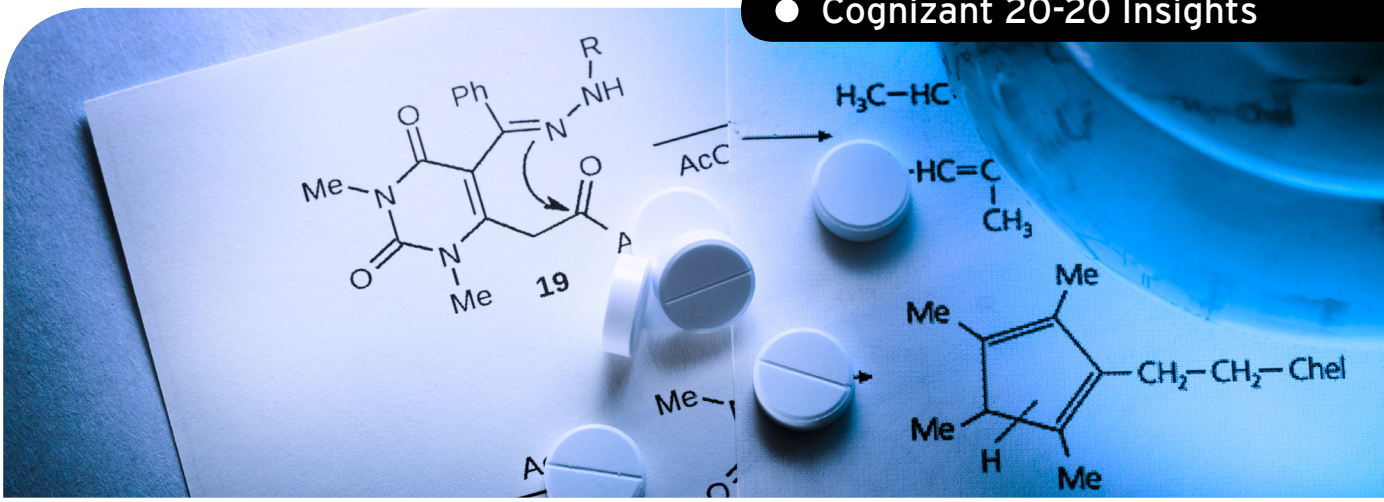

Patients Recruitment Forecast in Clinical Trials

Accurate patient recruitment forecasts are critical to the clinical trial planning process. Here, our recommendations on ways to remain on target and avoid huge losses in terms of time, effort and investment.

Executive Summary

Clinical trials are typically the most crucial part of a drug development cycle. After the manufacturer – a pharmaceuticals or medical device company – has spent a significant amount of time, effort and funds, it must test to make sure the drug is marketable and meets its therapeutic promise. Any failure at this stage can set the drug manufacturer back years.

Clinical trials are a long and tiresome process. Any misses here can delay time, add costs and result in missed opportunity. The leading culprit for missed clinical trial deadlines is the patient recruitment process. Patient enrollment is the most time-consuming aspect of the clinical trial process, estimated to take up to 30% of the clinical timeline. At the sensitive and crucial stage of development represented by clinical trials, optimizing patient enrollments with improved recruitment rates offers a clear advantage that results in time savings and reduced time to launch.

Clinical trials are the testing benchmark that make or break a drug. But they are imperfect, due to strict regulatory protections put in place to safeguard human subjects. The more patients needed for clinical trials, the greater the number of regulatory issues that typically arise related to patient safety and procedural validation. This, in turn, extends trial duration, and on a larger scale impacts multiple sites simultaneously. The impact often leads to increased demand for patient recruitment.

This white paper explores different approaches for forecasting patient enrollment, including basic guidelines for uncontrollable factors that may be quantified for better control over clinical trials.

From the Beginning: Patient Recruitment

Patient recruitment services annually contribute over $5.9 billion in expenses to the pharmaceuticals industry.[1] With such a significant amount of money being invested, the scope becomes so specialized that there are patient recruitment service providers that facilitate a variety of services to increase enrollment in clinical trials.

Like other industries that have evolved over time, pharmaceuticals and medical devices companies typically stick to their historical approach, at least in terms of infrastructural investments for clinical trials. With the correct protocol and investigator sites, patient enrollment should be facilitated.

When a a state-of-the-art site is installed, there is no logical reason to believe that it should

be difficult to recruit patients and provide treatment there. Unfortunately, this thinking, while delivering enormous success historically, has outlived its usefulness. Given how inherently complex the process is for industry, manufacturers and patients, nothing can be taken for granted and everything must be meticulously planned wherever possible.

The industry transformation that has led to such a complicated state can be understood in light of the following:[2]

- Roughly 80% of clinical trials fail to meet enrollment timelines.
- Approximately one-third (30%) of phase III study terminations are due to enrollment difficulties.

As these statistics make abundantly clear, better patient recruitment processes can drastically improve clinical trial success.

What Makes Patient Enrollment a Herculean Task

Pharma and medical device companies starting clinical trials are aware of the complexities involved in patient enrollment, but the tougher task is to identify the causes of obstacles. With each trial, a new set of conditions is available, with each condition requiring a different testing approach. In other words, the qualitative factors such as location, type of disease, drug and company reputation play an important role in shaping the trial. Therefore, many factors contribute toward making patient enrollment genuinely difficult and arguably the most challenging step in running a clinical trial.

Improper Estimation of Time Required for Patient Enrollment

Any big project with long-lasting and vital impact needs proper planning. Plus, companies must have a reliable estimate of what can be expected. If the company fails here, the reality will soon diverge from the plan. The primary problem faced during patient enrollments is improper expectations due to faulty trial forecasts. In short, a trial in actuality often takes a longer time than estimated to enroll the required number of patients. For example, a trial forecasted to have the right number of patients enrolled in, say, 20 months can actually take 22 months to accomplish this. This mismatch can easily lead to huge losses in terms of time, effort and investment. Any deviation from the forecast is not a good sign, and it is advisable to be absolutely certain about the trial planning process.

Patient Behavior and Drop Rate

Successful enrollment alone does not ensure the success of the entire trial. It is only the beginning stage, and there are many more uncertainties to account for. For example, a patient recruited is not bound to stay with the trial. The reluctance of a recruited patient can be attributed to a wide variety of reasons ranging from simple logistics, to fear, to any inconvenience in adhering to the steps in the protocol, or to the invasiveness of treatment and diagnostic procedures. This reveals yet another problematic issue: patient drop rates from trials.

The National Cancer Institute (NCI) has devoted efforts to research such factors, and has reported the following primary reasons offered by patients for a positive attitude and for trial participation:

- Recommendation or influence of a doctor.
- Hope for therapeutic benefit.
- Altruism or to advance science.
- Lack of other medical options.
- Access to leading specialists.
- Ability to receive cutting-edge care and the latest treatment discoveries.

Uncertainties in Estimations from Site Investigators

With all these uncertainties, sponsors often turn to the direct recommendation of site investigators for estimates of patient enrollments and recruitment success. Investigators provide recommendations using projected enrollment capacities. The most common way to collect these projections is through questionnaires. The questionnaires are rather simplistic, using questions focused on the number of patients the investigators treat who fit the study criteria and how many they believe they would be able to recruit for an upcoming trial.

Physicians are busy professionals who are intent on working in their patients' best interests. However, the aforementioned activities to determine patient counts are, at best, estimates gleaned through a summation of educated guesses. Moreover, a physician is not bound to answer this questionnaire, and feasibility surveys may go unanswered at some investigator sites. The major limitation that emerges from these estimates is that the site investigators tend to overcommit and are overly optimistic about their

ability to supply patients. In a typical trial, more than one-third of sites under-enroll patients and roughly one-tenth fail to enroll even a single patient.[3] Thus, site potential is unutilized and mismanaged.

Reestimation by Sponsors

The companies are aware of the "overestimation" issue and bring in their intuition and best judgment to manipulate the survey results to reestimate the time it would take to enroll all patients required for the trial. Even here, companies may err in putting intuition over estimates, with the aim to correct estimates that go astray from recruitment success rates.

All of these steps are part of the process, and with experience, calculated estimates and a bit of luck can generate a fairly workable enrollment schedule. The question is one of accuracy. Fortunately, statistical techniques are available that can process the rich and varied data through multiple scenarios to provide accurate information with confidence for various trial forecasts. The statistical methods are designed to work over the information gathered from physician surveys and can withstand the element of interference engendered by unintended company tampering. The output is a baseline forecast with a highly accurate predicted probability of enrollment success for the intended timeframe. Given that the proper data sources and analytical steps are used with correct statistical methodologies, companies can obtain the baseline estimates fairly quickly, with research steps that are performed concurrently.

Today (to the best of our knowledge when this white paper was written), the most popular techniques used by companies for recruitment and supply modeling use averages and other ad hoc techniques. These deterministic techniques are not devised to account for uncertainties arising from:

- Uncertain input information.
- Stochastic fluctuations over time.
- Change in recruitment patterns and rates across sites.

In our experience, over half the companies that are using statistical methods also fail to recruit in time. Companies using stochastic methodologies implement Monte Carlo simulation to bring in the uncertainties factor to predict patient recruitment. Stochastic and non-stochastic approaches with Monte Carlo simulation may provide similar results in some cases; even deterministic methods may perform better than stochastic ones, so the methodology selection should be based on the performance of both methods for the situation at hand.

Non-Stochastic Approach

In this approach, the accuracy of the outcomes is improved through known relationships among factors under consideration, removing the possibility of any random variation. With this approach, a given input always produces the same output.

Patient recruitment and recruitment duration are dependent on total number of patients (P); total number of sites (S); number of sites enrolled at the beginning (S_0); number of patients enrolled at the start of the trial (P_0); patient enrollment rate (λ); and average site initiation rate (S_s).

Forecasting clinical trial enrollment requires estimates of patient recruitment rate (λ); and sites start-up timing (S_s). Patient recruitment duration and patient recruitment can be forecasted at two stages of the clinical trial:

- At the beginning of the trial.
- At the interim stage of the trial.

The clinical operation department can provide minimum, maximum and average values of λ and S_s and these values can be used to estimate expected values and standard deviations of λ and S_s through the Program Evaluation and Resource Technique (PERT).

This approach assumes that sites start with an average initiation rate until all start enrolling. Initially, total recruitment is conditional upon the total sites available to enroll; it becomes unconditional and linear once all sites are enrolled.

Patient Recruitment

On or before enrollment completion of all sites, the number of patients enrolled (P_q) = $A\lambda + A^*\lambda + P_0$ Where $A=(1/2)rd^2$ and $A^*=S_0d$

After enrollment, completion of all sites number of patients enrolled (P_l) = $S\lambda d+P_q$

Recruitment duration can be calculated as follows:

- If the number of patients recruited is equal to total number of patients (P), then average site initiation time (S_s) would be equivalent to D.
- If the number of patients recruited is greater than P, then D would be the positive root solution of equation 1.
- If the number of patients are less than P, then

$D = ((P-P_q)/(S\lambda))+S_s$

In the special case where all expected sites enroll concurrently at the start of the trial, the above approach automatically reduces to the simple linear approach. The aforementioned approach is actually quite generic – a way in which investigators can estimate trials when enrollment starts at different points of time at various sites; in case a single site or all sites enroll patients from the beginning of the trial, this then becomes a special case of this method.

In this case, patient recruitment (P) and recruitment duration (D) can be estimated through ($S\lambda D+P_0$) and (($p-P_0$) + $S\lambda$), respectively.

One important assumption when explaining the non-stochastic approach is the use of aggregate estimates for site recruitment, total number of sites required and site enrollment rate, with no allowance for variability. The variability limitation can be addressed by randomly varying inputs from a plausible probability distribution function (e.g., beta function, log-normal or exponential) to provide Monte Carlo estimates of study recruitment duration and patient recruitment.

Stochastic Approach

The stochastic approach makes use of probability distributions functions to find the number of patients who may be recruited within a given duration and with a selected confidence interval.

Assume that a clinical trial study is spread over multiple sites, where p patients have to be recruited at S clinical centers. Considering a single site on this trial, it is assumed that there are no patients at the beginning when the site is initiated and there are no patients already in its database. In such a scenario, the patient recruitment process can be described by the Poisson process (with a general unknown rate r).

But for a larger multisite study, each site will be assumed to have a different recruitment rate based on internal and external, qualitative and quantitative factors. Factors may include size of the center, population of target patient in the region, length of study, etc.

Sen, Anisimov and Fedorov[4] have shown that the patient recruitment process at a particular center follows a Poisson process with unknown rate λ_i and variation in all rates at different centers can be described by a Gamma process. It means that the whole process can be explained by a Poisson-Gamma model.

Patient recruitment and enrollment duration at the initial stage of the trial, and in an ongoing trial, can easily be obtained using Anisimov's process.[5]

Predicting the number of patients to be recruited at a center "C" (in some region) during any time span involves a combination of probability distribution. Expected value, variance and confidence limit can be obtained using the formula below.

Suppose random variable X can take value x_1 with probability p_1, value x_2 with probability p_2, and so on, up to value x_k with probability p_k. Then the expectation of this random variable X is defined as:

$$E[X] = \sum_{i=1} x_i p_i$$

$$Var(X) = E[X^2] - (E[X])^2$$

An approximate p-confidence limit can be computed for any probability p using expected value, variance and a normal approximation as:

$CI = E[X] \pm \sqrt{(Var(X))} Z_p$; where Z_p is a p-quantile of a standard normal distribution

Anisimov has provided expected value and variance for the same in his research paper for the initial stage of the trial and for an ongoing trial.[6]

Significance Level	Z_p
0.80	1.28
0.90	1.64
0.95	1.96
0.99	1.58

Clinical Trial Recruitment Duration: Initial Stage Illustration

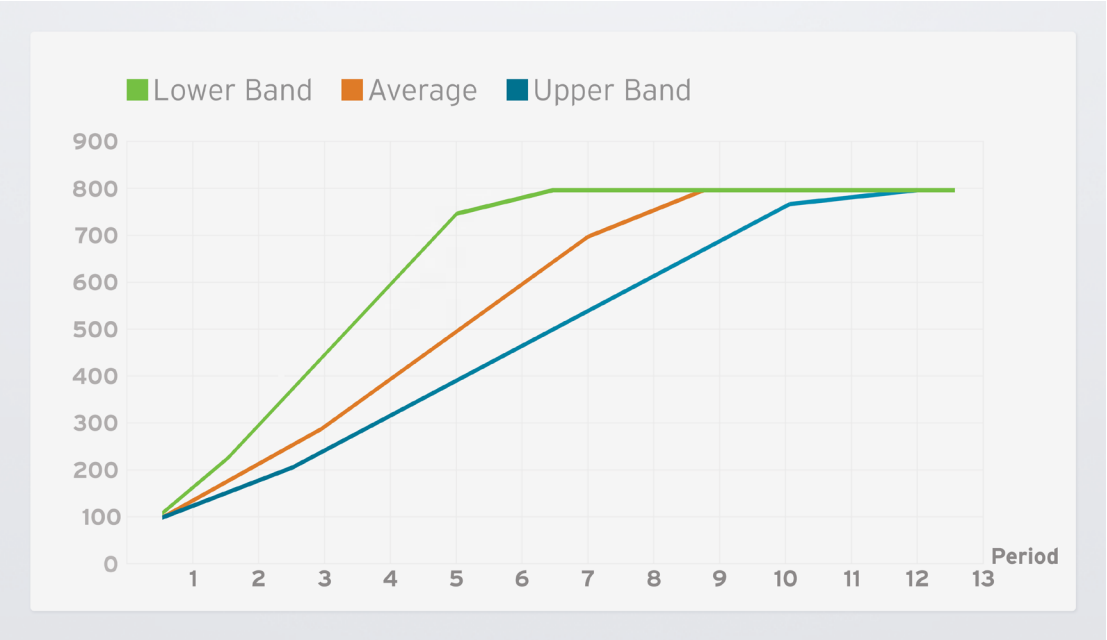

Figure 1

Clinical Trial Recruitment Duration: Interim Stage Illustration

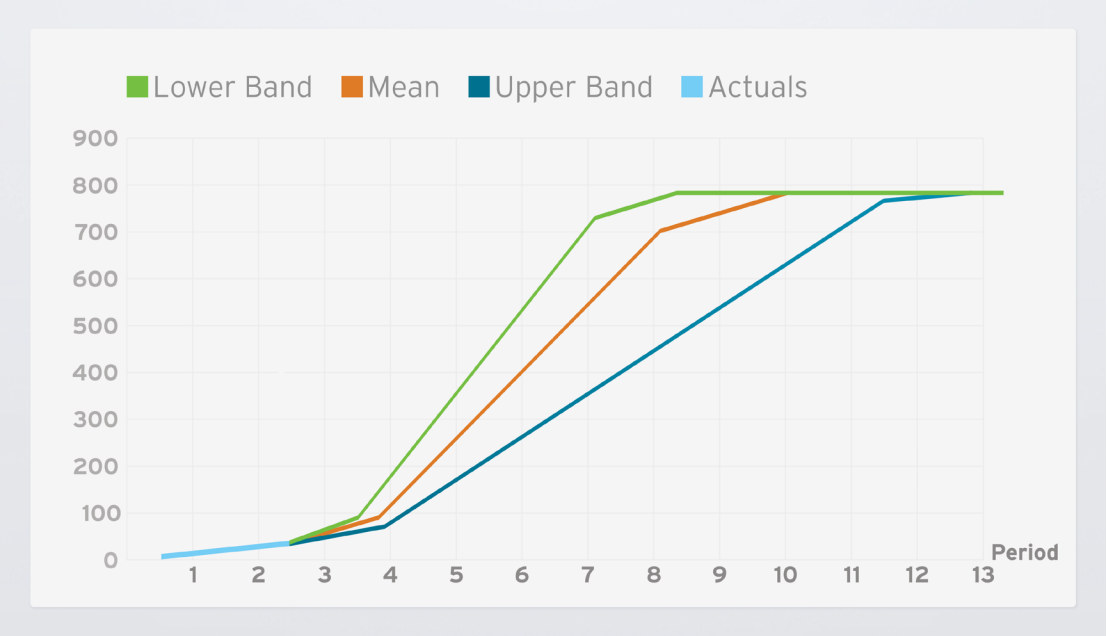

Figure 2

Figure 1 shows the recruitment duration and recruitment at the initial stage of the trial. Figure 2 shows the recruitment duration and recruitment at an interim stage of the trial (when actual numbers are also available). At this stage, the organization can make use of historical and actual data to create a forecast.

Looking Ahead

Though it has been observed and can be generalized that stochastic approaches perform better than non-stochastic approaches, it is recommended to test the suitability of the specific method on a case-to-case basis.

A simple approach would be to do a meticulous analysis of the past performances of both the methods and compare the outcomes from each of the methods against the actual; the method showing greater accuracy would be recommended since it provided better estimates. But in cases where a mixed trend is observed and no particular method is a clear winner – for example, in cases where in shorter periods of time one method performs better, and for longer periods the other method is the overall better performer – organizations should undertake a mixed approach that combines both the methods for improved accuracy.

Footnotes

[1] http://en.wikipedia.org/wiki/Patient_recruitment

[2] Source: White paper by Inventive Health, "Forecasting Trial Enrollment: More Data, Better Analytics, Greater Predictability."

[3] Stephen Young, Principal Engagement Consultant at Medidata, blogs on "Non-Enrolling Sites Come at a Price," http://blog.mdsol.com/non-enrolling-sites-come-at-a-price/.

[4] S. Senn, Vladimir Anisimov and Valerii V Fedorov are leading researchers holding doctorates in their respective specializations. They have authored and published several research papers on modelling and simulation in the pharmaceuticals industry, especially with relevance to clinical trials.

[5] Anisimov, V.V., "Predictive modelling of recruitment and drug supply in multicenter clinical trials," Proc. of the Joint Statistical Meeting, Washington, U.S., August 2009, pp. 1248-1259.

[6] Ibid.

Reference

Comfort, Shaun, "Improving Clinical Trial Enrollment Forecasts Using SORM," Applied Clinical Trials, May 2013, Vol. 22, Issue 5, p32.

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http://www.cognizant.com/enterpriseanalytics.

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