

The Use of @RISK for MS Project in Biopharmaceutical Schedule Risk Assessment, Team Building and Strategic Planning

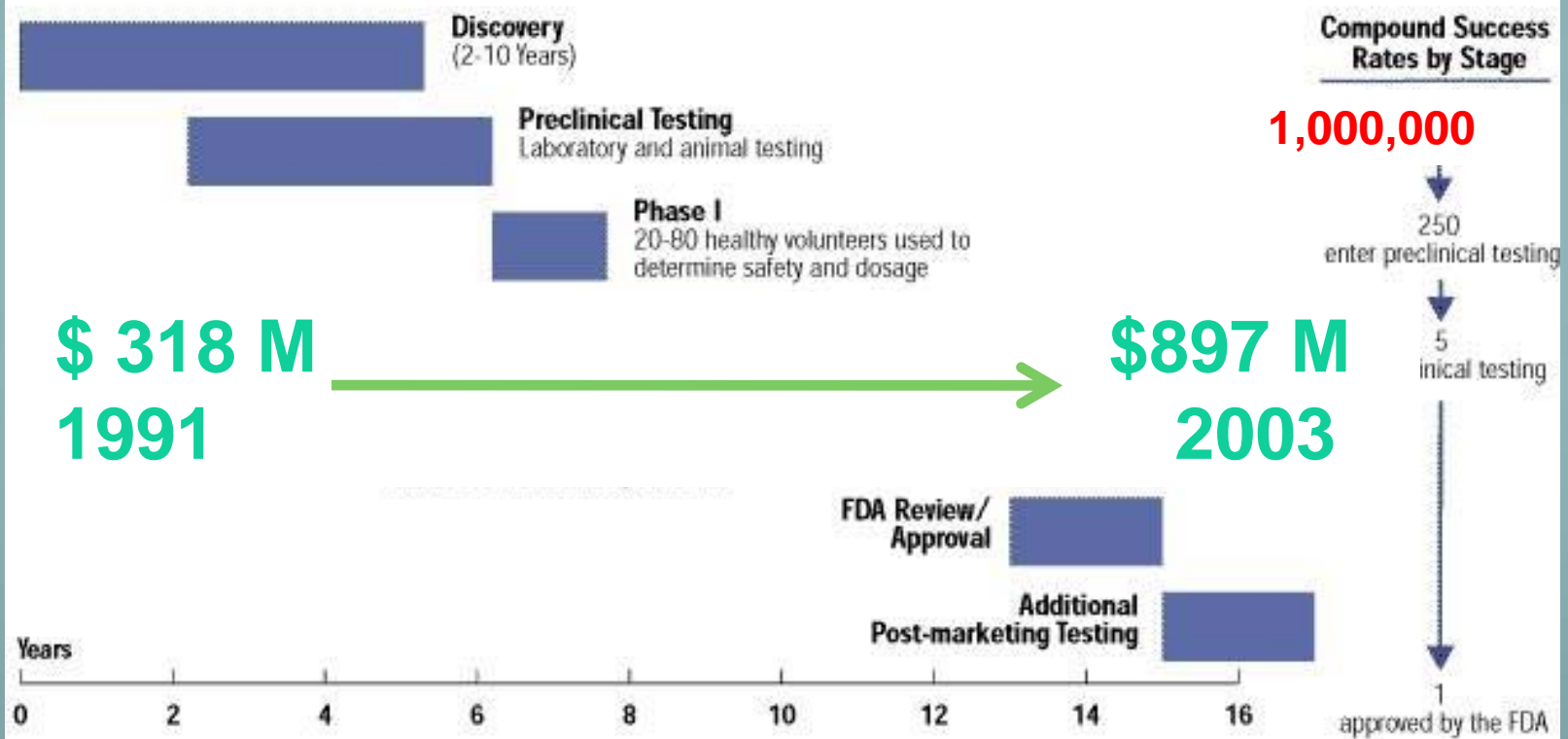
Palisade
Health Risk Analysis Forum
San Diego
March 31, 2010

Introduction

- Discovery to commercialization of biopharmaceutical products requires a complex integration of several disciplines
- Each discipline has inherent technical challenges
- @Risk for MS Project provides a measurable evaluation of overall project time and cost risk.
- Building a project model is useful for team building
- Timeline risk analysis and interpretation can illuminate options for portfolio and strategic decisions

Drug Development Statistics

Figure 3-1
COMPOUND SUCCESS RATES BY STAGES



Source: PhRMA, based on data from Center for the Study of Drug Development, Tufts University, 1995.



Drug Development Risk Analyses

- Drug development technical and timeline risk are unlike other industries e.g., construction or consumer goods
 - Longer timelines, high uncertainty at each step
 - Fewer “check points”
- Other systems are effective in analyzing specific activities
 - Earned Value Management System (EVMS) for manufacturing, contract monitoring
 - Decision Tools components for financial decisions and clinical trial planning

Stakeholders

- Internal
 - Project teams
 - Senior Management
 - Portfolio planners
- External
 - Investors/Shareholders
 - Granting agencies
 - Small Business Innovation
 - Department of Defense, DOE, DARPA, other federal agencies
 - NIH
 - Public (consumers)

Company Value of Modeling

- Start-ups
 - Stronger proposals to encourage investment
 - Better projections of development cost probabilities
 - Resource planning
- “Big Pharma”
 - Portfolio planning
 - Public relations
 - Internal resource logistics



Project Planning

- Integrated Project Plan
 - Assumptions
 - Milestones
 - Target product profile
 - Baseline Costs
- **Integrated Project Schedule**
 - Links activities to generate critical path
 - @Risk for MS Project simulations transmogrifies technical risk to statistical distributions



Integrated Project Schedule

- Project Team Value
 - Integrates functional activities
 - Quantifies anticipated uncertainties
 - Team members buy into the model because they provide the assumptions
 - Promotes team cohesion
 - Better understanding of functional challenges
 - Better cooperation and hand-offs
 - Enhanced credibility with Senior Management
 - In later development stages model can be adjusted to actual performance

The Project Team

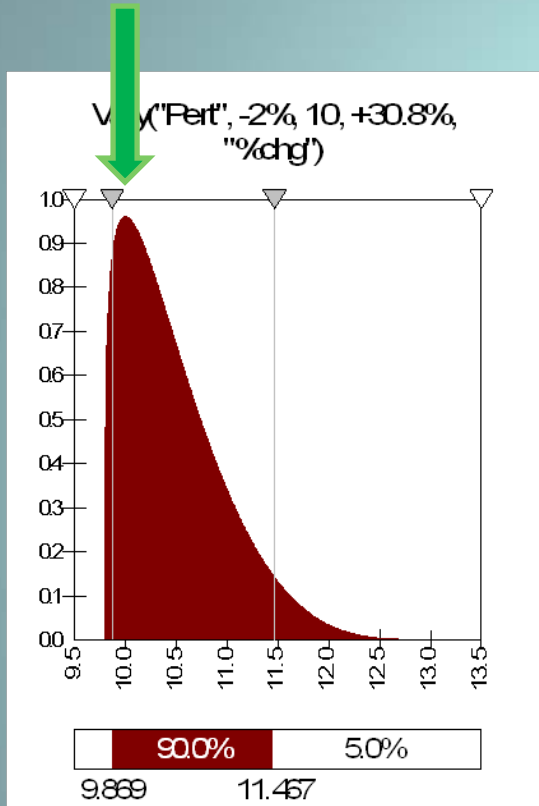
- **Project Manager/Leader**
- **Chemistry, Manufacturing, and Controls**
 - Manufacturing
 - Formulations
 - Quality Assurance/Control
- **Nonclinical**
- **Clinical**
- **Regulatory**
- **Research**
- **Sometimes**
 - Marketing
 - Finance/Portfolio Management
 - Business Development

CMC

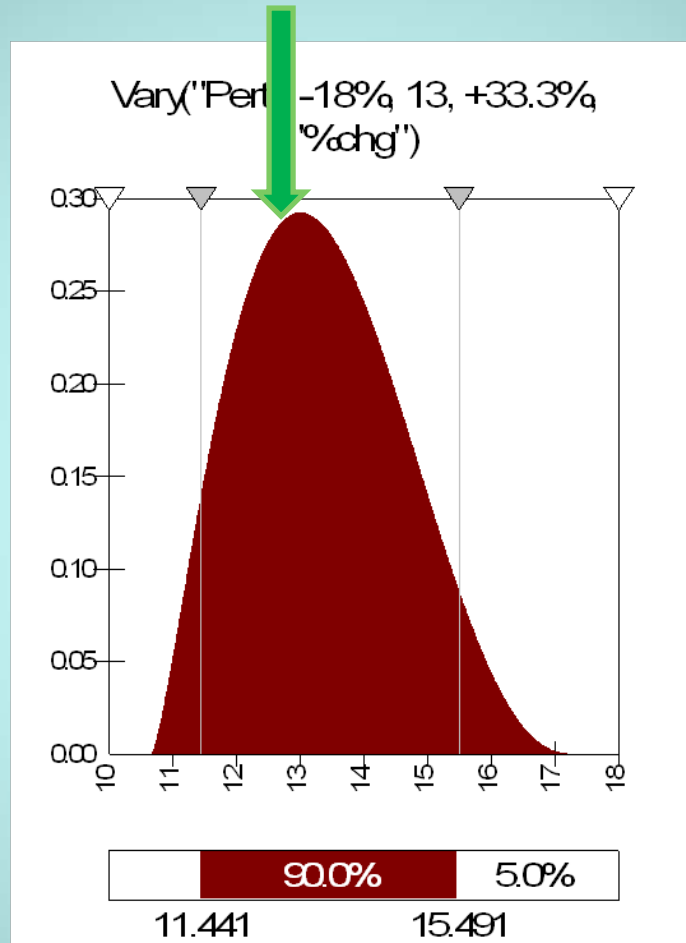
- Manufacturing of Active Product Ingredient (API)
 - Uncertainty at several stages of scale up and chemistry changes
 - Can take 9 weeks to 9 months to produce one batch
 - Each change in production must be validated by QA , which requires methods development
 - Critical Path to clinical and commercial supplies
 - API ultimately goes through formulations and delivery development that have their own risks

MS Project Plan

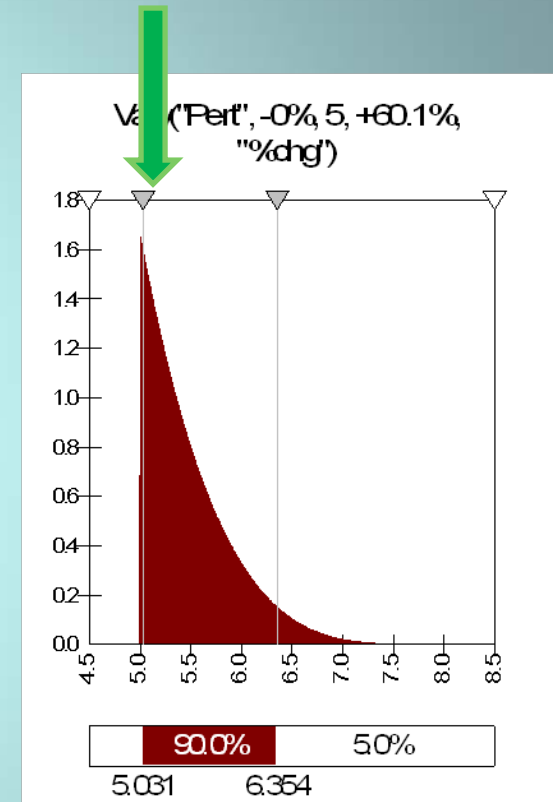
CMC



Raw Materials

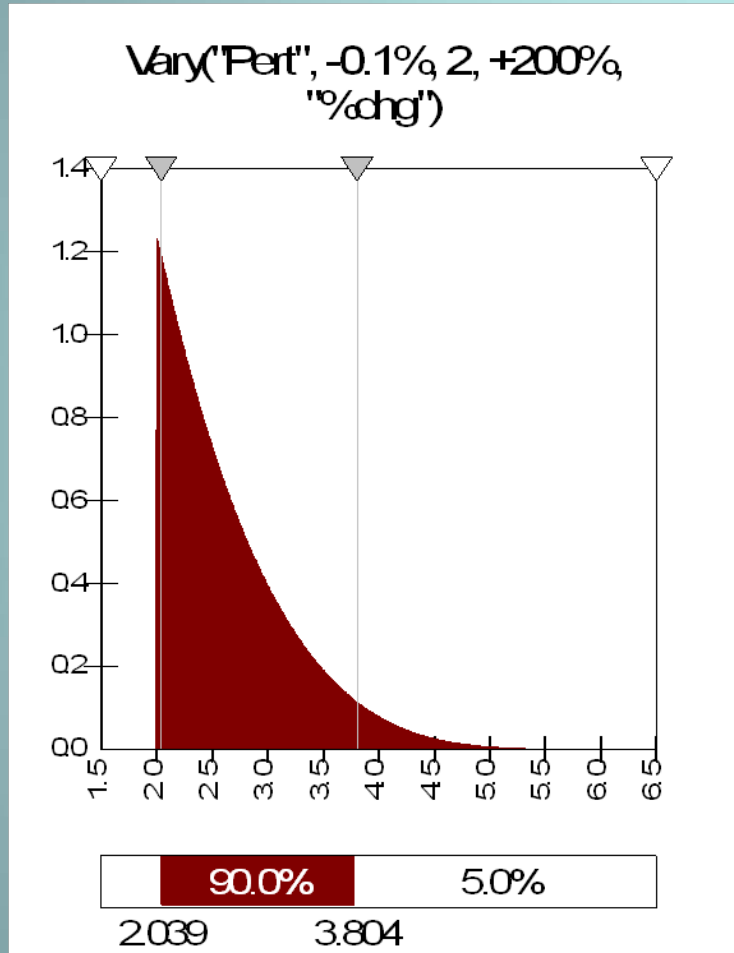


7 Kg Scale



Formulation

Nonclinical (Toxicology)



Weeks

Draft Study Reports

- Incorporates uncertainty in histopathology and interpretation reconciliation
- Integrating labs, histopathology, and clinical observations



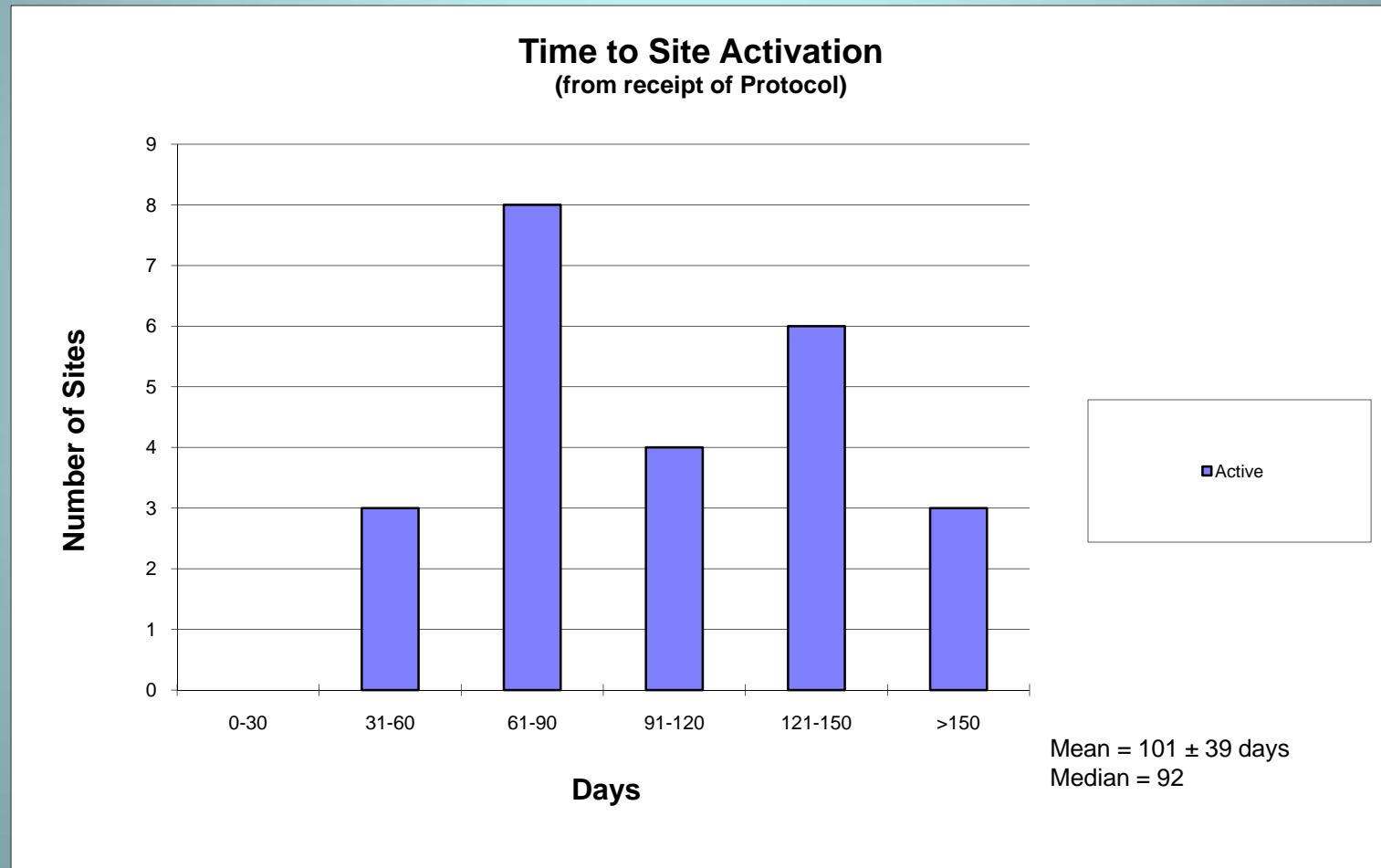
Advantages of Modeling Clinical Studies

- Clinical study enrollment is usually the most uncertain variable and correlates strongly to the overall timeline
- Patient terminations from studies
 - Usual assumption is that patients stay on for the entire treatment duration – modeling allows for probabilities of attrition
 - E.g., oncology patients stay on study until progression or adverse events – difficult to forecast drug supply

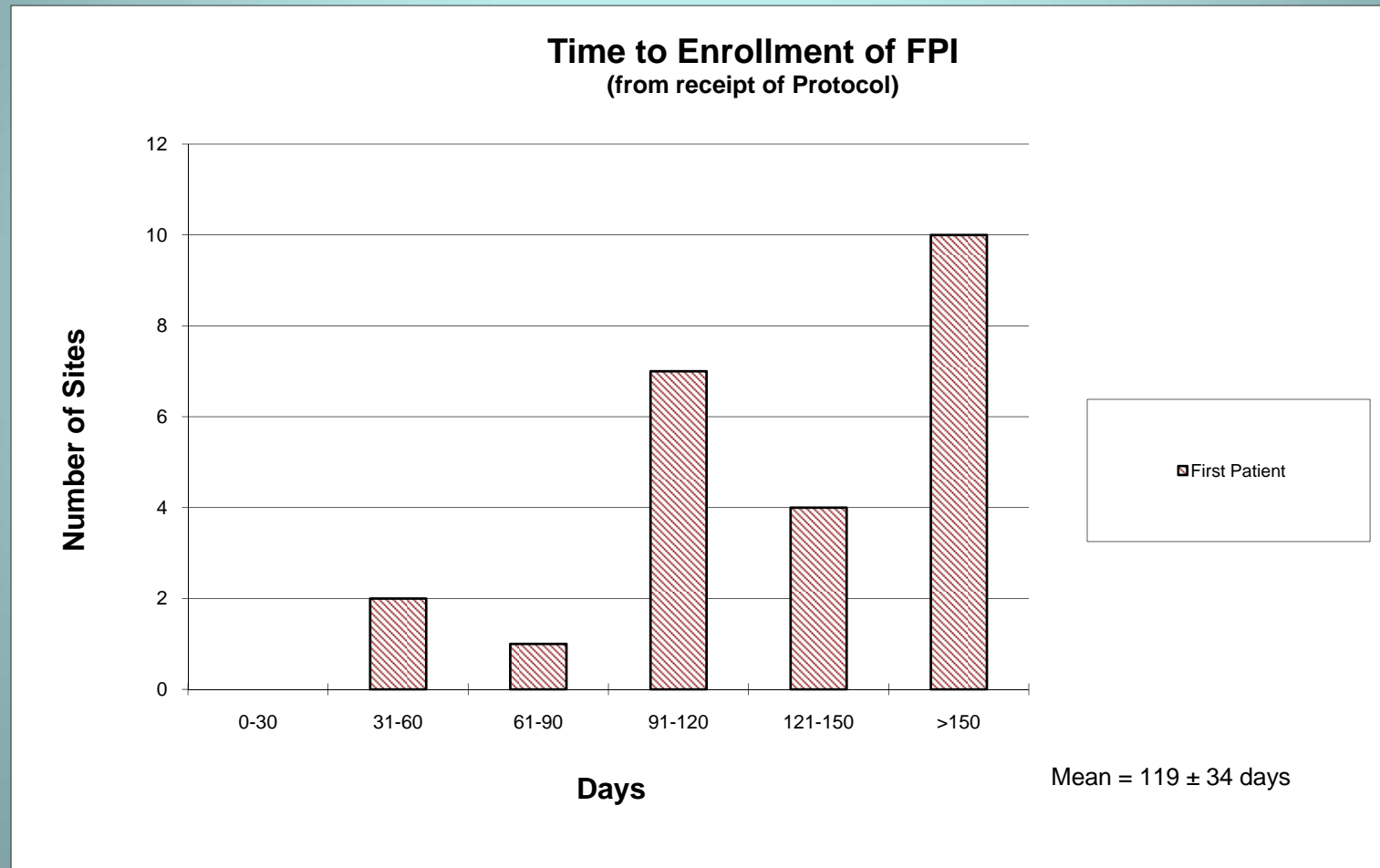
Clinical Operations

- Example from a 24-site clinical study
- All sites in the US
- Sites were academic and private practice
- To activate a site and start enrollment
 - Protocol and Informed Consent approved by Ethics Committee
 - Contracts in place with investigators
 - Recruitment of patients

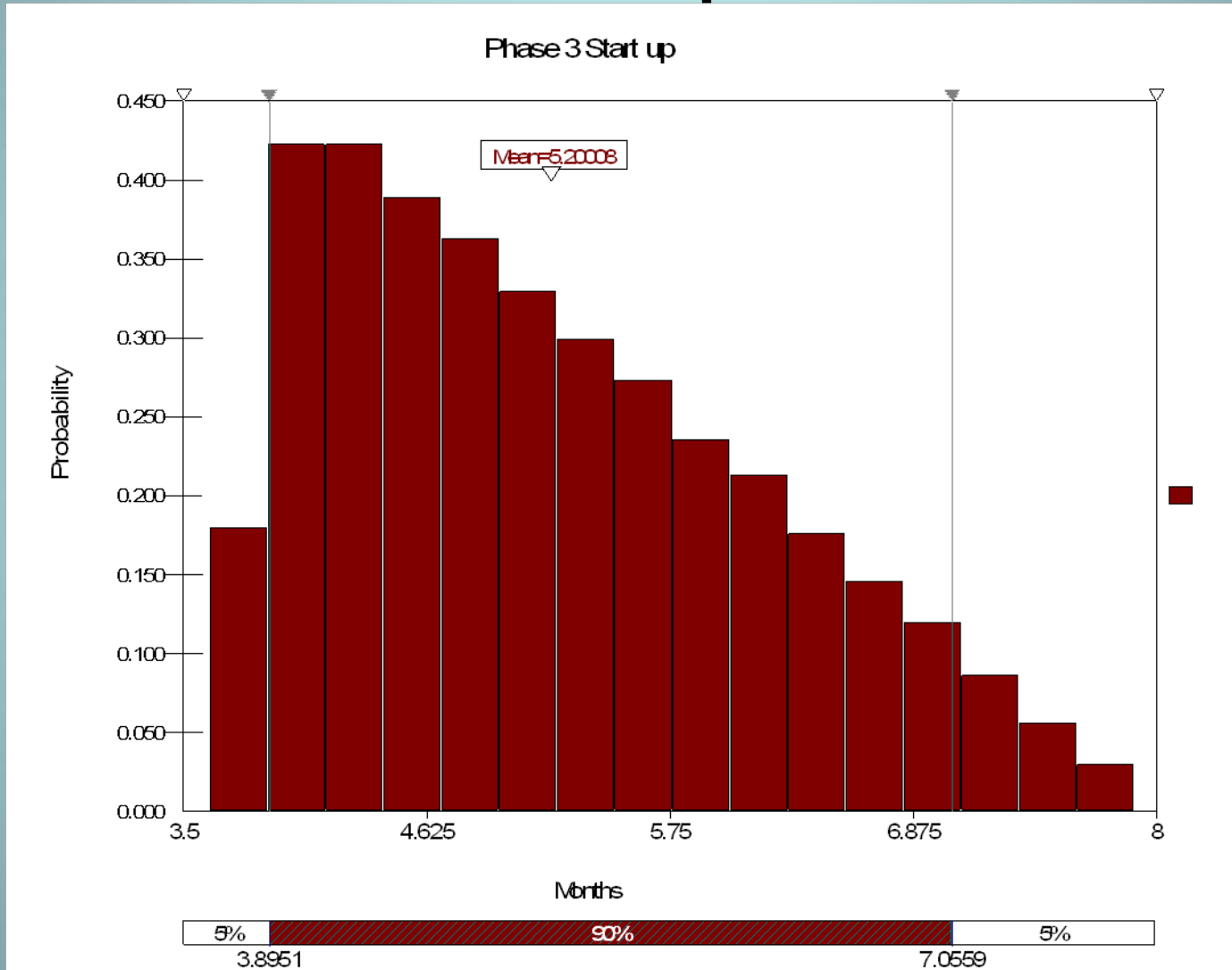
Clinical Start up



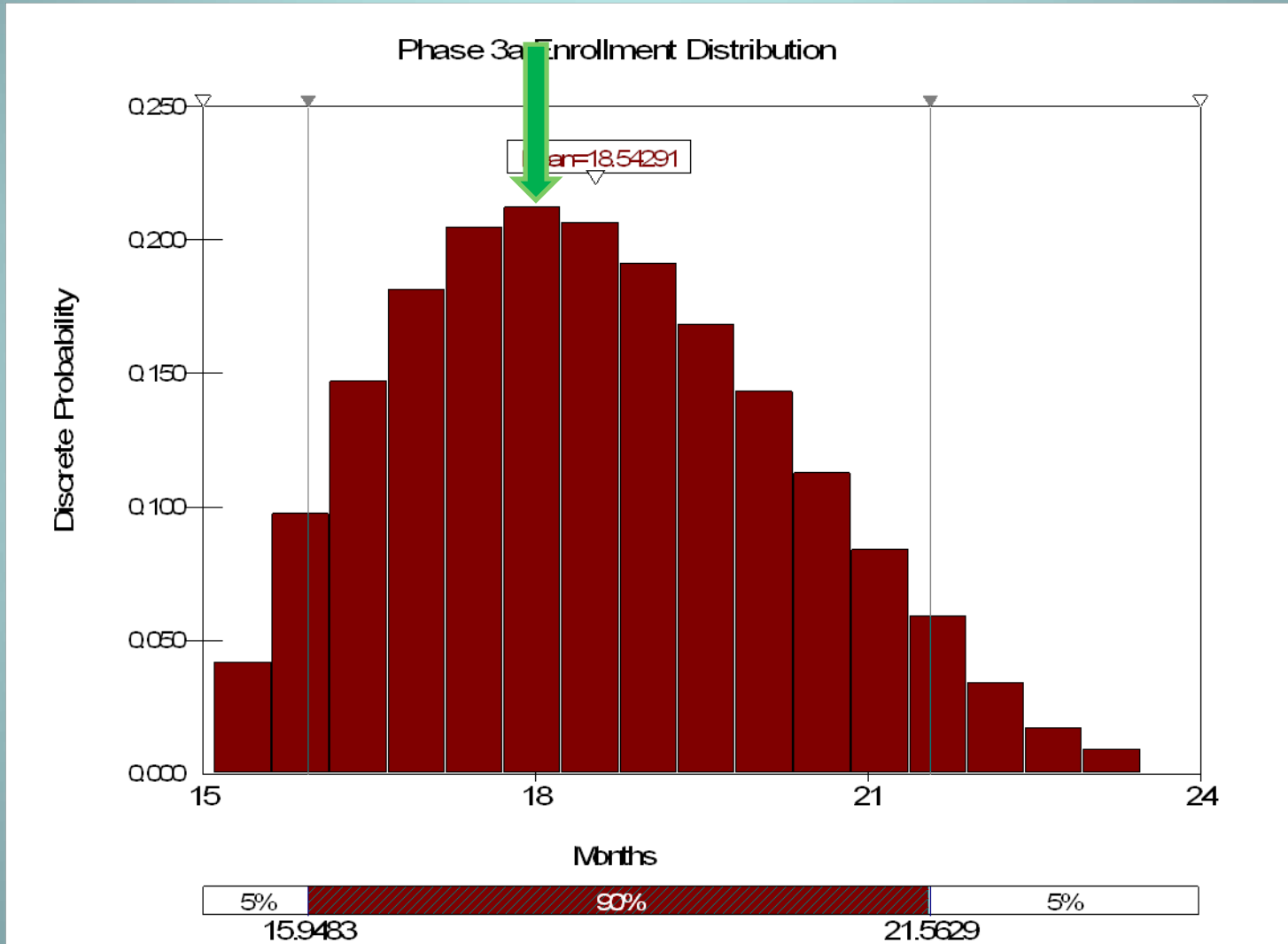
Clinical Start up



Phase 3 Start Up Distribution



Example for Phase 3



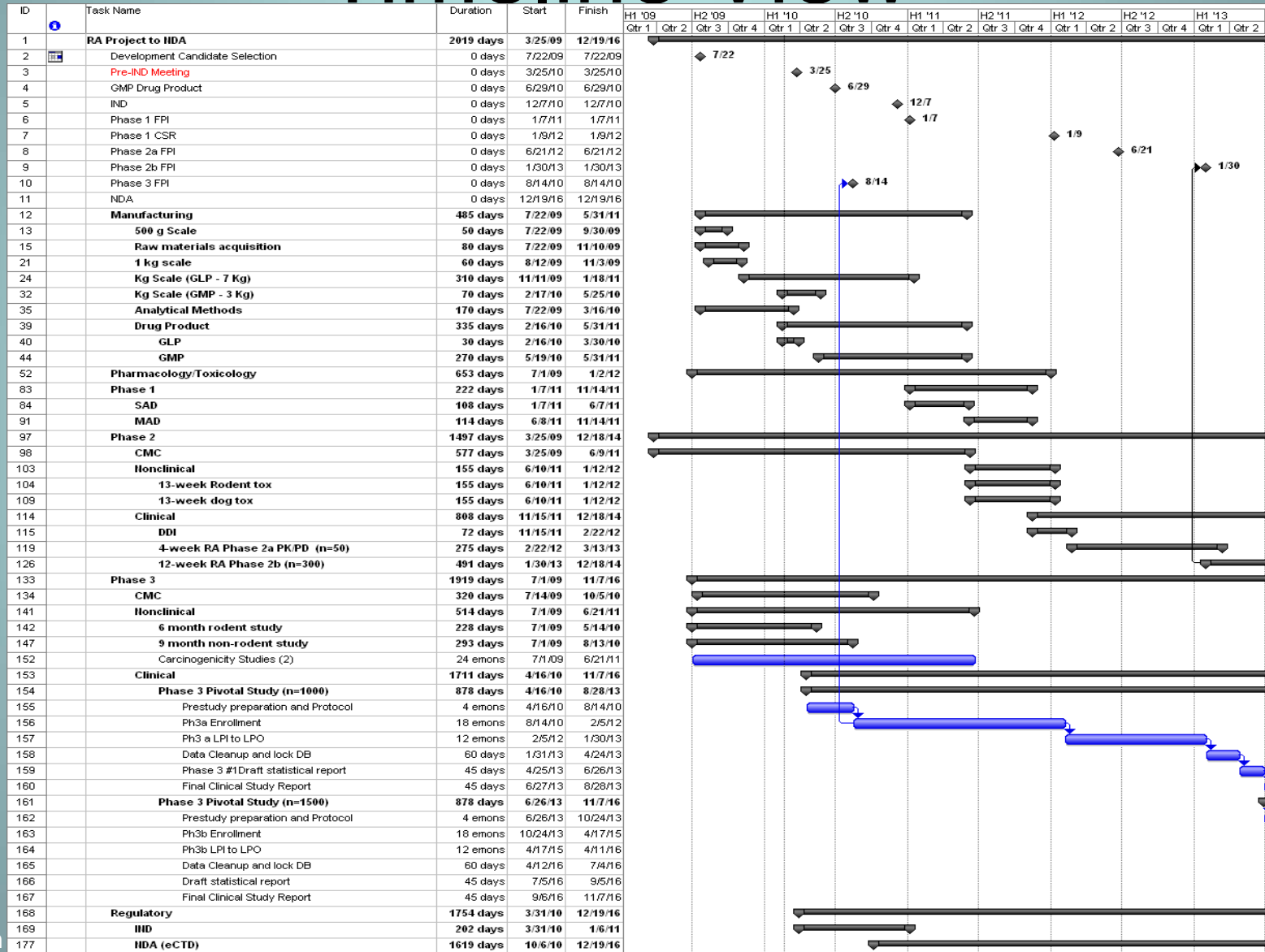
Example Case

- Drug being developed for Rheumatoid Arthritis
- Lead compound identified to start IND-enabling tox
- Current manufacture scale – 500 g
- Will require several Phase 1 and Phase 2 studies
- Will require at least one Phase 3 study
- Commercial manufacture will be on the order of 5 metric tons/batch

Major Milestones for Example

- **Chemistry, Manufacturing, and Controls**
 - Clinical drug supply will be available June 2010
- **Nonclinical**
 - Short-term (3 months) tox to support Phase 2 in January 2012
 - Phase 3 supporting tox in May and August 2010
- **Clinical**
 - Phase 1s complete in November 2011
 - Phase 2s done by December 2014
 - Phase 3a done by August 2013
 - Phase 3b (if needed) done by November 2016
- **Regulatory**
 - IND filed December 2010
 - NDA filed in December 2016

Timeline View



March

Clinical/Regulatory Scenarios

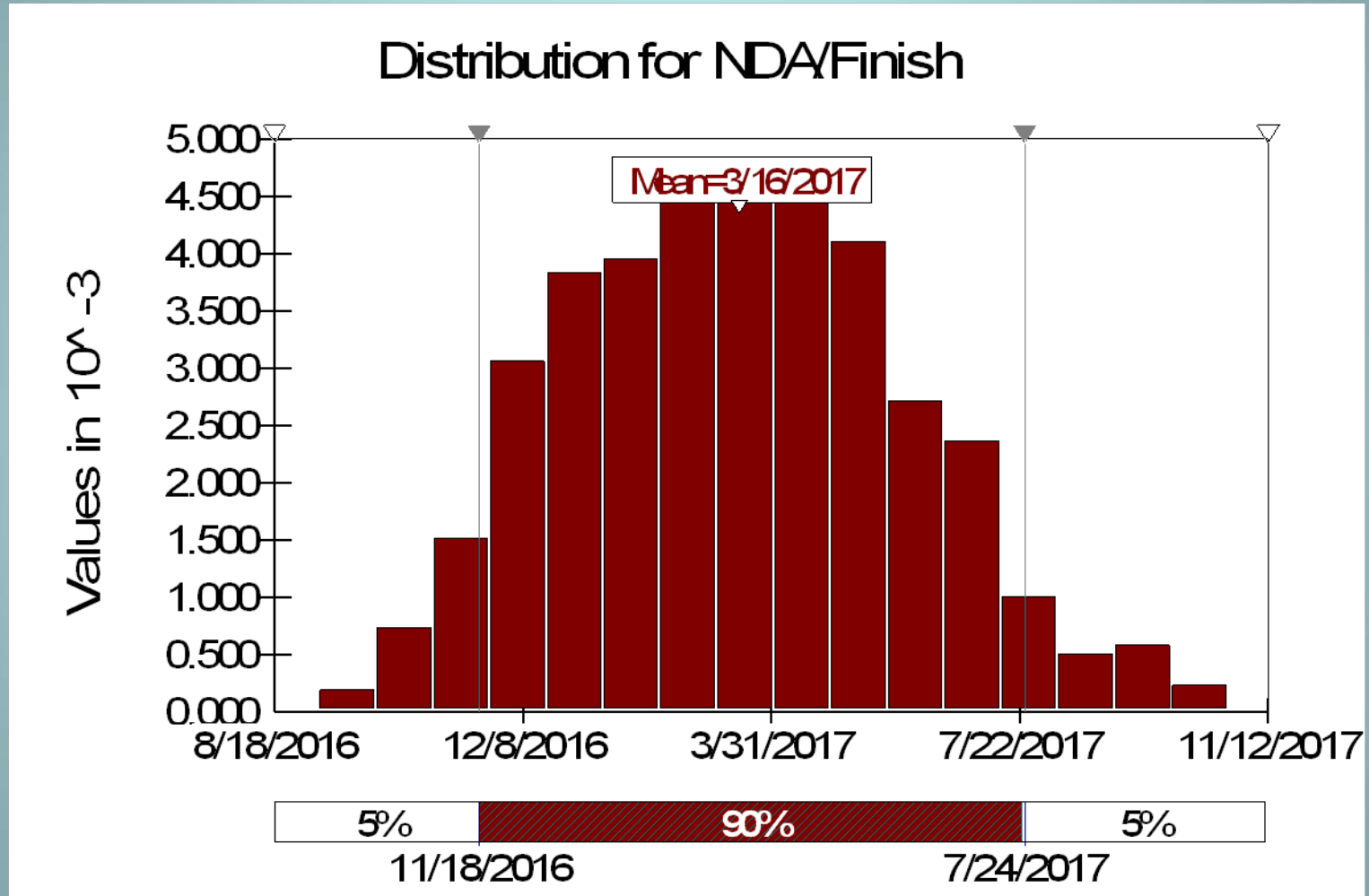
- Base Case – MS Project
- Base Case with @Risk
 - Assumes two Phase 3 studies
- Branched Case with @Risk
 - Provides for some probability that only one Phase 3 will be needed
- Branched and adjusted with @Risk
 - Provides for possibility of one study AND that a faster enrollment in the first Phase 3 predicts faster enrollment in the second Phase 3, if needed



Major Model Assumptions for Clinical Studies

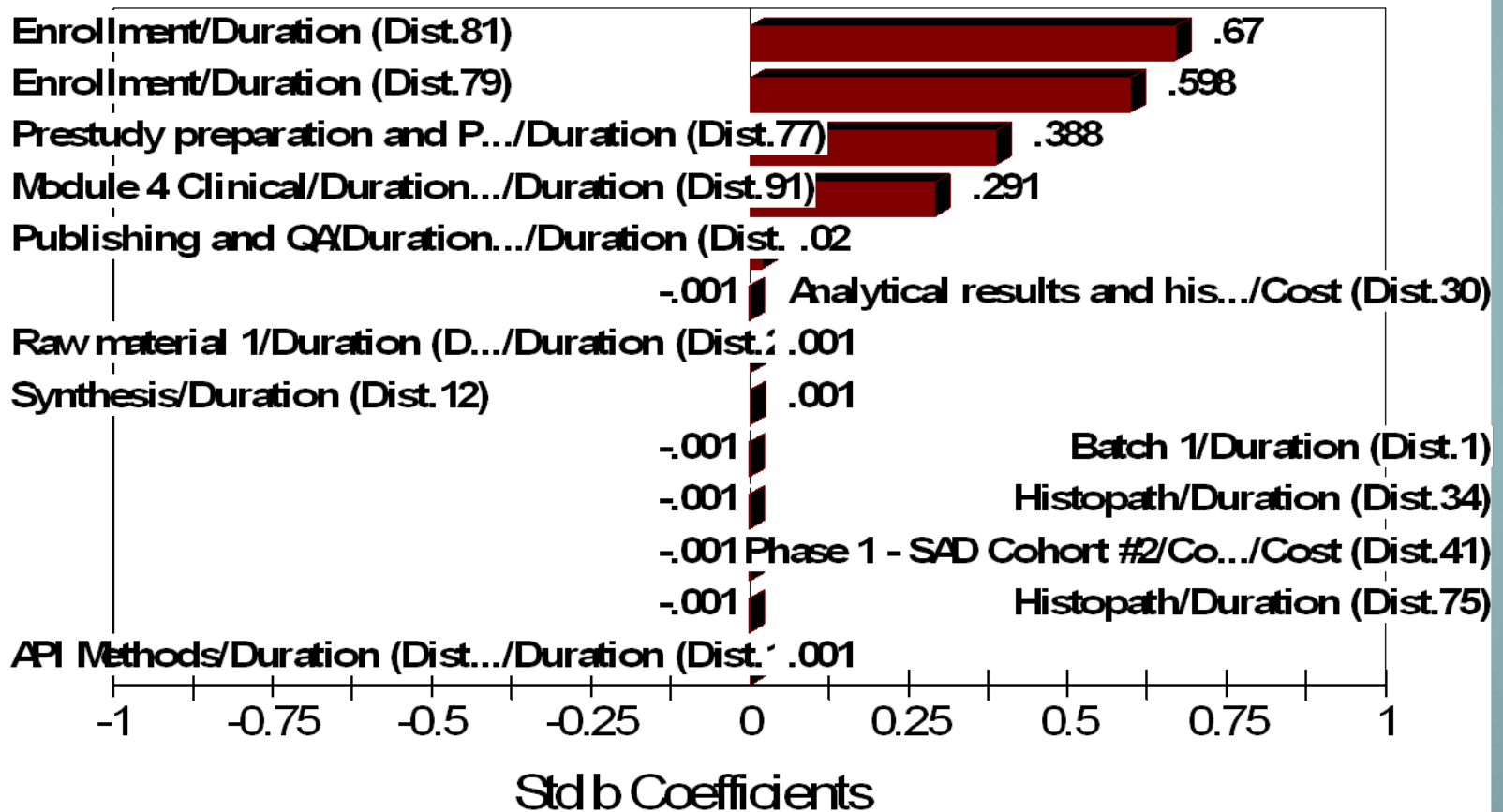
- Modeling allows scenarios
 - Probabilistic branching for this example
 - 0.3 probability a single Phase 3 study will suffice – branches to NDA
 - 0.7 probability that a second Phase 3 will be needed – branches to a second study
 - If/Then branching
 - In this example, if the first Phase 3 study enrollment is faster than planned (<12 months), then the second Phase 3 study enrollment is reduced from 18 to 14 months in the simulation
- Last Patient In (LPI) to Last Patient Out (LP) is defined treatment duration in protocols – could also model for early terminations.

“Simple” Model – Base Case



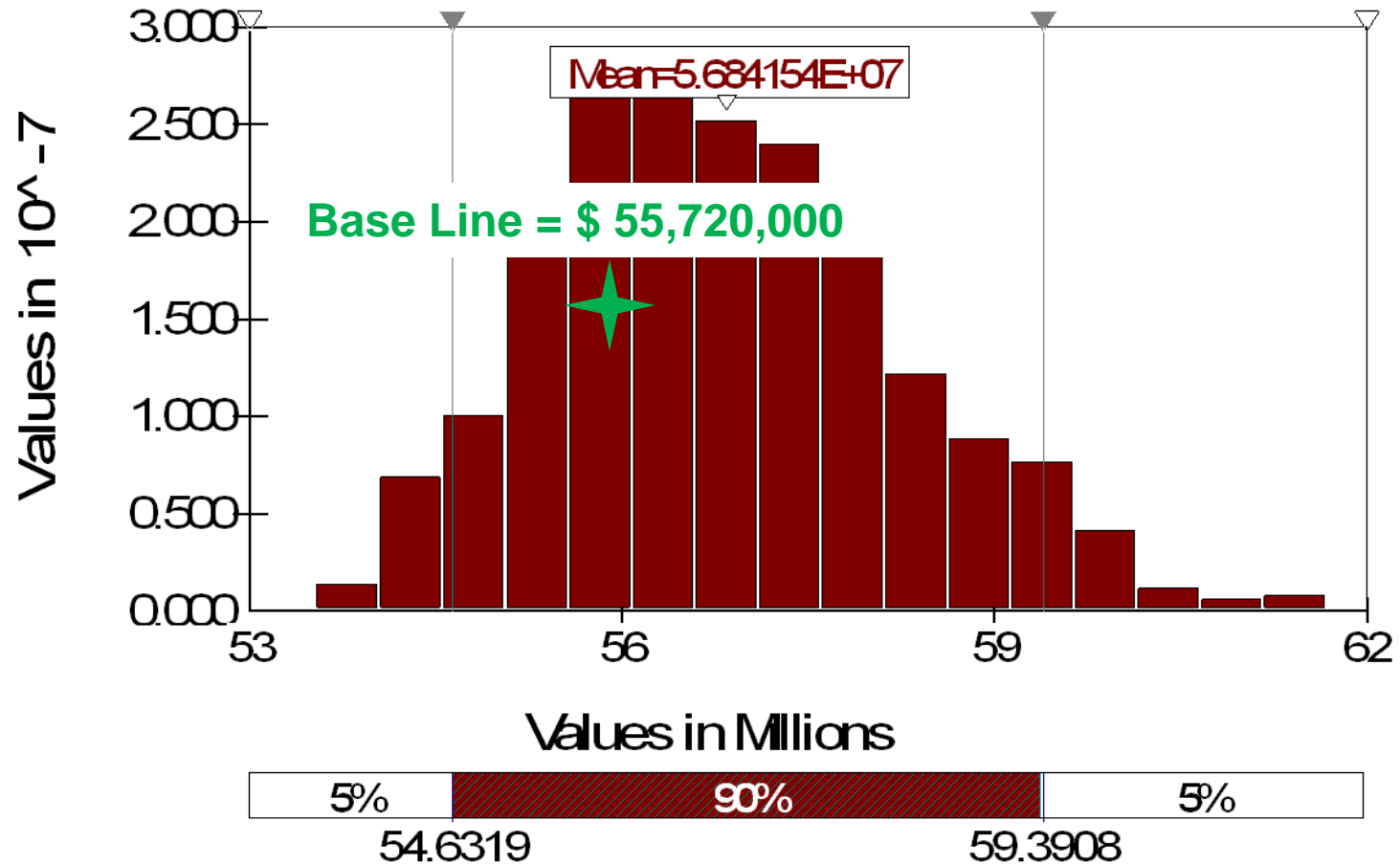
Sensitivity: "Simple" Model

Regression Sensitivity for NDA/Finish

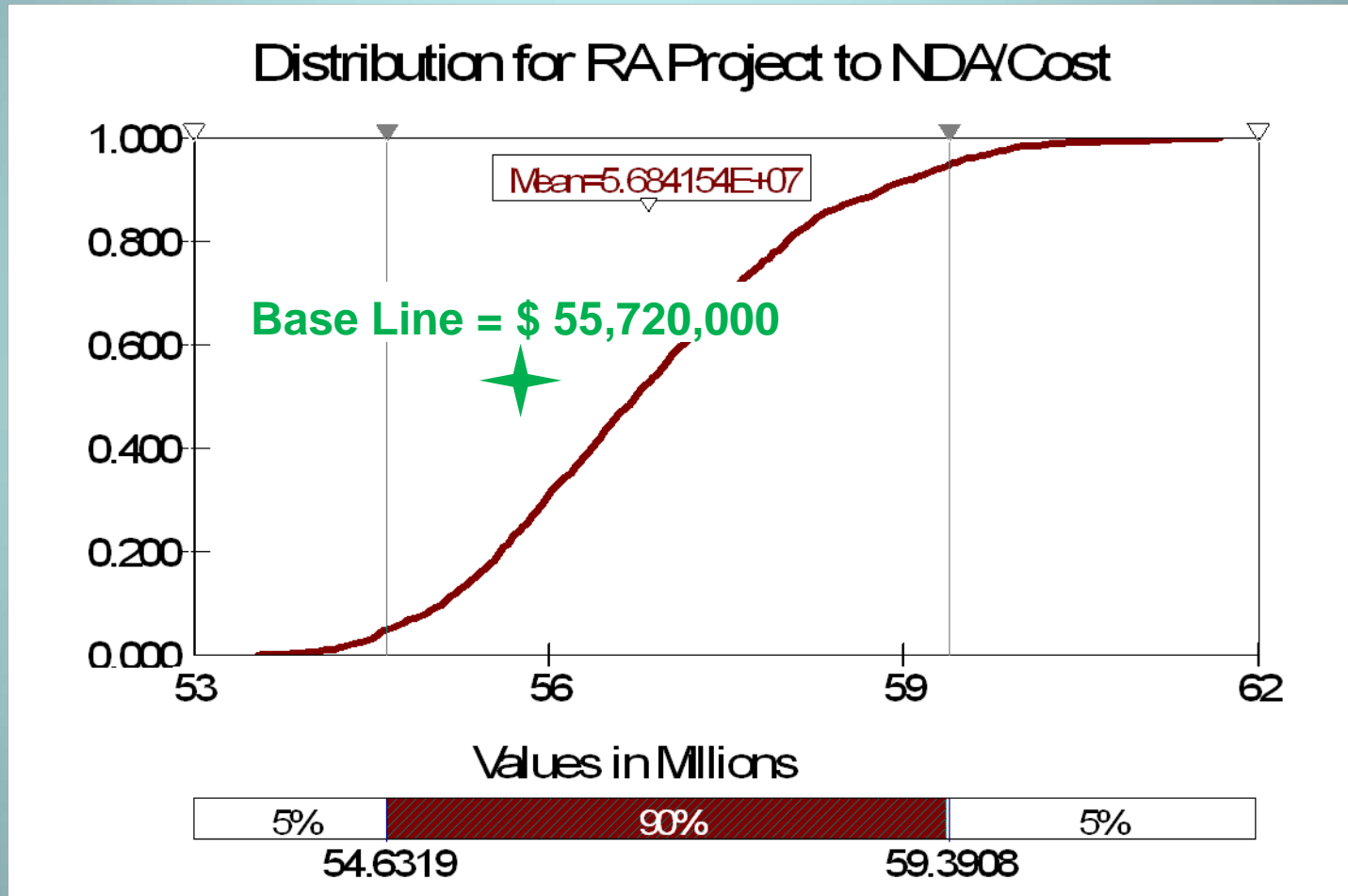


Costs: "Simple" Model

Distribution for RA Project to NDA/Cost



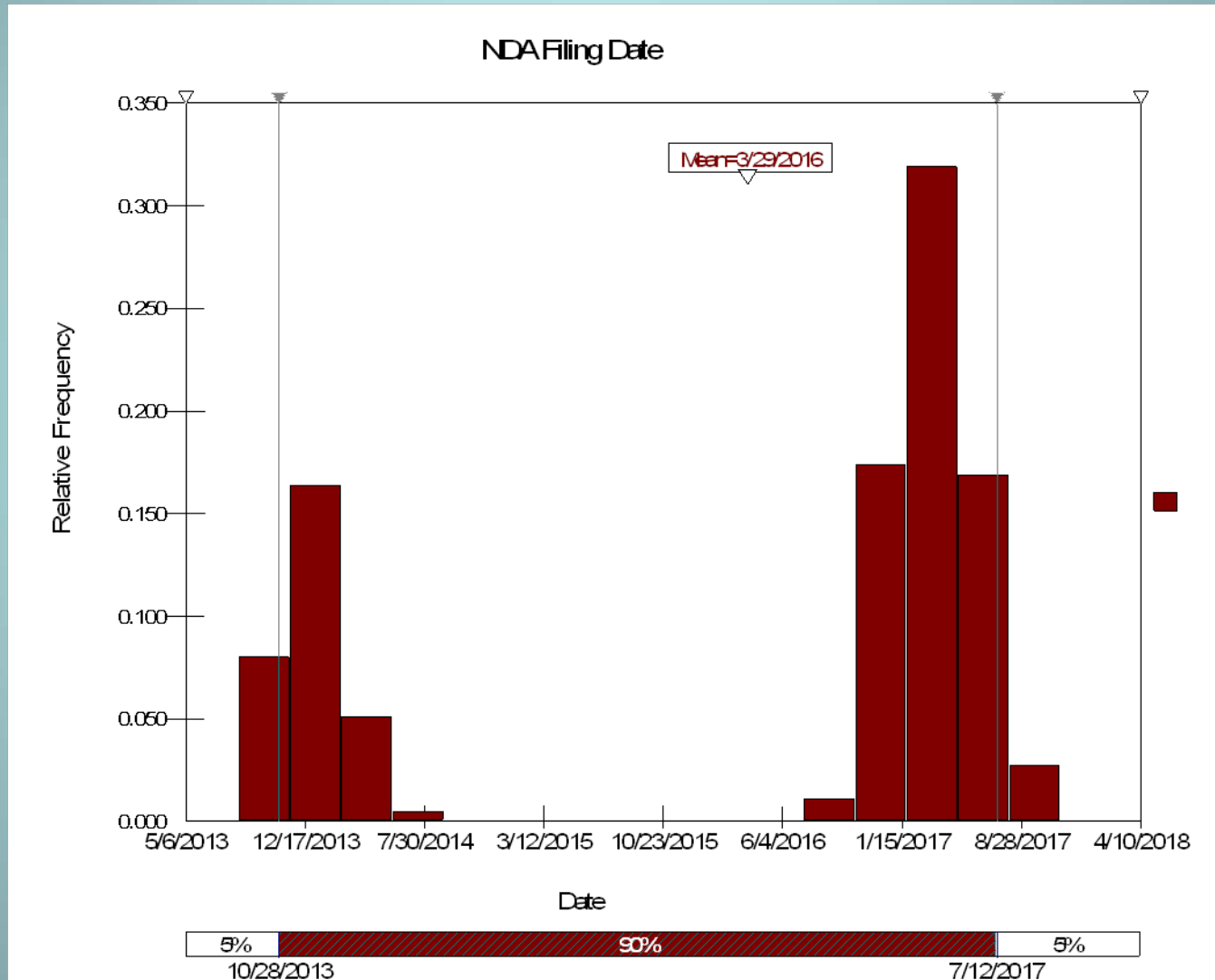
Costs: "Simple" Model



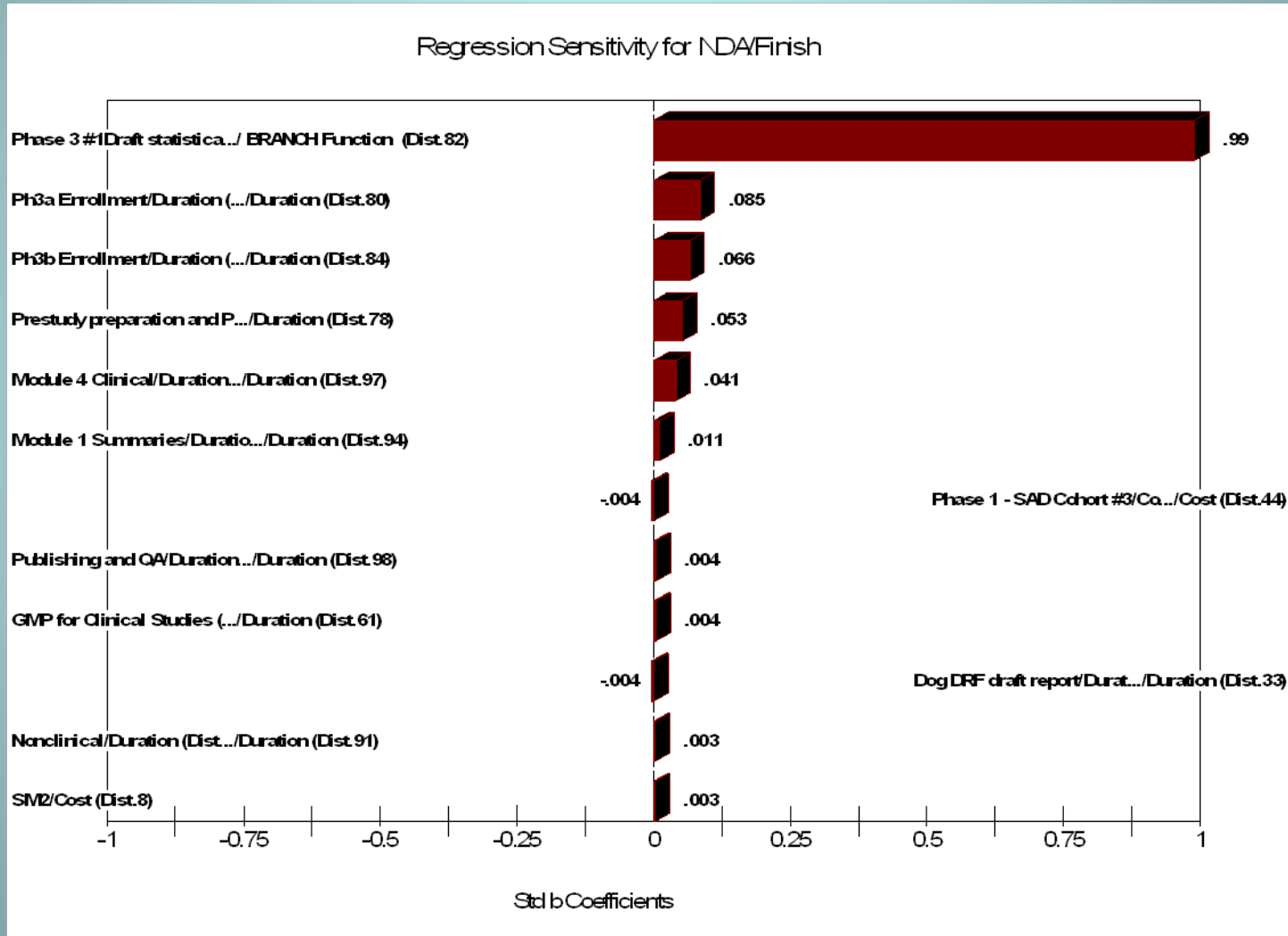
Branching Model

- Assumes that FDA will require a second Phase 3 study (probability of 70%)
- Won't start this study until the first Phase 3 has been preliminarily analyzed
- Utility of data:
 - Timing of financing that may be necessary
 - Partnering decisions

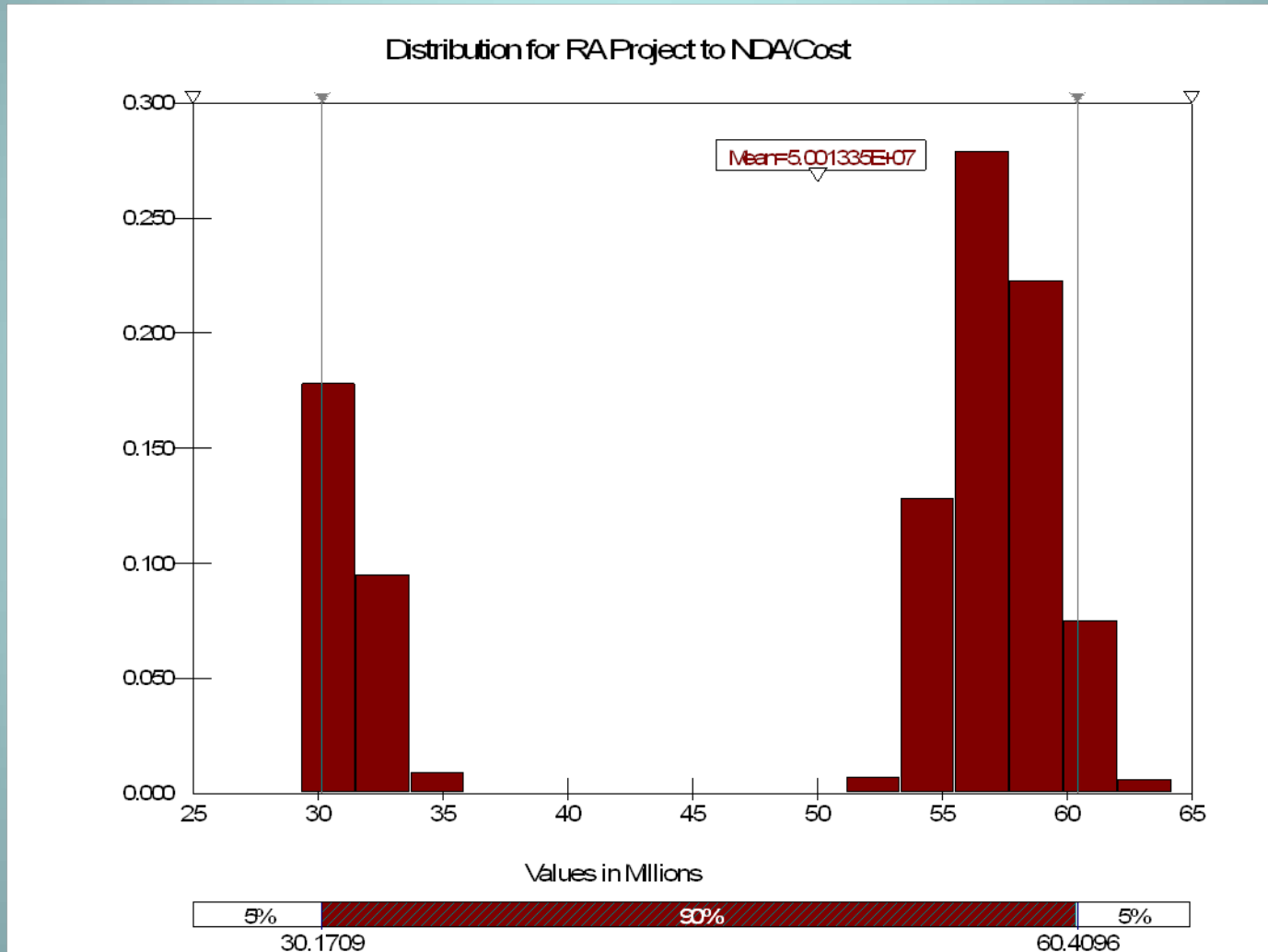
Simulation with Branches



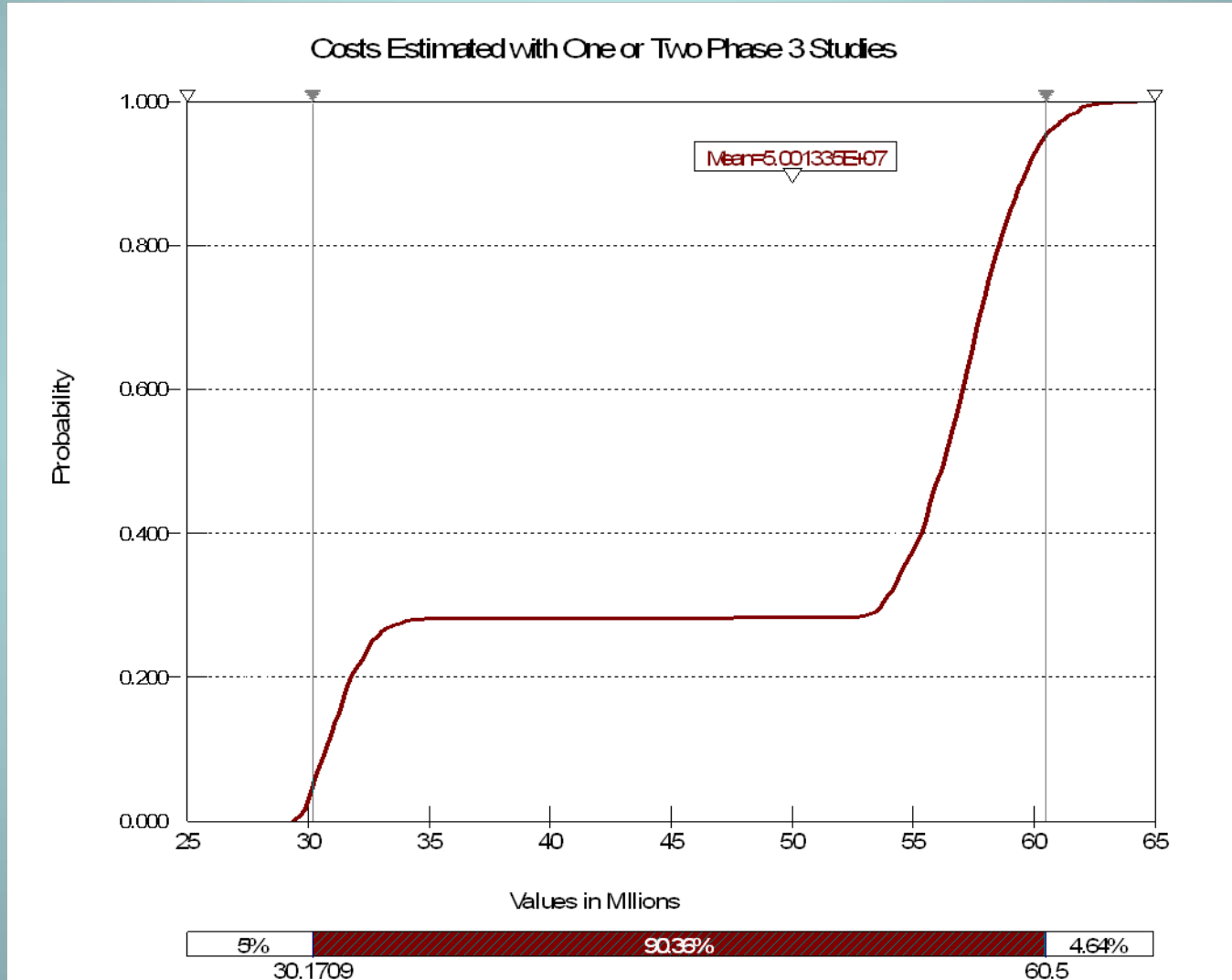
Sensitivity: Simulation with Branches



Cost: Simulation with Branches



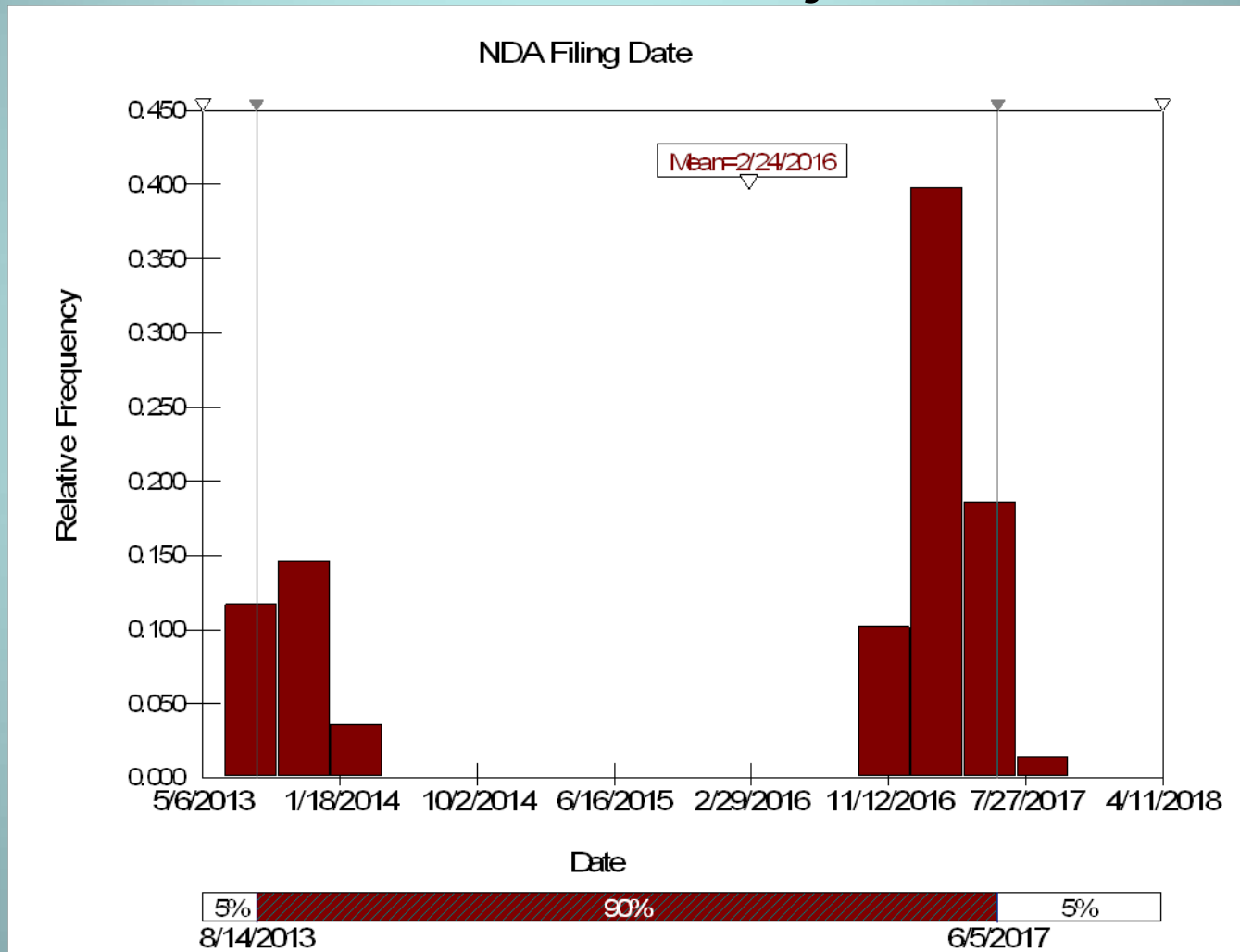
Cost: Simulation with Branches



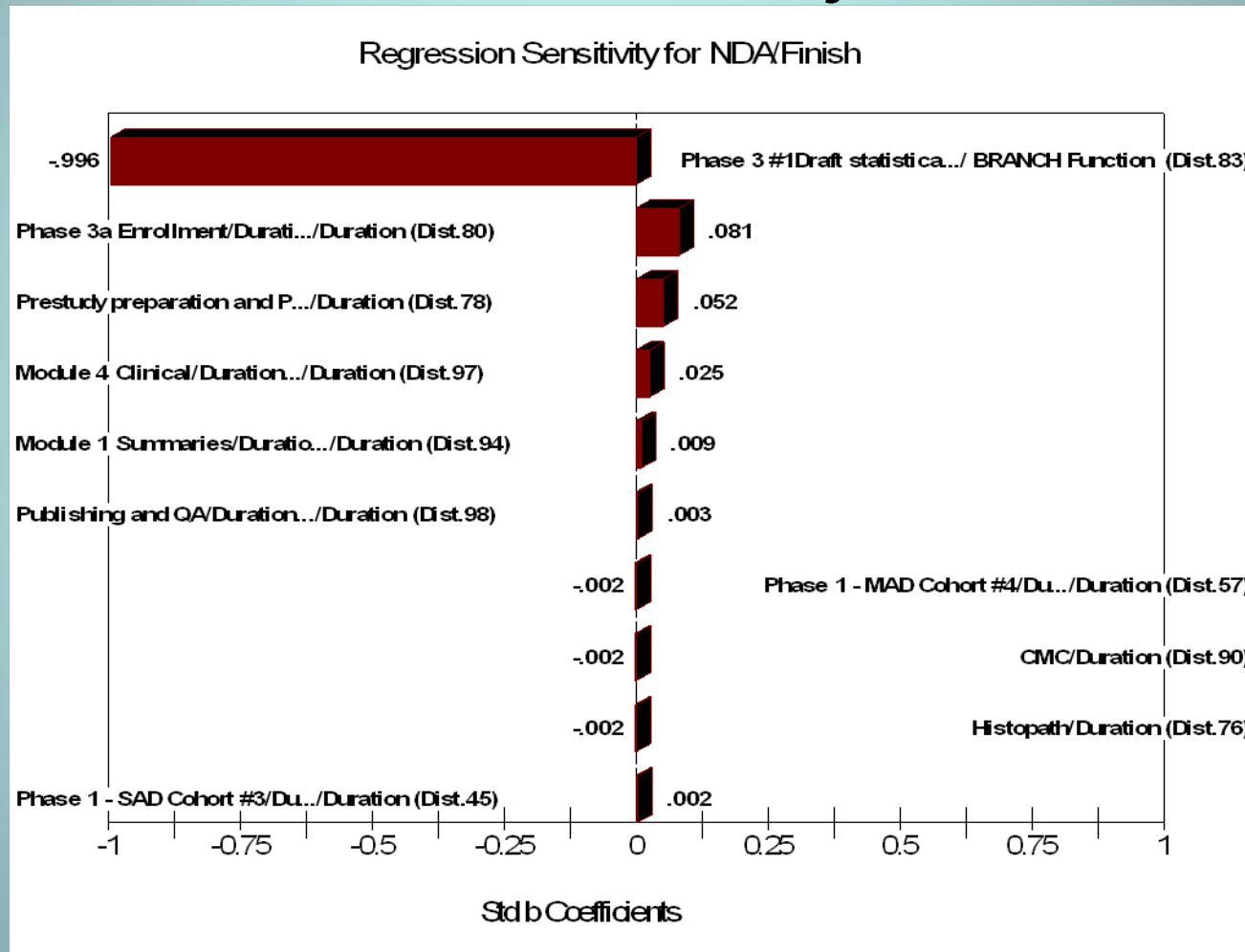
Branched Simulation with Enrollment Adjustment

- Assumes that FDA will require a second Phase 3 study (probability of 70%)
- Won't start this study until the first Phase 3 has been preliminarily analyzed
- If Phase 3a enrolls faster, then adjusts the Phase 3b study enrollment
- Utility of data:
 - Site selection and operations
 - Timing of financing that may be necessary
 - Partnering decisions

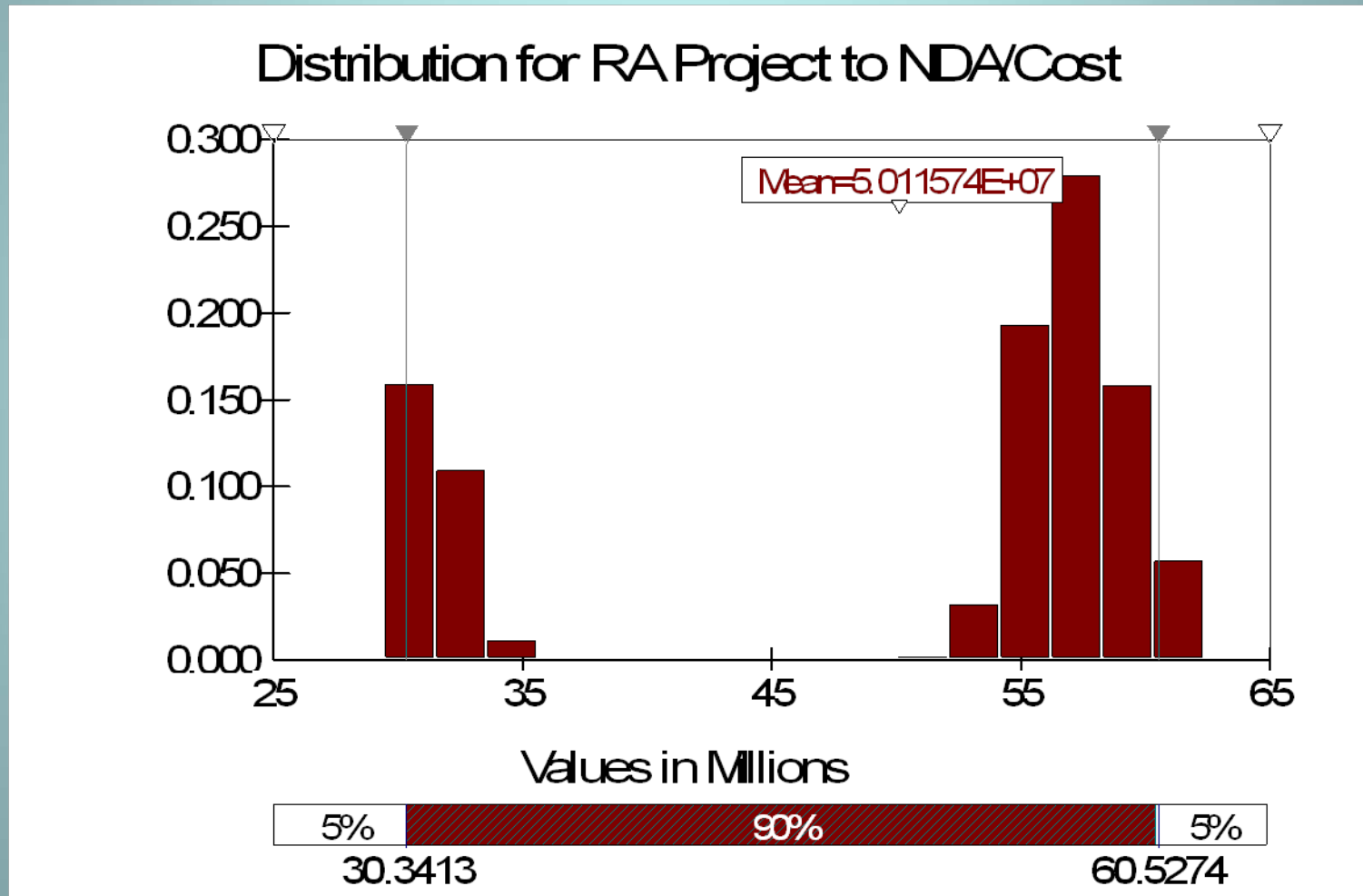
NDA Filing: Branched Simulation with Enrollment Adjustment



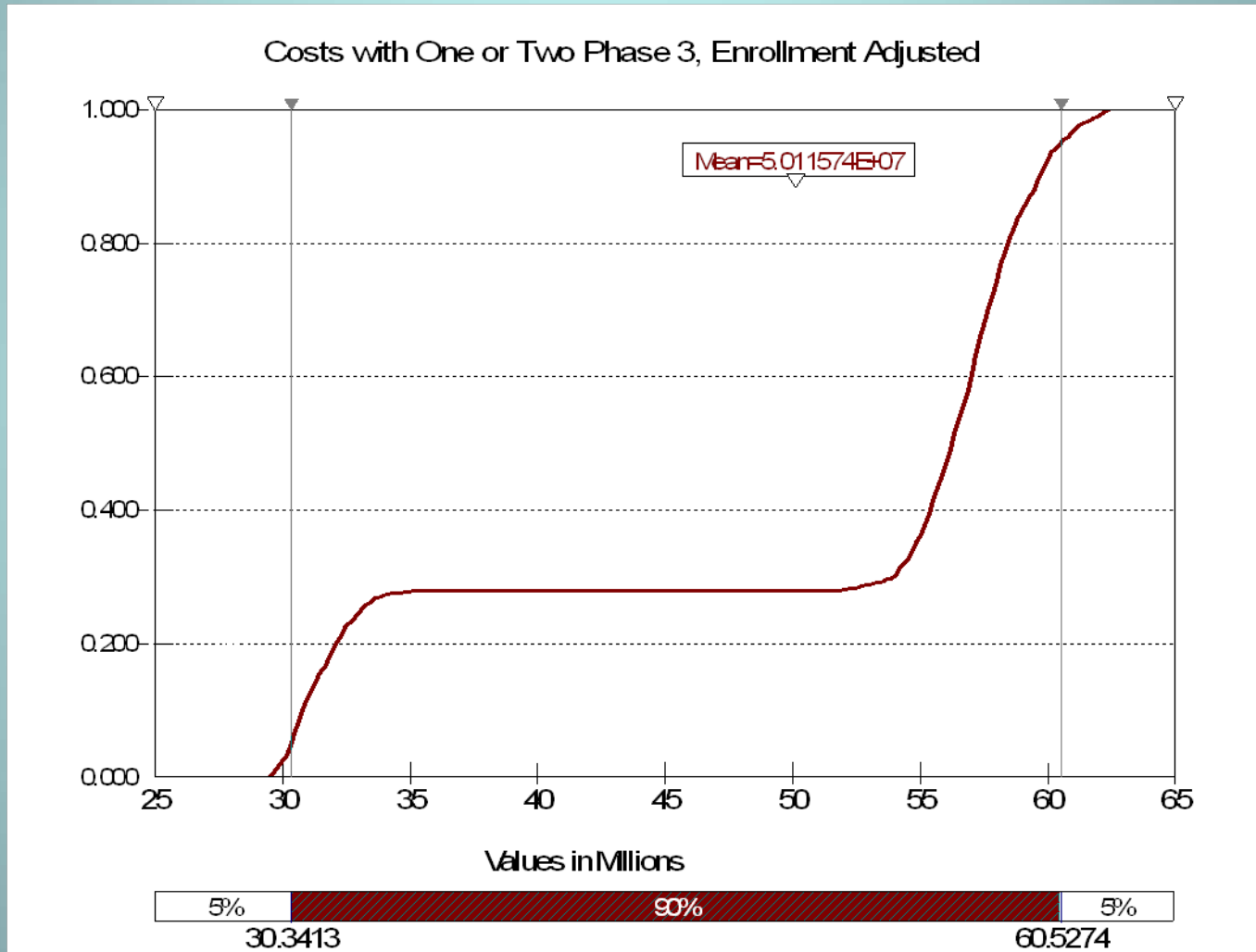
Sensitivity: Branched Simulation with Enrollment Adjustment



Costs: Branched Simulation with Enrollment Adjustment



Costs: Branched Simulation with Enrollment Adjustment





Scenario Summaries

Mean values

Scenario	Schedule (NDA date)	Costs (millions)
Base Case (no model)	Dec 19, 2016	\$ 55.72
Base Case with model	Mar 16, 2017	\$ 56.84
Branched to NDA	Q4 2013 or Q3 2017	\$ 30 or \$ 60
Branched to NDA & adjust enrollment	Q3 2013 or Q1 2017	\$30 to \$ 58

Conclusions

- A timeline will always be structured for “as soon as possible”
- Without modeling the timeline will provide the fastest time to completion
- With modeling the fastest time to completion will often be <5% probable
- As tasks complete, the actual values can be added to adjust the model. This is unlikely to change the mean, but can decrease the standard error.

Client Responses

- How can that be possible?
 - Can't argue if they provided the inputs
 - Team members may not like the result, but they also will be wary of making unrealistic projections
- This should be included across the entire portfolio
- From one CEO – “Why do you get out of bed in the morning?!”