow, with a review of key references that will provide clarity for these terms.

How Are These Terms Defined?

21 CFR 312.3 states that “investigator” means “an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject).” Similarly, 21 CFR 812.3 states that “investigator” means “an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered to, or used involving, a subject ...” Both of these definitions also specify: “In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team.” 21 CFR 312.53(a) states that investigators are “qualified by training and experience as appropriate experts to investigate the drug.”

The International Council for Harmonization E6(R2) Good Clinical Practice (ICH GCP) guideline^{2} states in section 1.34 that an investigator is “a person responsible for the conduct of a clinical trial at a trial site.” It further states: “If a trial is conducted by a team of individuals at a site, the investigator...may be called the principal investigator.” Therefore, the term principal investigator is an appropriate term whenever there are one or more team individuals in addition to a single investigator. However, “investigator” is primarily used throughout the regulations. The term co-principal investigator is not defined, as it is not possible to have more than one outright leader and, therefore, should not be used. Also, study sponsors will sometimes designate an investigator in a multisite study to be the study principal investigator and team leader over the other site investigators.

ICH GCP 4.4.1 adds that an investigator “should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial and should meet all the qualifications specified by the applicable regulatory requirement(s) and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the [institutional review board/institutional ethics committee (IRB/IEC)] and/or the regulatory authority(ies).” ICH GCP 2.7 adds that “the medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.”

The U.S. Food and Drug Administration (FDA) Compliance Program Manual 7348.811 for the agency’s Bioresearch Monitoring (BIMO) Program utilizes the term “clinical investigator” and states^{3}:

A clinical investigator is the individual who conducts the clinical investigation. The clinical investigator is responsible for overall conduct of the study at the clinical site, including directing the administration or dispensing of the investigational product to the subject and ensuring that data are collected and maintained in accordance with the protocol and applicable regulatory requirements. When the investigation is conducted by a team of individuals, the clinical investigator is the responsible leader of the team.

With that, the term clinical investigator encompasses “investigator” as stated in 21 CFR 312 and 812 and “principal investigator” as stated in ICH GCP 1.34.

The term “clinical investigator” is also used in a document on “Financial Disclosure by Clinical Investigators—Guidance for Clinical Investigators, Industry, and FDA Staff” from 2013.^{4} Those individuals who would be clinical investigators under 21 CFR Part 54 are individuals listed on lines 1 and 6 of the Form FDA 1572 (Statement of Investigator) (drug study) and the investigator and all individuals designated by him/her as sub-investigators (device study). Therefore, one must be careful of the context when referring to an individual as a clinical investigator. How the terminology differs from that of 21 CFR Parts 312 and 812 is further discussed below.

In a 2010 document on “Frequently Asked Questions—Statement of Investigator (Form FDA 1572)—Guidance for Sponsors, Clinical Investigators, and IRBs,”^{5} question 21 addresses the term co-investigator and states:

As commonly used, the term is meant to indicate that each co-investigator is fully responsible for fulfilling all the obligations of an investigator as identified in 21 CFR 312.60. Thus, under 21 CFR 312.3(b), each co-investigator is an investigator, and as such must sign a separate 1572.

Who Can Be a Principal Investigator?

Section 505 of the Food, Drug, and Cosmetic (FD&C) Act{6} requires the FDA to ensure that the investigational drug will be provided only to investigators who are “experts qualified by training and experience to investigate a new drug.”

The FDA has the following to say about non-physicians as investigators:

While technically a non-physician can be an investigator, this requires that the non-physician be qualified to personally conduct or personally supervise all aspects of the study. In practice, we have found it rare that a non-physician can comply with this requirement. In general, where we have seen non-physicians on the Form FDA 1572 as an investigator, we usually would find an MD as a sub-investigator to perform those study functions requiring the appropriate level of medical expertise.

Qualified individuals who are not (MDs/licensed physician) can participate in clinical trials as an investigator or sub-investigator provided that an MD, DO, DPM, or D.D.S. is listed in the [Investigational New Drug application] as an individual who will be responsible for diagnosis and treatment of disease, drug administration, and evaluation of safety.{7}

An FDA Office of Medical Policy communication has stated the following{8}:

Protocol-required tasks must be performed by the individuals specified in the protocol. For example, if the state [or jurisdiction] in which the study site is located permits a nurse practitioner or physician’s assistant to perform physical examinations under the supervision of a physician, but the protocol specifies that physical examinations must be done by a physician, then a physician must perform such exams.

As a result, a clinical psychologist could serve as investigator with an MD sub-investigator. Similarly, a Doctor of Pharmacy could serve as investigator of a pharmacological study with an MD sub-investigator. In theory, anyone qualified to conduct a clinical study who is not an MD or dentist could be an investigator, provided an MD or dentist handles the medical (or dental) decisions and care as sub-investigator or co-investigator.{7}

Nurse practitioners have full medical practice privileges in 22 states: Alaska, Arizona, Colorado, Connecticut, Hawaii, Idaho, Iowa, Maine, Maryland, Massachusetts, Minnesota, Montana, Nebraska, New Hampshire, New Mexico, North Dakota, Oregon, Rhode Island, South Dakota, Vermont, Washington, and Wyoming, as well as the District of Columbia.{9,10} In these states, nurse practitioners can be autonomous principal investigators; other similar emerging autonomous roles for nurses (e.g., advanced practice registered nurse [APRN]) are occurring in some states. However, that is currently not the case for physician assistants, who still work under the supervision of a physician, although there is currently legislation in several states to allow them to be independent practitioners.

Lastly, there can be instances where other healthcare practitioner/specialists can be an autonomous investigator based on their expertise, training, licensure, and the scope of the investigative study. Such an example would be an optometrist (OD) serving as the investigator on a study evaluating marketed pharmaceutical products or medical devices (e.g., contact lenses, lens care products, punctal plugs) where the inclusion of an MD on the 1572 or equivalent medical device form is not necessary.

Sponsors are responsible for selecting qualified investigators and often have the opportunity to discuss investigator qualifications with FDA prior to study implementation. The FDA's acceptance of an investigator may vary with the FDA division, the indication, safety risk, study phase, and approval status, but this individual should always be an expert qualified by training and experience to investigate a new drug or device.

Who Must Make Financial Disclosures?

The aforementioned FDA guidance on "Financial Disclosure by Clinical Investigators" states the following{4}:

Section III A specifies the individuals for whom reporting under this regulation is required. Generally, these individuals are the investigators and sub-investigators taking responsibility for the study at a given study site. The sub-investigators are delineated in Section 6 of the Form FDA 1572 completed by the investigator. The definition also includes the spouse and dependent children of each investigator or sub-investigator.

For purposes of [21 CFR Part 54], “clinical investigator” means a “listed or identified investigator or sub-investigator who is directly involved in the treatment or evaluation of research subjects,” including the spouse and each dependent child of the investigator or sub-investigator. (See 21 CFR § 54.2(d).)

Therefore, this would be the investigator and all of the individuals designated by him/her as sub-investigators (i.e., other physicians, pharmacists, research fellows, residents, study coordinators, data coordinators, etc.).

Section IV D of this guidance discusses how the above definition differs and is otherwise not equivalent with investigators as defined in 21 CFR 312 and 812:

For drugs and biological products, an investigator under 21 CFR Part 312 is defined as “an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team.” This is the individual listed on line 1 of the Form FDA 1572 of a research site.

For medical devices, investigator is defined under 21 CFR Part 812 as “an individual under whose immediate direction the subject is treated and the investigational device is administered, including follow-up evaluations and treatments. Where an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. (21 CFR § 812.3(i).)” This is the individual listed as the investigator on the medical device study Investigator Agreement.

Who is a Sub-Investigator?

The aforementioned FDA resource on “Frequently Asked Questions—Statement of Investigator (Form FDA 1572),” under Question 31, discusses how investigators and sub-investigators are defined and documented in a clinical study{5}:

FDA regulation 21 CFR 312.3(b) states: “In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. ‘Sub-investigator’ includes any other individual member of that team.’ 21 CFR 312.53(c)(1)(viii) requires the investigator to provide ‘a list of the names of the sub-investigators (e.g., research fellows, residents) who will be assisting the investigator in the conduct of the investigation(s).”

The purpose of Section #6 is to capture information about individuals who, as part of an investigative team, will assist the investigator and make a direct and significant contribution to the data. The decision to list an individual in Section #6 depends on his/her level of responsibility (i.e., whether they are performing significant clinical investigation-related duties). In general, if an individual is directly involved in the performance of procedures required by the protocol and the collection of data, that person should be listed on the 1572. For example, if the protocol notes that each subject needs to visit a specified internist who will perform a full physical to qualify subjects for the clinical investigation, that internist should be listed in Section #6.”

It is important to note that some sub-investigators will be licensed physicians/practitioners who were at one time an investigator for a study or have the qualifications to be one and thereby be appropriate for delegation of certain duties by the principal investigator. Further, sub-investigators have no automatic responsibilities—only those which are delegated to him/her by the investigator and which he/she is qualified to do.

Questions 32 and 33 offer clarification as to whether hospital staff, nurses, residents, fellows, office staff, pharmacists, or research coordinators should be listed on the 1572:

It is a matter of judgment, dependent upon the contribution that the individual makes to the study. For example, a research pharmacist may prepare test articles and maintain drug accountability for many clinical studies that are ongoing concurrently at an institution. Because the pharmacist would not be making a direct and significant contribution to the data for a particular study, it would not be necessary to list the pharmacist as a sub-investigator in Section #6, but he/she should be listed in the investigator’s study records.

Generally, a research coordinator has a greater role in performing critical study functions and making direct and significant contributions to the data. For example, a research coordinator often recruits subjects, collects and evaluates study data, and maintains study records. Therefore, the research coordinator should usually be listed in Section #6 of the 1572.

However, according to an informal response from FDA,{11} the Center for Devices and Radiologic Health would not consider research study coordinators to be sub-investigators unless they had the required expertise/training to also perform study-related procedures and this was noted on the study delegation log.

Sub-Investigators and the Assessment of Adverse Events

Just because someone is listed in the aforementioned Section #6 of Form FDA 1572 as a sub-investigator who will be assisting the investigator in the conduct of the investigation(s) does not mean they are qualified to be an investigator, can perform an investigator's tasks, or bear an investigator's responsibilities.

Per formal communication{8} with the Office of Medical Policy:

Listing someone [in Section #6] does not equate them to an investigator. In addition, the investigator is responsible for ensuring that any individual to whom a task is delegated is 'qualified by education, training, and experience (and state licensure where relevant) to perform the delegated task'—and is not assumed to be qualified only on the basis of belonging to a particular category of healthcare professional nor only from having been included [in Section #6] of Form FDA 1572. Per 21 CFR 312.3, sub-investigator means any other individual member of that (clinical) team.

The FDA also indicates “a sub-investigator role in the clinical investigation is more limited.”{5} A specific case in point is registered nurses performing causality assessments under the guise of being considered clinical investigators when included in Section #6 of Form FDA 1572 or clinical investigators per the financial disclosure regulation.

The following formal communications and references{12} offer clarity:

- *“While the investigator can delegate tasks to others in a study, it appears the investigator should assess Adverse Event (AE) causality and severity and report his/her findings to the sponsor. The investigator is required to report serious [AEs] to the sponsor and must include an assessment on whether there is a reasonable possibility that the drug caused the event (21 CFR 312.64). The sponsor is required to report serious and unexpected suspected adverse reactions to FDA and all participating investigators (21 CFR 312.32(c)(1)). That said, much of this depends*

upon who is required by the study protocol to make the AE causality and severity decision. If the sponsor specifically wants it to be made by the clinical investigator, then the investigator would be incorrect in delegating this responsibility and it would be considered a protocol deviation to do so.”

- *“Assessment of causality when evaluating [AEs] by the investigator is a complex clinical determination that requires an understanding of the risks of the investigational agent and an assessment of the totality of clinical factors related to the event, and such assessments are done typically by a licensed physician, whose qualifications are captured in Section 2 (of the Form FDA 1572).”*
- *The FDA Compliance Program 7348.811 Manual further implies that a clinical investigator should be performing safety AE evaluations and determined as such by the FDA Field Inspector when conducting a site inspection so, having someone other than a clinical investigator perform the assessment would pose an audit risk. The Field Inspector is to: “Compare the source documents with [case report forms] and any background information provided (e.g., data tabulations provided by the sponsor) per the assignment memorandum and sampling plan (if applicable) and...*

Determine: The clinical investigator assessed the severity of the [AE] and documented the relationship of the event to the test article, including any [AE] that was previously anticipated and documented by written information from the sponsor.

Determine: The clinical investigator assessed safety monitoring, including documentation of [AEs] (or other treatment-related safety concerns), assessment of the severity of the [AE] and relationship of the [AE] to the investigational product, and any changes to the subject’s participation on the study related to the [AEs] (e.g., study discontinuation/termination).”

The rules above for assessing AE causation also apply to signing lab reports and any other responsibility that requires the expertise of a physician or dentist.

Responsibilities Listed On the Form FDA 1572

Form FDA 1572 does not list all investigator responsibilities. Per the 2009 guidance for industry on “Investigator Responsibilities—Protecting the Rights, Safety, and Welfare of Study Subjects,”^{13} a more comprehensive listing of FDA’s requirements for the conduct of device, drug and biologics studies by investigators is found in 21 CFR Parts 11, 50, 54, 56, and 312/812.

Obtaining Informed Consent

In many states, the investigator has a specific role in or related to the informed consent process that cannot necessarily be delegated. The following are some examples:

Pennsylvania. A Pennsylvania Supreme Court ruling in the case of *Shinal v. Toms, M.D.* stated that a physician must obtain informed consent.^{14}

Indiana. A patient who has given informed consent for administration of experimental treatment in a clinical trial can only receive the treatment if a licensed physician has personally examined the subject and agreed to treat them. Mental health patients must be informed of the investigator’s credentials.^{15}

Minnesota. Subjects in state hospitals require the investigator to provide certification that the subject is competent to consent.^{16}

Montana. If a subject is a resident of a mental health facility, the investigator must send a notice of intent to enroll to the subject, their next of kin, and their attorney.^{17}

California. An investigator who negligently allows or willfully fails to obtain a subject’s consent is liable for fines to be paid to the subject per California Health and Safety Code §24176.^{18} The state also requires all subjects be given a copy of California’s Experimental Subject Bill of Rights (California Health and Safety Code §24172).^{19}

Other states in which the investigator has specifications or requirements for certain types of subjects include Delaware, Illinois, Maine, Missouri, Nevada, New Hampshire, New York, North Carolina, Oregon, Texas, Utah, and Wisconsin. Please note, each state's rules vary and a complete analysis is beyond the scope of the current article.

Conclusion

After evaluating all of the definitions and clarifications of misconceptions, we could expect that the investigator for a clinical trial will be a licensed physician identified as an investigator (or clinical investigator) in initial submissions or protocol amendments under an Investigational New Drug/Investigational Device Exemption whose name is listed in Section 1, qualifications (by training and experience as an appropriate expert to investigate the drug) are captured in Section 2, and who completes and signs the Form FDA 1572 (Statement of Investigator), assumes the responsibilities denoted on it including those outlined in 21 CFR Parts 11, 50, 54, 56, and 312/812, and completes a financial disclosure form. When the investigation is conducted by a team of individuals, the clinical investigator is the responsible leader of the team and is called the principal investigator.

In a small number of cases, an investigator can be an autonomous practitioner/specialist such as a nurse practitioner who meets the education, training, and experience requirements noted in 22 states and the District of Columbia.

Although very uncommon, there are scenarios where an investigator need not be a licensed physician, provided that a licensed physician(s) be included on the Form FDA 1572 as a sub-investigator to handle patient assessments, make medical decisions, provide care, and perform some or all safety review including AE severity and causality assessments. Responsibilities listed on the Form FDA 1572 and 21 CFR Parts 11, 50, 54, 56, and 312/812 therefore need to be handled by multiple personnel, including at least one licensed physician.

Equally uncommon is the use of co-investigators at a clinical site, both of whom would separately sign a Form FDA 1572. This would include at least one licensed physician/practitioner whose shared responsibility and leadership with another investigator would not necessarily be equal, but would include all obligations required of an investigator.

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PEER REVIEWED OPINION

A Conundrum of Trust: Addressing the Diversity Gap in Clinical Research

Awawu Igbinalolor, MD; Suvi Gross; Benjamin Karsai



As clinical research professionals, we are very proud of what our industry has achieved over the last 12 months. Countless lives will be saved by the COVID-19 vaccines and treatments produced by the tireless work of research sites across the country and the gracious contributions of study volunteers. However, the pandemic has also shined a light on the inequities of pharmaceutical clinical research. Many of these landmark trials were delayed due to their initial failure to enroll a sample of subjects reflecting the ethnic makeup of the country.

The failure of research sites to enroll a representative sample of the U.S. population is nothing new. Racial and ethnic minorities continue to be severely underrepresented in clinical trials investigating treatments for cardiovascular, pulmonary, metabolic, and infectious diseases. Considering that these diseases disproportionately impact the African American community, as researchers, we must frame the diversity deficit as nothing less than a scientific crisis. As our industry continues its fight against the pandemic, we must recognize that only through diverse clinical trial participation will the next generation of therapeutics benefit all Americans.

Since 2015, our research team has prescreened thousands of patients for clinical trial participation. Over these years, we were able to build a study patient database in which almost half of those prescreened are of African American descent. We are particularly proud of this achievement considering that African Americans are less than a quarter of our city's population. In this article, we will share our research site's best practices for fostering

diversity in patient recruitment. These adoptable site level strategies focus on garnering the trust of minority patients through education, access, comfort, and encouraging diversity within clinical research teams. Finally, we offer recommendations to pharmaceutical sponsors on how to promote diversity in trial enrollment more broadly.

I. A Call to Action for Investigators of Color

Twenty years of attitudinal studies examining clinical trial participation continue to confirm a stark reality: “mistrust of clinical investigators is strongly influenced by sustained racial disparities in health, limited access to healthcare, and negative encounters with health care providers.”^{1} Given this inequality, it is little surprise that “African Americans report concern that the findings associated with their participation will not benefit the African American community.”^{2}

Understanding these inequities is essential when considering solutions for closing the diversity gap in clinical research. As an industry, we find ourselves in a conundrum of trust. Without trust, we do not have access to communities of color. Without access, we cannot foster trust through education. One of the best ways we can address the conundrum of trust is by encouraging research sites to sprout from within communities of color. Medical doctors within these communities can educate patients about research with a baseline of trust, which in turn fosters confidence in clinical trial participation.

With more investigators of color, the conundrum of trust is replaced by a virtuous circle. As these efforts foster diversity in clinical trial enrollment, the clinical data collected will encourage more inclusive drug development. As newly developed treatments directly benefit these groups, more patients of color will be willing to enroll in clinical trials. This article is a call to action for more medical doctors of color to become clinical investigators.

II. Diverse Study Teams, Diversity in Recruitment

Any solution to bolster diversity in clinical research must acknowledge, empathize, and grapple with the historic abuses endured by the African American community in the name of science. As a clinical investigator of color, the lead author of this article is exceedingly

conscious of our industry's checkered past. From the exploitation perpetuated on unwitting African American test subjects at the Tuskegee Institute in Alabama from the 1930s into the 1970s to the enrollment of African American boys (without consent) into etiology research as recently as the 1990s, examples of malfeasance against blacks in clinical research are shockingly frequent and widespread. When considering this history, it is unsurprising that the primary impediment in African Americans' willingness to volunteer for a clinical trial is mistrust in academic and research institutions.

Garnering patient trust may be important in building a successful medical practice, but it is fundamental in developing a vibrant research operation. Many investigators fail to make the distinction between patients visiting a practice out of medical necessity and study subjects participating in research as volunteers. A study patient's decision to participate in a study stems, first and foremost, from the trust he or she has in the investigator and the research team.

In our industry, you often hear that "minority groups will only trust medical professionals who look like them." *This statement is an egregious oversimplification.* The conundrum of trust is much more nuanced. Considering the historic deficits and inequities suffered by ethnic minorities, patients of color require reassurances that they will not be treated differently due to their race. They will place their confidence in a medical team which will value their health and well-being irrespective of their identity. If a patient observes a study team comprised of many different backgrounds cooperating and valuing one another, then the patient will anticipate the same treatment in turn. Therefore, diversity in patient enrollment begins with a diverse study team.

Many site managers believe that promoting diversity requires hiring policies that give special treatment to candidates of color. In fact, the opposite is true. Impartiality in hiring practices should naturally result in a study team which reflects the local community. When our site's management interviews someone for an open position, we place zero emphasis on a candidate's ethnicity, religion, or sexual orientation. In fact, in our hiring process, traditional considerations such as prior experience or certifications are secondary to a candidate's attitude, amicability, and character. At our site, applying this approach over time has resulted in a remarkably diverse research team from many different backgrounds including African American, Caucasian, Hispanic, Mixed Race, and East-Asian descent.

Most importantly, as part of our hiring practices, our emphasis on character rather than professional background has garnered a study team with a passion for patient care and wellbeing. Clinical research is an exceptionally difficult profession because it is fundamentally a human enterprise. Our sponsors and monitors are human beings checking the compliance and safety of human volunteers participating in a human run clinical study. At the center of this human maelstrom is the site's staff. Our research center's management has committed extensive time and resources toward cultivating a company culture centered around patient care, comfort, and satisfaction. Our staff training emphasizes an etiquette toward study volunteers exemplifying empathy and respect. This attitude is immediately recognized by prospective study participants (of all ethnic backgrounds) and garners the baseline of trust necessary for diverse clinical trial enrollment.

III. Comfort and Trust Go Hand in Hand

As with other businesses, customer support and satisfaction are the benchmark of a research site's standards and quality service. At first glance, this statement seems obvious, but too often these fundamentals are lost on clinical investigators who fail to distinguish between sick patients in need of treatment and study volunteers offering their time for scientific advancement. In addition to outstanding medical care, the best way an investigator can show respect to his or her trial participants is through a steadfast commitment to a comfortable and positive study experience. A research center's investment in patient satisfaction garners trust overall and is critical for improving diversity in trial recruitment.

The professionalism and integrity of a research organization is immediately apparent upon entering an office. Our site has invested heavily in patient comfort and satisfaction. The research center is completely separated from the lead author's physician practice and is custom built specifically for study participants. The waiting room for study volunteers is spacious, cozy, and well lit. Instead of plastic or wooden chairs, patients wait for their study visit on wide recliners with massage capability. Our study volunteers have access to a wide variety of entertainment, including all the major movie streaming services. Whether a patient has arrived for a *prescreening*, or an *end of treatment* visit, they are welcome to all the snacks and refreshments they desire.

For longer visits, study participants receive catered lunches or dinners from the local restaurants of their choosing. In short, we strive to make our research center more comfortable than the study volunteers' own homes. At first glance, such investments might seem like a strain on a research center's budget, but in our experience, these expenses pale in comparison to the additional enrollment generated by these efforts. Our investments in patient comfort have improved our recruitment/retention efforts overall and resulted in consistent and ethnically diverse study enrollment.

Patient comfort and trust go hand in hand. A site's willingness to devote its resources toward a patient's satisfaction signals its dedication to the health and well-being of its study volunteers. Considering the historic discrepancies in minority access to quality healthcare services, a study team's devotion to its study volunteers' comfort and satisfaction is paramount in garnering the trust necessary for patients of color to participate in your site's clinical studies.

IV. Industry Level Recommendations

At the start of a clinical trial, sponsors often ask how they can best support our recruitment efforts, and may offer a selection of conventional flyers/posters or marketing items which fall far short of promoting diverse clinical trial enrollment. With more than a decade of experience working with major pharmaceutical/biotech firms and contract research organizations (CROs), our study team has identified three strategies which would greatly promote inclusive patient recruitment efforts across the country. These approaches involve targeted allocation of research funds and strategies for supporting medical doctors who would like to become investigators.

Supporting Education Within Local Communities

Encouraging diversity in clinical trial enrollment will require concerted outreach and education within communities of color. One of the most potent tools at our industry's disposal is advertising. Research centers are a part of their community and likely know how to allocate ad dollars to maximize a campaign's impact within the local culture. Offering sites strong discretionary budgets for local advertising and community events is one of the best ways pharmaceutical sponsors can support education, garner trust, and improve enrollment outcomes.

Rewarding Ethnic Diversity in Patient Enrollment

A track record of diverse patient enrollment assumes inclusive hiring practices, outreach to historically neglected communities, and considerable investment in study participants' care, comfort, and satisfaction. If the industry values such efforts, then ethnically inclusive patient recruitment should be considered a specialized skill and, as such, be compensated accordingly. Through greater financial incentives, study sponsors encourage research sites throughout the country to make the investments necessary to help close the ethnic diversity gap within pharmaceutical clinical research.

Access, Training, and Support for Investigators of Color

There is a considerable barrier to entry for medical doctors looking to participate in clinical research. Sponsors and CROs will usually only work with investigators who already have a substantial research pedigree. Many doctors gain study experience by acting as sub-investigators on clinical trials. However, considering that there are 8,350 principal investigators in the United States, of which only 9.8% are black, it is safe to assume that the doctors of color have limited options in building their research resumes. {3}

Industry could foster more investigators of color through events which not only aim to educate existing investigators of their study pipeline, but also facilitate networking opportunities for medical doctors looking to get involved in clinical research. These efforts could further be supported by providing grants to research centers willing to offer mentorship and sub-investigator opportunities to medical doctors underrepresented in our industry.

V. Conclusion

As an industry, we have made real strides in recognizing and acknowledging this scientific crisis. To close the diversity gap in clinical trial enrollment, we must place a greater emphasis on the ideals of education, impartiality, and exceptional service. On the site level, more medical doctors of color must take the initiative to become clinical investigators. Site managers should encourage and value diversity within their clinical trial teams and invest more in the comfort and satisfaction of their study participants. Finally, study sponsors should support these efforts through financial incentives and networking opportunities for new investigators of color.

There is no single solution which will address the conundrum of trust between researchers and minority patient populations; however, together we can take the necessary steps to ensure that our clinical trials produce groundbreaking therapies that serve all Americans.

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PEER REVIEWED

Adapting to the Evolving European Clinical Trial Regulatory Scenario: An Overview of the Current State of the European Clinical Trials Regulation and Clinical Trials Information System

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Since 2014, clinical trials within the European Union (EU) are conducted in accordance with the established EU Clinical Trials Regulation (CTR). The European Medicines Agency (EMA), in collaboration with the European Commission and EU Member States, is developing a centralized portal and database, the Clinical Trials Information System, to harmonize all clinical trial requirements and improve trial data transparency across the EU. This paper will briefly focus on the impact of the transition from the existing processes and systems, including the European Union Drug Regulating

Authorities Clinical Trials (EudraCT) database, to the forthcoming centralized system. Furthermore, it will focus on a perception on the ways to overcome the potential challenges that may be experienced by study sponsors during this transition.

Glossary

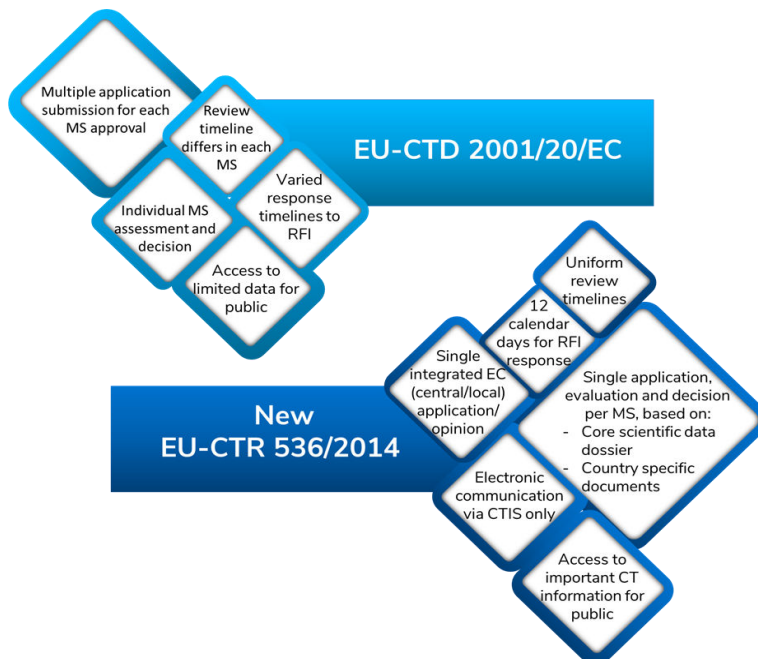
CRO	Contract research organization
CTA	Clinical trial application
CTD	Clinical Trials Directive
CTIS	Clinical Trials Information System
CTR	Clinical Trials Regulation
EC	Ethics committee
EEA	European Economic Area
EMA	European Medicines Agency
EOT	End of trial
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
GCP	Good Clinical Practice
IT	Information technology
MS	Member States
RFI	Request for information

Background

The conduct of any clinical trial generates extensive patient data, which are very sensitive in nature. Revealing any such data requires a unique approach in presenting the key trial data to regulatory authorities, healthcare professionals, patients, or other sponsors. Currently, clinical trial conduct in the EU is highly regulated and requires trial registration with the EudraCT database.{1,2}

In April 2014, the European Parliament and the EU Council released the Clinical Trial Regulation (EU-CTR) No 536/2014 regarding clinical trials on medicinal products for human use repealing EU Clinical Trial Directive (EU-CTD) 2001/20/EC. The primary goal of this new regulation is to protect the rights, safety, dignity, and well-being of the trial participants and to generate reliable and robust clinical trial data. The regulation was intended to facilitate harmonization of the assessment on medicinal products and supervision of processes for conducting clinical trials throughout the EU using a centralized Clinical Trials Information System.{3,4} The highlights of EU-CTD 2001/20/EC and EU-CTR 536/2014 are presented in Figure 1.

Figure 1: Comparison of 2001 Directive with the New 2014 EU-CTR



(CT=clinical trial); Source: CTIS-highlights, December 2020.{5}

The 2014 regulation will be fully implemented after the publication of the notice confirming the full functionality of the EU portal and the EU database by the European Commission.{4}

CTIS—A Cornerstone of the Clinical Trials Regulation EU No 536/2014

The key highlight of EU-CTR 536/2014 is to provide a single, unified portal and database, which is the Clinical Trials Information System (CTIS), available for both trial sponsors and regulatory authorities of each Member State. The CTIS will be a centralized, paperless, integrated, single-entry point for submission, evaluation of data, authorizing, supervising, and reporting any trial-related information between the relevant Member States. The EMA will set up and manage the CTIS, in collaboration with the Member States and the European Commission. {5} The purpose of this system is to considerably facilitate the process of clinical trial conduct across EU, starting from the initial submission to authorization, providing corrective measures, inspection information, and publication of relevant documents for the general public and substantial updates over time. {3,4}

Overview of CTIS Workspaces

The CTIS will provide dedicated workspaces to enable sponsors, regulatory authorities, and the public to access a suite of functionality. For sponsors and regulatory authorities, common roles in the portal include User Administration, Clinical Trial Information, Notices and Alerts, and Annual Safety Reporting. The various workspaces within CTIS include:

- **Sponsor Workspace**

Sponsors, academics, and others (including regulatory project managers, in-country specialists, and CTIS submission managers) will use the Sponsor Workspace on the tool, enabling them to apply for their trial authorization using a single application for up to 30 EU/European Economic Area (EEA) countries.

- **Authority Workspace**

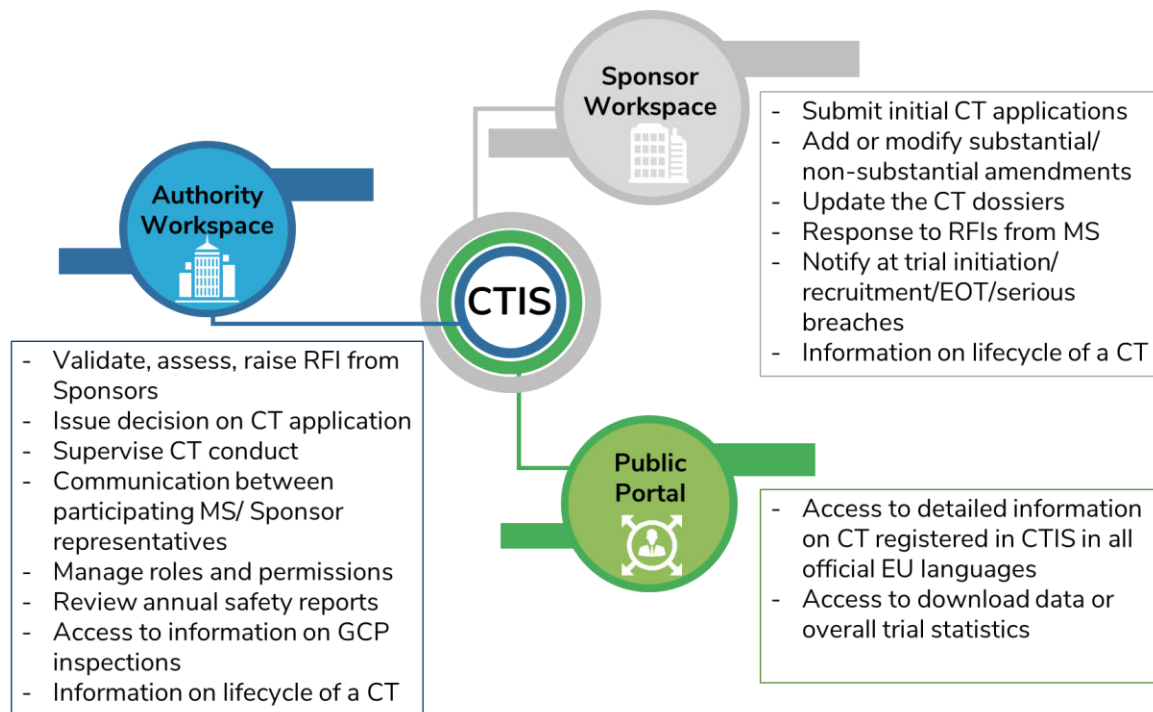
Member States from different participating countries, national competent authorities, and ECs can coordinate and promote harmonization of clinical trial assessment decisions and administrative processes.

- **Public Portal**

The general public will be able to access clinical trial data in all official EU languages in compliance with the disclosure policies (EU-CTR 536/2014 and Policy 0070). Data and information submitted through the EU portal will be stored in the EU database, and shall be publicly accessible unless confidentiality is established on any grounds as stated in Article 81, paragraph 4 of the EU-CTR 536/2014.

A pictorial representation on the functions of CTIS for the different user workspaces is provided in Figure 2.

Figure 2: Functions of CTIS for User Workspaces



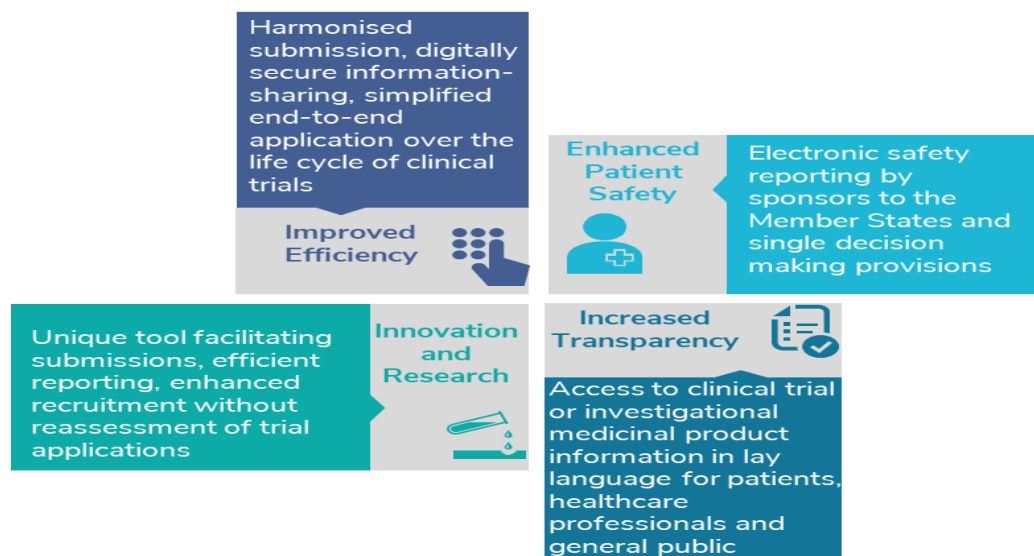
(CT=clinical trial); Source: CTIS-highlights, December 2020.{5}

Dedicated workspaces with restricted access to multiple stakeholders are expected to enhance support in daily business processes throughout the lifecycle of a clinical trial. Business experts are focused on continuous development of the CTIS to ensure whether it is fit for purpose. Since June 2019, the areas of consideration included document management, enhanced submission, and facilitating overall scientific and regulatory review and monitoring.{6} In April 2021, following a successful independent audit, the EMA’s Management Board confirmed that CTIS is fully functional and meets the specifications as stated in the Article 82, Paragraph 2 of the EU-CTR. The European Commission will further publish a notice in the Official Journal of the EU, six months before the planned CTIS launch date.

Benefits of the CTIS Workspaces

The CTIS is intended to provide an improved and more collaborative environment for the user community. Some of the key benefits of the system include efficiency, increased transparency, patient protection, and better capability to facilitate effective submission processes (see Figure 3).

Figure 3: Key Benefits of the CTIS



Source: CTIS-highlights, December 2020.{5}

Transition to the New Regulatory System

The new clinical trial system is planned to be fully functional after a three-year transition period (2022–2025) for all clinical trials to go through CTIS.{7} The EMA announced the CTIS go-live date as January 31, 2022. During the first year, new clinical trial applications (CTAs) may be submitted either under the new regulation (via the EU portal and database) or under Directive 2001/20/EC. Over the second and third years (from January 31, 2023 onward), all initial CTAs will be submitted through CTIS; however, old trials will continue to be governed by the Directive. From January 31, 2025 onward, all ongoing clinical trials will be governed by the Regulation and must go through CTIS.{8}

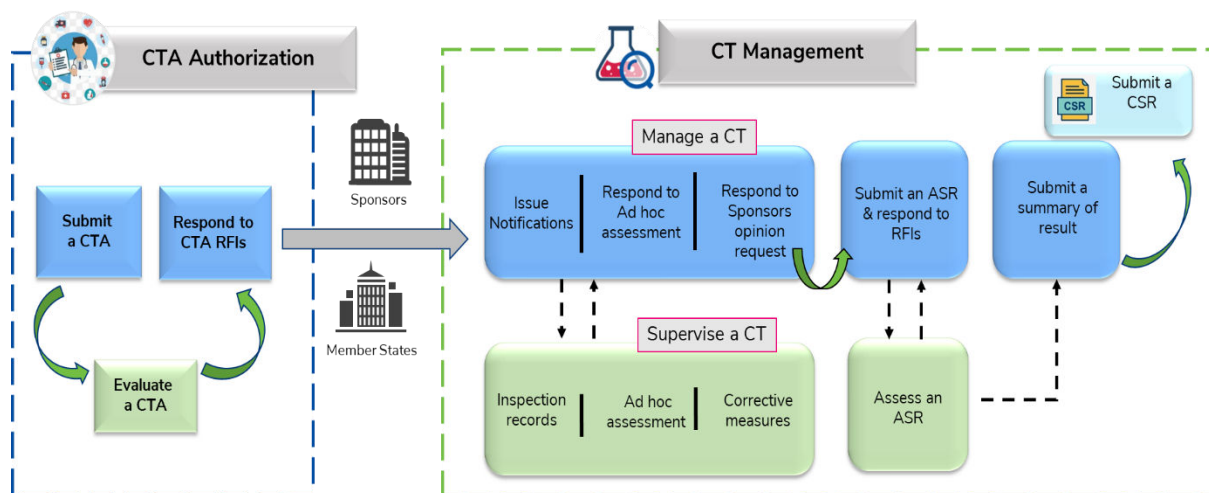
A well-planned CTIS training programme is already under way to provide users with the required skills, capabilities, and knowledge for successful adoption of CTIS. {5} EMA’s training materials are tailored for clinical trial sponsors and staff of the EU Member States, European Commission, and other organizations who will use the system. Presentations, quick guides, frequently asked question sheets, e-learning, webinars, and short videos are available online, which will help in the preparedness for CTIS end-users. The training is scheduled in three main programme streams for sponsors:

1. **Sponsor Master Trainers** are conceptualized to use the train-the-trainer approach for the Member State users aimed at CTIS functions applicable for commercial sponsors and contract research organizations (CROs), which are likely to submit several CTAs and have multiple CTIS users across various organization models.
2. **A two-day webinar** for users from small and medium-sized enterprises, academia, and other non-commercial clinical trial sponsors will disseminate the knowledge on applicable CTIS functions.
3. **Training catered on specific CTIS functions** was planned to be initiated in the fourth quarter of 2021 for end-users from all sponsor groups. {9}

More information on the CTIS training programme is available [here](#).

An overview and a high-level illustration on the possible lifecycle of a clinical trial via the new portal, supporting various user groups including sponsors, Member States, the European Commission, and the public is presented in Figure 4. {10}

Figure 4: Lifecycle of Clinical Trials in CTIS



(ASR=annual safety report, CT=clinical trial, CSR=clinical study report); Source: Guide to CTIS Training Material Catalogue. {10}

Potential Challenges for Sponsors During the CTIS Transition

Currently, separate CTAs and submissions are globally initiated and updated locally by the in-country personnel for multiple Member States. With the introduction of CTIS, sponsors need to assess change in the processes across the lifecycle of a clinical trial. Most of the users from sponsors, small and medium-sized enterprises, and academia are now involved in allocating time and resources to align with the transition to the new system. Many users with limited resources are also dependent on CROs, making it a huge responsibility to decide on the user management for each trial, especially for those complex trials with more than one vendor.

Nevertheless, the transition to the new system is leading to increased risks regarding trust, accuracy, costs, and workload. While the small and medium-sized enterprises are planning to train on the available resources, the large sponsors are preparing to align several hundreds or thousands of resources with the new processes. { 11 } Some of the possible common challenges faced by sponsors are listed below:

1. **Administrative burden for new user access:** Sponsors will need to configure Administrative User accounts, which will be obtained only upon EMA's validation of certain documents, to perform their responsibilities and meet their business needs. Administrative sponsors will be responsible for user management by assigning, amending, revoking, or approving user roles; therefore, the more users there are tied to a sponsor, the more responsibility there will be for the sponsor administrator. It is therefore critical for sponsors to maintain the right balance in assigning roles to their resources within the CTIS.
2. **Training for end-users:** Sponsors need to carefully identify the resources (or vendors) who will undergo the EMA training programme and in turn develop training materials and train other resources within the organization. The programme should be lined up with the roles assigned in CTIS to ensure that employees efficiently perform their activities within the stipulated timelines.
3. **Revealing sensitive data:** As CTIS has open access for the general public, it is critical for the sponsors and/or any end-users to ensure that no personal or sensitive information is used within the CTIS while considering the transparency guidelines wherever appropriate. Coordinating with translations and redaction of trial-related documents in multiple languages could possibly burden the trial timelines.
4. **Increased cost and administrative burdens:** Sponsors and institutions were accustomed to their company-specific standard operating procedures and workflows in preparing submission documents as per country-specific requirements, which may need to be revised to cater to the new requirements. In addition, essential trainings for individuals and upgrades in the IT infrastructure could lead to increased costs and administrative burdens.

5. **Tight submission timelines**: Upon the implementation of CTIS, sponsors need to closely coordinate with regulators for initial applications and all subsequent clinical trial modifications. Any lapse in the timeline might result in legal consequences, such as lapsed application; therefore, sponsors need a strong strategic plan and timelines defined for all studies of the same product. Ongoing assessment in one Member State will put a hold on any substantial modifications for other Member States.

Other Considerations for Preparedness for CTIS

Planning new clinical trials: Sponsors planning to conduct any new trials within the EU should be mindful of the transition period and ensure compliance either with the old Directive or new Regulation, based on the duration of planned clinical trial. In addition, it is important to plan timelines and trial-related activities well in advance.

Adaptability to the new Administrative User system: As CTIS will have dedicated sponsor workspaces, all sponsors (including institutions, academia, or other organizations) should develop the expertise to adopt and compile CTA dossiers in compliance with regulations for any new or ongoing trials on the new secure workspace.

Well-established IT Infrastructure: Sponsors will need to upgrade their IT/technical/infrastructure to gain access to the new secure workspace for preparing and compiling data submitted to the Member States for assessment of any new and updated trials, and to avoid any delays. Further IT infrastructure upgrades may be necessary whenever the CTIS platform is updated.

Define workflows: Sponsors may need to create new or revised standard operating procedures and workflows for dossier preparation, compilation of all CTA authorizations and related documents for multiple Member States assessments through the CTIS.

Conclusion

The much-awaited digital transformation of the healthcare industry has been setting its roots for almost a decade. The EU-CTR and CTIS will streamline the process for seeking approval for the conduct of clinical trials and harmonize the end-to-end electronic application procedures over the lifecycle of trials across the EU.

It is expected that the new, centralized CTIS will improve collaboration among sponsors, innovators, researchers, Member States, and regulatory authorities with enhanced patient safety and knowledge-sharing, reduced delays in clinical trial approvals, and increased efficiencies in trials within the EU. Furthermore, it is expected to prevent redundancy in clinical trials and unnecessary duplication of research.

The fully implemented EU-CTR will foster innovation and competitiveness of European clinical research by bringing together methodological data quality and ethical integrity. It will further enhance trial data transparency for improved patient safety. {4}

A well-planned and detailed training programme on CTIS has been initiated by the EMA, in order to prepare all the end-users ahead of its launch. The CTIS training material is also tailored in various modules for different end-users based on their roles and responsibilities. It is important that every responsible individual complete the prerequisites to fully enable a smooth transition to the new and secure system.

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SPECIAL FEATURE

Preparing for the Future: Data Collection and Technology Deployment in Decentralized Clinical Trials

Stacy Weil; Nicole Carswell



The data are clear: Decentralized clinical trials (DCTs) are on the rise.

In July 2021, the *Industry Standard Research (ISR) Report on Hybrid/Virtual/Decentralized Clinical Trials Market Outlook* surveyed 109 industry leaders worldwide who had been involved in DCTs over the past year.^{ 1 } Respondents anticipated a 12% increase in hybrid trials over the next two years—and predicted that DCTs would outstrip

traditional trial models within three years. They praised the increased ease of patient recruitment and improved patient compliance that DCTs generate. They were also impressed with the access to rich data—often sampled multiple times a day—representing a trove not possible with traditional trials.

Yet that does not mean all is perfect. DCTs—including for our purposes the range of hybrid onsite/offsite, siteless, remote, and virtual trials, depending on your favorite terminology—rely heavily on technology for data capture, and immature technology can pose problems. Therefore it is critical that sponsors choose a contract research organization (CRO) with the specialized experience to foresee and forestall this new breed of potential issues.

Wearables: Drivers of DCTs—And Many of Their Headaches

From a CRO's standpoint, decentralization is not revolutionary. Technologies used for electronic patient-reported outcome (ePRO) collection and electronic informed consent (eConsent), just to name a few, are longstanding facets of trial management, and other technologies have steadily gained broad-based acceptance and popularity. Further, as wearable technologies and home monitoring devices become standard accessories for the health-conscious, their data gathering in clinical trials seems increasingly natural.

These devices are also producing better results. The rising popularity of DCTs is based primarily on their ability to better support patients—saving them time and out-of-pocket costs while minimizing their exposure to outside pathogens. That increased support has led to improved compliance and better data, which are, after all, the holy grail of any trial.

Yet the sheer volume of data produced is one of the key challenges created by the surge in wearables. Data arrive day by day—sometimes minute by minute—often from multiple devices. Accurately collecting, managing, and analyzing all these data can be overwhelming. Yet, those processes are also critical to trial success—adding pressure to the task of choosing a CRO wisely.

How Accurate is That Avalanche of Data?

The ISR report reveals that the selection of apps, monitoring devices, and online platforms rests primarily with the sponsor. That makes sense since the ultimate responsibility for accuracy also remains with the sponsor. Current International Council for Harmonization (ICH) guidelines specify, “The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions that are subcontracted to another party by the sponsors’ contracted CRO(s).” Yet, the CRO still bears day-to-day responsibility for the data.

The deluge of data not only needs to be managed, it also needs to be verified. After all, the patients responsible for much of the collection aren't tech experts.

Some of this is business as usual for professionals at CROs. Just as they have ample experience utilizing technologies to alleviate paperwork and decentralize data input, they have been assimilating data from multiple sources through multiple systems for a long time. The issue now is one of scale: DCTs may produce 10 times the volume of data as a traditional trial.

As for patient control of data generation, the ISR report indicates that wearable sensors and connected health devices are the top hybrid trial-related areas in which sponsors invest significant resources; they are also the technology ISR respondents ranked as needing the most improvement, with user-friendliness deemed a key concern.

Many CROs are primed to address patient tech challenges, too. A core competency in developing a DCT is the ability to make it accessible in all ways to a range of patients; that includes helping and supporting patients in using the chosen trial technology.

Can Your CRO Handle a DCT? (How to Judge Before You Hire)

While many CROs are technology-savvy, not all are. Here are eight key areas to consider as you are choosing a CRO partner.

1. **A track record of success.** This may seem obvious, but it is not as straightforward as it may sound. Be sure to understand exactly how the CRO measures success—and what its role was in every aspect of a “successful” trial.
2. **The overall approach to DCTs.** Some CROs develop specialized personnel focused solely on DCTs; they may have different offices, different leadership, and different trial teams. This may seem preferable—a group of experts wholly focused on this new way of operating. We respectfully disagree. We see DCTs as a continuum of the traditional model, and advocate actively ensuring that all team members are well versed in what we believe will be the future of clinical trials.
3. **Optimal protocol support.** As sponsors prepare their trial, they should consider which aspects of the protocol can be decentralized; they can then discover whether the risk management and associated technology abilities of the CROs under review have evolved to support those key aspects.

4. **The vendor management process.** DCTs may require many more vendors than a traditional trial—and sponsors need assurance about data quality. How do the CROs vet the vendors? Can a CRO or its vendor access the right data, process that data, and perform risk management during the clinical trial? We have had sponsors request that we partner with a specific vendor, then found during the request for proposal process that the vendor would be unable to transfer the data without relying on a third party. By identifying these sorts of stumbling blocks in advance, we can circumvent them.
5. **Flexibility and nimbleness.** DCTs require partnership with a wide range of companies, some of which may not be precisely aligned in their approach to this evolving process. Does the CRO have a proven method for collaborative vendor management, proactively addressing risks and minimizing quality concerns while remaining collegial?
6. **The breadth of in-house technologies available.** One way to streamline third-party vendors is to partner with a CRO with several in-house technologies making them more of a one-stop-shop. Ideally, this would comprise a comprehensive data collection, management, and analysis system.
7. **Transparency into data lineage.** Assuming that a clinical trial is successful, at some point, the sponsor will need to show its data to various regulatory bodies. If regulators have questions, the ability to track and instantly retrieve each piece of data—along with records on how it was collected, queried, and stored—is invaluable.
8. **Adoption support.** Does the CRO have strategies in place not only to train and support patients on the various technologies, but also to train and support its own clinical trial team?

Data and the technology required to deliver those data accurately are core components of DCTs. By using these eight parameters, sponsors can ensure their CROs can effectively deploy the technology to deliver the necessary data—organized, analyzed, and verified.

DCTs: Delivering On the Future of Clinical Trials

There is no question that COVID-19 accelerated the adoption of DCTs. Previously, the change-averse healthcare industry had been moving slowly and ponderously in that direction; now, there is no going back. Patients prefer DCTs—a preference that has bolstered recruitment, retention, and even compliance. Technology has kept pace, adapting and advancing to support larger, more complex trials while allowing patients to reduce clinical visits. CROs, too, are growing more comfortable, either by creating freestanding DCT teams or developing company-wide expertise.

While there are many questions regarding best practices in DCT management, specifically ensuring data quality, our observations of how data and technology trends are stacking up against quality, utility, accessibility, and patient privacy metrics have cemented our belief that careful vendor management, flexibility, transparency, proactive adoption support, and a fully integrated team can deliver superior DCT results.

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“Be Well to Manage Well”: Clinical Project Managers’ Well-Being in the Pandemic and Beyond

Zoran M. Pavlovic, MD



A growing interest in workplace well-being demands a paradigm shift in how society thinks about and treats employees—not just as they go about their jobs, but as they manage all aspects of their lives. Such interest is prompted, in part, by studies showing that physically and mentally healthy workplaces can lead to more engaged, committed, and productive workers and an organization’s sustainability, despite ongoing economic turbulence caused by the COVID-19 pandemic.

According to Duran and Sanchez,^{1} there are five factors (the “five Cs”) that influence and reinforce employee engagement since the start of the so-called “New Normal” of pandemic conditions. All of them are either direct or indirect moderators of workers’ well-being:

- **Conciliation:** reconciling work and home life, with remote working and flexibility acquiring considerable importance;
- **Cultivation:** development schemes for employees;
- **Confidence:** through the health and safety of employees, as well as through hands-on leadership;
- **Compensation:** rewarding employees’ efforts and covering the additional costs of these difficult times; and
- **Communication:** achieving employee participation and engagement.

Reasons for Investing in Workplace Well-Being Interventions

- When an intervention to raise subjective well-being is utilized, performance and productivity can improve.
 - The productivity difference between high and low well-being employees can be significant.
 - Gains in employee well-being and engagement have been linked to increases in annual per-employee productivity.
 - Organizations with satisfied employees do better on the stock market.
 - Happiness at work is contagious. The mood of one employee might affect the mood of others. The happiness of close contact enhances a person's chances of happiness.
 - Absenteeism is linked to low well-being. Mental health issues such as stress account for many missed days. Similarly, improving an employee's well-being can cut health absenteeism costs.
 - Low personnel turnover is linked to high well-being. Employee turnover costs are reduced significantly when employees are happier at work.
 - Employees having higher well-being are promoted more quickly.
 - Well-being is linked to positive working connections. The quality of one's professional relationships affects one's mental health.
 - Presenteeism is typically manifested by symptoms of poor mental health such as depression, anxiety, and work-related stress. Its costs are much higher than absenteeism, and employers have reported a significant return on investment from spending on mental health promotion activities.
 - People who have high psychological well-being are far less likely to develop a cold.
 - People with high psychological well-being are less prone to cardiovascular illness.
 - Happy people are healthier and live longer.
-

Now let's look at a number of factors affecting project managers' well-being and how to overcome them.

Skills Gap

According to an Australian Institute of Management survey of project managers (PMs), the most significant negative impact of the skills gap on PMs' well-being and productivity is related to increased levels of stress (71 %), followed by lower morale (56%), loss of high-performing employees (48%), and reduction in customer service standards (41%).{2} The same survey reported that the most prominent skill gap was in "leadership," which affected 46% of interviewed PMs.

Another well-being survey of project professionals by the Association of Project Management{3} in 2019 showed that the most underdeveloped skill was communication. Therefore, training that includes upskilling project-related leadership and communication capabilities would be the most beneficial for individuals, teams, and organizations. This training can also serve as an effective stress management and well-being enhancement strategy.

The same survey also identified crucial high-risk areas impeding PMs from experiencing a sense of wellness compared to the general working population (norm group). In the following eight sections, I have selected those that, in my opinion, have the highest priority in terms of affecting the PM's well-being and suggested types of training that aim to mitigate these risks.

Job Control

From the 2019 survey, the most concerning item related to job control was "the account not taken of ideas and suggestions about the job." Such perceived lack of control, or decision latitude, over how people choose to do their work or whether they feel able to influence their situation can be a leading source of stress and decreased psychological well-being.

The perception of control over their situation empowers PMs to make active attempts to resolve problems and encourages them to approach their work positively. High internal locus of control can also safeguard against the adverse effects of other pressures, such as work-life imbalance and heavy workloads.

Job control could be increased through participatory, organizational-level interventions. These would concentrate on improving work policies, practices, and procedures where managers and employees collaboratively decide on the intervention's method (design and implementation) and content (changes to work policies, practices, and procedures). On the individual level, PMs could enhance their self-directed behavior and autonomy through various types of self-leadership training.

Work/Life Balance

Project professionals were worse off than the norm group due to poor work/life balance and increased workload. When individuals can maintain a good work/life balance, they are less inclined to get overstressed and more likely to enjoy their work, and thus feel happy about what they do.

Organizational factors that promote this balance include synergies of work-family practices and job crafting, flexible working hours, job sharing, part-time work, compressed workweeks, and access to programs that encourage physical and mental fitness. Provision of training opportunities, rewarding and praising for good performance, organizational justice, trust in leadership, and promotion significantly affect employees' perception of company efforts to help workers balance work and family.

Personal resources such as psychological capital (i.e., HERO: Hope, (Self-)Efficacy, Resilience, and Optimism), including trait and state mindfulness and high emotional intelligence, positively predict better work/life balance. These facts indicate that the employer's imperative is to improve the PM's coping strategies and psychological resilience by providing mindfulness, behavioral monitoring, and emotional intelligence training, thus enabling positive, "spill-over" effects between their working and family roles.

Work Relationships

Certain work relationships measures (including those involving such themes or issues as "a boss/manager-aggressive management style," "unclear what boss expects," "boss forever finding fault," "support/relations with colleagues-support from others," "isolation at work," and "poor

relations with colleagues”) were found to be high-risk items among PMs compared to the norm group, except for an item on “others not pulling their weight,” which was approaching high risk.

Good relationships at work can be energizing and contribute to high levels of engagement and satisfaction, helping people cope with work pressure and maintain performance under challenging conditions. The employer should initiate emotional intelligence training and enable the engagement of PMs in interventions based on the ASPIRE (Agency, Safety, Positivity, Inclusion, Respect, and Equality) framework. These programs would help identify counterproductive behaviors and improve upon skills tied to social situations, self-awareness, interpersonal relations, and conflict management, leading to better working relationships and improving associated psychological, emotional, and social well-being parameters.

Sense of Purpose

The “sense of purpose” subscale of the psychological well-being scale was approaching high-risk among PMs compared to the norm group, meaning that project professionals found job goals to be less well-specified than those in the general working population. Similarly, job goals and objectives were less clear, resulting in a relatively lower commitment to achieving them.

A sense of purpose enhances the effect of positive emotions (positive emotions were aligned with the norm group in this survey), so this finding indicates the PMs’ underachievement of overall psychological well-being due to a diminished sense of purpose and direction. PMs could gain better insights into their unique individual goals through organization and human resources–initiated personal development activities, supporting them in taking appropriate/value-congruent actions at the workplace and in their private lives.

Organizational culture must enable clear vision and mission sharing at all levels, serving as a compass for all employees to make decisions and choose goals. In this respect, interventions that increase affective, normative, and continuance commitment, as well as a sense of belonging and citizenship behavior, are strongly encouraged. Self-awareness and self-reflection exercises can also help PMs find their sense of purpose. Other practices that strengthen social bonds and work relationships, thus building a shared sense of purpose, could also positively impact PMs’ well-being.

Personal Growth and Career Prospects

Two studies that directly assessed the happiness of PMs reported that the opportunity for personal growth{4} and career prospects{5} significantly affect PMs' happiness levels. Personal growth initiative (PGI) refers to active and voluntary engagement in personal growth as the primary driver of individual development. PGI includes both cognitive and behavioral aspects related to intentional personal development. People with high PGI consciously intend to develop and actively find and utilize developmental opportunities.

Robitschek, et al.{6} identified four components of personal growth, including readiness for change, planfulness, using resources, and intentional behavior. Strengths-based training that promotes the acquisition of new cognitive-behavioral habits leads to increases in readiness for change (preparedness for undertaking self-change), planfulness (planning for the necessary processes and implementing self-change), the wise use of resources (adapting resources outside oneself to help self-change), and intentional behavior (purposeful engagement in behavior for self-change). Such training is particularly effective in driving personal growth in work environments.

Strain On Physical Health

Getting back to the 2019 Association of Project Management survey, project professionals were aligned with the norm group regarding strain on physical health, but the item "feeling sick" was high risk, with significantly more women than men reporting it. Additionally, PMs spend most of their time in sedentary activities, positively correlated with cardiovascular and metabolic morbidity (overweight, obesity, and type 2 diabetes mellitus) and mortality risks.

These harmful effects could be mitigated or even eliminated by engagement in regular, brief physical activities. For instance, training such as that found in *10-minute Workout Anywhere* from the American Heart Association during lunch break could be one of the options. Other types of more passive exercises that primarily involve a mental component, such as mindful walking, yoga, and positive emotion-focused stress management programs like *Inner Quality Management*®, were proven to decrease blood pressure in hypertensive individuals.

Wellness experts from the Mayo Clinic also recommend discussing barriers to exercising, such as overcoming self-defeating cognitions like “I do not have time for exercising” or “exercising is boring,” especially if physical activity is performed remotely.

Strain On Psychological Health

Only three of the 11 items in the “strain on psychological health” subscale were not high risk compared to the norm group, indicating that PMs experience a high level of pressure on their psychological health mainly because of the stressful working environment. Employers should enable PMs’ participation in programs that increase mental toughness, psychological resilience, and grit. Stress management programs should use simulation-based “learning by doing” exercises to mimic various stress-inducing, work-related scenarios. This type of training would empower PMs to learn “situation-specific” stress management approaches, thus minimizing their “real-life” stressful experiences more efficiently.

Engagement

The results on the “engagement” subscale put PMs in the approaching high-risk category compared to the norm group. Three causes of this can be identified by the items “put myself out for the organization,” “committed to achieving job goals,” and “committed to organization,” which indicate that PMs were less inclined to agree with these statements than the norm group.

The relatively low level of engagement is a huge problem, given the link between engagement and individual/organizational performance outcomes. Classroom and on-the-job training that promotes the development of agile and entrepreneurial skills boosting persistence, self-starting and future-oriented behaviors, and gaining knowledge and experience about synchronizing their individual with pro-team and pro-organizational proactivity should be considered central to the learning and development strategy.

Future Directions

The development of a PM's agile, entrepreneurial, mindful, and compassionate leadership skills will take precedence over coaching on traditional leadership styles such as “transformational” and “authentic” due to the better alignment of the former four with business models showing superior performance in today's VUCA—V(olatile)U(ncertain)C(omplex)A(mbiguous) economy. Concerning the wellness programs, training and access to holistic wellness services encompassing physical, nutrition, self-management, psychological, and spiritual well-being domains will become an integral part of a PM's benefits package.

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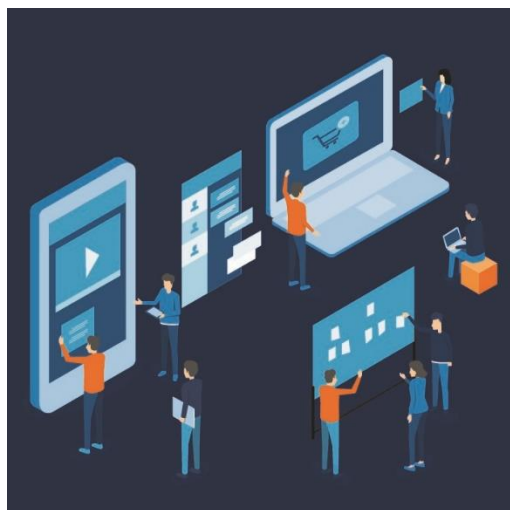


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SITES & SPONSORS

Establishing a Site Engagement Strategy for Greater Efficiency and Speed in Study Start-Up

Anusha Shetty



Nearly one out of every 10 clinical trials launched never enrolls a single patient.^{1} This is costly and time-consuming for all stakeholders, yet a failure to meet patient recruitment targets is one of the most common reasons clinical trials are stopped or delayed. Of the suspended studies between 2011 and 2021, 30% were due to a low number of participants.^{2}

Starting trials with the right clinical research sites can drive better patient recruitment, streamline execution, and improve study quality. To help clinical leaders develop strategies for efficient site feasibility and selection, we'll explore the key challenges the industry faces, areas in need of improvement, the role of technology, and what the future holds for study start-up.

Poor Site Engagement is Holding Trials Back

Selecting the right research site is vital to the success of a study, but finding a partner that can maximize patient enrollment has been an industry-wide issue since 86% of clinical trials don't meet recruitment targets within specified periods.^{3} The first step to establishing a successful site engagement strategy is understanding key study start-up challenges and how they impact trial outcomes. Let's consider four of these challenges, just to warm ourselves up to the topic.

Lengthy and complex questionnaire process. Feasibility surveys are typically long (including approximately 40 to 75 questions) and many of the sites' responses are applicable across studies, such as the total number of exam rooms. Yet, site responses aren't being reused or pre-populated on subsequent questionnaires. This becomes tedious and inefficient for site staff, many of whom are short on resources.

Siloed information. After completing a successful study, many sponsors and contract research organizations (CROs) don't save and reuse the data captured about investigators and their sites. While valuable data about a site's performance exist in the hands of individuals on spreadsheets and in e-mails, there is no easy way to query and leverage this information for future studies. Without a reliable database and a central repository of site profiles, everyone loses costly time, including principal investigators and their staff.

Site accessibility and availability. Selecting a site that has delivered in the past provides a sense of security, but this approach can be problematic because it narrows the reach of the proposed research. By not conducting thorough site selection, sponsors and CROs can miss out on talented investigators who don't have the resources to promote their areas of expertise.

Add on the intense competition for sites and the pressure to engage quickly (sometimes within two weeks), and it might seem like using the site you know is the best option. However, this isn't always a best practice that delivers results, since it limits access to new patient populations in previously untapped areas.

Too many systems for sites. Sponsors and CROs have different software systems and security, privacy, and regulatory standards for every study, placing an additional burden on already resource-strapped sites. Many opt to use manual or paper-based processes to overcome this challenge, increasing quality and compliance risks because investigators can't use the technology provided for a trial.

Enabling Seamless Study Start-Up

It's time to reimagine site engagement and implement new strategies that make it easier for sponsors/CROs and sites to work with one another across multiple studies. To begin this transformation, organizations should prioritize evaluating and adopting modern study start-up technology, especially since 81% of sponsors and CROs still use spreadsheets to manage start-up processes.^{4} A shift in strategy and use of purpose-built study start-up applications can help drive long-lasting, positive change. Here are three steps companies can take now to enable a more seamless trial tomorrow.

Establish a data-driven site identification strategy. Leverage public domain data and internal resources to collect critical data about site capabilities. Information should be stored in a format that is easy to access and analyze. Key examples are details like after-hours contact information and specific site successes and failures.

With this information readily available, sponsors and CROs can efficiently conduct queries and make more informed decisions. Figure 1 provides an example of what can be accomplished with better site performance data.

Figure 1: Better site performance data lead to more informed decisions in study start-up.

Information	Decision
Past performance issues	Rule out under-performing sites
Recruitment track record	Ensure the site has a sufficient patient population
Specialty areas	Confirm if the site has the expertise needed
Principal investigator biography	Confirm if the site is a relevant fit for the study
Length of time to complete contracts	Eliminate if working within a limited timeframe
Equipment and facilities	Ensure sites have the necessary resources
Confidentiality disclosure agreement (CDA)	Share protocol synopsis with sites that have an active CDA with your organization

Simplify feasibility questionnaires. Capture precise data about a site with a questionnaire that delivers valuable insight into a site’s suitability for the upcoming study. Instead of *how many patients are in your database*, edit the question to *how many of your patients have this specific disease*. Framing the questions to draw out detailed information will help companies make more informed decisions. In addition, developing a library of standard questions allows for the reuse of questions in other studies and responses for future trials.

Evaluate how pre-study visits (PSVs) or qualification visits are done. Establish clear criteria around whether a PSV is required or can be waived to proceed with site selection. With the advancements in decentralized and digitally connected trials, remote PSVs are becoming more commonplace. This can provide cost and time benefits and accelerate site activation.

Sponsors and CROs can enable faster site engagement by establishing a site selection strategy focused on data, simplifying questionnaires, and clearly defining PSVs. Paired with modern study start-up applications, this approach can help the industry improve site engagement long-term and reduce the burden of using numerous systems for sites.

Tapping the Power of a Modern Study Start-Up System

A purpose-built solution can help sponsors and CROs bring together start-up activities and processes in one system. This includes building workflows, tracking and analyzing data, and leveraging automation to speed site engagement.

More importantly, sponsors and CROs can establish reusable data-driven exchanges with sites. An effective study start-up system should deliver a global directory of contacts, accounts, and site information; connected workflows, milestones, and documents that automate processes; reusable documents and data; and end-to-end reporting. With advanced capabilities, companies can eliminate wasteful manual steps from their site engagement strategy.

Using a single system to manage study start-up activities also establishes a strong data foundation, enabling real-time metrics and reports. This allows clinical leaders to prioritize and manage critical tasks and milestones across multiple studies. If issues can be identified and resolved quicker, teams can execute faster.

Here are key considerations for clinical leaders assessing study start-up solutions to advance their site engagement strategy:

- *Alleviate the site burden.* Sponsors and CROs should make every touchpoint with sites as seamless as possible. A one-stop shop study start-up system replaces spreadsheets, paper, and disparate tools while simplifying the site experience.
- *Enable connected processes and workflows.* Seamless information and document sharing between study start-up and other clinical applications, like clinical trial management systems and electronic trial master files, reduces administrative tasks for study coordinators and eliminates costly and complex integrations. The system should enable data flow based on sequential processes.
- *Establish a site and investigator database.* Gather and store clean, accurate data, including site performance statistics and facility information. Companies should gather information from site engagement to study completion for continuous use across all trials.
- *Prioritize user experience.* A user-friendly, role-based platform that provides a consistent user interface drives effective and consistent processes.
- *Build a roadmap for the next five years.* The path to streamlined study start-up and site engagement is a marathon, not a race—map details with clear goals, requirements, and expectations to drive continuous improvement.
- *Evaluate trusted technology partners.* Look for vendors with a proven track record of success. They should provide training and change management strategies and be equally invested in your success throughout the journey.

Enabling Long-Term Stakeholder Collaboration

Addressing the critical challenges during site selection and leveraging the power of modern systems can significantly improve how trials are run. Looking ahead, sponsors, CROs, sites, and patients should have one source to find each other easily. A platform that allows sponsors to

search based on criteria, sites to share credentials and information, and patients to find trials will improve engagement and collaboration in trials.

Bringing stakeholders together to seamlessly share and access information can drive transformational change for the industry. If we can speed study start-up and clinical execution, life-changing medicines can reach patients faster.

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PRESCRIPTIONS FOR BUSINESS

The Real Reason Behind the Growth of Decentralized Clinical Trials? It's the Patients

Jaydev Thakkar, MBA



The concept of “patient-centered care,” loosely defined as situations in which clinical decisions are based on the needs, goals, and preferences of the patient—not the physician—is decades old and broadly accepted among most healthcare providers. Patient-centered care is believed to encourage patient engagement by involving the patient in more care decisions and collaboratively helping him or her overcome obstacles that could interfere with an optimal outcome.

Patient-centeredness, however, is only now—in part thanks to the COVID-19 pandemic—reaching a tipping point in clinical research. Although flexibility and excellent care are expected, historically, clinical trials and other types of research were driven by the needs of site-centered research, which could require extensive travel and time lost for study participants. The pandemic initially brought travel and many types of elective healthcare procedures to a halt, and likewise, clinical trials. New participant enrollment in April 2020, for example, was down 79% compared to the previous year.^{1}

Research to develop new therapies that could improve outcomes and quality of life—and even save lives—needed to continue despite patient reluctance to participate. Enter decentralized clinical trials (DCTs). Although not a new concept, DCTs have accelerated in recent years^{2} due to the expanded capabilities of wearable sensors and other monitoring devices that can be easily, or even passively, operated in the patient’s home.

More importantly, though, many patients prefer DCTs because the practice allows them to stay in the comfort of their home for most of the trial. On the other hand, while patient-centeredness can be advantageous for recruitment and retention, a DCT could end up posing greater challenges for life sciences companies and contract research organizations (CROs). Deciding what type of research to conduct virtually is important, for example, as is the technology used to gather and analyze data. Leading companies are even developing digital therapeutics along with pharmacotherapy to be co-prescribed for maximum efficacy.

When the optimal strategy is chosen, however, DCTs and hybrid models that include remote and in-person elements can result in significant cost savings and can accelerate timelines for clinical researchers. Essential to this outcome is to stay focused on the patient in all aspects of trial design and execution.

Why DCTs?

As of late 2020, more than three out of four (76%) life science organizations report at least some of their trials have already been decentralized, and 38% indicate more than half are decentralized.^{3} Other than COVID-19, one of the reasons for this shift is nearly 70% of potential clinical trial participants live more than two hours away from a study center.^{4}

Similarly, survey results from 2017 show that nearly one-quarter (23%) of participants in a clinical research study reported that the location of the study was what they liked “least” about the research, which was a close second to “possibility of receiving the placebo” (24%) as their top concern.^{5} More than 1 in 10 participants (11%) said site visits were too time-consuming. Other survey results of patients with chronic conditions found “inconvenience of travel” as one of the most common reasons for non-participation.^{6} These obstacles to participation and retention for an onsite research study can be worsened by the frequency of visits, patients’ out-of-pocket costs, and patient frailty.

Meanwhile, patient comfort with telehealth and remote patient monitoring is high. A 2020 survey of patients found 98% of patients reported satisfaction with telehealth.^{7} Likewise, 74% of patients with COVID-19 reported satisfaction with a remote patient monitoring program that included around-the-clock tracking of their vital signs.^{8} An even earlier

survey of post-lung transplant patients found that 90% of participants were satisfied with a home spirometer program that included electronic transmission of data as well as assessment and management by remote clinicians.{9}

DCT Use Case Example: Heart Failure

DCT or hybrid models can engender high satisfaction levels by eliminating logistical challenges for patients. In addition, these models are applicable for a wide range of therapeutic areas, such as heart failure, where timely initiation and dose intensifications of guideline-directed medication therapy (GDMT) continue to be a major challenge despite the availability of guidelines from professional societies, such as the American Heart Association and the American College of Cardiology. Less than 1% of heart failure patients are on the optimal dose of their heart failure medication and less than 25% of eligible patients receive all of their GDMT medications.{10}

Clinical decisions regarding the use and dosing of GDMT among heart failure patients must take into consideration various factors, including medical history, vital signs, laboratory data, and patient symptoms, as well as medication-related side effects. Currently, medication decisions are made by the care team periodically during in-person or virtual clinical interactions based on data gathered from disparate data sources.

Digital Therapeutics and DCTs

Decentralized and hybrid trials and research are now under way to study more efficient ways to identify optimal medication and dosage using digital therapeutics. By combining wearable sensors, an artificial intelligence algorithm based on real-world data and patient-facing tools, digital therapeutics can help investigators more quickly achieve optimal therapy because they help clinicians more accurately assess a patient's health status and drug tolerance through continuous physiology monitoring and inclusion of lab assessment results for analysis.

Digital therapeutics, which are typically categorized as software-as-a-medical device (SaMD), also improve engagement and retention by automatically prompting clinicians and patients for medication initiation and up-titration while the burden of site visits is eliminated

through a patient-clinician communication system that can include streaming video encounters through a mobile device. Lastly, using a SaMD to support DCTs requires fewer resources than nurse-led programs because safety management and titration recommendation management guidelines can be distilled in the system.

Not only are such digital therapeutics being used to study drugs, but leading pharmaceutical companies are developing solutions that incorporate a SaMD to be co-prescribed as a companion to the drug to help determine efficacy and tolerance sooner and develop personalized treatment options. Likewise, the technology also enhances clinical research as a care option by flagging early deterioration in a patient's condition well before a medical crisis would have otherwise occurred. This tap on the clinician's shoulder enables him or her to intervene early to avoid costly and devastating medical issues and to improve outcomes overall—all while advancing clinical research.

Avoiding the Technology Burden

While site visits and travel can be a burden for patients, so can the care-at-home technology used during decentralized and hybrid clinical trials. If the technology is too complicated, or trial demands are too onerous for patients at their homes, engagement and retention can suffer despite patients' growing acceptance of telehealth and home health devices. Some technology factors clinical researchers should consider include:

- *Patient burden.* How much data entry will be required of the participant? If there are too many daily or weekly forms to fill out, too much testing to perform, or complex software to navigate, then investigators can expect more dropouts, or even worse, inaccurate or unreliable data. The technology platform should offer a simple user interface while automatically collecting as much physiologic data as possible, alleviating the patient from conducting their vital signs testing and reporting. The research should not require the patient to repeatedly fill out long, complicated forms, but rather questionnaires that take only a few minutes to complete.
- *Clinician burden.* Emerging technologies inevitably prompt the need for education and support for patient questions or technical troubleshooting. Also, site staff can be overwhelmed by inventory management and logistics. Investigators and site staff, however, should be focused on patient care, reviewing actionable alerts, and promoting patient engagement with excellent care, not technology issues. Life science

companies and CROs should select a technology partner that will support the complete platform with helpful, knowledgeable patient-facing representatives to troubleshoot and resolve challenges. Also, ensure that a technology partner can handle logistics and inventory management of devices, shipping direct to patients' home when needed, remotely onboarding patients on the technology platform, and tracking patient compliance.

- *Device agnostic.* The platform selected should also not limit investigators to what type of device they can use to drive their research. A device-agnostic, fully integrated remote patient monitoring platform also limits the number of vendors that researchers must manage and makes trial participation more seamless for patients.
- *Modular and scalable.* Few life science firms or CROs study just one therapeutic area. By choosing a highly modular and scalable digital therapeutic platform to support research, investigators can pursue DCTs and hybrid studies across a wider range of conditions and easily expand the number of participants as needed.

Beyond Trial Support

DCTs can be leveraged to investigate drugs as well as digital therapies. For example, a rather remarkable study found patients receiving chemotherapy for metastatic solid tumors survived longer when they used a web-based tool to document their symptoms compared to those who did not. {11} Instead of talking with a nurse or physician by phone or a site visit, a randomly selected group of patients answered a simple weekly questionnaire online about the side effects of chemotherapy. Researchers determined that health-related quality of life improved for the intervention group, the members of which also survived for a median five months longer than those in the control group, which is an outcome that some oncology drugs would hope to deliver.

Researchers did not conclude that reducing site visits or travel influenced this outcome, but the study and others demonstrate the possibilities of clinical research and therapeutic solutions that enable patients to remain in the home more often. With a focus on patient-centeredness and using technology solutions that alleviate participant burden, life sciences companies and CROs can not only improve their recruitment and retention, but also arrive at meaningful results sooner using fewer resources and driving optimal outcomes.

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Challenging the Conventional in a Post-COVID-19 Era: Why it is Time for Innovation in Clinical Trial Technology

Ricky Lakhani



With accelerations in medical science and the advent of personalized medicine and patient centricity, drug and device developers have the chance to tackle unmet needs and grow their businesses like never before, but only if they make wholesale changes to the way “do” clinical trials.

Spiralling operational costs, strict compliance procedures, and difficulties in recruiting and retaining participants are age-old barriers to efficient development. Trends such as more complex trial designs, ever tightening regulations, and targeted therapies reducing the pool of potential study subjects are only serving to compound these problems.^{1} In addition, there is a growing supply and demand issue—since the arrival of COVID-19, the overall volume of clinical trials and the number of procedures and endpoints they include has skyrocketed, yet sites are facing increasing financial and staffing pressures.^{2}

The time is right to shake off these shackles and realize the potential of innovation. How the industry responded to COVID-19 has proved that it is possible, and now it must elevate the conversation and realize that cutting-edge science needs cutting-edge technologies.

Pandemic Change

Digital solutions are nothing new, but COVID-19, which demonstrated the need for agile, adaptable trials and for better risk management, also highlighted just how far clinical trial technology has come in recent years.

According to an article published in *The Lancet* in August 2020,{3} thousands of trials were suspended at the start of the pandemic to comply with social distancing and lockdown rules. As these studies came back online, sponsors and contract research organizations (CROs) turned to clinical trial technology to get back up and running quickly, safely, and cost effectively. What they found was that today's digital platforms are faster, easier, and cheaper to implement than their traditional counterparts, and that they were more suited to modern trial conduct than ever before.

These digital platforms can, for example, generate the high-quality, clean data needed to support the focus on data-driven decision making. In addition, thanks to their greater usability, they can support trial continuation in rapidly evolving work environments, where some study team members are still working remotely and many companies are opting for hybrid home-/office-based models.

In essence, we have witnessed a monumental, and possibly unprecedented, change in clinical trial conduct. It was born of necessity but would not have been possible without agility—the hallmark of any sustainable business. The last 18 months have shown that the typically slow-moving industry can adapt to changes in the marketplace and seize new opportunities.

Further, while it may have taken a pandemic for the industry to wake up to the advantages of advanced clinical trial technologies, the benefits will extend much further than simply addressing the challenges of COVID-19.

Unified Trial Management

From supermarkets to the automobile industry, insurance to hospitality, most sectors understand the key to business growth is digital transformation. The integration of digital technology into all areas of a business fundamentally changes how it operates and delivers value to its customers. However, it is about more than just technology—it is a cultural change that requires businesses to continually challenge the status quo, experiment, and become comfortable with failure.{4}

To date, pharmaceutical, biotech, and medical device companies have been slow to rise to the digital transformation challenge. In the main part, they have taken an operational, one-

dimensional approach to clinical trial technology. Individual solutions to individual problems have been employed on a piecemeal basis with little effort to “connect the dots,” but next-generation clinical trial technology has the potential to offer so much more. It can provide strategic, enterprise-wide oversight that leaders can use to identify unmet needs, ensure risk management, build in agility, and, ultimately, direct company growth.

A crucial missing part of the jigsaw is represented by clinical trial management systems (CTMSs), which are often considered discretionary. In many cases, more precedence is given to operational technologies like electronic data capture (EDC), interactive response technology (IRT), and electronic trial master files (eTMFs). However, intelligent CTMSs can be central to some of the master data required to drive the operational systems, and can be a place to unify data.

A standalone eTMF, for example, requires the duplication of master and operational data, much of which are sourced from, and reside within, the CTMS. Intelligent CTMSs can unify these disparate technologies, reducing unnecessary duplication. In turn, this increases quality and proactivity, drives process optimization, and boosts collaboration between clinical teams.

CTMSs do this in a number of ways; for example, through the eradication of spreadsheets and other manual tools, they reduce the risk of human error, thus protecting safety, easing compliance, and leading to valuable gains in clarity and efficiency in a fast-paced environment. By being at the center of an ecosystem of inbound and outbound data, intelligent CTMSs also increase transparency, aiding data reporting and informed decision making.

This not only enables the effective, efficient management of individual clinical trials, it also gives organizations access to the information they need to make C suite-level decisions. In short, modern clinical trial management technologies give organizations greater strategic oversight by making the workings of disparate trial processes more visible, thus increasing the speed and agility of trial managers as they respond to changing market conditions.

If they are to embrace these new possibilities, leaders must be willing to change. If they are bold, the return on investment will be clear across a number of factors, including cost, efficiency, transparency, and, crucially, quality. For example:

- CTMSs increase access to and transparency of data, allowing for more proactive decision making based on issues and trends that are identified more quickly.
- These systems reduce duplicate data entry and errors, and aid in reconciliation through a single source of truth for data that is shared across what would otherwise be unconnected systems.
- Clinical teams are brought together, working in harmony and reducing operational overheads in training.
- Quality system overhead is reduced through the addition of vendor validation capabilities, which focus internal validation on user acceptance testing. This shrinks in-house bureaucracy, speeding up implementation and upgrades and allowing for more frequent innovation adoption.

Post-COVID-19 Action

Unifying trial management technologies will change how clinical trials are managed post-COVID-19. Staying on top of trends and accurate analysis is, now more than ever, paramount to managing uncertainty and change, and continuously adapting to new and evolving situations. CTMSs for effective trial management can be the “new normal” and ensure that trials are ready for anything.

While standalone, siloed solutions will always have a place, the advantages of unification are clear. For one, it secures data assets in the medium to long term; this helps to guide learning and inform decision making, and reduces the risks associated with moving legacy data between systems. It is also worth noting that unified systems can greatly increase adherence and compliance with industry standards and best practices.

We need to dispel the myths about who needs to adopt such technologies and clearly demonstrate that every company involved in clinical research stands to benefit. One such myth concerns CTMS as a monolith enterprise system that takes time and expertise to set up, and so is only used across multi-study programmes. The truth is that modern systems can come with built-in standards, configuration options, and validation templates, for example, meaning they can be up and running in weeks (not months) with limited in-house knowledge. This accelerates the

speed of implementation, allowing it to be used for single studies. What's more, when it is unified with eTMF, CTMS is the “brain” and eTMF the “memory” combining processes via a consolidated, single solution.

A CTMS also allows CROs to cut the number of systems they need to adopt, validate, and integrate, reducing overhead costs and increasing efficiency. By maintaining all data assets, sponsors can clearly demonstrate proactive oversight, build an evolving knowledge base of their clinical trials, and ensure they are always compliant.

For medical device companies, embracing the unified approach can help them prepare for the forthcoming electronic medical device reporting (eMDR) regulations. Traditionally, technologies such as CTMS have not catered to these companies' needs, but things are changing. Modular, configurable systems, with built in templates and support-as-standard, offer an easy to set up, configurable, compliant solution.

Of course, a unified trial management platform will not replace every system. Rather, it will sit at the center of an ecosystem. It will collapse some siloed processes and systems and consolidate data across different sources, offering a view of the data that fall outside the boundaries of a single study, supporting business intelligence across the board, particularly at therapeutic, portfolio, and compound levels.

Challenge Convention

If the industry is to continue to make landmark breakthroughs, it must disrupt the status quo—the digital transformation of clinical trials requires a wholesale change to the established norm. Digitalization and unification have already transformed our personal lives—a phone is no longer just a phone—but what about our professional lives?

To secure successful product development for the future, clinical operations executives must be proactive and focus on the organization as a whole. Business success depends on seeing things through a strategic lens and having the ability to adapt when necessary. Advanced clinical trial technology provides that overview.

Ultimately, the time is ripe to challenge convention in clinical trials. The science required to develop life-changing interventions exists, as does the technology needed to inform decisions and drive business growth; and if COVID-19 has taught us anything, it is that the two go hand in hand.

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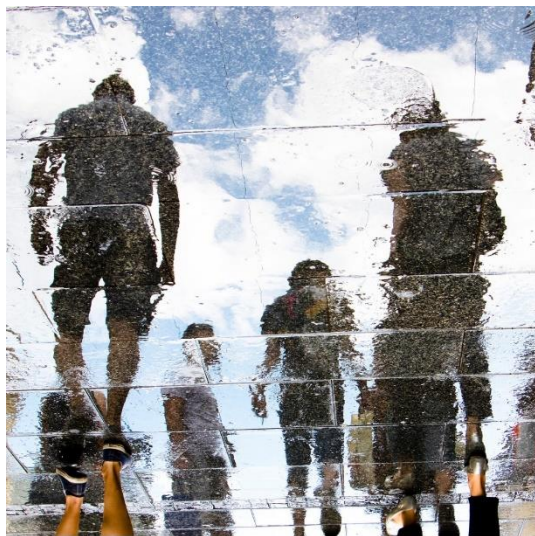
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OVER THE TRANSOM

I Can See Clearly Now

Gary W. Cramer

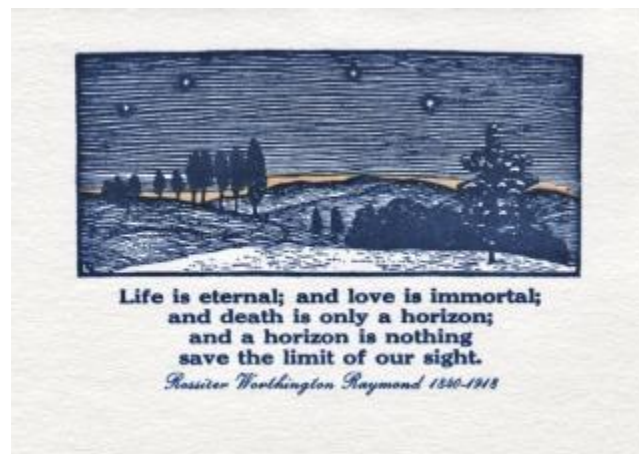
Life is eternal; and love is immortal; and death is only a horizon; and a horizon is nothing save the limit of our sight. — Rossiter Worthington Raymond (1840–1918)



As we are concentrating on the power of new perspectives on the clinical research workforce in this issue, I offer up the above words from a gentleman whose career surely must have benefitted from the ability to look at the world from many different angles at once. Rossiter Worthington Raymond was an American mining engineer, legal scholar, and author. At his memorial, he was [described](#) as “one of the most remarkable cases of versatility that our country has ever seen—sailor, soldier, engineer, lawyer, orator, editor, novelist, story-teller, poet, biblical critic, theologian, teacher, chess-player—he was superior in each capacity. What he did, he always did well.”

Well known as he may have been in his lifetime, I only ever came across his name because that inspiring quote is used in a woodcut bookplate by [J.J. Lankes](#) (1884–1960) that caught my eye in a quaint bookstore some years ago. Both quote and bookplate remain favorites of mine, serving as reminders that what we can readily see ahead of us falls far short of telling us all there is to be known about the true extent of any particular subject.

So it is with clinical research in these challenging times when so much that we thought we knew about the workings and limitations of the enterprise being fixed has been upended, reconsidered, rearranged, and reconstituted to the betterment of patients and practitioners. Here are some examples of how new perspectives are being put into practice by various players in the field (no endorsements implied) who are helping us see clearly things which were once obscured. Also shared is a cautionary tale about comeuppance for thinking no one in authority will ever see past any deceptions you may be guilty of in the pursuit of knowledge.



Alternative Statistical Method Could Improve Clinical Trials

Researchers say they have honed and advanced an alternative statistical method that can make clinical trials more reliable and trustworthy, while also helping to remedy what has been called a “replicability crisis” in the scientific community. In [a new paper](#) in the *Proceedings of the National Academy of Sciences*, the researchers further the “fragility index,” a method gaining traction in the medical community as a supplement to the p -value, an often-misunderstood measure used to determine whether study results have merit or are just a chance occurrence. The paper is written by statisticians from Cornell and doctors from Weill Cornell Medicine and the University of Toronto.

“Clinicians trust that the procedures and protocols they carry out are informed by sound clinical trials. Anything less makes surgeons nervous, and rightly so,” said Martin Wells, a professor of statistical sciences and a paper coauthor. “We’re discovering that many of these consequential

trials that showed promising results and that were published in top journals are fragile. That was a disconcerting surprise that came out of [this research](#).”

Skepticism surrounding the p -value’s reliability, when used on its own and without supporting methods, has grown in the last 15 years, particularly as past trial results initially deemed strong couldn’t be replicated in follow-up trials. In [a 2014 study](#) using the fragility index, researchers analyzed 400 randomized clinical trials and found that one in four with “statistically significant” p -values in fact had alarmingly low fragility scores, indicating less reliable results. The fragility index investigates what number of patient outcomes could tip a trial in either a successful or unsuccessful direction.

Placebo Effect Accounts for More Than Two-Thirds of COVID-19 Vaccine Adverse Events

In [a new meta-analysis](#) of randomized, placebo-controlled COVID-19 vaccine trials, researchers at Beth Israel Deaconess Medical Center (BIDMC) compared the rates of adverse events (AEs) reported by participants who received the vaccines to the rates of AEs reported by those who received a placebo injection containing no vaccine. While the scientists found significantly more trial participants who received the vaccine reported AEs, nearly a third of participants who received the placebo also reported at least one AE, with headache and fatigue being the most common. The team’s findings are published in [JAMA Network Open](#).

“Adverse events after placebo treatment are common in randomized controlled trials,” said lead author Julia W. Haas, PhD, an investigator in the Program in Placebo Studies at BIDMC.

“Collecting systematic evidence regarding these ‘nocebo’ responses in vaccine trials is important for COVID-19 vaccination worldwide, especially because concern about side effects is reported to be a reason for vaccine hesitancy.”

Senior author Ted J. Kaptchuk, professor of medicine at BIDMC, and colleagues are known for a large and growing body of evidence showing that full disclosure of placebo treatment, what he calls “open label placebo,” can actually improve common chronic conditions without any nocebo effects.

Younger Parkinson's Patients Show Strong Interest in Trial Participation

Writing for SubjectWell [in January](#), Ivor Clarke describes how, in order to better understand the sentiment of patients with Parkinson's disease (PD) toward both their specific symptoms and their attitudes about clinical trials, SubjectWell fielded a survey to 217 patients with PD.

One finding of the survey is that 77% of respondents are likely to participate in a trial focusing on the treatment of Parkinson's motor symptoms versus 66% in a trial for non-motor symptoms caused by Parkinson's. Further, younger respondents were more likely to report high interest in trial participation. Of those 59 and younger, 91% responded with a high likelihood of participation in a trial for PD, significantly higher than all older age groups.

Respondents were also asked about their comfort level completing a variety of digital tasks on a smartphone or digital tablet as part of a daily electronic diary. A majority of respondents (72%) rated highly their comfort level with digital tasks.

Research Site Co-Owner Pleads Guilty to Falsifying Trial Records

According to [a report](#) from *Mintz*, on January 12, 2022, Olga Torres, co-owner of the clinical research site Unlimited Medical Research (UMR) in Miami, Fla. pleaded guilty to one count of obstruction of justice after she knowingly [lied to a United States Food and Drug Administration \(FDA\) investigator](#). The conduct that led to the charge stemmed from a clinical trial run at UMR to evaluate the safety and efficacy of a pediatric asthma drug. Torres admits having made a number of false statements to FDA investigators to create the appearance that the trial had been conducted legitimately and honestly when she knew that it had not. For example, she told FDA investigators that UMR prepared accurate and complete medical records in conjunction with the trial and that study subjects were seen at UMR and not another location. In fact, the records of the study subjects had been falsified and UMR had fabricated data showing that subjects had attended study visits at UMR. [Previously](#), the principal investigator and others involved in the trial had pleaded guilty to wire fraud in connection with the study.

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