



Monte Carlo Simulations for Patient Recruitment: A Better Way to Forecast Enrollment

Introduction

The clinical phases of drug development represent the eagerly awaited period where, after several years of research and development, promising treatments become available to volunteer patients. The stakes at this stage are high: while less than two-thirds of Phase 3 trials are successful [1], they represent the most costly and time-consuming period of drug development. According to a paper published in the Journal of the American Medical Association [2], the most common cause for incomplete Phase 3 trials is related to enrollment. This is not surprising when as many as 37% of trial sites miss enrollment targets, and 11% fail to enroll a single patient [3].

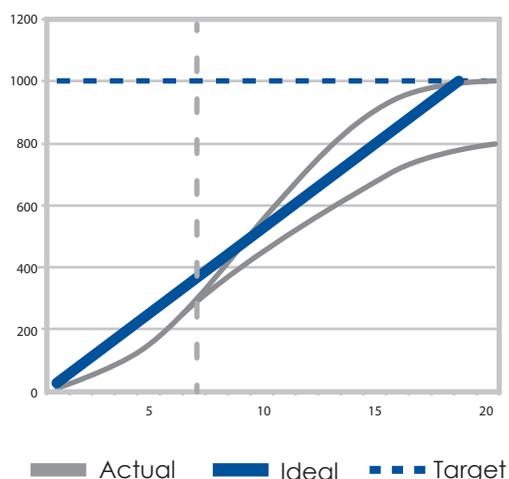
A vast majority of clinical trials experience delays in enrollment, and in the worst cases, these delays lead to discontinued trials. Even for successful trials, however, enrollment delays impose a substantial cost on the sponsor by increasing clinical operations expenses and loss of revenue due to delayed submissions. On the other hand, over-enrolling patients can also waste resources. Thus, optimal planning of patient enrollment – a key component of trial success - remains a difficult balancing act.

One of the critical questions facing trial planners is: "Can we recruit the required number of patients (e.g., 1000) within the assigned time (e.g., 25 months)?" A trial planner's experience and judgment is certainly useful for addressing this question. However, as demonstrated below, intuitive judgments alone may be ill-suited to manage all the complex uncertainties and interdependencies between relevant variables.

A Conventional Approach

Figure 1 shows an example projection that is based on a set of simplistic assumptions about trial performance, including:

Figure 1



- All sites will be ready to recruit from the same start date.
- No sites will fail to recruit patients.
- Patients will arrive in a strictly linear fashion.
- There will be no pauses in enrollment during the trial.

Using conventional tools such as spreadsheets, it is difficult to relax these assumptions because the computations required become impractical. In contrast, a more rigorous approach uses Monte Carlo simulations for data-driven trial planning. Such an approach can allow the trial planner to encode more complex assumptions into their projections.

The Simulations Based Approach

Our proposed technique, known as **Monte Carlo Simulation**, is commonly used in scientific, industrial, and business applications, to make realistic forecasts about uncertain outcomes [5]. This approach captures two realities of the enrollment process. The first reality is that enrollment is **nonlinear**. Different sites may open at different times, for example, so that enrollment starts very gradually, but then accelerates over time as more sites come on board. The second reality is that enrollment is **random**. A different number of patients will be recruited from one week to the next, simply due to chance. A data-driven approach should easily accommodate these two basic facts (nonlinearity and randomness), which would be impossible using conventional methods alone.

The first step when using the simulations based approach is to specify the relevant inputs, or factors that will affect enrollment. The target sample size and study duration are two such inputs already mentioned. Others include region or country specific data, patient accrual rates, and the sorts of inputs mentioned in the box at the left.

Other key inputs required for the model include:

- *Regions / countries and potential investigator sites*
- *Maximum number of patients to be enrolled at each site*
- *Percentage of sites failing to recruit any patients*
- *Time window for site initiation*
- *Average number of patients screened per week*
- *Chance that a screened patient will fail to be randomized*

It is relatively straightforward nowadays to gather data - whether internal, proprietary, or public - to provide reasonable values for these inputs.

Once this model is set up, the trial planner can use a computer program to simulate a virtual run. A virtual simulation displays one possible result given the set of inputs. These virtual runs can be repeated (e.g., 1000 times), with different random values all within the constraints specified by the key inputs. The end result provides a range of possible outcomes and their associated probabilities.

Simulation Outputs

The outputs of these simulations can be visualized in various ways. For example, Figure 2 displays the predicted study duration, defined in this case as protocol approval to last subject randomized. Due to the randomness associated with many of the key

inputs, this plot quantifies the inherent uncertainty about the study duration. For example, if asked to provide a single “best guess,” we can report the average predicted time of 16 months. In addition, there is a 95% chance that the trial duration is between 11 and 25 months, since 95% of the simulated trials fell within that range. In the

Figure 2

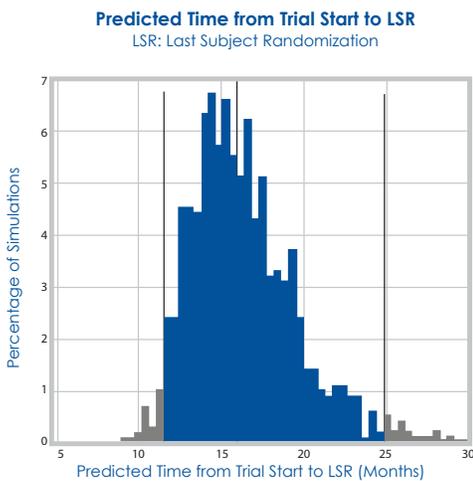
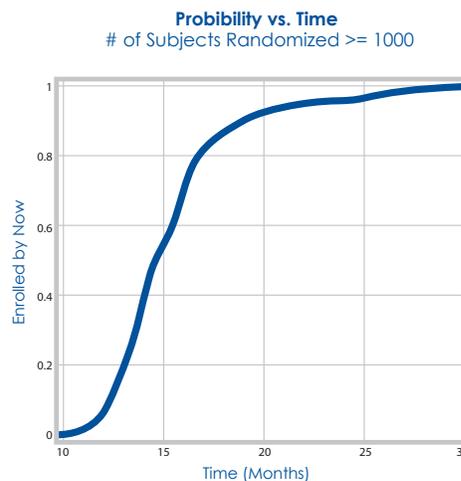
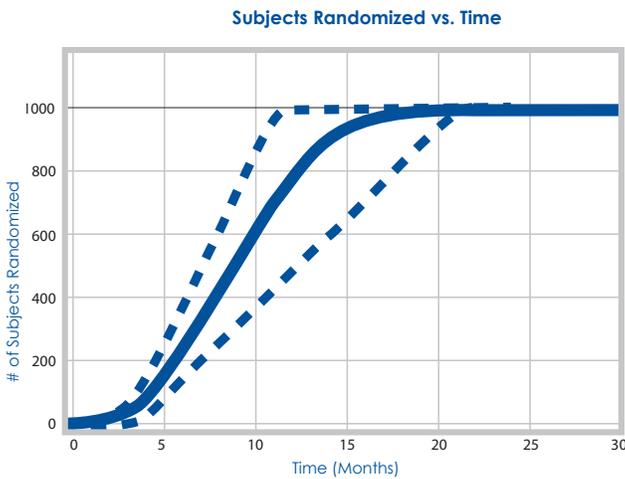


Figure 3



“worst case scenario,” there is a 2.5% chance that the duration will exceed 25 months. Therefore, we can be very confident that the target sample size will be achieved in the scheduled timeframe. Similar plots can reflect other desired outcomes, such as the time from trial start to first patient randomized.

Figure 4



These same simulated outputs can easily transform into a curve showing the probability of achieving a key milestone (in this case, the target sample size) before any given time [Figure 3].

As a final example, Figure 4 displays the predicted cumulative enrollment over time until the target sample size of 1000 patients. The solid blue line represents the average prediction, while the dashed blue lines represent 95% probability intervals. Put into words, this means that in 95% of the simulations, the simulated trial was within those bounds. Corresponding plots can display other metrics, such as the predicted cumulative sites that will open over time.

Acceleration Strategies

Armed with these sophisticated simulations, which reflect more realistic assumptions about trial performance, we are now in a much stronger position to address the critical question: “Can we recruit the required number of patients within the assigned time?” If such outputs indicate that achieving the milestone is not highly likely (i.e., the simulated probability is less than some threshold, such as 95% or 90%), then we can consider a number of strategies, while still at the planning stage, to remedy the situation.

Common acceleration strategies include:

- *Varying countries or sites to minimize site initiation times or site failure rates.*
- *Adjusting the protocol (inclusion/exclusion criteria) to reduce the screening failure rate.*
- *Advertising and awareness campaigns to boost enrollment rates.*

Moreover, if we discover that an aggressive target will lead to significant benefits, we might want to pursue the aggressive target. For example, if we discover that a 10% chance of a particular trial site hitting an enrollment milestone will result in three months off of a trial, we may want to pursue a low probability event.

Planners can evaluate the relative effectiveness of these strategies quite conveniently via simulation, and compare different scenarios on meaningful quantitative measures. Implementation of such strategies will of course be much less expensive when considered before the trial than in the middle of the trial.

Conclusion

Compared to conventional approaches, the Monte Carlo Method for patient enrollment provides a more realistic forecasting technique which captures the possible risks and outcomes for any given scenario. It accounts for the nonlinearity and randomness of real-life enrollment processes. It identifies how different inputs like accrual rates and site-specific screening can affect the patient recruitment strategy. Given the right computer programs, it can provide substantially greater accuracy than conventional and other methods.

Advantages Of A Simulations Based Approach

- **Identify Strategic Relationships:**
For example, if enrollment targets are met in one country, what needs to be done for enrollment plans in other countries?
- **Depend on Data-Driven Decisions:**
Since the relationships between key events becomes clear, there is greater understanding between stakeholders regarding strategic decision rules.
- **Enhance Financial Decision-Making:**
The probabilities associated with model-based outputs can easily integrate with dollar amounts. These can support or oppose decisions on the basis of expected risks and rewards.

Across many functions within the drug development industry, modeling and simulation methods are already gaining popularity [5], and will soon become an indispensable tool for clinical operations. Trial planners who take advantage of such methods will be able to significantly reduce their study costs and timelines, while maximizing their chances of study success.

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