Connecting the Right Sites to Promising Trials:

The Role of Web-Based Feasibility Assessment

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The fact that clinical trial planning bottlenecks have become a significant burden for the pharmaceutical industry is well-known. The number of New Drug Application approvals by the U.S. Food and Drug Administration is declining, despite greatly increased research and development (R&D) spending. A large number of subjects need to be recruited in a timely fashion, and there are growing pressures for time and cost containment. Time to market is critical, and any delay in a clinical drug development program will diminish the market value of a drug.

The "fear" of a delay constitutes an immense driving force in the process of site selection. In a study of several hundred global clinical trials, sponsors found out that 11% of sites, on average, in any multicenter clinical trial will fail to enroll a single patient, and 39% will under enroll.[1] This is testimony to the fact that the site selection process is still painfully broken, despite the overwhelming available information about the inefficiencies incurred through the existing processes.

This article examines the root causes behind the inefficiencies in site selection and engagement, and presents available and promising solutions to the problem, with specific emphasis on web-based tools, including in particular online feasibility assessment.

Background

Selection of the right sites for a promising clinical trial is clearly the most relevant step in the planning process for subsequent successful study conduct. Many obstacles stand in the way of efficient implementation of this process, and the figures speak for themselves:

- Today, developing a drug can cost more than US $1 billion, and a single clinical trial can cost more than US $100 million.
- Between 50% and 60% of research sites enroll fewer than two patients in their studies,[2] and about 80% of clinical trials are delayed[3] because of unfulfilled enrollment.
- An estimated US $10 billion a year is wasted because of poor site selection,[4] which is due to a failure to match trial planners with appropriate, efficient research sites.
- In the case of oncology, less than 5% of patients currently participate in clinical trials.[5] If 10% participated, studies could be completed in a significantly shorter period instead of the current three to five years.[5]

Thus, poor site engagement is an impediment to medical innovation. A new approach is needed. Proper planning of clinical trials is key to the success and efficient use of R&D investments so that new therapies can reach patients.

The Causes of Site Selection Inefficiencies

Pharmaceutical Company Practice

Although sponsors are aware of the need to change the established way of preparing and conducting clinical trials, they have been thwarted by the lack of appropriate tools and approaches to follow up on this insight.

In their article, "Fixing the Protocol Feasibility Process,"[6] Beth Harper and Nikki Christison summarize the root causes of poor site selection: "Assessment teams are often given unrealistic timelines, use tools they know to be ineffective, and follow inefficient processes they know prevent them from doing their work properly."

Site selection is very often influenced by a variety of complicated considerations. Sponsors appear to believe at times that the more key opinion leaders for the given indication are involved in a clinical trial, the better it is for the trial; but are key opinion leaders or the best prescribers of drugs always the best investigators? Daily experience very often reveals the opposite, and the following example clearly indicates what is involved.

During a site selection visit for an international diabetes trial, one of the authors of this article witnessed the coordinating investigator for the trial, a key opinion leader who was chosen by the sponsor, telling the project leader directly: "But you have to know that I do not feel confident about the comparator that is used." Given the obstacle created by the opinion leader's obstinacy, this site enrolled only three patients. Two patients were screening failures and the remaining patient withdrew from further participation after several weeks. The site enrolled no further patients through the end of the study, although several other sites enrolled more than 15 patients each in the same period.

For the performance of a site in a clinical trial, the number of publications of the investigator is not a truly hard parameter. The setup of a site and its performance in previous trials (e.g., recruitment capabilities) are much more important for the success of a trial. However, when selecting sites for a new trial, sponsors often do not take these crucial parameters into account. They tend to place trust in unreliable and/or outdated information, or the site selection is often influenced by personal and marketing considerations.

A recent analysis by the Tufts Center for the Study of Drug Development (CSDD) involving 150 studies and nearly 16,000 trial sites revealed that 90% of clinical trials meet their patient enrollment goals, but in many cases do so only by doubling their original enrollment timelines.[7]

Flawed site selection is not the only reason for this time-, money-, and resources-wasting reality. As mentioned above, 50% to 60% of research centers end up with fewer than two patients in any given trial, falling behind the recruitment expectations.[2] Tufts CSDD also found out that pharmaceutical companies and contract research organizations (CROs) rely very often on a limited number of traditional recruitment and retention tactics, and the same seems to apply for the identification and selection of trial sites.

Site-Related Issues

A number of factors behind these difficulties are directly related to the sites themselves. As explained by Kenneth A. Getz at Tufts CSDD: "The site landscape has been in a perpetually nascent and fragmented state." It is "a landscape that has been spinning its wheels for 30 years, unable to mature or achieve scale efficiency and operating sophistication."[1]

At the same time, given the global expansion of clinical trials, there are more than 400,000 disease-specific research sites worldwide in more than 59,000 institutions.[4] Trial planners simply do not have adequate analytics about investigators and their teams, research centers and the locations where they operate, the local number of enrolled and available patients, and regulatory timelines. Information is often inaccurate and outdated, or simply does not exist.

Moreover, this information disconnect has forced trial planners in pharmaceutical companies and CROs to compensate by overloading the centers with detailed requests for information (feasibility questionnaires), which can be voluminous (up to 40 pages) and often go unanswered. In addition, communication is inefficient during feasibility assessment; there is a lack of harmonized and integrated epidemiological and demographic data; and critical information about the highly complex, dynamic, and global regulatory environment is not easily accessible.

The big question is whether or not the feasibility and final site selection process leads to accurate knowledge of the site and its real capabilities with respect to patient recruitment. Questionnaires often need to be completed with very tight, unrealistic deadlines—perhaps even several times for the same trial when a number of CROs are involved. Information provided is taken at face value (or discounted using arbitrary "correction factors"); and the same sponsor commonly repeats information requests on general site capabilities in every questionnaire.

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Furthermore, no information is given as to when and how the selection decision will be made. Since a large proportion of the questionnaires do not lead to site selection, the sites are seldom informed officially when rejected. For the few that are informed, there is no information on what criteria were used to make the decision.

This whole process leaves the sites in limbo, with uncertainty over whether a rejection was related to site capabilities, geographic distribution of the study, or simply cancellation of the program. It creates the impression that sites are commodities, with no sense of partnership and no learning takeaways to be gained through the feasibility process. Thus, sites struggle to communicate their capabilities to trial planning professionals globally. Moreover, they need to involve expensive staff to respond to the feasibilities, which turns into business in less than 5% of cases.[8]

The Way Forward

Is it so difficult to get reliable and up-to date information about professional and successful working trial sites worldwide? One of the main difficulties has been the absence of a structured venue for sharing information about sites, site investigators, and the environment in which they operate. However, there is increasing awareness of the potential of "Big Data." The tools of information technology can be put to good use to organize and share information, keep it up to date, and improve communication among all stakeholders toward the goal of streamlining trial planning processes.

Recent years have seen the development of new, innovative, and neutral tools for site selection that can significantly address the current dilemma. Deborah Borfitz, in an article in *Clinical Informatics News,*[9] presented several of these new tools, including:

- Citeline's Sitetrove, with profiles from a large number of investigators at many sites;
- BioPharm Clinical's Study Advisor, for timeline and enrollment forecasting;
- ViS' online feasibility platform; and
- IMS Health's SiteOptimizer, which uses history and predictive analytics to improve clinical trial enrollment.

For some companies, the primary goal goes beyond providing information about the most appropriate investigators and trial sites to sponsors/CROs. An online feasibility platform may, for example, focus also on the reduction of the administrative burden related to feasibility questionnaires for the sites, while facilitating personal contact between trial planners and research sites.

Online feasibility assessments consist of the efficient use of digital capabilities to enable sites to complete site assessments more quickly and with less effort. Sites can thus complete their profiles, answering more than 85% of the general and disease-specific questions raised in feasibility assessments, keep them up to date, and share them as many times and with as many sponsors/CROs as they want, for free. In turn, sponsors and CROs have free access to thousands of feasibility profiles at their fingertips.

Online feasibility assessment offers three main benefits for sites:

- Visibility—Site personnel are able to showcase their disease-specific capabilities and gain direct exposure to decision makers, therefore increasing revenue from more trial participation.
- Cost savings—Sites are able to reduce expenditure related to marketing and feasibility assessments, and reduce waste from inefficient communication.
- Communication—Site staff are able to efficiently exchange technical information with sponsors, CROs, and other sites, reducing duplication of efforts and starting trials that can bring in revenue more promptly.

The implications for sites are substantial. Site staff need to fully understand their capabilities and be willing to share this information transparently in a very comprehensive manner, in order to proactively promote their capabilities to sponsors. The current options are clear, in particular those who have a crowd-sourcing platform, where the sites provide comprehensive and standardized data. (Crowdsourcing is the practice of obtaining needed services, ideas, or content by soliciting contributions from a large group of people and especially from online communities, rather than from traditional employees or suppliers. In the case of an online feasibility platform, crowdsourcing means the possibility for research centers and other parties to provide structured data online, making it possible to efficiently aggregate and organize information and keep it up to date.)

The time has come for sites to take the front seat and actively help to change the current business model of passively waiting for questionnaires that have been shown to be irrelevant in improving the site selection process. If sites are successful in making this happen, then the sponsors will need to

show that they can use these data to select the right sites and accomplish their critical goal of getting medicines to market on time.

The industry as a whole is increasingly aware of these challenges and opportunities to make an impact. A number of initiatives address such inefficiencies, harmonize data, and streamline the clinical trial process. In particular, TransCelerate Biopharma Inc., created in 2012 by 10 leading pharmaceutical companies, has taken a number of significant steps, with initiatives related to site qualification and training and the establishment of a shared investigator portal.[10] The Alliance for Clinical Research Excellence and Safety (ACRES),[11] established to enhance safety, quality, and operational efficiency across the entire clinical research enterprise, supports the collection, sharing, and analysis of information.

Conclusion

Increasingly, the clinical research enterprise is moving in the direction of sharing data and fostering a more collaborative approach, a key aspect of which can be called "collaborative analytics."

Just as everybody is using new tools when buying a camera or a car, sponsors are beginning to do the same for the preparation of their trials and the selection of trial sites. Beyond the benefits to sites and sponsors, patients deserve a dramatic improvement in the whole operational model. Not only will they get breakthrough drugs sooner, with the promise of a more efficient development process, they will also have access to medical innovations at lower prices.

Despite the need for a fundamental paradigm shift, it will take significant investments of time and effort for all players to embrace new operational models. At the same time, people are quickly getting used to the now pervasive access to data and online communications. Technology platforms like Google maps, LinkedIn, and Bloomberg (in the financial industry) are now enabling all of us to quickly navigate complexity, find answers, and immediately connect with the people who can best perform a task. Such smart navigation and live connections are welcome innovations for the clinical research enterprise.

Clinical trial planning is one of the major bottlenecks in pharmaceutical drug development. Reliance on feasibility questionnaires has proven to be highly inefficient. New digital technologies, including an online feasibility platform, produce significant improvements in terms of efficient site selection, crucial cost reductions and time savings, and welcome access to new treatment possibilities for patients.

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