

Better than a Crystal Ball

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Clinical research professionals often dream of having a crystal ball that can accurately and precisely predict enrollment performance. Long-used in other industries, modeling and simulation tools represent the future of clinical research planning. They may, in fact, do better than the elusive crystal ball we long for.

Just knowing that a trial will take X months to enroll is one thing. Insight about the drivers of enrollment success and the impact of manipulating various factors is quite another. Here we explore the basics of modeling and simulation and their use and value in aiding enrollment planning and management decisions.

Modeling and Simulation

Think of operational modeling and simulation tools as a virtual planning sandbox that enables decision makers to practice the performance of their clinical trial. Those exercises take place without exposing real people to real products, without waiting months or even years to see how long it will take to reach target enrollment or how a study might perform. The goal and focus is to understand the impact of different factors on the outcome. For example:

- If we add 10 sites, how much faster could we complete enrollment?
- If we spend \$1 million on a recruitment program, how much faster can we realistically expect to complete enrollment?
- If we add sites in China, what impact will that have on projected enrollment time?

How it Works

The nuances of technical definitions and differences between modeling and simula-

tion are beyond the scope of this article. It is useful, however, to briefly define some terms and describe some important elements of operational modeling and simulation as they pertain to enrollment planning.

A model is a hypothetical description of a complex process. Simulation enables study decision makers to practice various scenarios in a computer generated model of a clinical trial. Both techniques are typically used when the real process (e.g., conducting a trial) is complex, time-consuming, expensive, and/or dangerous.

For our purposes, models range from simple mathematical equations of a few key metrics to full-blown computerized simulation systems that represent an entire clinical trial process.

Mathematical models (i.e., equations) are created to explain how a certain process (e.g., country allocation or subject recruitment) might work. In computer simulations, professionals build entire processes that reflect real-world activities: the flow of subjects from identification and prescreening through informed consent and randomization, through to trial completion.

Planning Enrollment

With modeling and simulation, study planners can run multiple trial scenarios, which can reveal missed opportunities or valuable insights. For example, the project team may discover that countries not previously considered could contribute subjects at a lower cost or that a trial could be enrolled in the same time with 45% less sites.

Some industry experts suggest that it costs \$25,000 to \$40,000 to initiate a site; not having to initiate additional sites represents huge cost and time savings. Multiple

Cycle Time What-if Scenarios



simulation runs may reveal that a trial could take twice as long to enroll as originally planned, which may lead to a decision to cancel the study before it is launched.

Study Scenario. Let's say we're planning a large, global Type II diabetes trial of 700 subjects. Very early in study planning we might ask a simple question: Is a six-month enrollment period realistic?

Using past enrollment metrics from a database, some simple modeling could look at various combinations to determine that we could realistically meet the six-month

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enrollment goal and that several options exist for the possible mix of countries and sites that would allow us to meet that goal. With little difference in the enrollment and total cycle times, we may choose a scenario with fewer sites and countries to minimize study start-up and monitoring costs.

Multiple stakeholders then weigh in with country recommendations and strategically important factors. The marketing de-

partment has requested including China and enrolling a minimum of 10%, or at least 70 subjects, into the trial.

Although the company has never worked in China, its CRO partner advises them that China's activation process can take about a year. Because a year is an unrealistic time to wait to see whether China can meet the enrollment commitments, the study team does further in-depth modeling and simulation to assess the impact of that wait before making

a final commitment. They learn that adding China will come at a cost of approximately seven additional months from protocol approval to last patient enrolled.

Both the simple quick trial modeling and the country allocation modeling examples use an algorithm with a series of ranking and weighting calculations based on past performance data. The results optimize the mix of countries most likely to meet the enrollment goal of 700 subjects in six months.

China is strategically important, so the study team agrees to include it and revises their enrollment timeline estimate to a more realistic nine months (see Figure 1).

While study implementation activities in the rest of the world proceed, the team now turns its attention to planning U.S. enrollment. They explore options for accelerating enrollment to accrue 300 subjects so that an interim analysis can be completed. The team wants to determine time:cost trade-offs for the following scenarios:

- Invest \$1 million in an advertising campaign expected to accelerate the study enrollment rate in 40 U.S. sites
- Add an additional 10 sites in the United States (a total of 50 U.S. sites)
- A combination of adding 10 more sites and a \$1 million recruitment campaign.

Figure 1 shows estimated enrollment

curves for the three options, and Figure 2 shows a comparison of the time:cost trade-offs for the various scenarios.

What we learned from simulating these scenarios is that we are likely to gain only about one month in cycle time and two weeks additional enrollment by spending more than \$1 million to add more sites and run a recruitment campaign. With that insight, the team may opt to go with their baseline scenario of 40 sites and invest the \$1 million in other improvement initiatives.

Benefits Realized

The true power and value of operational modeling and simulation decision-aiding tools is the ability to run unlimited what-if scenarios in a matter of minutes.

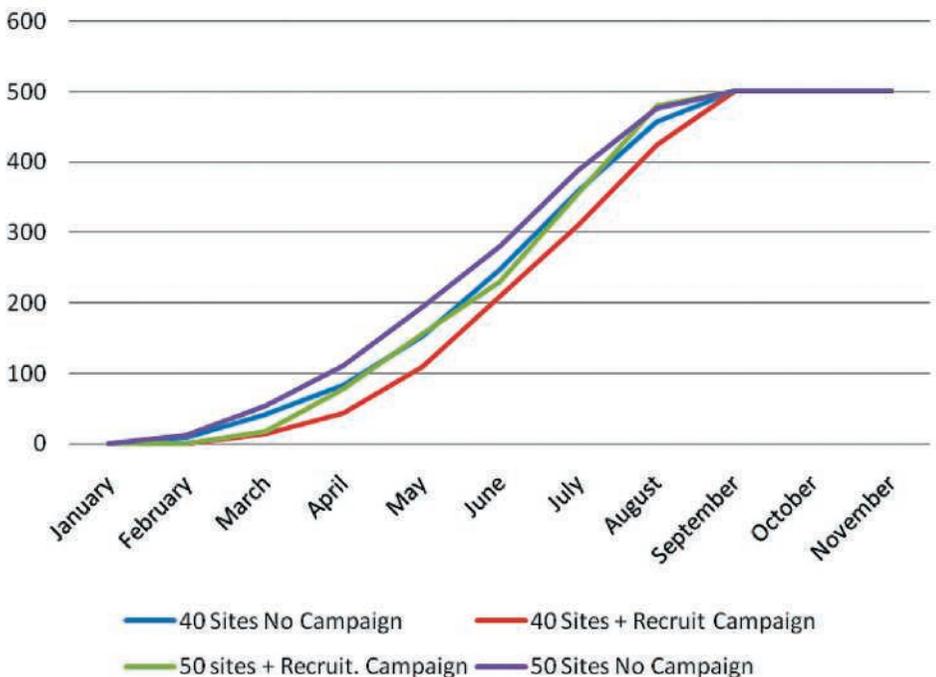
Gaining insight into the likely outcomes may come from various scenarios without actually having to implement those plans, which saves valuable time, money, and re-

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sources. If such decision-aiding tools enable study planners to “practice” their trials in a safe simulated environment—and if practice makes perfect—then modeling and simulation tools give the industry an opportunity to perfect the planning and execution of clinical trials.

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Simulated Scenario Enrollment Curves



Source: Internal SAI CTInsight Simulation Run Results, Jan. 2009

Figure 2. The estimated patient enrollment curves for the four scenarios listed.