

Clinical Researcher

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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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Steven Eric Ceh, DPM, (sec_consulting@sbcglobal.net) is a Consultant with SEC Clinical Consulting, Ltd. In Westerville, Ohio.

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.

Reference

1. <https://isrreports.com/reports/hybrid-virtual-decentralized-clinical-trials-market-outlook/>



Stacy Weil is Senior Vice President of Clinical Data Operations with Premier Research.



Nicole Carswell is Executive Director of Patient Engagement and Recruitment with Premier Research.

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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3. <https://www.statnews.com/2019/08/23/clinical-trial-recruitment-diversity-community-engagement/>



Anusha Shetty is Director of Clinical Strategy for Vault Study Startup at Veeva Systems.

ACRP HOME STUDY

CLINICAL RESEARCHER—FEBRUARY 2022 (VOLUME 36, ISSUE 1)

I Can See Clearly Now (The Power of New Perspectives On the Clinical Research Workforce)

Article #1: The Clinical Research Investigator: Clarifying the Misconceptions

LEARNING OBJECTIVES

After reading this article, the participant should be able to differentiate between terms for investigator positions according to their officially defined qualifications, roles, and responsibilities; cite several U.S. regulations and international guidances on the subject; and explain the work of sub-investigators.

DISCLOSURES

Steven Eric Ceh, DPM: *Nothing to disclose*

- 1. The definitions of “investigator” found in portions of 21 CFR 312 and 812 in the *Code of Federal Regulations* agree on which of the following?**
 - a. The investigator bears the full financial impacts of the success or failure of a clinical investigation he/she initiates.
 - b. Investigators must personally recruit all human subject volunteers into any clinical investigation at their sites.
 - c. The investigator is the responsible leader of the team if multiple people are conducting a clinical investigation.
 - d. Investigators cannot be held legally responsible for the conduct of any of their staff involved in clinical investigations.

- 2. A stated expectation of the ICH Good Clinical Practice guideline is that an investigator should provide evidence of his/her qualifications for conducting a trial to which of the following, among others?**
 - a. Regulatory authorities
 - b. Contract research organizations
 - c. Potential volunteers
 - d. Data and safety monitoring boards

- 3. The Compliance Program Manual for FDA’s BIMO Program uses which of the following terms to encompass “investigator” and “principal investigator” as stated in other sources?**
 - a. Sub-investigator
 - b. Co-investigator
 - c. Co-principal investigator
 - d. Clinical investigator

- 4. Which of the following is the stance of the FDA regarding non-physicians serving as investigators?**
 - a. They may readily do so, as long as a co-investigator of more senior standing is also listed on the Form FDA 1572.
 - b. They should only do so in cases where a physician investigator has to drop out of a study due to an emergency.
 - c. Although they can do so, it is rare for them to be qualified according to the agency’s requirements.
 - d. There are no circumstances under which a non-physician can conduct a clinical trial as an investigator.

5. Nurse practitioners may serve as autonomous principal investigators in which of the following locations?

- a. In all U.S. states and in the District of Columbia.
- b. Wherever they are certified through the American Nurses Association.
- c. In all states except Alaska, Hawaii, and Massachusetts.
- d. In states where they have full medical practice privileges.

6. FDA guidance on “Financial Disclosure by Clinical Investigators” states which of the following?

- a. Only investigators and any of their staff who own stock in the study’s sponsor must make financial disclosures to the FDA.
- b. Investigators and any sub-investigators taking responsibility for a study at a given site must report under the regulation.
- c. Financial disclosures are to be made to all potential human subject volunteers prior to the informed consent process.
- d. Investigators are only required to make financial disclosures when a study is completed successfully and fully registered.

7. How does 21 CFR 312.3(b) characterize who a sub-investigator is on a study team?

- a. As any other individual member of a team being led by an investigator.
- b. As any member of an investigator’s study team who also holds a medical degree.
- c. As a member of a study team who is not responsible for making a financial disclosure.
- d. As the individual member of a team most likely to handle data-entry tasks.

8. What are the responsibilities of a sub-investigator?

- a. Any tasks assigned to him/her within the study protocol which a licensed physician/practitioner is qualified to do.
- b. Only those which are delegated to him/her by the investigator and which he/she is qualified to do.
- c. Overseeing and documenting the completion of study-related tasks by clinical research coordinators.
- d. Determining the causes and severities of any adverse events and serious adverse events on behalf of the investigator.

9. Who should report findings about adverse events to the study sponsor?

- a. The clinical research associate
- b. The data and safety monitoring board
- c. The investigator
- d. A sub-investigator

10. Where can a comprehensive listing of FDA’s requirements for the conduct of studies by investigators be found?

- a. In ICH GCP E6(R2)
- b. In various parts of 21 CFR
- c. In Form FDA 1572
- d. In the FDA Compliance Program Manual

[Home Study continues on next page]

Article #2: Preparing for the Future: Data Collection and Technology Deployment in Decentralized Clinical Trials

LEARNING OBJECTIVES

After reading this article, the participant should be able to highlight factors sponsors should consider when choosing contract research organizations to manage decentralized clinical trials, discuss the role and challenges of wearables in modern trials, and explain sponsor and vendor responsibilities for data quality.

DISCLOSURE

Stacy Weil; Nicole Carswell: *Nothing to disclose*

11. Respondents to a 2021 industry survey predicted which of the following about the use of decentralized clinical trials (DCTs) in the near future?

- a. That DCTs would increase by nearly one quarter in just a few years.
- b. That DCTs would soon be more common than traditional trials.
- c. That DCTs would fail to catch on to any significant degree.
- d. That DCTs would be over-regulated and more difficult to conduct.

12. The authors cite which of the following as examples of decentralized technology that has already been used for a long time?

- a. eConsent and ePRO
- b. TMFs and CRFs
- c. IVRS and EHRs
- d. CAPAs and eRegulatory

13. DCTs' ability to better support patients is said to lead to which of the following results?

- a. Trial timelines and expenses cut nearly in half
- b. Easing of regulatory oversight and reporting
- c. Increased PI compensation and study awards
- d. Improved compliance and better data

14. Who typically selects the online platforms to be used during a DCT?

- a. The sponsor
- b. The study site
- c. The FDA
- d. The patients

15. Respondents to the industry survey cited which of the following as a factor in need of improvement for wearable sensors and connected health devices?

- a. Adverse event detection
- b. Insurance coverage
- c. User-friendliness
- d. Regulatory acceptance

- 16. The authors recommend that contract research organizations (CROs) do which of the following in terms of staffing and training for DCTs?**
- a. Develop specialized personnel focused solely on them.
 - b. Defer to staff at study sites on how best to conduct them.
 - c. Ensure that all team members are well prepared for handling them.
 - d. Wait for regulatory guidance on how to assign team members to them.
- 17. DCTs may require more of which of the following than traditional trials?**
- a. Principal investigators
 - b. Patients
 - c. Coordinators
 - d. Vendors
- 18. The authors suggest that an ideal technology system for DCTs would encompass which of the following?**
- a. Patient recruitment, retention, and reimbursement
 - b. Data collection, management, and analysis
 - c. Regulatory training, reporting, and compliance
 - d. Staff onboarding, tracking, and communications
- 19. What should a CRO have in place in terms of adoption support for DCT-related technologies?**
- a. Clearance from regulatory authorities to use the latest data-collection methods.
 - b. Clinical Trial Agreements signed by the principal investigators using the technology.
 - c. Strategies for training and supporting patients and trial team members.
 - d. Memoranda of understanding with sponsors that any tech may become obsolete.
- 20. The authors cite which of the following as a factor bolstering the success of DCTs?**
- a. Guaranteed better data quality.
 - b. Non-U.S. sponsors avoid them.
 - c. Privacy issues are eliminated.
 - d. Patients prefer them.

[Home study continues on next page]

Article #3: Establishing a Site Engagement Strategy for Greater Efficiency and Speed in Study Start-Up

LEARNING OBJECTIVES

After reading this article, the participant should be able to summarize key challenges to study start-up in terms of site engagement, describe how feasibility questionnaires and qualification visits could be improved, and address the role of technology in future site/sponsor relationships.

DISCLOSURE

Anusha Shetty: *Nothing to disclose*

21. Nearly one-third of clinical trials suspended over a recent 10-year period were due to which of the following?

- a. Insufficient study budgets
- b. Not enough human subjects
- c. Poorly trained coordinators
- d. Not enough sponsor support

22. How successful are trials in terms of recruitment of patients within specified periods?

- a. Nearly half meet their recruitment targets just in time.
- b. Most meet their targets in less than half the time allowed.
- c. Almost none require extra time to meet their targets.
- d. Most of them do not meet their recruitment targets.

23. The author cites which of the following as a problem with site feasibility surveys?

- a. Most questions asked are not applicable to many smaller study sites.
- b. Sponsors rarely make use of them despite demanding their completion.
- c. Site responses aren't being saved for use on later questionnaires.
- d. Site personnel filling them out too often supply incorrect data.

24. The author cites which of the following as a barrier to investigators being noticed by potential study sponsors/contract research organizations (CROs)?

- a. Sponsors and CROs not conducting a thorough site selection process.
- b. Regulatory restrictions on how many sites sponsors/CROs may consider.
- c. Sponsors and CROs won't select sites that have been used by competitors.
- d. Investigators are not allowed to market their sites to sponsors/CROs.

25. The author suggests which of the following as a tactic for improving site identification and study start-up?

- a. Sites and their staff should regularly be reevaluated through an independent certification process.
- b. Patients should share post-study feedback on their visits to sites with the study's sponsor/CRO.
- c. Sponsors/CROs should leverage data from the public domain and internal resources regarding sites.
- d. Clinical research associates should be better trained for interviewing investigators and selecting study sites.

- 26. Which of the following is suggested by the author as a means for simplifying feasibility questionnaires?**
- a. Strictly limiting them to a dozen questions.
 - b. Developing a library of standard questions.
 - c. Eliminating multiple-choice questions.
 - d. Requiring all answers in essay format.
- 27. What does the author suggest regarding pre-study or site qualification visits?**
- a. At least three different sponsor/CRO representatives should visit each site.
 - b. Such visits are almost never necessary following a thorough questionnaire.
 - c. They should only be conducted by independent, unbiased contractors.
 - d. Establish clear criteria as to whether they are required or can be waived.
- 28. Among others, the author says which of the following features ought to be included in an effective study start-up system?**
- a. Connected workflows and end-to-end reporting.
 - b. Billing and payment triggers for sponsor reimbursements.
 - c. IRB meeting notes and FDA Form 483 information.
 - d. Patient study diaries and feedback on site staff.
- 29. The author cites which of the following as an example of connected workflows?**
- a. Regulatory filings shared between site binders and the ClinicalTrials.gov registry.
 - b. Document sharing between clinical trial management systems and electronic trial master files.
 - c. Data safety and monitoring board report sharing between sponsors and CROs.
 - d. System password sharing between clinical research coordinators and clinical research associates.
- 30. A site and investigator database should include information covering what span of time?**
- a. From initial site contact to feasibility study completion.
 - b. From Clinical Trial Agreement to site initiation.
 - c. From site engagement to study completion.
 - d. From completion of one study to start of the next.