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Take a Chance

Taking on a digital approach changes the dynamics of patient enrolment in clinical trials and removes over-reliance on luck – bringing with it a wealth of advantages, not only to patients but also to the economy as a whole

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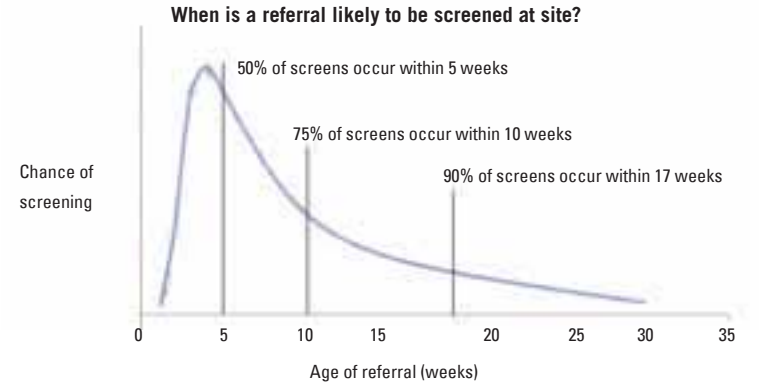
Site enrolment performance is a fundamental factor in determining whether a clinical trial will follow its pre-trial plan, including the planned recruitment period and interim analyses regarding milestones (1). While it is particularly difficult to use historical metrics to predict which sites will perform well or not, digital advertising for clinical trials lends itself to real time enrolment prediction models. These electronic marketing methods allow advertising to be strategically channeled by sites, so that advertising investment is commensurate with site recruitment rates to optimise overall execution.

Enrolment Performance

Since site enrolment performance varies greatly – with some sites taking on a high number of referrals from digital marketing, and others enrolling no patients at all – this customised investment approach to recruitment advertising is critical. Monitoring performance can identify high-, low- and non-enrolling sites, and can signal over-enrolment – which, in turn, plays a role in safeguarding the validity of the trial. A comprehensive site monitoring and support strategy, which identifies sites that enroll well, and also provides them with a sustained flow of patient referrals, will result in increased enrolment rates and shorter recruitment timelines.

Sponsors and CROs put significant effort into forecasting clinical trial timelines, and in particular predicting site performance rates. Many of these feasibility teams use historical metrics to calculate these predictions.

Figure 1: Graph showing the weeks between a site receiving the contact details of a referral, and when a site screening appointment is likely to occur. 75% of screens take place within 10 weeks



However, due to the fragmented landscape of investigator sites, in which the larger proportion of sites are research-naïve or inexperienced, success has been limited because of a lack of historical data. Pfizer and Lilly identified four promising predictive factors based on retrospective analysis: sites' historical performance; trial experience; research focus; and time to first subject enrolled, following initiation (2).

Research Experience

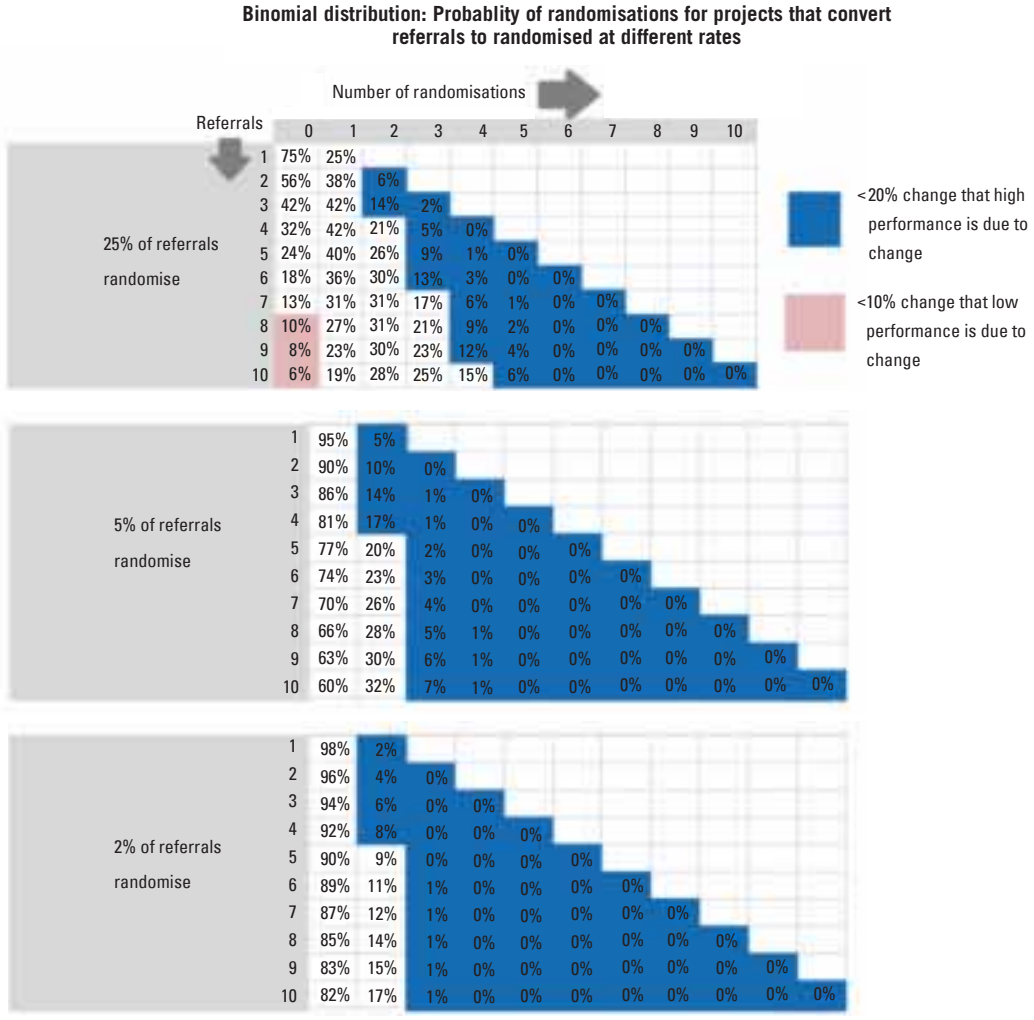
Clinical research experience remains a significant challenge. For example, of the 23,000 FDA-regulated investigators in the US that conduct at least one trial per year, only 35% of these were more experienced community-based study sites, or those associated with an academic health system – with the majority being stand-alone sites undertaking research in a clinical practice (2). Unless the investigative landscape becomes less fragmented, metrics-based enrolment predictions are of limited use. In lieu of this, there is a need to analyse real time site performance data on an ongoing basis during clinical trial conduct, in order to make swift, strategic decisions during the recruitment phase. Digital trial recruitment plays an important part in decreasing recruitment investment commensurate with such information.

Unpublished data from three Phase 3 studies within a digital recruitment agency showed that of the performing sites that received three or more referrals, the top third of sites enrolled 58% of digitally sourced subjects; the middle performers enrolled 42%; and approximately the remaining third of sites enrolled no subjects. These figures demonstrate the variability of site performance statistics. Looking at the wider picture of recruitment as a whole, a 2012 Tufts Center for the study of drug development looked at 151 Phase 2 and 3 trials involving 16,000 investigative sites, and found that 11% failed to enroll a single patient; 41% missed their target enrolment number; 40% met their target; and 15% exceeded their number (3).

Digital Advantages

Enrolment success is predicated on studying site enrolment rates in real time

Figure 2: The probability that a site will enroll x% of the referrals it receives by chance. If the probability is small, this means it is unlikely that random chance is the only factor at play, and warrants an investigation to determine what is driving the unusual enrolment rate



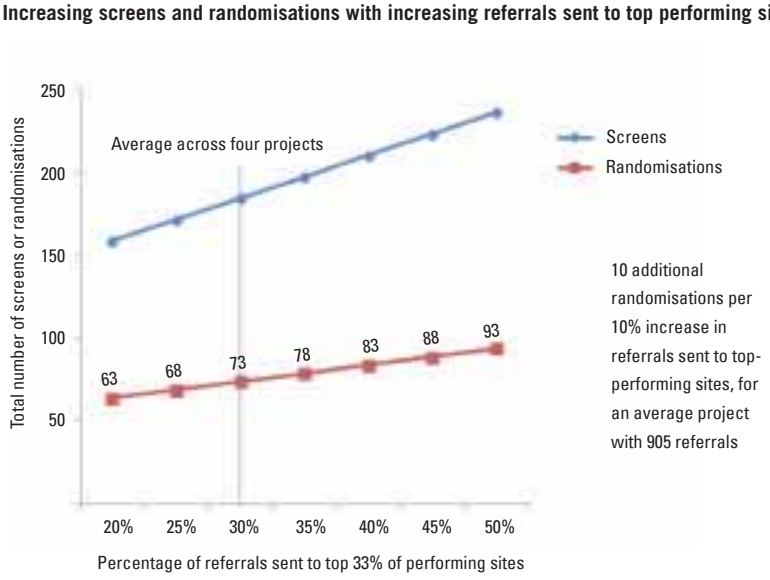
and throughout the recruitment phase. Digital recruitment methods are conducive to this approach, which enable media performance metrics to be collected in real time, and site performance metrics to be collected in near time. Using such metrics allows decision-making to be made on a site-by-site basis, so that the campaign can be flexibly adjusted and refined to match individual site performance. This methodology not only increases enrolment rates, but also safeguards the validity of the trial itself by setting performance benchmarks that trigger monitoring – to catch any sites that may be over-enrolling. When dealing with inclusion and exclusion criteria that are subjective – such as the assessment of medical images – a significant portion of subjects may be erroneously entered into the trial, due to inherent biases and incentives (4).

This was demonstrated by a recent study examining the importance of centralised endoscopy readings in trials, which found that 31% of subjects were incorrectly entered into the trial following local endoscopy readings at sites. Analysis of the remaining 69% of subjects resulted in the investigational product being proven effective – but with the erroneous cohort included, there was no significant difference found between the treatment and placebo groups (5). High enrolment performance can be used as part of a risk-based-monitoring strategy to reduce misleading enrolment rates, safeguarding the trial from type 2 (false negative) errors.

Coordinated Approach

In-depth enrolment data, from which important trends can be identified, take time to collect. However, as Figure 1 demonstrates, 50% of patient screening visits at study sites occur within five weeks of study candidates being referred to a research site, and 75% occur within 10 weeks – yet a significant percentage (25%) of referrals remain ongoing for various reasons, such as being unreachable, unable to commit time to attend study visits, or they have reconsidered their decision to participate altogether. These pending patient referrals should be given more time to evaluate

Figure 3: As high-enrolling sites receive more referrals, the number of screens and randomisations achieved by digital marketing increases. The model is based on 905 referrals, the average number of referrals across the four projects considered



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their options, or screen at a site before not considering them as a potential study candidate anymore. While this belief can delay the performance monitoring process, its trade-off can result in more patients being screened.

Rather than relying solely on enrolment data, which inherently requires a delay before high-enrolling and low- or non-enrolling sites can be identified, the assessment of site performance should follow a comprehensive suite of data. By combining enrolment statistics, real time site efficiency data and input from site support specialists, a better picture of site proactivity and enrolment practices can be captured, helping reduce delays in identifying site performance. Sites should also be engaged in regular communication, offered support and best practice training. Real time data on the status of each referral, the efficiency at accessing referral information, and the outcome of each patient referred was used to help determine sites likely to perform well or underperform, in advance of actual screening and randomisation data.

More than Chance

An element of chance is involved when considering response rates to advertising, which can, in turn, influence enrolment rates at study sites. A site may receive a disproportionate number of ideal pre-screened study candidates or, alternatively, 'non-viable' candidates, despite initial pre-screening. Additionally, a site may be lucky or unlucky in terms of the number of pre-screened patient referrals received, which are then further filtered to confirm interest in study participation, willingness to be screened, medical eligibility, and availability for enrolment. Data that carefully tracks each filter in the qualifying process can be used to flag sites that are either too lenient, or too restrictive in applying inclusion and exclusion criteria. Furthermore, this information enables marketing investment to be correlated with performance rates.

Statistics

So when is site enrollment performance the result of chance, over-enrolment or skill? To find out, statistics – followed by further investigation into what is going on at site-level – is employed. Without appropriate statistical consideration, there is a danger of drawing incorrect conclusions due to a tendency to interpret patterns where none exist. While there will always be variability in enrolment due to the 'luck of the draw' in terms of referrals received, skill, best practice and subjective interpretation of eligibility all play a role.

Statistical tests pinpoint those sites where enrolment outliers are identified, and these can be investigated to determine what is driving these metrics. For example, as Figure 2 (page 53) shows, if a site receives and randomises two referrals in a study where 25% of referrals are randomised, there is a 6% probability that chance alone is responsible. In a study where 5% of referrals are randomised, this approximates to 0% – which warrants further investigations. Sites that quickly convert a high proportion of referrals to randomised subjects are easier and faster to identify as high enrollers. On the other hand, sites that do neither are statistically slower and more difficult to identify as non-enrollers, as explained below.

Consider the following scenarios (see Figure 2):

- In a study where 25% of referrals are randomised, one out of four sites that receive five referrals are likely to randomise, none of them due to chance alone
- In a study where 5% of referrals are randomised, three out

of four sites that receive five referrals would be expected to randomise none of them, simply due to chance

- In fact, in this case, roughly half of sites that receive 14 referrals would be expected to randomise, none of them due to chance

This demonstrates how difficult identifying non-performing sites can be, in projects with mid- to low-range enrolment of referrals. It is important not to react and halt marketing to sites that have not enrolled any patients, without being relatively certain that the results are valid – since doing so means no further data is collected, or time delays in enrolment can result in late assessments to validate whether a site is proven to be an underperformer. In this case, additional data sources are essential before taking action such as marketing hold, or labeling a site as a poor performer. Comprehensive site support, regular communication and real time metrics identify which sites are proactively and efficiently engaging with referrals.

High Performers

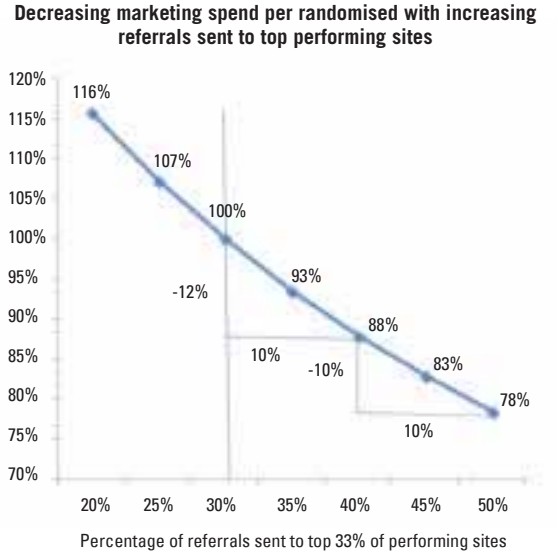
High-enrolling sites have increased rates of randomisation than average and non-performing sites. By identifying these sites – retraining those that are too lenient, or too restrictive with the inclusion and exclusion criteria, and increasing the proportion of referrals received by those applying criteria correctly (safeguarding the trial from ineligible subjects) – more randomisations for the same marketing investment can be achieved. The recruitment timeline can further be shortened by increasing the conversion rate of referrals to consent and randomisation, thus reducing trial costs.

Feasibility assessments can predict return-on-marketing investment and estimated response rates, by recognising that specific patient populations in a site catchment area are limited. Placing more than one site location in areas of low patient counts can also increase spend, cannibalise the flow of patient referrals to sites, and result in a plateauing of enrolment rates. As long as the overall referral rate of potential study candidates is monitored and maintained throughout the process, the speed of enrolment can be enhanced by higher enrolment rates at preferred sites. Essentially, this is a careful balancing act, informed by metrics.

Figure 3 (page 54) shows what happens to the number of randomisations in a study when more referrals are sent to top-enrolling sites, and uses unpublished data from four case studies. Boosting referrals to top sites by 10% gives a linear increase in randomisations; in this case, 10 additional randomisations across an average-sized project involving approximately 900 referrals. Figure 4 shows what happens to marketing spend per randomisation when top sites receive more than their share of referrals. If the top third of enrolling sites receive 40% of the referrals, this minimises marketing spend per randomisation by 12%. A subsequent increase from 40% to 50% reduces marketing spend per randomisation by a further 10%.

A realistic proportion of referrals to send to known top-performing sites should be defined in advance, and adjusted

Figure 4: As top-performing sites receive more referrals, marketing spend per subject decreases non-linearly



About the authors

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Liz Moench is President at MediciGroup. Her achievements include launching the industry's first direct-to-consumer advertising campaign in 1983 for Boots-ibuprofen, and pioneering the first direct-to-patient recruitment for clinical trials in 1991. Today, her pioneering initiatives include optimising digital strategies and social media for patient recruitment and engagement.

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