Chapter 5

Increasing trial productivity: Addressing site-specific challenges to improve site engagement

Executive Summary:

Every clinical trial involves a complex ecosystem of diverse trial sites. Site-to-site variability is influenced by a number of factors—including experience with prior trials, the level of existing clinical and administrative expertise at the facility, overall size, geographic location, access to target patient populations, existing equipment and technology infrastructure, and more. Drug developers and their chosen clinical research organization (CRO) can benefit the trial by working closely with each candidate trial site to identify and rectify site-specific challenges promptly and embrace insights from sites about how the trial might be conducted more efficiently. This demonstrably improves individual site engagement and competence, driving the overall trial effectiveness and efficiency. This article reviews common causes of productivity lapses and offers actionable recommendations for how to tailor the interventions so that individual sites can improve the speed of patient recruitment and the predictability and productivity of trial operation.

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Clinical trials play a pivotal role in advancing therapeutic innovation. Specific issues that can hinder trial productivity will vary from trial to trial, from site to site, and from drug sponsor to drug sponsor. Further compounding the challenge, the overall clinical trial landscape has become more complex in recent years, as drug developers have continued to pursue targeted, specialty and personalized therapies, treatments for rare diseases, and other niche indications in recent years.

Factors that contribute to site-to-site performance variability include prior trial experience, expertise within the specific target therapeutic space, overall staffing, facility size, technology infrastructure, and more. When trial site engagement and productivity lags at particular sites within a complex trial, it can depress overall trial productivity. But it also creates many opportunities for improvement.

Inefficient or ineffective workflows, a lack of experience and expertise, and other structural issues at individual trial sites can create delays, cost overruns, and potential quality issues. Thus, to optimize overall productivity, any trial will only be as strong as its weakest site. Typically, measures are built into the trial to mitigate this weakness, but inefficient or ineffective workflows must be addressed at every site that is part of the integrated trial ecosystem. When minor productivity lapses compound across multiple sites, it negatively impacts the entire trial and, importantly, can result in delayed regulatory filings and market entry. Both have costly implications for drug sponsors and the healthcare community.

To enhance site-by-site engagement and productivity, drug sponsors and their CRO collaborators should use a strategic approach to critically evaluate the strengths and weaknesses of each potential trial site. Such an approach will highlight key deficits and specific pain points, informing problem-solving efforts.

Defining clinical trial productivity

As discussed throughout this multi-part thought leadership series[1], within the context of any clinical trial, productivity is typically measured in terms of performance benchmarks related to the trial's ability to:

- Remain on budget and reduce avoidable cost overruns
- Stay on the timeline and minimize avoidable delays
- Minimize costly and time-intensive protocol amendments
- Reduce frustration and burnout among trial investigators
- Reduce frustration and satisfaction issues among patients and care providers
- Maximize patient adherence and minimize dropout rates
- Optimize overall quality
- Ensure the statistical viability of the data findings (by ensuring that trial participation does not fall below threshold levels)

1 All chapters in Fortrea's productivity series can be found at **www.fortrea.com/insights**

Variability requires a nuanced approach

Given the overall complexity of today's clinical trials, there is no single blueprint for success in optimizing site engagement and productivity for individual trial sites. When individual sites—regardless of their size or prior trial experience—are able to develop a close working relationship with the drug sponsor and its chosen CRO(s), the collaboration helps to establish a road map for sustained success over time.

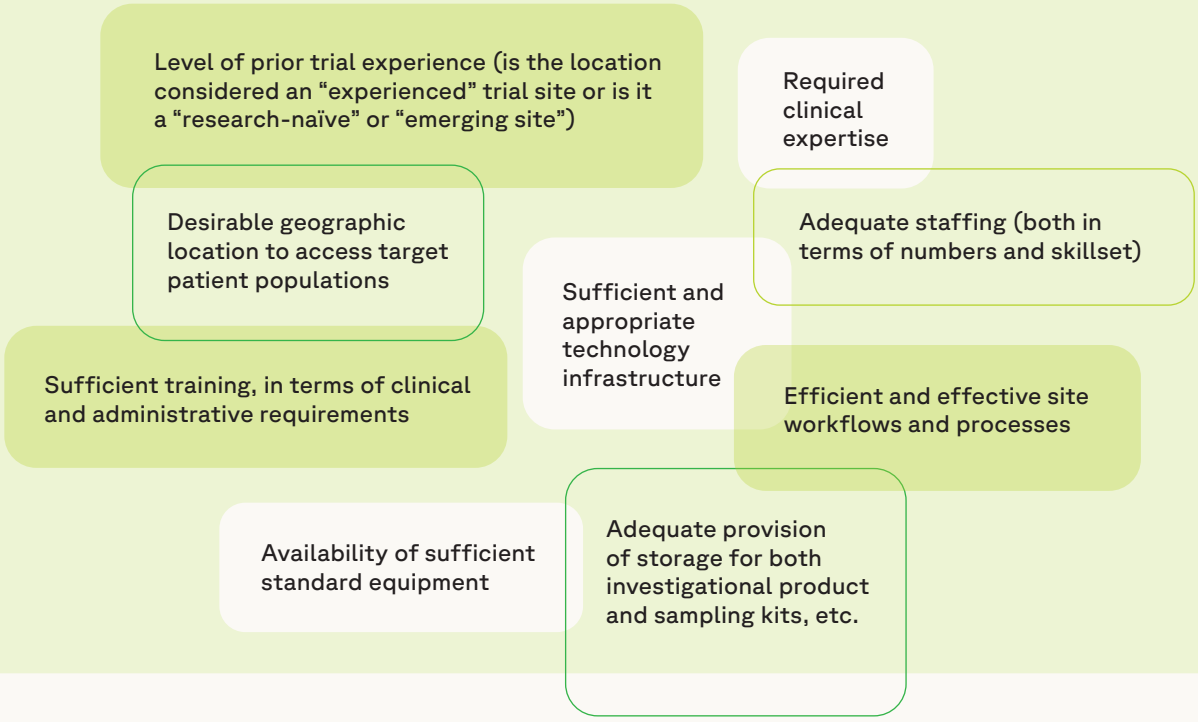
For instance, such collaboration can provide opportunities for the candidate site to evaluate the trial protocol as early as possible and to assess what will be needed to ensure a speedy trial start. Similarly, working in close collaboration with the CRO, sites may be able to conduct "dry runs" to better anticipate the patient experience and assess site readiness. Dry runs are especially useful for large cohorts or visit days that may require a large number of clinical tests to be carried out.

A collaborative relationship encourages the exchange of timely feedback and insights that inform ongoing improvement efforts. However, developing the right environment for collaboration to thrive requires explicit, active intent, open communication channels, and relationships built on shared values.

Resisting the urge to rely solely on "experienced" trial sites

As drug sponsors and their chosen CROs assess competing sites for any given clinical trial, there are downsides associated with leaning too heavily on well-known, experienced trial site locations. The inclusion of a more diverse selection of trial sites—even if additional work is needed to ensure "less-experienced" sites are ready to meet the trial requirements—typically pays dividends over time and helps to build future capabilities and institutional knowledge.

During the process, the particular strengths and weaknesses and overall trial readiness of each candidate site must be assessed in terms of a range of factors:



Don't overlook the importance of emerging or "research-naïve" sites

It is worth noting the oversight of characterizing sites as "research naïve". On an initial read, "naïve" might suggest a lack of experience in operating clinical trials. Yet new site businesses do not typically start from scratch, rather they start with a team that will have some experience of trial conduct—merely labeling a site as "naïve" because it is a new name or new physical location in a database overlooks the opportunity of the experience of the team setting themselves up at that location. Indeed, new site businesses competing against established names may help invigorate a trial through greater availability.

Determining suitability and readiness can only be done by taking a holistic view of each site. Drug sponsors and CROs stand to gain by assessing the level of "naïve" site suitability at the outset, and then ensuring that proper training, resources, and other forms of scaffolding are provided to enable that specific site to operate successfully.

Factors that inform site selection are varied. Some drug sponsors believe it is easier to engage primarily with well-established trial sites that have extensive prior trial experience or access to a large patient population. However, this approach is short-sighted and can miss meaningful opportunities that can arise when smaller, emerging "research-naïve" sites are integrated into the trial ecosystem.

Balancing a mix of investigator sites that are experienced, emerging, and "research-naïve" can deliver significant productivity benefits. Consider the following:

- Experienced, high-volume trial locations may be reflexively prioritized, but such sites may also be saturated in terms of their current clinical trial commitment. This saturation can create delays, impact investigator availability, and create competition for a finite number of potential trial participants
- Over-reliance on a finite pool of experienced researchers may be counter-productive, as these individuals are typically in demand. A more productive long-term strategy is to consistently identify, engage, and nurture the next generation of experienced trial investigators and key opinion leaders (KOLs)
- Some drug sponsors may exhibit a reflexive bias toward conducting their trials primarily in large academic settings rather than smaller community care settings. The truth is, that each type of trial site provides distinct advantages, so including a diverse mix of both can create a stronger trial ecosystem and provide access to a broader cross-section of patients
- Broadening the geographic reach of any trial has numerous benefits, including helping drug sponsors access desired trial participants more effectively and mitigating trial delays:
    - Such an approach is especially important for rare diseases and trials that have very narrow inclusion/exclusion criteria
    - Broader geographic reach also helps to reduce the travel burden for patients in those locations, and creates more opportunities to reach patients in trusted community healthcare settings
    - Broader geographic spread can also mitigate exposure to regulatory delays, logistical challenges, and complications caused by political instability
    - Access to trials for patients outside of the major, traditional trial conduct geographies through decentralized and digital methodologies

Actionable recommendations to help trial sites thrive

Discussed below are some of the opportunities drug sponsors and their chosen CROs can use to help individual sites.

1.

Prioritize diversity when finalizing site-selection decisions. As discussed above, there are numerous benefits to creating a heterogeneous mix of sites to participate in any given clinical trial.

2.

Foster open conversations with key stakeholders to ensure the site has the necessary bandwidth and capabilities. The CRO and drug sponsor must thoroughly assess overall site readiness, identify the gaps, formulate a plan that sets the site up for success, and then prioritize and pressure-test the proposed scenarios for improvement. This is especially important for smaller sites that have had little or no trial experience to date. The goal is to implement strategic process improvements and to enable technology adoption and/or upgrades that can expand the site's existing capabilities and streamline workflows and outcomes. Similarly, efforts to reduce the overall number of parallel technology platforms and to integrate technology systems wherever possible will help to improve workflow and transparency and drive efficiency. However, fundamental to all this is the need to maintain ongoing collaboration and communication.

3.

'Right-size' all productivity-related initiatives and interventions. The most effective CROs do not presume a site is ready to take on the trial responsibilities. Nor do they arrive onsite with a pre-determined list of improvements to make. Taking the time to truly understand what is happening at each site helps stakeholders identify the prevailing challenges and then prioritize tangible opportunities for improvement.

4.

Develop a road map to address each deficiency and enable self-sufficiency over time. It is critical for each site to understand what interventions are needed to make it a high-performing and sought-after candidate for trial participation. Does the site have the necessary equipment? Is all calibration testing up to date? Does the site have the needed staffing and clinical expertise? Do they have access to the right patient population? Does the site have positive work experience with the drug sponsor and the CRO (based on prior trial experience)? Are internal workflows as streamlined and efficient as possible?

5.

Streamline the number of steps and touchpoints within all internal workflow processes. The ability to reduce redundant or unnecessary processes or steps provides a critical opportunity for any trial to stay on schedule and under budget. A critical assessment of daily workflows can identify specific steps in various processes or workflows where inefficiencies can be reduced. This may involve providing additional training or implementing specific technology systems to automate data capture and streamline access to it.

6.

Utilize "enabling technologies". The judicious use of digital tools and techniques can reduce or eliminate mundane tasks over the life of the study. Such efficiencies can help to reduce investigator and staff burnout and improve site engagement. One example is to enable the use of readily available devices (such as smartphones or tablets) to scan documents right at the point of care. Another is the use of barcodes in individual rooms within the clinical setting, allowing investigators to immediately confirm the availability of the required equipment. Automating and streamlining mundane tasks also reduces delays and the opportunity for human error.

7.

Streamline and prioritize payments to trial sites to reduce delays. Being respectful about site payments and cash flow coming from the drug sponsors and the CRO to the trial site is essential to reduce delays and foster goodwill. Efforts to stay cash-neutral and make payments on a more frequent basis go a long way to reduce frustration and improve goodwill, allowing the site to operate smoothly and efficiently, and reduce delays in patient recruitment.

8.

Invest in clinical research associates (CRA) capabilities. CRAs work with sites to ensure that protocols are followed in accordance with regulatory requirements. Improving their effectiveness has downstream benefits, such as the availability to invest in CRO-site relationships and listening to opportunities to improve.

9.

Budget time and resources for patient training. Technology has made an invaluable contribution to improving and increasing patient participation in clinical trials. Such systems are an increasingly common part of the clinical trial paradigm for data collection, patient-reported outcomes, and more. However, the selection and use of technology needs to be carefully made and properly supported. To ensure the most reliable and appropriate uptake of the technology tools that are used at any trial site, the drug sponsor and CRO must not assume that enrolled patients will take the selected technology tools and use them appropriately. Rather, the drug sponsor and CRO must invest in proper training and clear communication to reduce patient frustration and help them to use the technology interventions confidently. This will help patients adhere to the required treatment protocols and improve clinical outcomes. Site staff training, local language support, and patient-appropriate user guides should be carefully considered.

Closing thoughts

The ability to build a strong, diverse, and integrated ecosystem of trial sites, and to proactively improve site engagement at each location, is a critical objective for both drug sponsors and CROs. Such diversification helps to distribute the workload and improve patient access to participate in potentially lifesaving or life-altering clinical trials. It is also an important aspect of building the next generation of experienced trial sites and supporting the professional development of the next generation of clinical researchers and KOLs.

Since all trial sites are not equal, drug sponsors should partner with a CRO that thinks holistically when assessing potential trial site options and has the capabilities, experience, infrastructure, and technology toolkit to set each site up for success—no matter how variable the individual site capabilities are at the start.

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Alison Foster has over 26 years of experience in the pharmaceutical and CRO industries, with a strong background in project management and strategic delivery. For the past 12 years, Alison has led teams focused on driving efficiency and innovation. Currently, Alison oversees departments covering strategy, feasibility, site engagement, partnerships, digital health, patient recruitment, and innovation.

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