

Using Simulation to Create Enrollment Plans

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ABSTRACT

Developing a plan to reach a Study Enrollment goal can be a tricky business. Choosing countries and sites with their associated rates and costs complicates things. Simulation is an excellent way to understand sources of variability and comparing options to meet the enrollment goals.

INTRODUCTION

One of the most important things to do once a clinical trial has been designed is to figure out where the subjects are going to come from. Decisions about what countries to use and what sites in those countries are driven by striking a balance between the enrollment rate and the cost of countries and sites. Many assumptions are made on these rates and costs, usually from combining previous experience and a feasibility study. In a feasibility study, a team will contact many potential sites and ask questions about the types of patients they typically see with the therapeutic area of interest. Those questions tease out the following information:

- How long will it take to get your site initiated (ready to enroll subjects)?
- How many subjects can you enroll each month?
- How much will it cost to get initiated? How much will it cost to treat the subjects per the protocol?

For example, a site might say it will take six months to get initiated and they will enroll 10 patients per month, so the site will contribute zero for the first six months and 10 per month after that. In general, when putting together an enrollment plan for a proposal, this sort of estimation is done for several sites and summed up over time until the required number of subjects are enrolled. This is a reasonable approach to get a ballpark estimate of how long enrollment would take, but it is missing a key component: an understanding of the expected variation. Simulation is a way to get an understanding on the width of possibilities for a given enrollment plan, and also provides a method of comparing possible scenarios.

SIMULATION METHODS

There are multiple ways to approach simulation, but for a problem of this nature, discrete-event simulation (DES) is an excellent modeling approach. DES looks at how a system changes over small slices of time. A typical application is in modelling customers interacting with a queue – arrival times are sampled from a distribution, customers wait in line while tellers are seeing other people, and finally they are seen by the teller and leave the system. The simulation tracks the individuals as they go through the system, and the state of each individual changes over time. Subjects going through a clinical trial can be modeled in the same way. Figure 1 shows a very simple approach to enrolling patients at a single site.

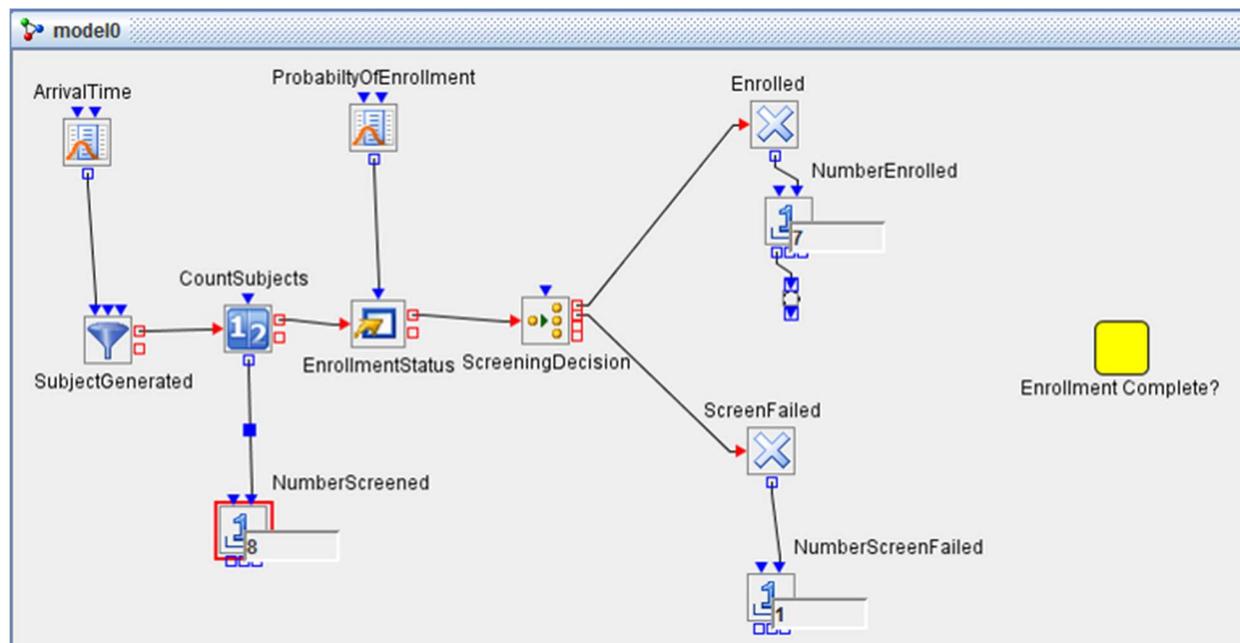


Figure 1. Discrete Event Simulation Flow for Single Site Enrollment

First we simulate the time for the next arriving subject from some distribution (for example, we set a distribution that will have 15 patients per month arrive, so on average a new patient arrives every two days). Once the subject is in the door, the screening process starts. In this simple example, we determine the enrollment status right away by sampling from a binomial distribution (essentially flipping a coin with a 90% chance of enrolling and a 10% chance of screen failing). That probability sample determines if they go up the top path and enroll or down the bottom path and screen fail. In DES, you also provide a stopping criterion – in this case we'd let the simulation run until 50 subjects were enrolled, and then shut the door to new subjects. The simulation keeps track of time as they system runs, so at that point we'd know how long it took to get the targeted enrollment.

The most important thing about these simulations is that we will repeat the process multiple times (each time is called an iteration or replication of the simulation). Instead of just running the simulation once and getting a snapshot of what we might expect, we would run the simulation 100 times and get a range of how long it took to enroll the 50 subjects. Each time we run a new replication, we sample new random values from the ArrivalTime and ProbabilityOfEnrollment distributions, and this would give a distribution of values for the time to finish enrollment – that's the true value of simulation.

SIMULATION PARAMETERS

The example in Figure 1 is of a very simple process; the entire study simulation is much more complex, and there are a lot of values to keep track of. At a high level, we can look at the study timeline as following this path:

1. We establish a start time (Day 0) for the study
2. Each country gets approval for the study and can start site selection. A scenario might have multiple countries, each with a different startup time.
3. Sites are initiated in a country and can enroll.
4. Subjects start screening at sites
5. Some subjects fail screening; others start the study treatments.

6. As the subjects progress through the study, some discontinue early or are lost to follow-up.
7. The study hits the enrollment target and no new subjects enter the screening process.
8. The study remains operational until all subjects either complete or end the study.

At the same time you are tracking the progress of subjects through the system, it's also helpful to keep track of the costs generated, which will differ between countries and also between sites.

When designing a discrete-event simulation of a system like this, you must identify some key parameters that will be used to define the probability distributions. These parameters may be very different for different therapeutic areas, and will be different across all sites and countries. Some of the key parameters to consider are as follows:

COUNTRY-LEVEL PARAMETERS

- **Startup Time** – how long does it take to get a country from the decision to start a trial (Day 0) until it can start the site initiation process.
- **Startup Cost** – how much does this cost.
- **Startup Probability** – it's useful to consider the chance that approval will never be achieved in a country as you are working through the startup process – maybe there is a 99% chance of getting approval in the US vs an 85% chance in Brazil – some of the replications of the study might have only one country successful started up.
- **Concurrent Site Startups Possible** – this is a constraint to the system. For example, you may plan on starting up 40 sites but only have the personnel for 30, so the 31st site to attempt to start up would sit in a queue until staff became available.

SITE-LEVEL PARAMETERS

Once the country successful starts up, the site initiation process can begin. There are two ways to think about sites: you may have some specifically identified sites that you have used before and understand (primary sites) and you may have more general ideas about groups of sites (candidate sites). An example of candidate sites may be classified as “fast enrolling, central IRB sites” or “medium enrolling, local IRB” – these groups would each have a distinct set of parameters and would apply to groups of sites.

- **Time-to-Identify (Candidate Sites Only)** – a distribution of the number of days it will take to find specific sites from this candidate group
- **Number Available (Candidate Sites Only)** – how many sites you can get from the specific candidate group
- **Startup Time** – distribution of the number of days between when the site is ready (identified and country is approved) and the site is ready to open for enrollment
- **Startup Cost** – the cost for getting the site through the initiation process
- **Startup Success Probability** – a value that represents the chance a site will successfully get through initiation
- **Probability of Zero Patients** – there is always a chance that the site will get initiated and can enroll, but for whatever reason never does – essentially the site gets lost to follow-up
- **Expected Recruitment Rate** – this is generally expressed as the number of patients per month to start the screening process. Often, sites are overly optimistic about how many patients they will see per month, and it is useful to have a way to address that. One approach is to break this rate

into two periods – for example, the site will get 20 patients per month for the first six months, then see 12 per month after that.

- **Available Subjects** – it is a good practice to have a cap on the number of subjects that could possibly come from one site
- **Per Subject Cost (Screening)** – this is the cost incurred by the site to screen subjects
- **Per Subject Cost (Enrolled)** – this is the cost incurred by an enrolled subject who completes the study. Subjects who discontinue early would get a pro-rated value allocated to them.

STUDY-LEVEL PARAMETERS

- **Discontinuation Rate** – the percent of subjects who discontinue early for any reason. It can be useful to split this up into cohorts – for example, the 60% in the active arm will see a 20% dropout rate, while the 40% in the control arm will see a 25% rate
- **Schedule of Assessments** – Identify the study days for visits. At each of the study visits, there would be a chance for each subject to discontinue, to get the overall discontinuation rate identified above

SCENARIO-LEVEL PARAMETERS

Scenarios are a combination of countries, sites and a study that the simulation will be executed on. Generally, you will be looking at multiple scenarios to determine which approach is better. For example, you may be looking at a trial that will be run in 10 specific sites in the US as one scenario, and then compare that to the idea of adding 10 possible sites in Brazil, with the understanding that it will take longer and cost more to get Brazil up and running, but once it is operational, you think the sites will enroll faster and the subjects will cost less. Will this have a positive impact on enrollment times and cost? The ability to address such a question is the key benefit of doing simulation.

- **Country Selection** – identify which countr(ies) you want to include in the simulation
- **Country Screen Failure Rate** – each country will have its own probability of a subject failing screening
- **Site Selection** – identify which sites to include in each country. If using candidate sites, provide the maximum number of sites
- **Target Enrollment** – this is the total number of subjects you are trying to enroll. Once this target is reached, enrollment stops, but the simulation continues until every subject exits the trial
- **Maximum/Minimum Subjects per Country** – consider putting caps on the total number of subjects who can enroll from any specific country
- **Target Start Date** – this is Day 0, the start date of the simulation. All other dates are in reference to this.

RESULTS & BENEFITS

The results from running multiple replications of a scenario will provide a good understanding of the possible variation. Figure 2 shows the results of the scenario with using just the 10 sites identified in the US.

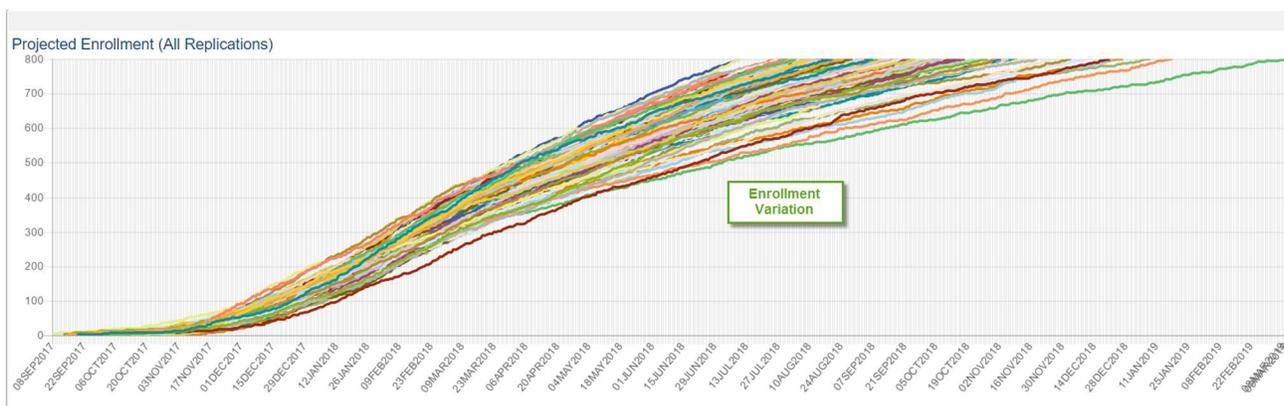


Figure 2. Simulation Results for a Single Country Scenario

The observed variability is due to randomness in startup times, enrollment rates, and the number of sites that successfully enroll any subjects. Having a greater appreciation for what might reasonably happen allows for better planning.

Figure 3 shows a scenario using the same 10 US sites, but also including up to 10 sites in Brazil. The Brazil sites have a higher risk of failure to start (as does the country startup), but once started will contribute subjects faster.

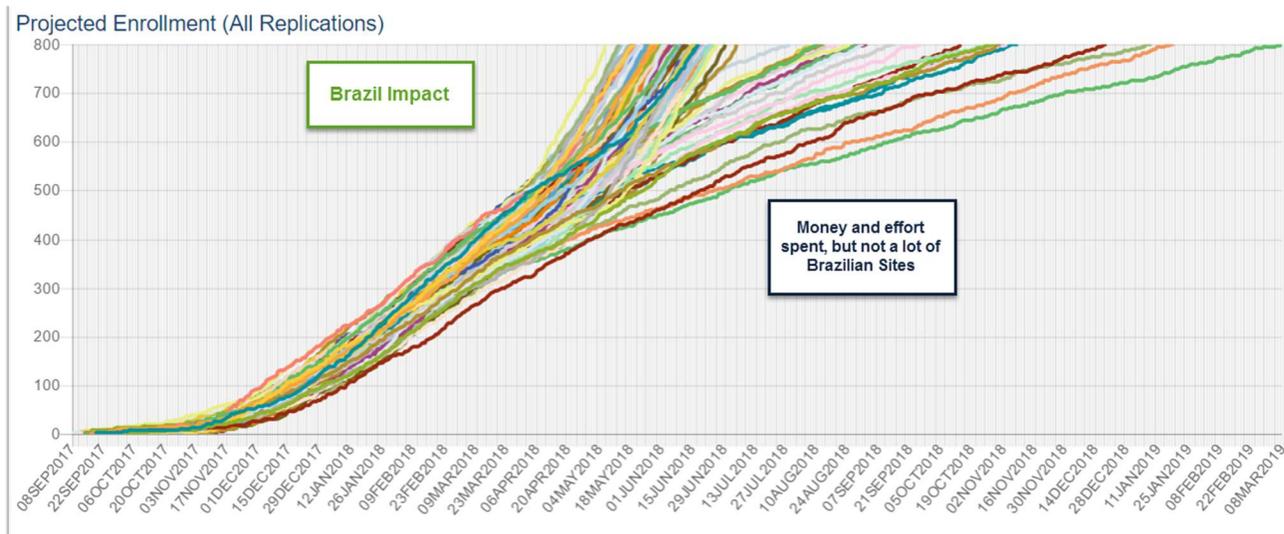


Figure 3. Simulation Results for a Two Country Scenario

Once a scenario is chosen and an enrollment plan is created, one of the replications from the scenario is chosen to anchor the expectations. Generally, the median replication is the best choice, but it might make sense to choose a different one, depending on the amount of risk involved for the team.

One of the key benefits of doing simulation is the creation of subject-level datasets for each replication. These datasets allow for further analysis and planning opportunities. Figure 4 shows the expected trial visits for a chosen replication. This can be used for managing supply chain and for developing

expectations around monitoring visits.

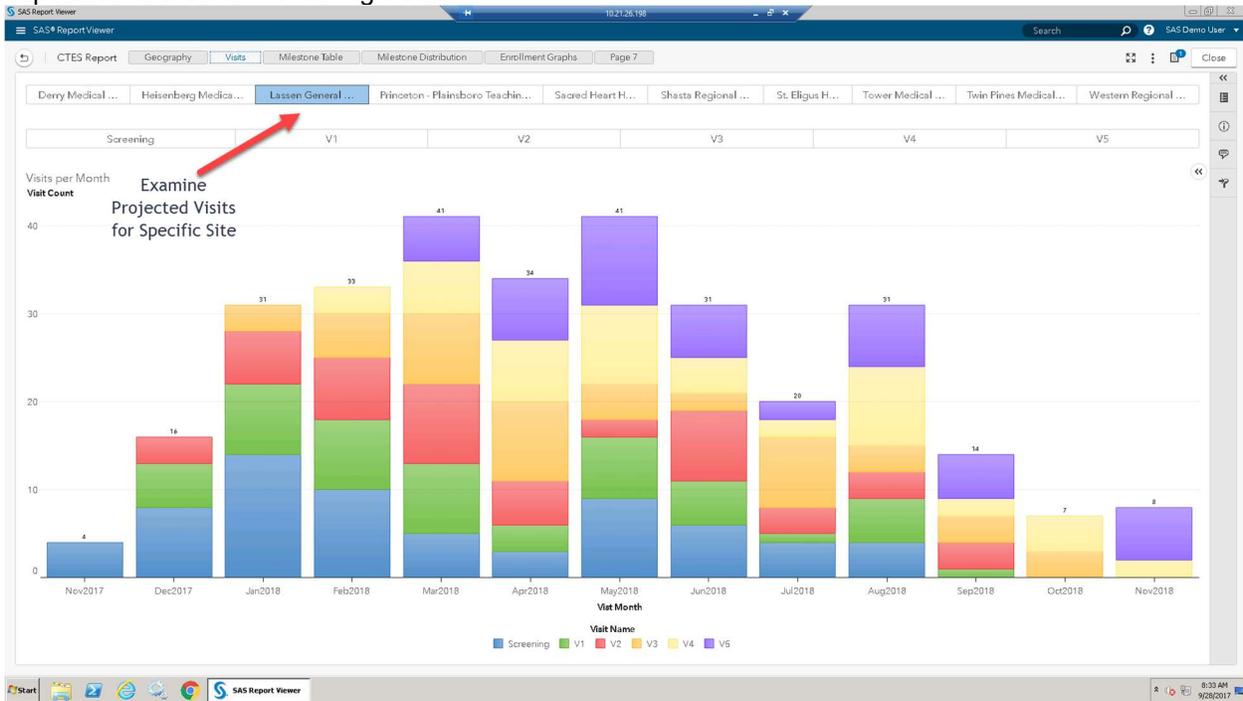


Figure 4. Projected Site Visits for a Chosen Replication

Figure 5 shows a distribution of the last patient last visit dates – this could be useful to evaluate the overall acceptability of the scenario. For example, we might learn that there is a 5% chance the LPLV will not happen by the desired end date, and other scenarios must be explored.



Figure 5. Distribution of Last Patient Last Visit dates

Figure 6 shows a cost breakdown by all subjects for a specific replication. This can be used for budget forecasting, and can easily be broken down by site and by time, to further aid in budget creation.

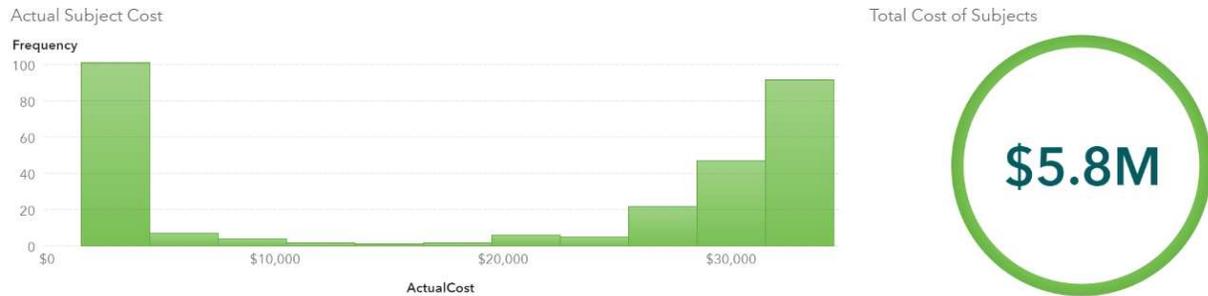


Figure 6. Distribution of Subject Costs for a Chosen Replication

CONCLUSION

Creating enrollment plans for clinical trials is a complicated endeavor. Static methods can give a reasonable ballpark estimation, but simulation methods can give a much deeper understanding of possible outcomes. Discrete-event simulation allows for the comparison of many potential scenarios, and is a source of rich data that can be used to project key milestones and costs that allows for more comprehensive clinical trial planning.

CONTACT INFORMATION

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