The Balanced Approach to Optimising Clinical Trial Design and Execution

With clinical trials proving to be a large risk to run and fund, receiving answers to essential questions is of the utmost importance. Therefore, ensuring the greatest chance of a successful trial should be a prominent feature when designing trials, and artificial intelligence may hold the key

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According to internal Phase 2 termination analysis, as many as 17% of clinical trials fail to answer the questions their sponsors had aimed to address (1). These failed trials end up wasting significant time, money, and resources, effectively ending with a whimper instead of a bang. Moreover, such failures are especially upsetting to patient communities, who must wait longer for new treatments.

In many cases, sponsors conduct dozens of trials at once without comprehensive data-led design and planning. All too often, sponsors activate hundreds of sites for a single trial without thoroughly analysing investigator site performance data. Even when a trial results in regulatory approval, it may have been dogged by a lack of operational excellence.

The fine line between success and failure in clinical trials underscores the importance of a simple, yet essential, formula:

Flawless design + top performing sites + accelerated site activation = smarter trials and faster cures

However, all too often, trials founder because of a failure to integrate one or more elements of that equation. Indeed, a well-designed protocol is no guarantee of success. Even when a protocol has a sound design, the trial can fail due to insufficient attention to site selection and activation.

Fortunately, these inputs can be optimised through use of data via artificial intelligence (AI) platforms. Today, vast

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amounts of commercially available data can be processed and analysed to inform algorithms that facilitate site selection and activation. Such a data-driven approach enables prediction of baselines for key measures of trial performance, allowing sponsors to monitor these parameters.

Improving Protocol Design

When trials are terminated due to enrolment challenges, suboptimal protocol design is often the culprit. For example, trials in non-small cell lung cancer (NSCLC) typically define a patient Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 and a patient age of 18 years or older as the mode values for inclusion criteria. However, to generate clinically meaningful results, a trial may need to include patients with more serious prognoses, such as an ECOG PS of 2 or older patients (eg, 70 years or more). Thus, more restrictive inclusion criteria may shrink the eligible patient population and make enrolment more difficult, but the impact of those criteria can still be objectively measured and planned accordingly.

Figure 1 maps the gross site enrolment rate ([GSER], defined as the number of patients per site per month) for 178 NSCLC trials, with each bubble representing an individual trial; the larger the bubble, the longer of the enrolment cycle time (ECT). The white bubbles represent trials that included older patients (ie, 70 years and older). With few exceptions, those white bubbles are significantly below the red curve, which indicates the expected median enrolment performance. Consequently, the median ECT for the trials including older patients is 822 days, versus a median ECT of 618 days for all 178 trials (1). Even a minor change to the trials' design criteria can significantly impact key metrics and deliverables such as ECT.

Figure 2, which charts the GSER based on ECOG PS scores, shows a similar relationship. In this figure, the white bubbles represent trials that only include patients with an ECOG PS of 2; for those trials, the median ECT is 1,445 days, compared to 618 days for the 178 trials as a whole (1).

This analytical approach allows us to understand the significant implications for one Phase 2 NSCLC clinical trial, which was targeted to include patients 70 years and older and with an ECOG PS of 2. The trial was initially planned to enroll 121 patients, but was terminated after enrolling only 54 patients because the recruitment rate was "slower than expected", according to the sponsor (1).

Optimising Site Selection

Just as a professional sports team can use predictive analytics to identify underrated (and hence, less expensive) players to propel the team to success, as described in Michael Lewis's book, *Moneyball,* so, too, can trial sponsors and CROs employ a predictive analytics platform to illuminate factors that can impact clinical trial success in the design, planning, and execution phases. Predictive analytics quantify the effect of inclusion and exclusion criteria on enrolment and allow the organisation to address other factors such as site selection and activation in an integrated scenario modelling. Many trial sponsors and CROs employ site selection platforms informed by AI to score sites based on predicted performance, yielding a ranked order of sites so that the selection process is objective, methodical, and most likely to meet enrolment

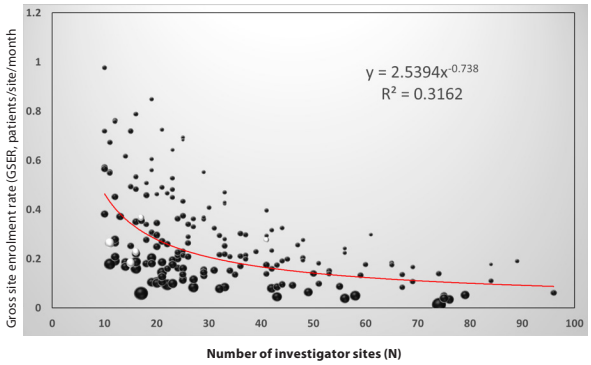

Figure 1: Gross site enrolment rate (GSER) for NSCLC trials enrolling older patients (≥70 years old) and a secure private cloud

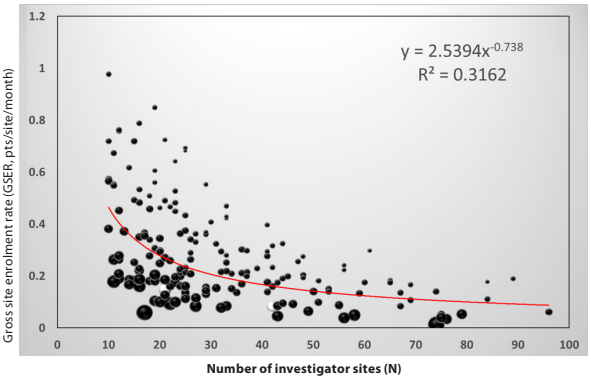

Figure 2: GSER for NSCLC trials enrolling only patients with ECOG PS = 2

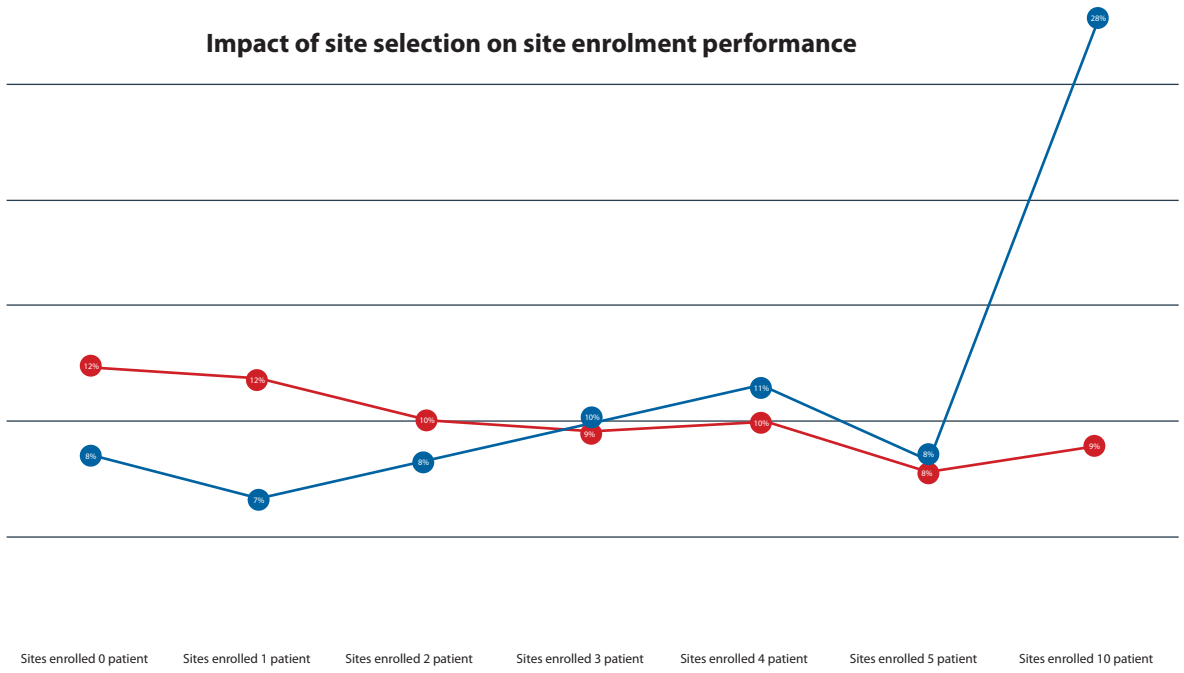

Figure 3: Impact of site selection on site enrolment performance

targets. Leading AI platforms are fully integrated and can make linkages with the protocol design features, enrolment predictions, and selection of high-performing centres.

As can be seen from the above examples in NSCLC, the ability to analyse the impact of apparently minor changes to the study design (eg, inclusion/exclusion criteria, treatment duration) and their impact on-site selection and enrolment can be a competitive differentiator and particularly advantageous in relation to the 'digital dashboards' that companies such as AbbVie and Novartis have introduced to design and track the progress of individual studies (2-3). The industry needs to move from the question of 'how' to collaborate more efficiently to the question of 'what' predictive analytics inputs are needed to improve decision-making. Refocussing the question involves shifting one's perspective: it is less about the command and control centre flat screens and more about the robust aggregate data and information analytics environment that can be seen on screen.

Site selection platforms quantitatively assess investigator site performance in relation to peer sites, whether for a single clinical trial or a set of similar trials. Figure 3 illustrates the potential benefits of using an AI site selection platform to improve site enrolment performance.

Figure 3 is based on a recent site performance analysis of seven similarly designed double-blind clinical trials, involving 1,521 randomised patients with Type 2 diabetes enrolled at 292 investigator sites. It shows the distribution of non-performing sites (ie, the percentage of sites enrolling zero patients on the far left) and the best-performing sites (ie, the percentage of sites enrolling 10 or more patients on the far right) (1).

The blue curve shows the performance profile of 'recommended sites', which were identified via a site selection platform; the red curve shows the performance profile of the non-recommended sites (ie, those activated without input from the platform). Whereas the red curve clearly trends downward, the blue curve shoots upward for sites enrolling 10 or more patients, illustrating the effectiveness of the platform (1).

However, the site selection platform approach has its limitations. Although a highly effective platform can minimise the number of non-performing and poorly performing sites, it cannot eliminate them. Similarly, a highly effective platform can maximise the number of best-performing sites, but cannot guarantee that every recommended site is a high performer.

Most trial sponsors can reasonably expect a 20% to 40% improvement in enrolment performance through the use of a highly effective site selection platform. However, even the most efficient platform cannot disguise an unpleasant fact that plagues most clinical trials: the activated sites do not enrol patients quickly enough. It would seem logical, then, to address this problem by activating a large batch of high-

performing sites. If only it were that simple. The problem is compounded by the lack of an organic connection between different functional areas within sponsors' organisations, in which one group may coordinate protocol design, another group may handle site selection, and a third group may oversee execution of the trial. Even when individuals within an organisation are aware of the factors that contribute to delayed or inefficient enrolment, a compartmentalised organisational structure can make it difficult to communicate the importance of those factors to the various responsible stakeholders. Moreover, when an organisation fails to conduct a coherent, quantitative analysis of those factors and of how certain factors affect others, communication about these is hindered, if not impossible.

Optimising Site Activation

Inefficient site activation is one of the major contributors to clinical trial enrolment delays. This was illustrated in a recent gastrointestinal (GI) trial that had activated 29% of eligible sites, well short of the 58% activation rate of a comparable trial (see Figure 4) (1). Based on that metric, the CRO that was managing the GI trial assumed it was on track to enrol only half of the requisite number of patients to keep the trial on target.

Using a quantitative formula known as the site effectiveness index (SEI), a patented algorithm was used to calculate the optimal number of sites for this trial to be 142 sites (1).

Notably, at the time of the analysis, the CRO had already activated nearly 200 sites. Site optimisation analysis showed that, for studies of this type, only about 120 sites were required (1). The trial was in trouble because the significant over-usage of sites was hindering adequate support for all sites, at the expense of those with the best enrolment potential.

Instead of adding more sites to expedite patient enrolment, the situation called for more active monitoring of the already-activated sites' performance and immediate closure of sites that had not enrolled any patients in more than five months. By implementing these recommendations, the trial completed enrolment in October 2017, exactly as forecasted, and saved between US $3 million to US $5 million of CRO change orders that would have worsened the situation, rather than helped (1).

Fine-Tuning the Recipe

The challenges that plague clinical trial planning and execution have existed for decades, and various corrective approaches have been tried without material improvement, as revealed through extensive benchmarking analyses over the past decade. The challenges defy simple solutions and the solutions cannot be identified quickly. However, the situation is about to change. A massive, dynamically updated, integrated, and well-structured AI clinical development platform, supported by validated quantitative measures of trial performance, can identify and analyse the variables

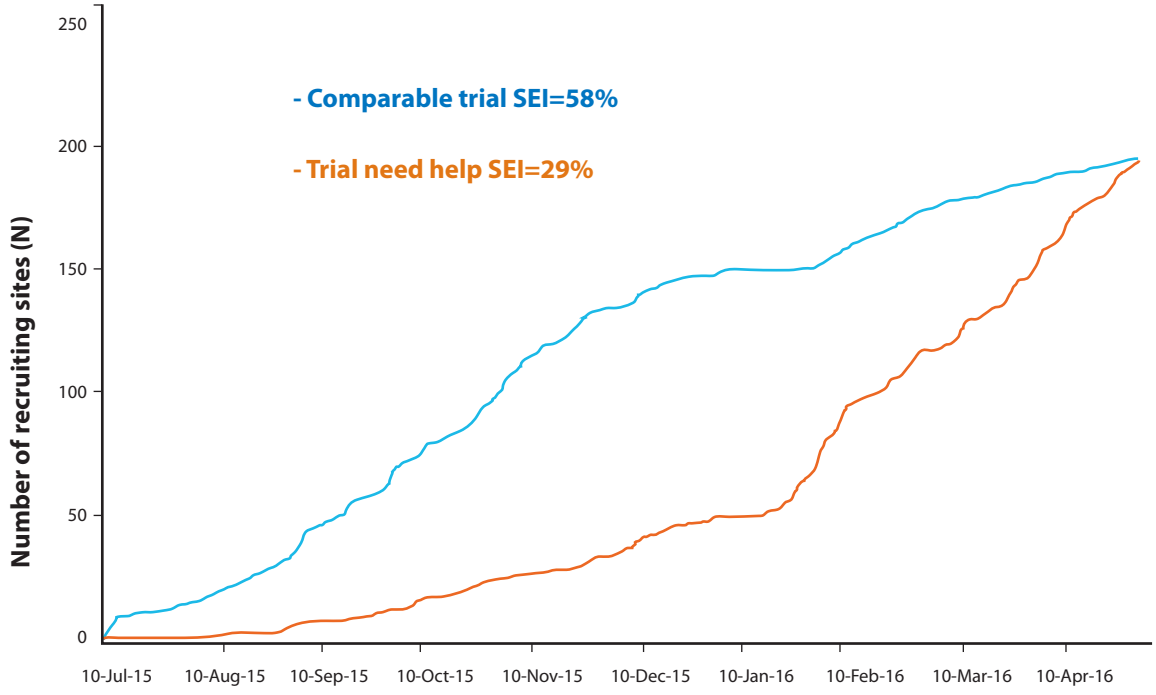

Figure 4: Recent gastrointestinal trial results

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that affect performance and the relationships among these variables. The availability of the platform will transform clinical trial design, planning, and execution, as it will give sponsors and CROs the opportunity to take corrective actions in an intelligent, data-led approach. Given the three-to-five-year cycle time to plan and complete a clinical trial, using an AI platform informed by such a database can be crucial to success.

The recipe for success in clinical trials relies not on any single ingredient, but on effectively integrating all of the elements of the clinical development plan, including protocol design, site selection, and site activation. Similarly, while various analytical platforms can be utilised to positively affect trial performance, it can be misleading to assess the value of each individual platform in isolation. It is also unreasonable to expect additive impact from deploying multiple platforms concurrently. Rather, the platform framework described herein should align with a set of strategic objectives defined by the clinical development organisation and should reside within one platform to support adoption by the user community. For example, while shortening ECT is a strategically important goal in most cases, some organisations may prioritise minimising trial costs over reducing ECT. Whatever the strategy, an effective platform can facilitate scenario planning in real time, enabling clear and efficient tracking of each scenario as it unfolds.

This is an exciting time for medical innovation, one that hints at numerous possibilities for addressing the dire needs of patients around the world who are living with serious diseases. Nevertheless, even with the advent of Big Data and predictive analytics, clinical development remains fraught with inefficiencies. While one can get lost in the apparently dry and abstract numbers generated by a clinical trial database, those numbers may, one day, lead to the development and adoption of powerful, innovative approaches to clinical trial design and execution, allowing drug companies to alleviate patients' pain, frustration, and struggle. At the very least, an AI-based approach to predictive analytics and clinical trial design, planning, and execution will enable practical solutions to help trial sponsors and CROs manage these challenges proactively.

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3. Visit: linkedin.com/in/vas-narasimhan-a5943912/detail/recent-activity/shares

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Gen Li PhD is founder and President of Phesi and is passionate about improving patients' lives. Prior to founding Phesi in 2007, Gen was Head of Productivity at Pfizer in clinical development, following Pfizer's acquisition of Pharmacia where he delivered the first implementation of clinical development productivity measurement. At Pharmacia/Pfizer, Gen significantly contributed to the Centre for Medicines Research international database for pharmaceutical R&D performance. Previously, he led the creation of the first computer-automated resource management system at Bristol-Myers Squibb. He earned his PhD in biochemistry from Beijing University, China, and an MBA from the Johnson Graduate School of Management at Cornell University, US.

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