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Qpinion: *The Investigator Site of the Future*

The perspectives offered in this opinion piece come from the author, who works in a contract research organization (CRO) with a site alliance; from two investigators and a study manager who conduct clinical research; and from personnel at a CRO-like organization with a new hybrid approach that offers staff and processes to help investigators conduct clinical research.

PEER REVIEWED

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The investigator site of the future will look dramatically different than it does today. To a great extent, investigator frustration with the current environment will drive change as the industry seeks to eliminate inefficient processes that create redundant activities, slow patient recruitment and enrollment, and complicate trial execution. Such processes are harmful in that they distract physicians from patient care and discourage others from considering clinical research.

The frustration experienced by investigators and other site personnel often stems from their increased responsibility for activities tied to contracts, budgets, new software, training, and other mundane, though necessary, tasks, when they would prefer to focus primarily on patients. For example, they must navigate multiple levels of government and private-payer policy to determine which study treatments and services are (and are not) eligible for insurance coverage, often creating uncertainty that can complicate billing.[1] Meanwhile, delayed reimbursement and inaccurate payments reportedly contribute to a 40% investigator turnover rate, fostering the "one (trial)-and-done" investigator phenomenon.[2]

Moreover, growth in global clinical trial grant spending—by both government and industry—has slowed significantly in recent years, even as industry-sponsored clinical trial activity has continued to increase.[3] Given the average per-patient cost of $36,500 for clinical trials of any phase or condition,[4] such financial and administrative volatility can significantly impact site revenue streams and resource planning.

Trial sites are further burdened by the proliferation of multiple technologies. The typical site uses 12 different systems for data collection[5] and has increasing responsibility for deploying devices and wearables for patient use. While these technologies are meant to increase efficiencies, the lack of standardization across the industry, in fact, often makes their use a hassle.

All these factors—combined with increasingly stringent regulatory and administrative requirements—serve to drive up costs and increase the burden on investigators and sites, dissuading many from participating. This situation must change.

ENVISIONING THE SITE OF THE FUTURE

Overcoming the challenges of the current site environment will entail extensive consultation and rethinking among trial sponsors, CROs, and regulators about how they can reduce investigator turnover and encourage more physicians to participate in clinical research, while also streamlining patient

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recruitment and retention. Certain aspects of site operations will therefore need to be optimized to accelerate and improve clinical research.

"To be successful, sites will need both the right resources and the right processes," said Ravi Thadhani, MD, MPH, chief of the Division of Nephrology at Massachusetts General Hospital and adviser to various healthcare organizations. "There isn't going to be one solution, but multiple solutions. There will need to be modifications in processes, incentives, and organizational activities."

RUNNING THE SITE AS A BUSINESS

For sites to truly become better centers for high-quality clinical research, each site should be professionally managed as a proper business.

"Sites need to change the way they operate to become more efficient and profitable, especially during study startup, and they can do so by streamlining ideas and establishing a sound infrastructure," said Manuel Montero, MD, who serves as a principal investigator at Eastern Nephrology Associates.

CROs can facilitate this by helping sites implement professional financial systems as well as new tools, technologies, and services to expedite payments and provide more transparency for sponsors and investigators. Sites also can make greater use of resource planning tools to optimize resources, possibly transitioning from the decentralized (silo) operational and administrative model to one in which some or most research activities are standardized and controlled by an umbrella core organization.[6,7]

"It is very difficult to redirect medical providers to a business mindset," Montero said. "We need them to understand that research is not just about medical care, but about helping patients in the future."

While the concept of patient centricity is nearly ubiquitous in the current environment, it needs to be incorporated into strategies and value propositions, helping sites to sell their services and expertise to sponsors and/or CROs. Having an experienced study manager on staff with project management expertise will enable sites to prioritize study demands and oversee the adoption and implementation of new technologies.

THE POWER OF CLINICAL SITE NETWORKS

The future may see the rise of clinical investigative site networks, which are groups of independent clinical sites that function as one entity. In one model, the typical network is managed by a central administrative staff that oversees and streamlines financial, regulatory, safety, data management, business processes, quality assurance, and site selection matters for each trial.

Unless affiliated with a CRO, these networks typically require sponsor monitoring, are regionally structured, and further divided by disease state, with each region assigned a lead investigator for a specific disease state.[8] Whether structured in this manner or in some version of this model, networks offer value by centralizing services.

"There's a need for independent research sites to group together to reduce their overhead costs," said John Potthoff, PhD, CEO of Elligo Health Research. "Technology, systems and training applied to one site per year is a heavy cost. If the same processes and infrastructure can be leveraged across many sites, it eases the burdens of study conduct."

It remains to be seen whether site networks can take over such tasks as overseeing general feasibility assessments, licensing, annual Good Clinical Practice (GCP) training, and internal audit programs to eliminate redundancies and optimize site qualification visits. However, networks can be particularly effective in leveraging recruitment campaigns—even those not specific to a study, but which target patients expressing a general interest in participating in clinical research.

Such networks may be able to obtain more studies through competitive pricing, making it harder for non-affiliated sites to compete. Some of the larger networks may also be able to negotiate better payment terms.

ADOPTING AND OPTIMIZING NEW TECHNOLOGIES

The site of the future will almost certainly feature new technologies that dramatically improve management of data, documentation, workflow, and compliance. When sites effectively use the technology available, patients can benefit.

"We can begin to utilize remote consenting with live chat and remote monitoring to include more patients in clinical trials," said Thadhani. "When patients have the opportunity to be more involved—in activities like filling their own kits, for example—they feel like they are actively participating in the research."

Another advance that can be implemented is to automate the processes for sharing trial performance–related information with sponsors, which can potentially save 40 hours a month alone for CROs per study[9]—a benefit that can result in shortened trial timelines and significant cost savings.

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However, efforts to optimize the drug development process may backfire if these new technologies do not fully integrate with each other. Multiple technologies can be more burdensome because of training requirements at the site level, along with the added weight of managing sign-on credentials across a large number of platforms. Even investigator portals—specifically meant to ease investigator burden—can be troublesome.

"From a technology perspective, we continue to see the deployment of investigator portals to accommodate study startup and data collection, but it's very challenging to maintain sign-on credentials for each individual sponsor," said Morgan Moore, CCHT, CCRC, clinical research site operations manager at Eastern Nephrology Associates.

As new platforms are developed and tested, the number of adopted technologies will likely consolidate over time, with some clear winners emerging, especially given the favorable valuations of technologies in the clinical space. The site of the future will benefit from this consolidation with fewer, more powerful tools such as mobile-friendly electronic data capture systems, clinical data management programs, clinical endpoint adjudication software, genetic analysis software, online risk assessment tools, and cloud-based clinical trial management systems.

Nevertheless, even with consolidation, sites will need to overcome lingering "technophobia" if they are to take full advantage of new technologies. In a 2006 survey of representatives of academic institutions, drug and device companies, CROs, clinical research sites, consultants, and third-party service providers, investigators and their staffs were the least accepting of Big Data and innovative processes in clinical trials, and were the second most resistant group to paperless trials and wearable mHealth technologies; their resistance was largely due to concerns about cost and data integrity.[10]

Technophobia is not limited to trial site personnel. "In our patient population, participants frequently have device limitations, or a lack of familiarity with technology or Internet access," Moore observed. "They prefer the additional one-on-one interactions with our staff during clinical studies."

In the future, patients and site staff alike will benefit from new technologies that work more like apps, require little or no training, and use plug-ins to integrate multiple technologies. There will also be increasing use of telemedicine and wearables to collect and track vital signs and facilitate ongoing monitoring.

Additionally, consumer advertising and retargeting technologies will facilitate patient recruitment, allowing sponsor companies and CROs to drive more patients to sites, while reducing the recruitment burden at the site level. Other advances such as home-based video conference equipment to enable "virtual" physician visits/examinations and drone-delivered medication may yield further efficiencies.[11]

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"Patients want to feel engaged and connected with the research," Thadhani said. "These are technologies that can connect patients to investigators and improve connections among research staff and administrators."

EFFECTING DISRUPTIVE CHANGE

The site of the future will be the product of disruptive change that transforms the industry and eliminates redundant activities; it is almost ridiculous the way current practices needlessly ask investigators to do certain things over and over from trial to trial. Rather, by centralizing and standardizing key processes, disruptive change can accelerate study startup and drug development, while also cutting costs.

To a great extent, disruptive change can ameliorate many of the inefficiencies in the current site environment, particularly those pertaining to patients. "Having a streamlined process to screen patients would greatly assist the whole industry," said Montero. However, getting patients in the door can be a resource-intensive pursuit.

"While ongoing patient engagement and education programs can be instrumental in getting more patients interested in clinical research, a comprehensive program that includes 'lunch and learns,' educational materials, slide shows, collateral, etc., as well as database maintenance, requires a lot of resources—and resources at sites are limited," said Moore. "At industry conferences, there is a lot of talk about Big Data, but right now, we are not seeing it effectively translated to the site level."

To get more patients involved in clinical research, Elligo Health Research is improving the accessibility of studies in terms of potential participants. The company is using electronic health records and other data to first identify patients. Once patients are identified, the company provides their physicians with the infrastructure to conduct the studies with their own patients in their own clinics.

"We need to look at healthcare and where the patients are really treated—not where should we run the trials," said Potthoff. "Patients want the familiarity and consistency of their trusted clinician."

This approach is a new way to tackle the problem of low patient and physician participation

levels. In addition, the industry must evaluate many options and implement those that truly help us meet our challenges. Some disruptive changes that can be considered include:

- U.S. Food and Drug Administration or other centralized organization takeover of responsibilities for collecting licenses and conducting annual GCP training, as well as development of an audit program to enable research sites to eliminate redundant per-study requirements and site qualification visits.
- Improvements to ClinicalTrials.gov to make it more user friendly, up to date, and compatible with other tools.
- Streamlining insurance cost analysis so that the sponsor can conduct a single analysis for the largest providers, rather than requiring each site to expend time and resources on multiple analyses across the sites.
- Centralization and expansion of site data to reduce the volume of feasibility questionnaires for every study.
- Collaboration between industry and regulators to improve guidance on "serious and unexpected" adverse events, and to reduce the burden of over-reporting of all adverse events.
- Adoption of centralized, risk-based monitoring to lessen the burden on the entire system.

CONCLUSION

Although forecasting change is an inexact science, it is possible to envision how trial sites will evolve into more efficient engines of clinical research. Indeed, many of the procedural and technological advances described in this article are already under way and are expected to yield benefits in the not-so-distant future. As these benefits are realized, skeptics and others reluctant to adopt new technologies and practices may become proponents of change in order to capture labor and cost savings.

As Thadhani said, "Research complements and can enhance clinical care." This is at the heart of our efforts—the desire to complement clinical care now and to enhance it in the future. To truly succeed, all stakeholders—sponsors, CROs, investigators, site personnel, and even patients—must be willing to embrace the changes necessary so that we can realize the broader benefits of more streamlined and more efficient clinical development.

The future may see the rise of clinical investigative site networks, which are groups of independent clinical sites that function as one entity.

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