

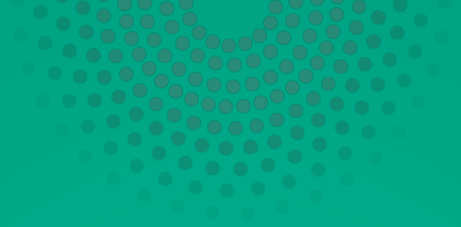


Simulating Enrollment Plans

Jim Box, SAS Institute

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Enrollment Plans

Typical Approach

Enrollment Plan Development

Understand the Problem

- Request for Proposal comes from Sponsor
- Goal – Enroll N subjects on the study as quickly as possible
- Feasibility Analysis Performed
 - Historical Data
 - Discussions with potential sites
 - Educated guesses

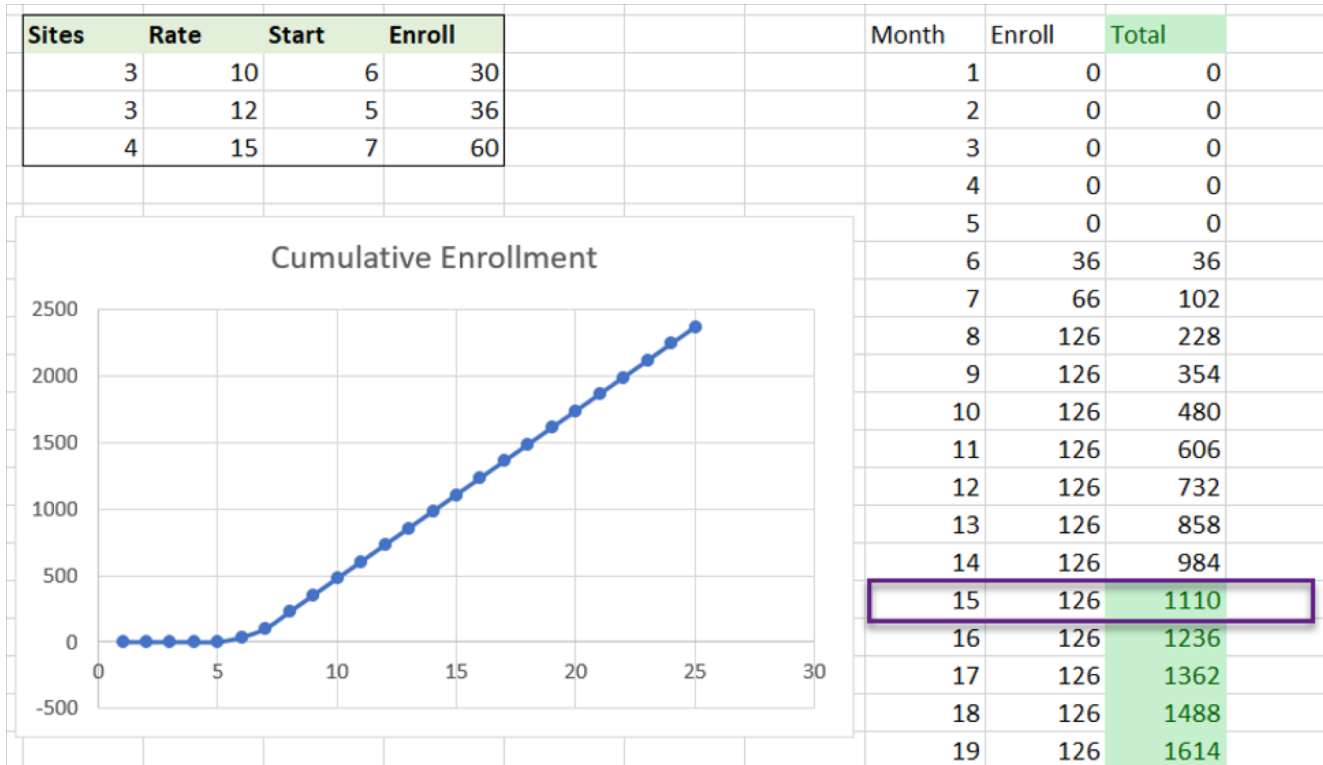
Enrollment Plan Development

Understand the Problem

- Basic Inputs Determined:
 - What countries do we target?
 - How many sites can we get from each country?
 - How long will it take to get the sites enrolling?
 - How many patients per month can each site expect?
- Perform some calculations
 - To Excel we go ...

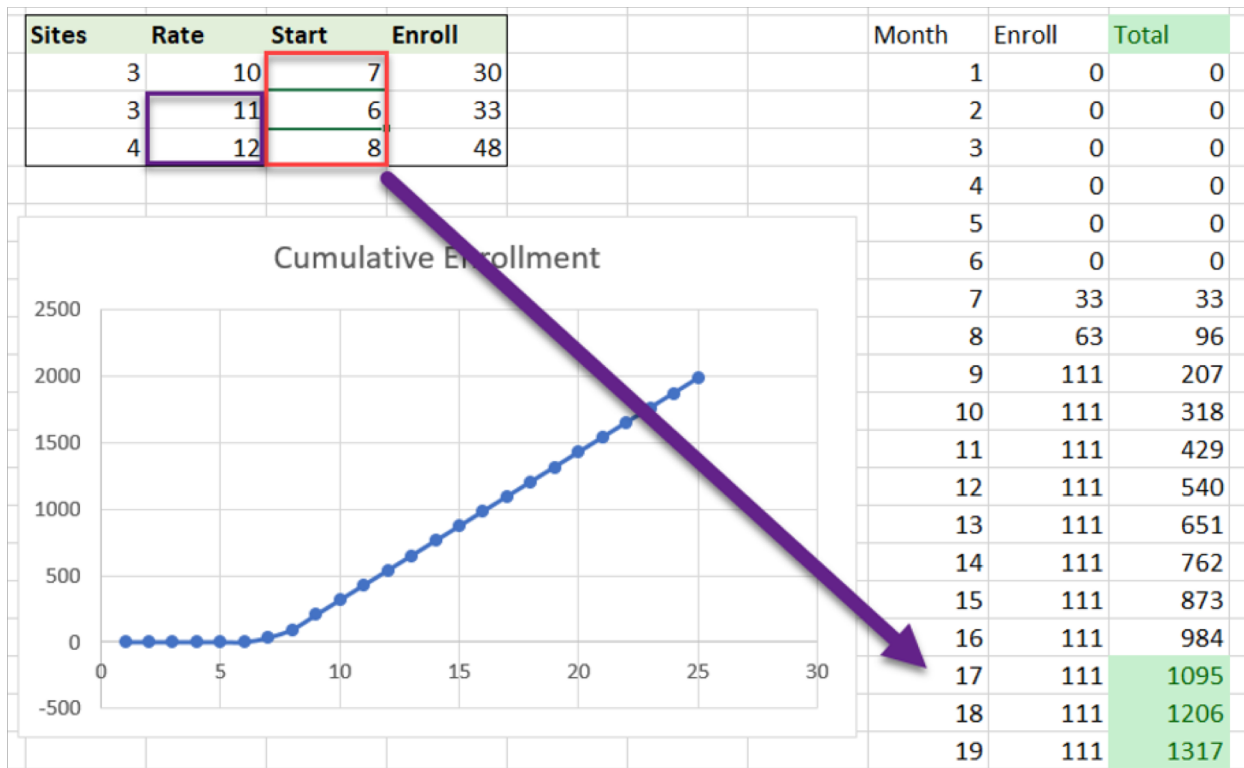
Enrollment Plan Development

Excel Calculations



Enrollment Plan Development

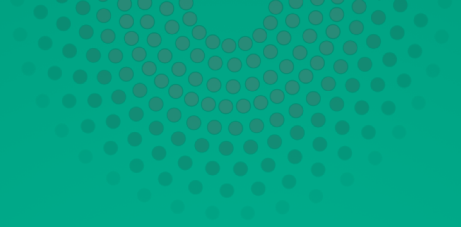
Excel Calculations – Exploring Possibilities



Enrollment Plan Development

What's Missing from the Calculator Approach

- Variability
 - Both in estimated inputs and outcomes
- More parameters to explore as inputs
- Cost estimates
- Ability to track different scenarios to determine best outcome



Enrollment Plans

Simulation Approach

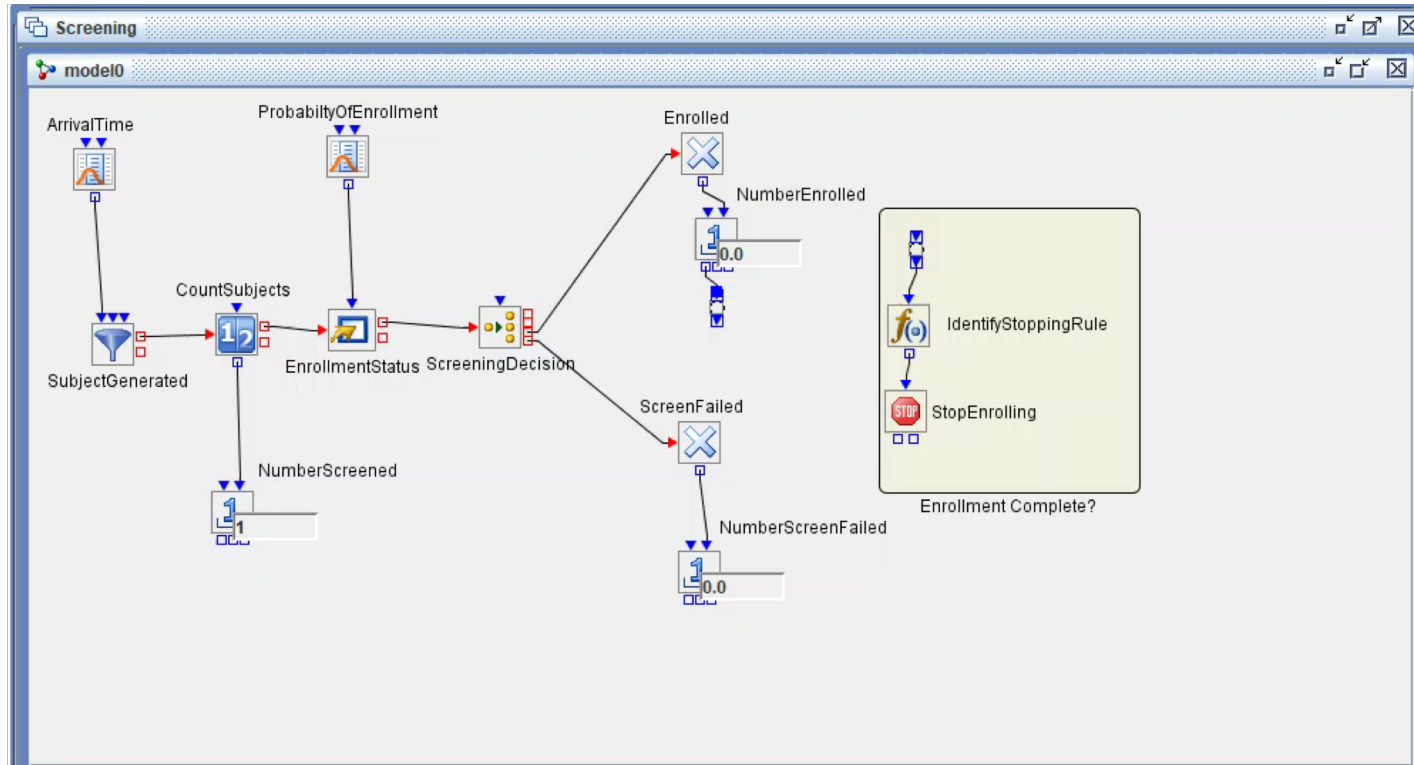
Simulating Enrollment Plans

Methodology – Discrete Event Simulation

- Models the system as a discrete sequence of events in time
- Each event marks a change in system
- Entities pass through the system
 - Countries
 - Sites
 - Subjects
- Typically used in queuing system simulation

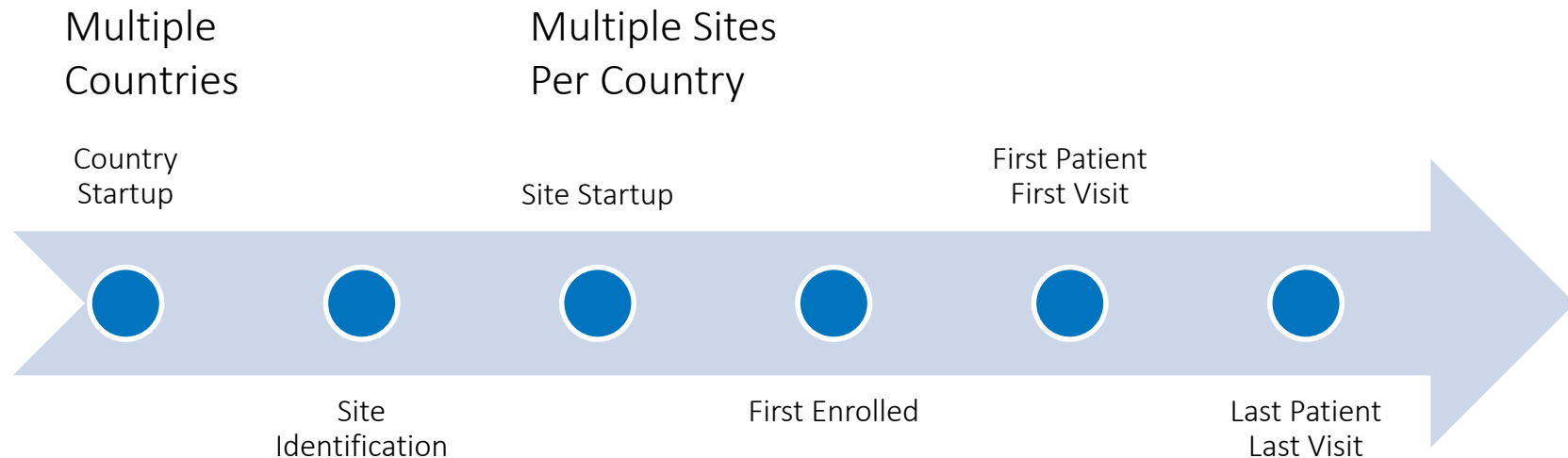
Simulating Enrollment Plans

Example – Discrete Event Simulation



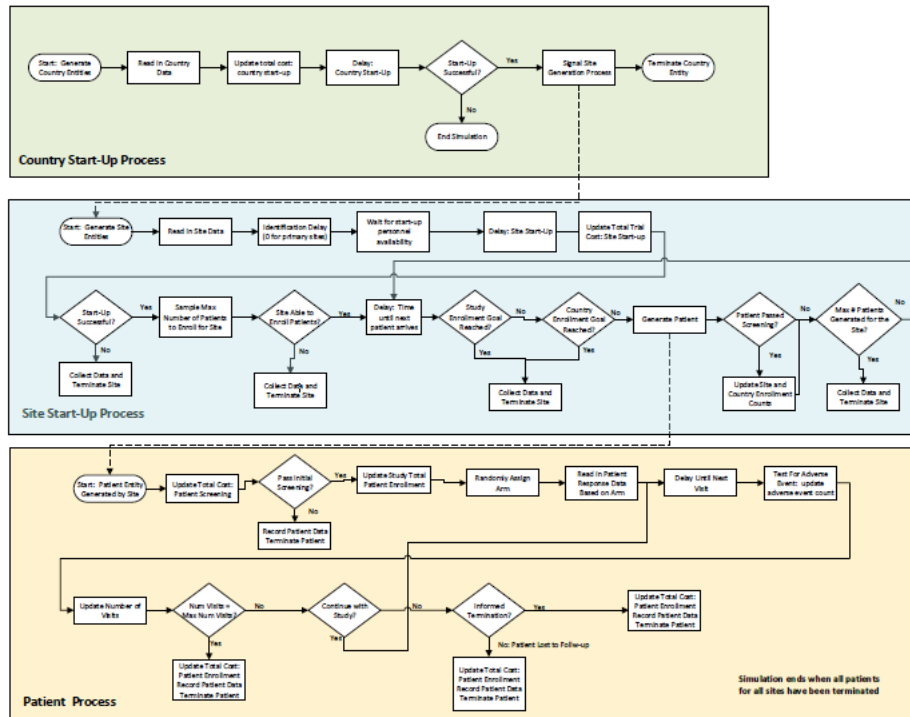
Simulating Enrollment Plans

Real System is Complex



Simulating Enrollment Plans

Real System is Complex



Simulating Enrollment Plans

Parameters – Study Level

- Number of Subjects required
- Schedule of Visits
- Dropout Rates
- Milestone Targets
 - Cost
 - Key dates
 - First Site Initiated
 - First Subject Enrolled
 - Last Patient Last Visit

Simulating Enrollment Plans

Parameters – Country Level

- Startup Time (time until site selection can begin)
- Startup Cost
- Startup Success Probability
- Number of Concurrent Site Startups

Simulating Enrollment Plans

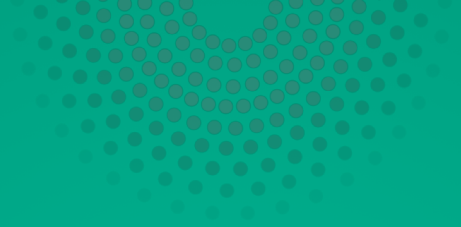
Parameters – Site Level

- Individual Sites vs Groups of Sites
 - Site Initiation Time and Cost
 - Site Initiation Success Probability
 - Chance of never enrolling a subject
 - Expected Enrollment Rate (with a decay)
 - Enrollment Cap
 - Cost for Screening and Completed Subjects
 - Time to identify sites

Simulating Enrollment Plans

Parameters – Scenario Setup

- Scenarios for the Enrollment Plan consist of:
 - Study
 - Group of countries (with max/min enrollment)
 - List of sites for each country
 - Overall enrollment target
 - Start Date
 - Number of Replications
- Add the ability to override country and site settings at the scenario level

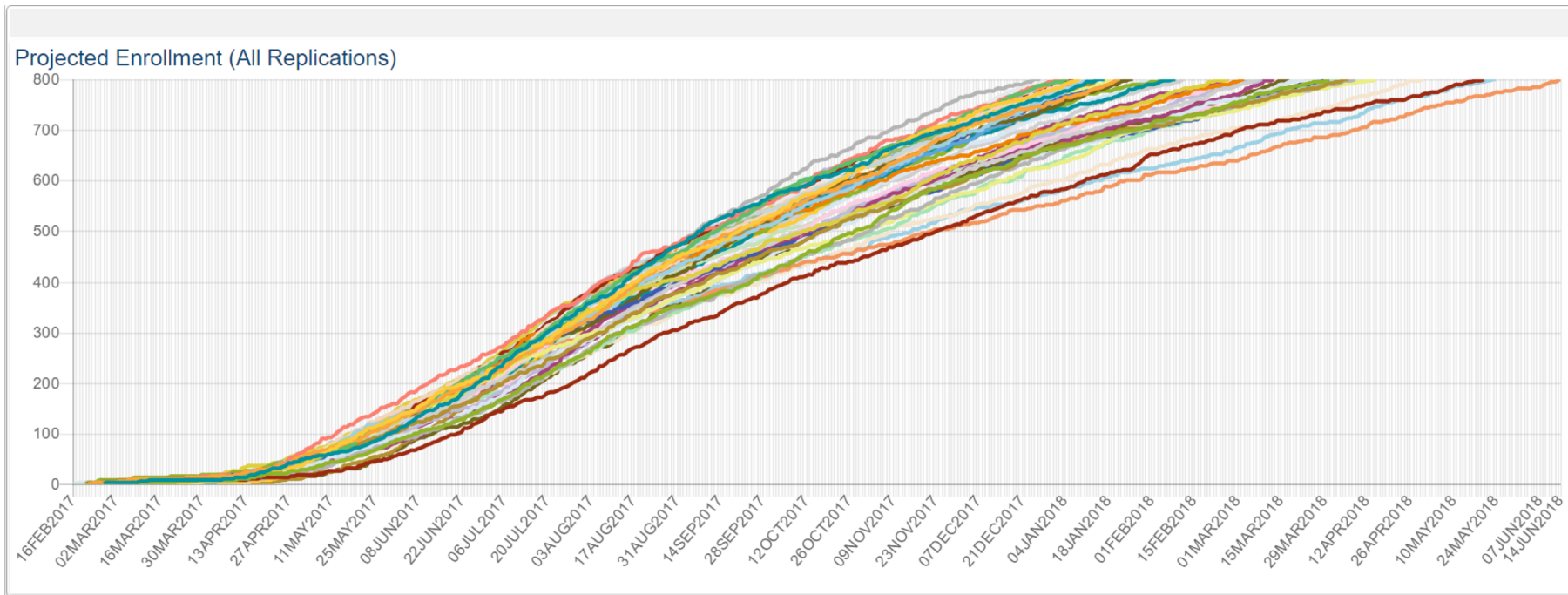


Enrollment Plans

Simulation Results

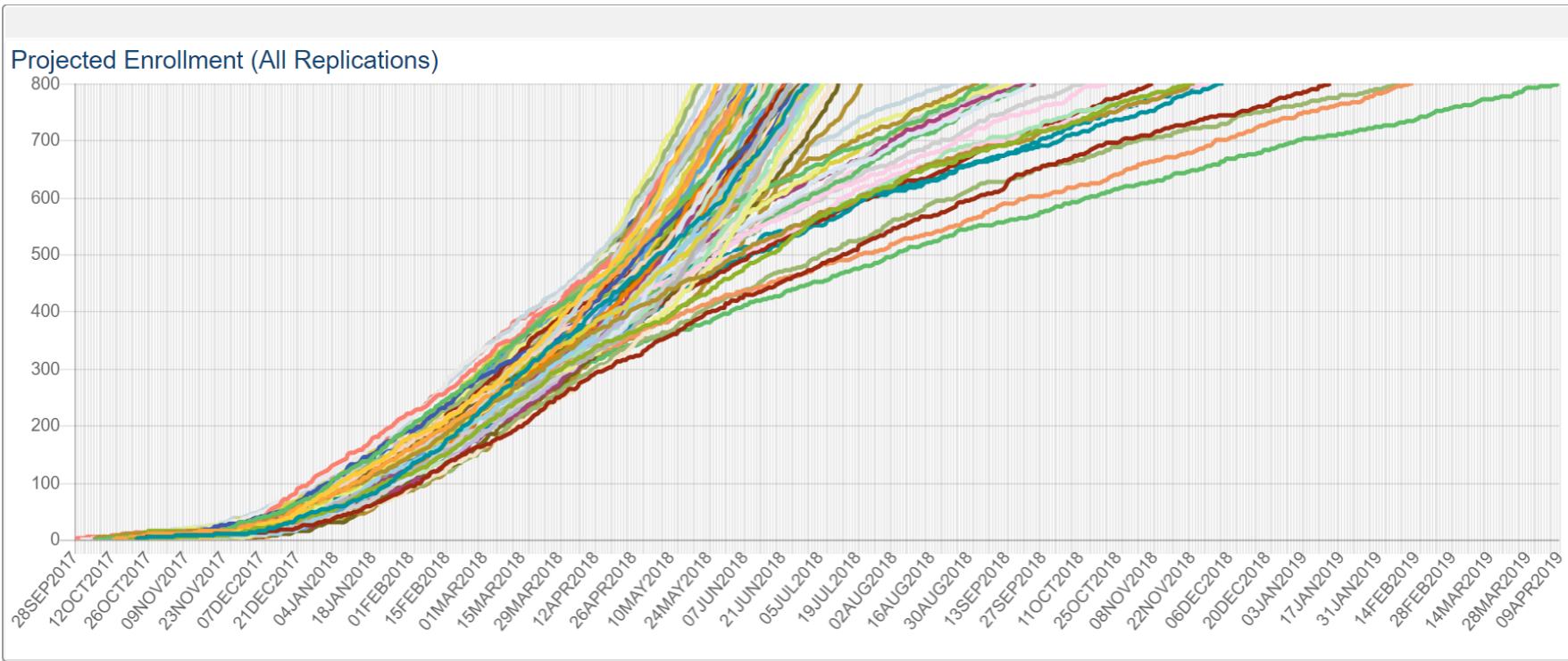
Simulation Results

Enrollment Variability



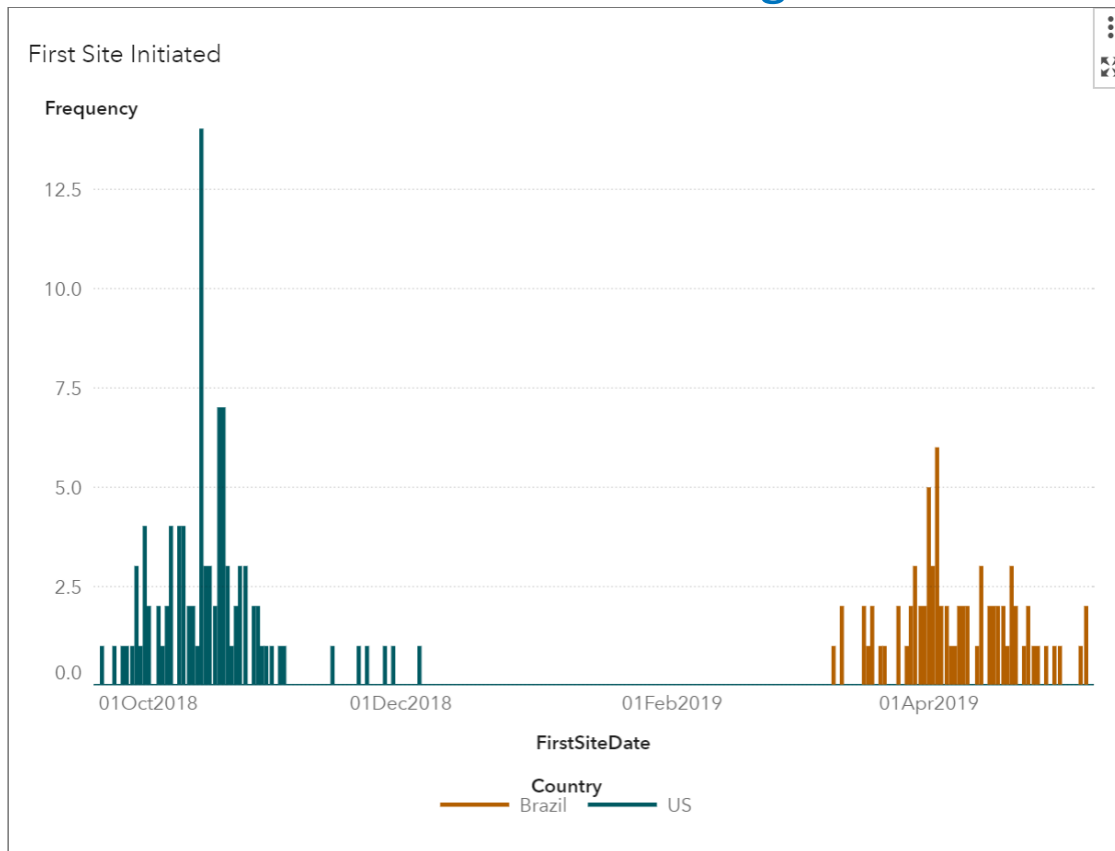
Simulation Results

Enrollment Variability

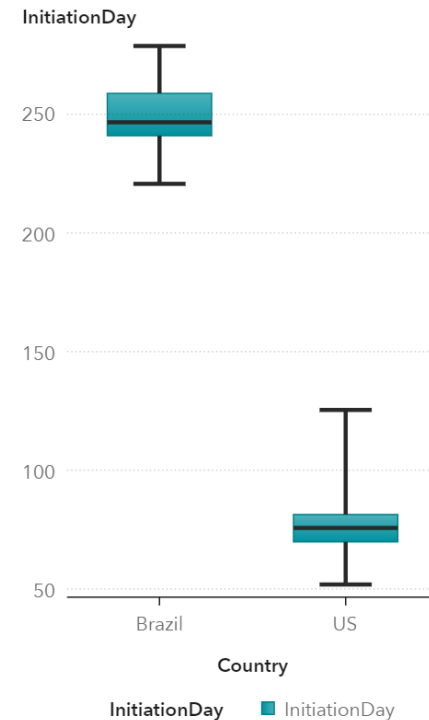


Simulation Results

Target Dates



InitiationDay by Country



Target Dates



Simulation Results

Milestone Tables

Study Milestones By Replication:																		
Country	Site	Number Screened	Number Enrolled	Screen Failure Rate	Number Completed	Percent Completed	Number Withdrawn Consent	Number Lost to Follow-Up	Date First Patient Screened	Date Last Patient Screened	First Patient First Visit	Last Patient First Visit	Last Patient Last Visit	Enrollment Period (Months)	Total Study Length (Months)	Screening Cost	Cost of Enrolled Patients	Total Cost
Replication #1:																		
US	Derry Medical Center	78	66	15.4%	55	83.3%	1	10	30NOV2017	09AUG2018	01DEC2017	10AUG2018	21NOV2018	12.3	15.7	\$156,000	\$484,000	\$640,000
US	Heisenberg Medical Center	67	59	11.9%	53	89.8%	0	6	18SEP2017	03AUG2018	19SEP2017	02AUG2018	13NOV2018	12.0	15.4	\$134,000	\$442,667	\$576,667
US	Lassen General Hospital	73	64	12.3%	55	85.9%	1	8	26NOV2017	06AUG2018	27NOV2017	07AUG2018	18NOV2018	12.2	15.6	\$146,000	\$468,000	\$614,000
US	Princeton - Plainsboro	76	66	13.2%	55	83.3%	1	10	16DEC2017	07AUG2018	17DEC2017	08AUG2018	19NOV2018	12.2	15.6	\$190,000	\$505,750	\$695,750
US	Sacred Heart	95	82	13.7%	70	85.4%	1	11	10JAN2018	03AUG2018	11JAN2018	04AUG2018	15NOV2018	12.1	15.5	\$190,000	\$758,333	\$948,333
US	Shasta Regional Hospital	64	52	18.8%	47	90.4%	1	4	16DEC2017	05AUG2018	17DEC2017	06AUG2018	17NOV2018	12.2	15.5	\$160,000	\$363,750	\$523,750
US	St. Eligus Hospital	100	90	10.0%	75	83.3%	0	15	13DEC2017	04AUG2018	14DEC2017	05AUG2018	16NOV2018	12.1	15.5	\$300,000	\$747,000	\$1,047,000
US	Tower Medical Group	105	91	13.3%	81	89.0%	1	9	31OCT2017	29JUL2018	01NOV2017	30JUL2018	10NOV2018	11.9	15.3	\$210,000	\$599,667	\$809,667
US	Twin Pines Medical Center	141	122	13.5%	105	86.1%	3	14	31JAN2018	07AUG2018	01FEB2018	04AUG2018	13NOV2018	12.1	15.4	\$352,500	\$857,500	\$1,210,000
US	Western Regional Hospital	119	108	9.2%	99	91.7%	2	7	05NOV2017	07AUG2018	06NOV2017	08AUG2018	19NOV2018	12.2	15.6	\$119,000	\$679,250	\$798,250

Simulation Results

Individual Replication Results



Simulation Results

Scenario Comparisons

Enroll Time (Months)

14.7
14.0
12.0
10.0
8.0
6.3

US with Brazil

Cardio US Only

Simulating Enrollment Plans

Conclusion

- Enrollment Estimation is well-suited for simulation
 - Parameters are readily available
 - Adds value to the process
- Simulation provides deeper insights
 - Understanding of variability
 - Distributions of hitting targets
 - Simulated trial activity for other usage



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