
# Fixed and Adaptive Clinical Trial Simulator

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# What is FACTS?

- A powerful platform to design, simulate, and compare both ***fixed*** and ***adaptive*** clinical trials

- Accessed through an interactive graphical user interface – does not require programming knowledge to use

- Built on compiled low-level languages (Fortran and C++) – ***very FAST***!

# About FACTS

- FACTS has modules ("design engines") to simulate:
  - ***Dose Escalation trials*** (phase 1 and phase 2a)
    - dichotomous or ordinal endpoints
  - ***Dose Finding trials***
    - continuous, dichotomous, time-to-event endpoints
    - multiple endpoints (up to 4 continuous/dichotomous)
  - ***Enrichment trials***
    - continuous, dichotomous, time-to-event endpoints

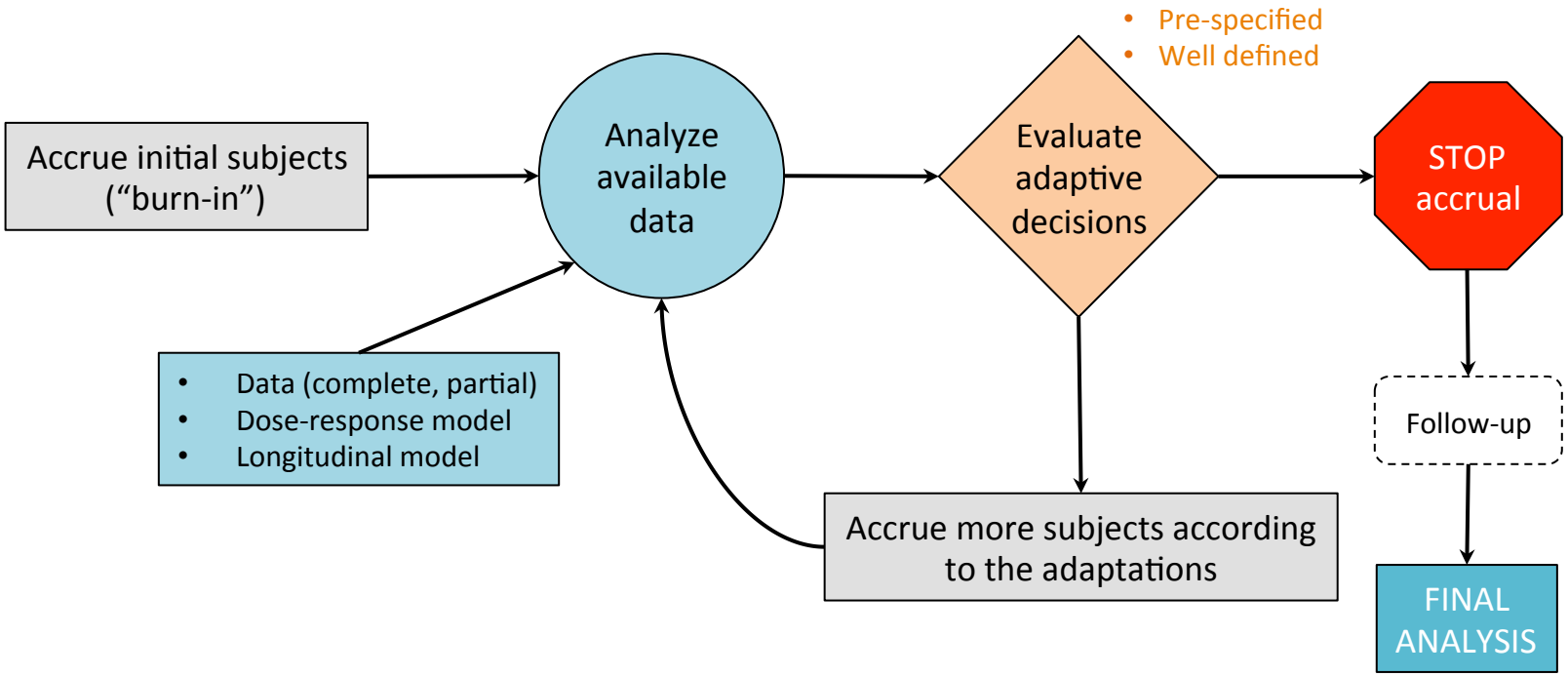
# Adaptive Designs

- Allow information that accumulates during the trial to modify key design parameters according to ***pre-specified*** and ***well-defined*** rules

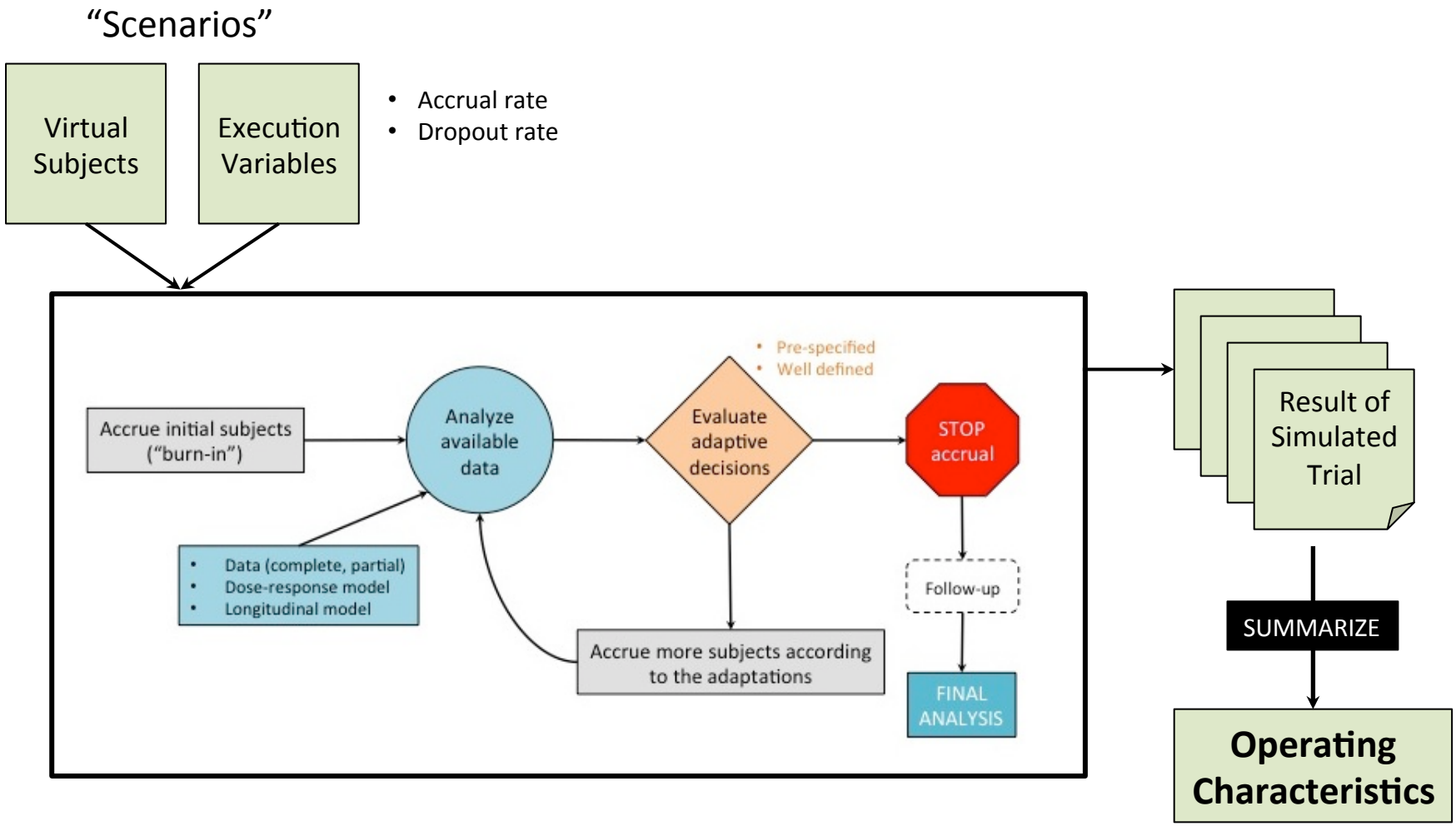
- Adaptable components may include:
  - treatment arms (dose, frequency, duration, etc)
  - allocation to the different arms
  - the patient population
  - the sample size

- By learning from the accruing data, a well-planned adaptive design may:
  - improve efficiency and reduce cost
  - maximize the information obtained
  - minimize risk to subjects and sponsor

# The Adaptive Process



# Simulating Clinical Trials



# Why Simulate Clinical Trials?

- Enables clear understanding of the design's operating characteristics
- Clarifies how design choices affect the behavior of the trial
- Facilitates communication and provides justification of the design for the study team, regulators, funders DSMB, etc.
- An incredible learning tool!


# SIMULATING TRIALS IN FACTS

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# Specifying Design Features

***Adaptive vs. Fixed***

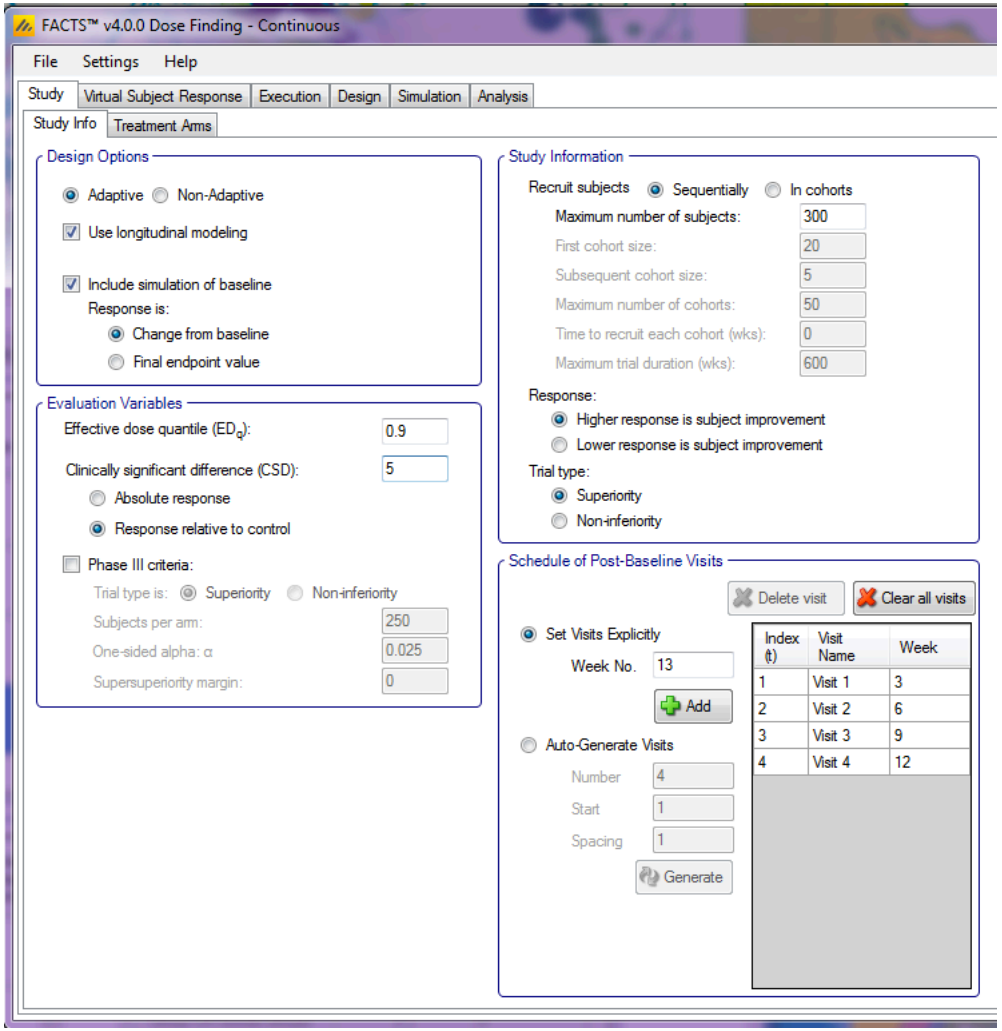
***Maximum Sample Size***

***Superiority vs. Non-inferiority***

***or Super-superiority by defining a margin (CSD)***

***Visit Structure***

***etc…***

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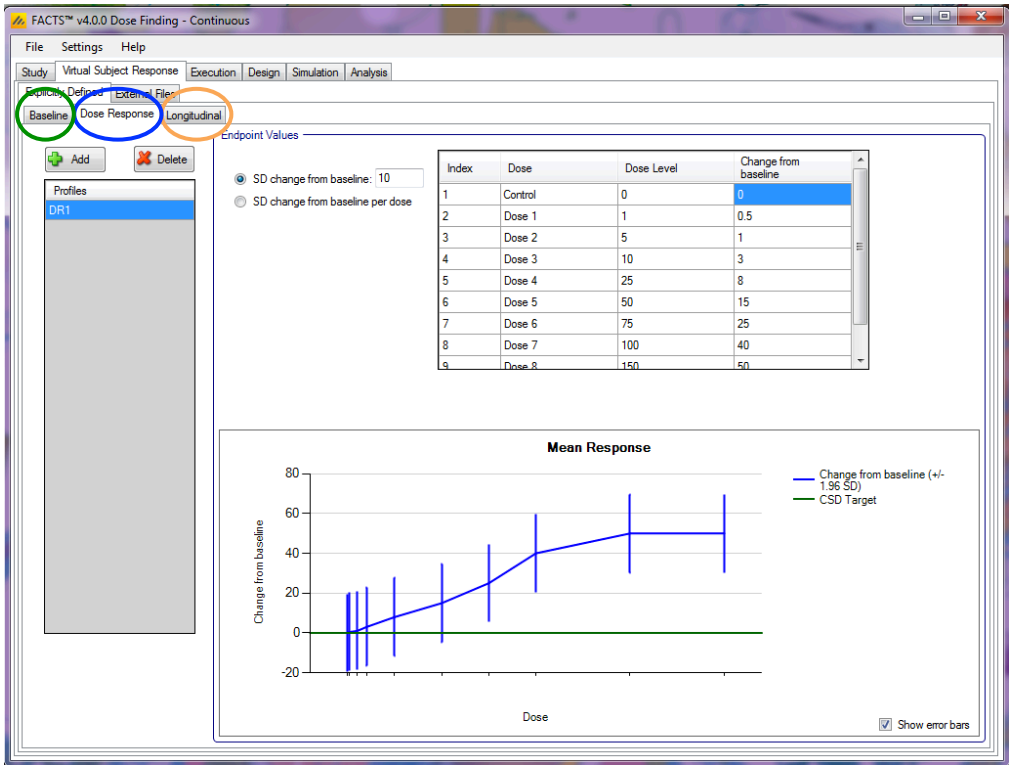
# Simulating "Virtual Subjects"

- Built-in facilities for simulating:
  - Patient responses
    - baseline, final response, multiple visits
    - either simulated internally or sampled from an external file
  - Patient accrual
  - Patient dropouts



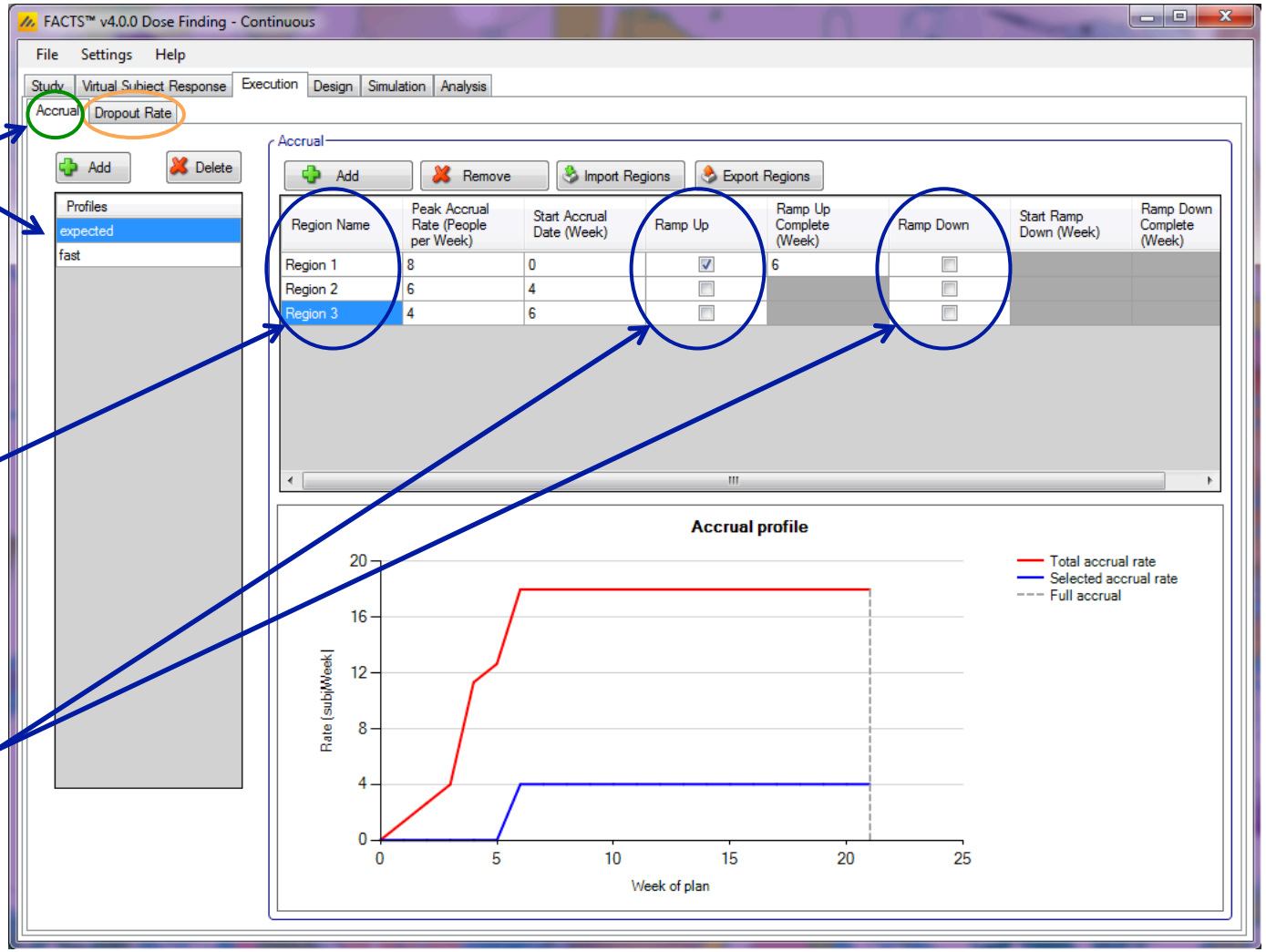

- Keeps track of how much data would be available at each interim analysis

# Simulating Accrual and Dropout

*Create multiple scenarios for accrual and dropout rate*

*Enable different enrollment profiles by region*

*Ramp up and ramp down options allow differential accrual over time*

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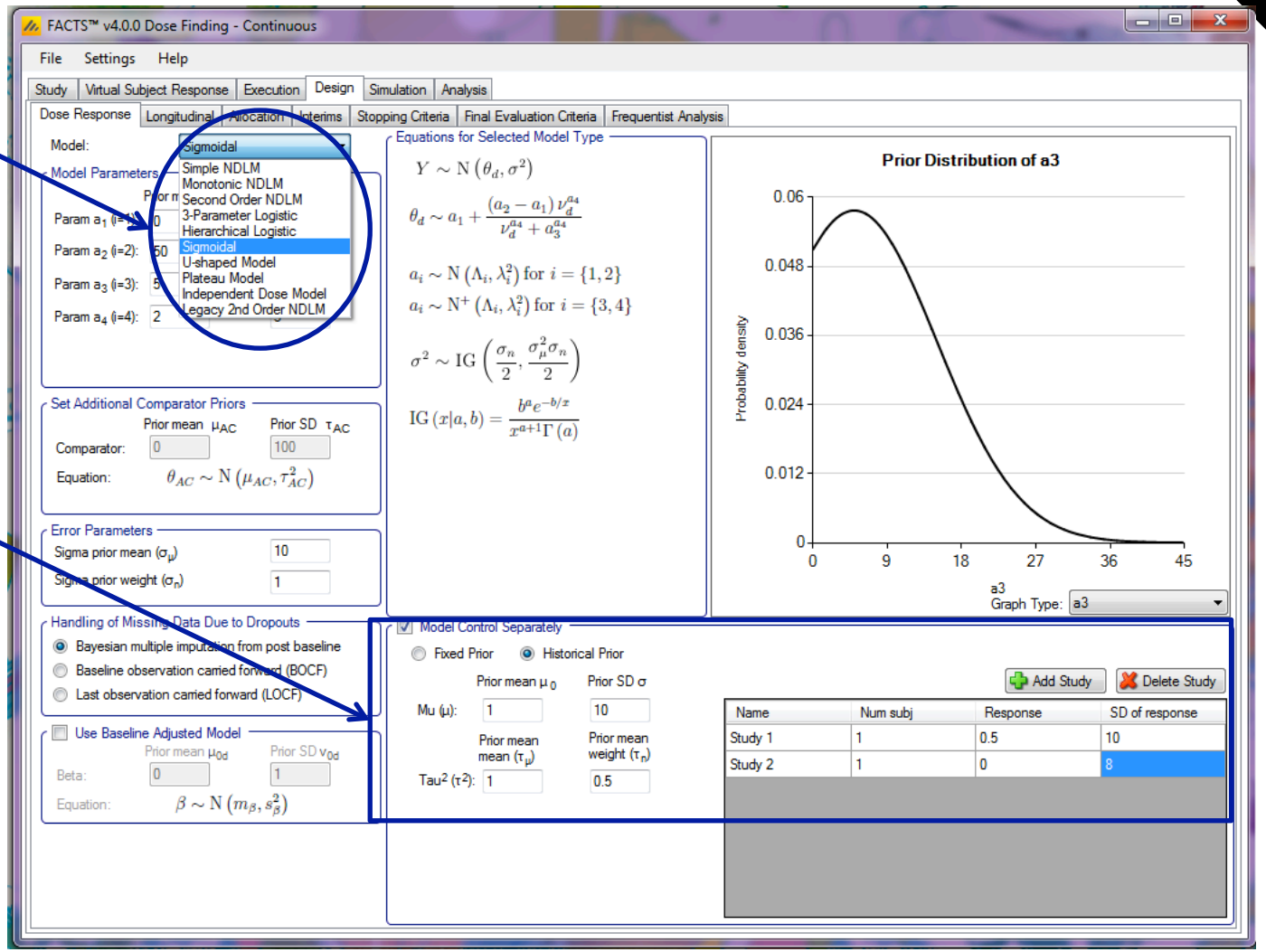
# Dose-Response Models

***Multiple options for modeling the dose-response curve***

***Hierarchical borrowing of historical control data***

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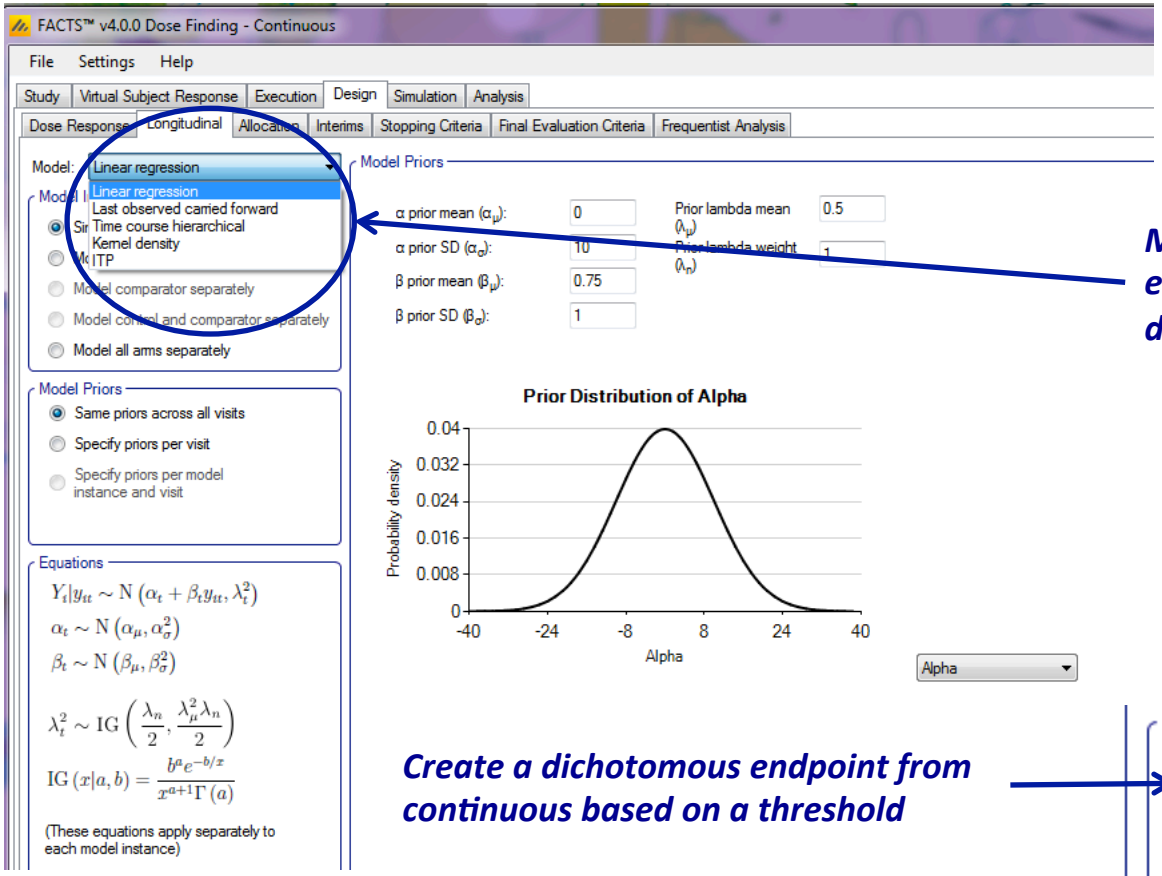
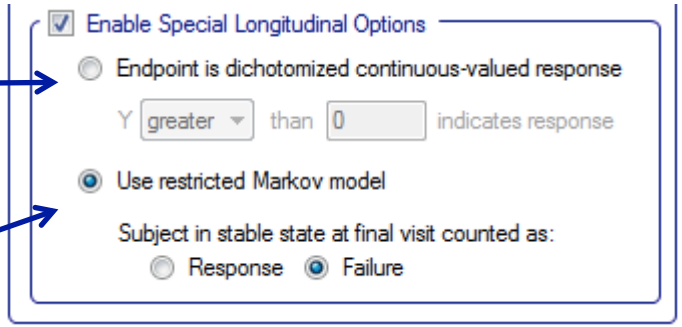
# Longitudinal Models




***Multiple options to impute the final endpoint for subjects with incomplete data at an interim***

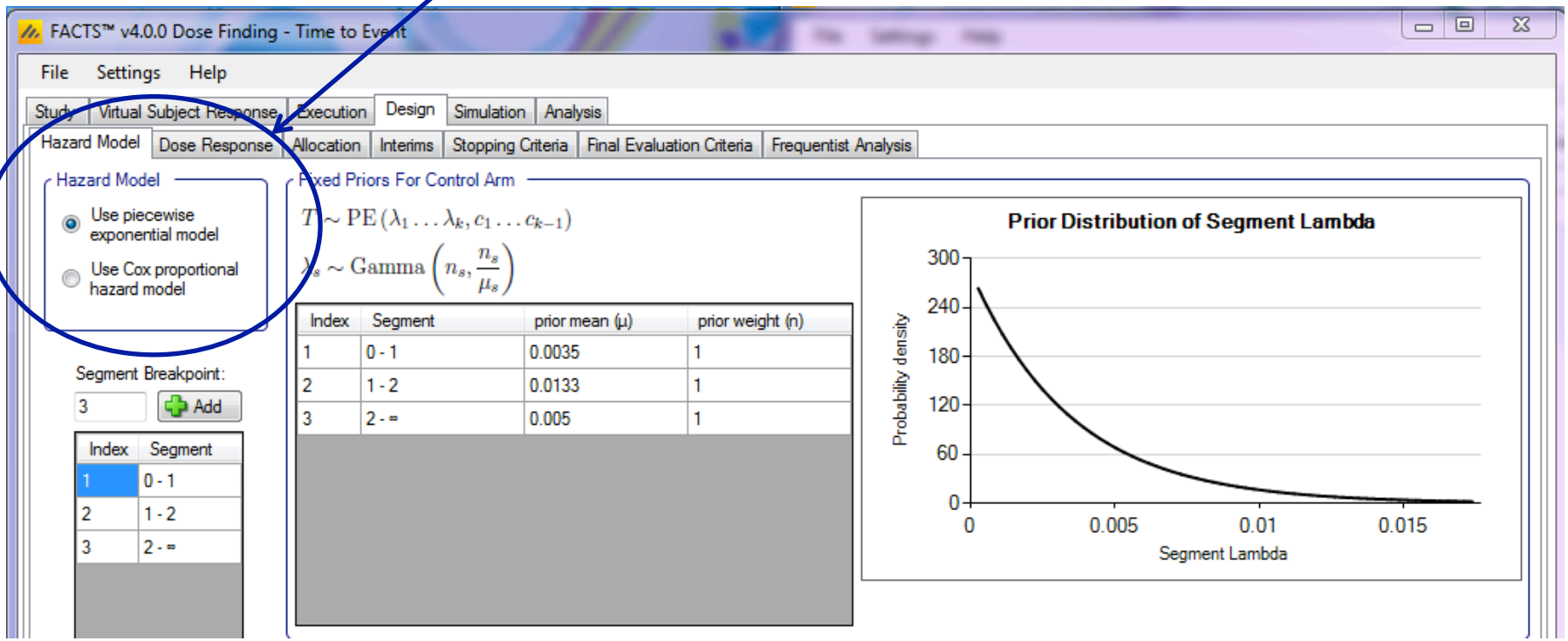
***Create a dichotomous endpoint from continuous based on a threshold***




***Absorbing Markov Chain Model (dichotomous endpoints)***
***Subject can be "failure", "stable", or "response" at interim visits, with failure or response being absorbing states***

# Time-to-Event (TTE) Models

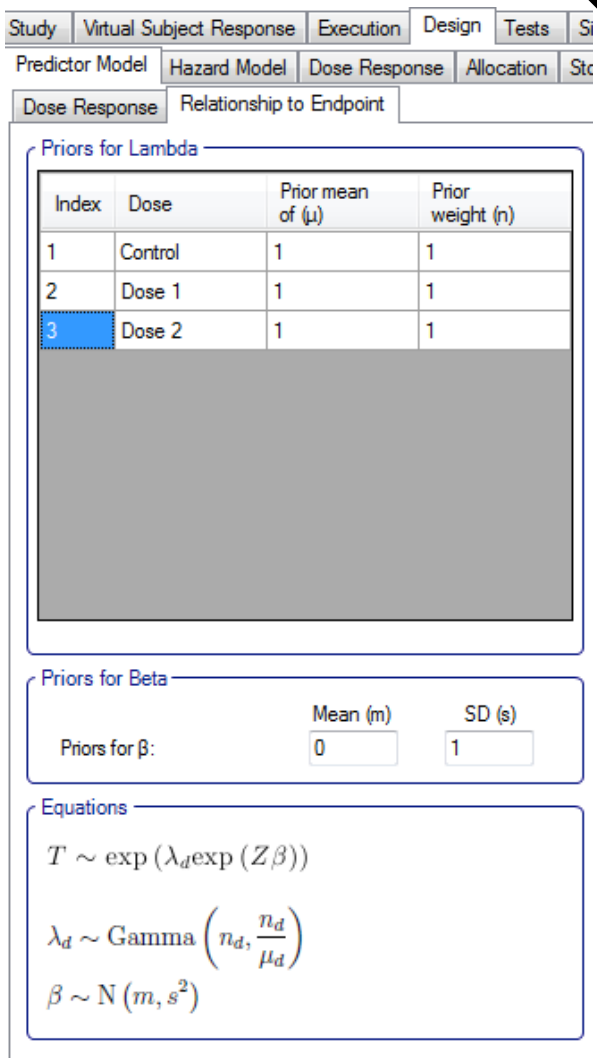
***Piecewise-exponential***
***or***
***Cox proportional hazard***

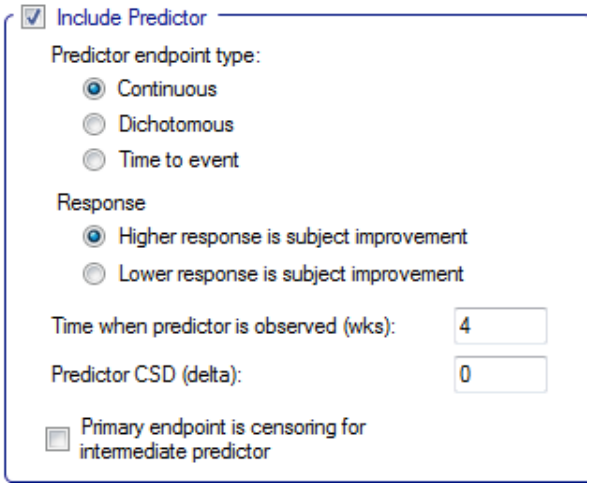


# Early Predictors for TTE

Allows incorporation of an early predictor (continuous, dichotomous, or time-to-event)

- e.g. Progression-free survival (PFS) predicting overall survival (OS)
- Predictor may be used to impute final endpoint values for incomplete subjects at an interim
- Can adaptively stop accrual based on predictor information

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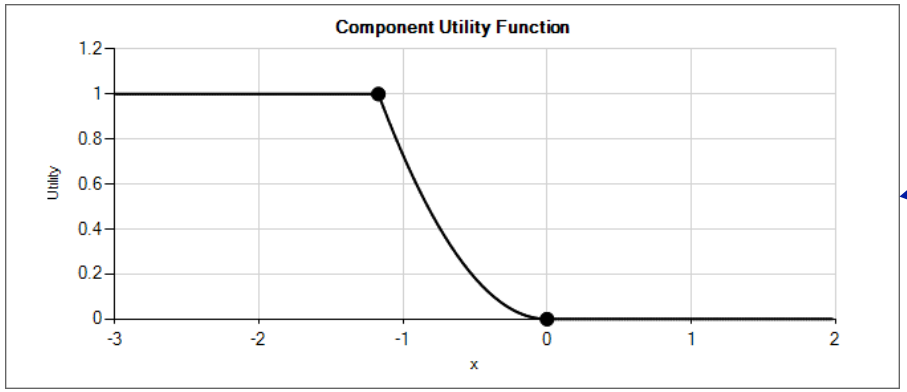
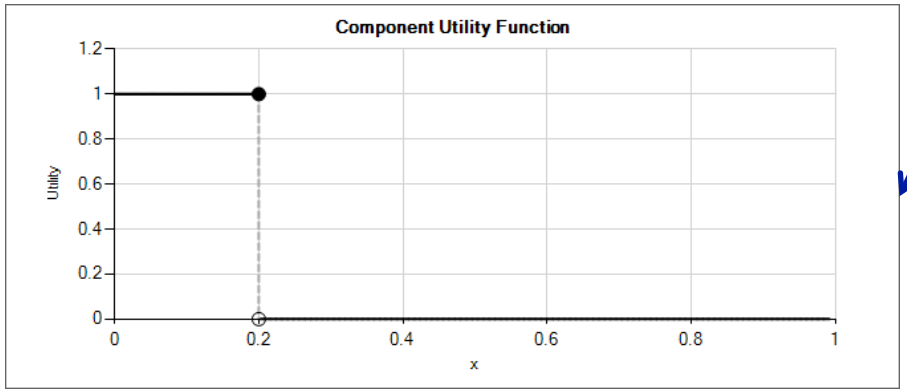
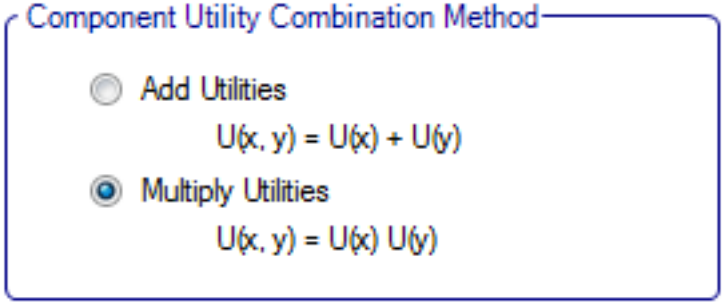
# Utility Functions: Multiple Endpoint




***Specify utility (weight) functions for each endpoint***

***Combine utilities either additively or multiplicatively***



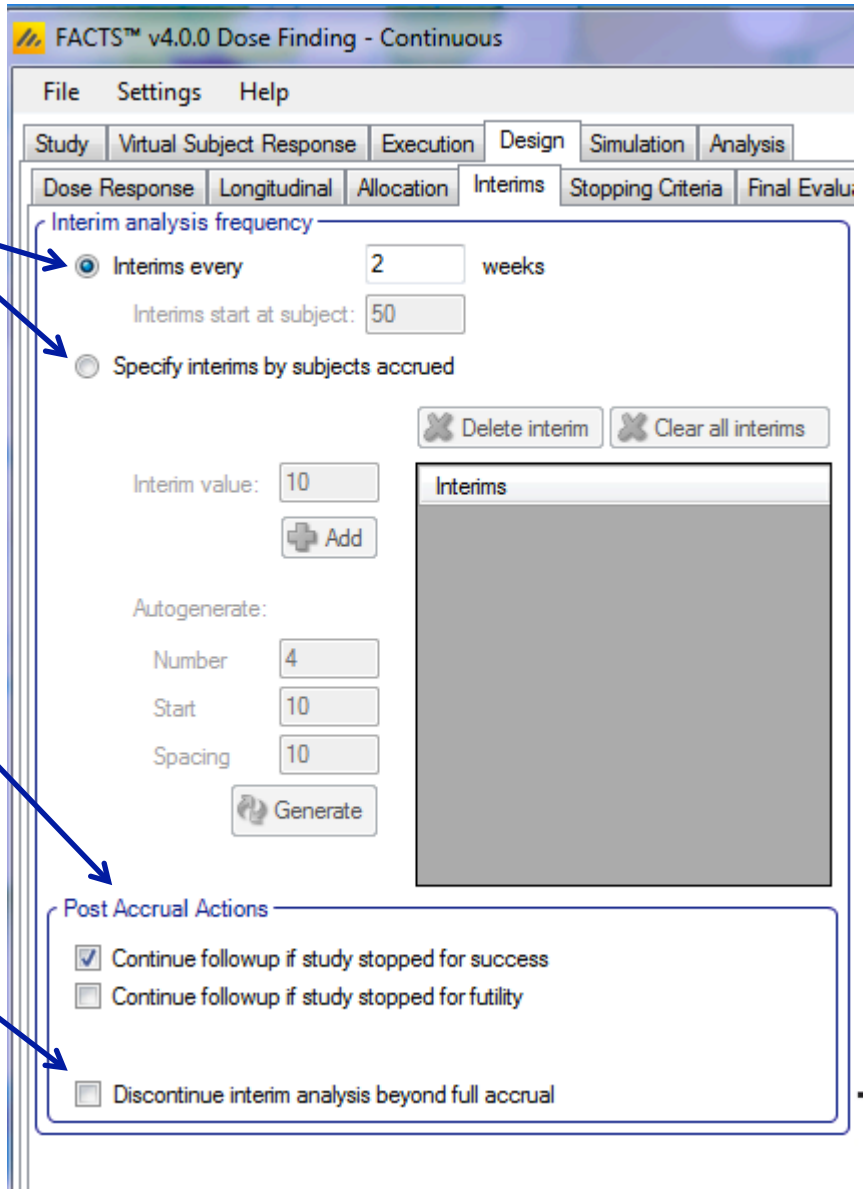

***Adaptations and evaluation criteria are based on the estimated utility***

# Timing/Frequency of Interims

***Specify frequency based on number of subjects enrolled, number of events (TTE), or by time, e.g. every 2 weeks***

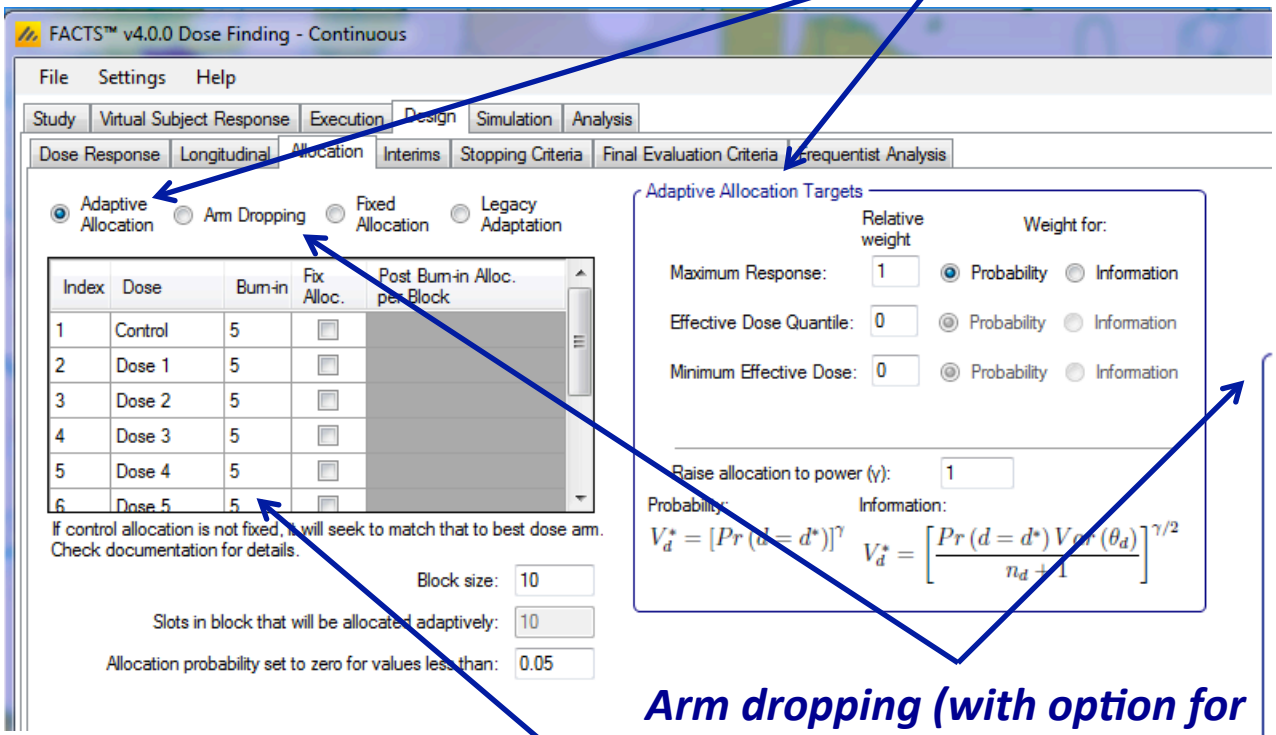
***Options for discontinuing follow-up after early stopping***

***Interims conducted during and possibly after full accrual***

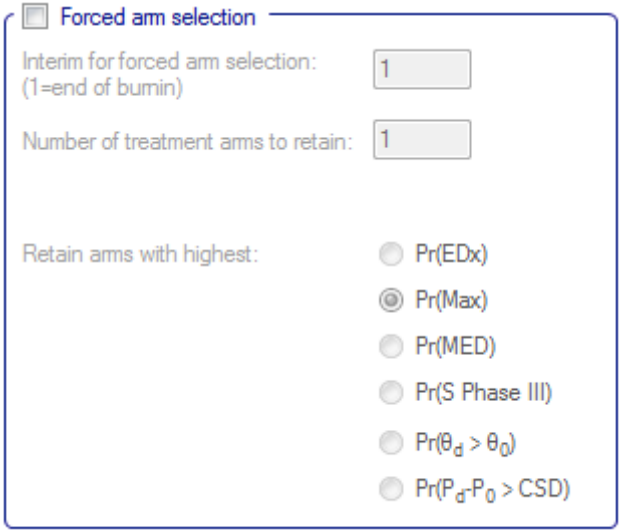


# Adaptations

***Response adaptive randomization***




***Arm dropping (with option for forced arm selection)***




***Flexible specification of burn-in period and post-burn-in blocking***

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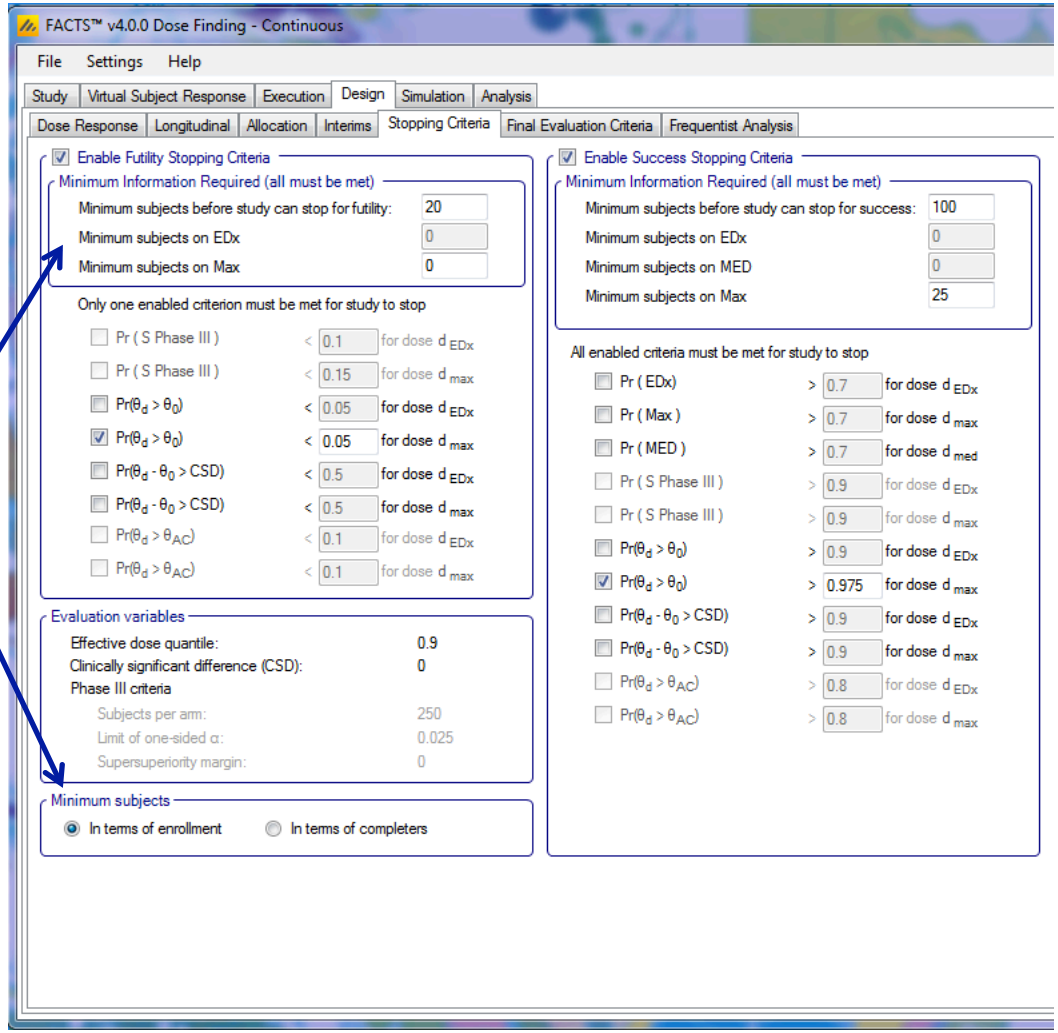
# Early Stopping Rules

***Highly customizable early stopping for success and/or futility***

***Minimum requirements for number of subjects enrolled or complete (or number of events for TTE)***

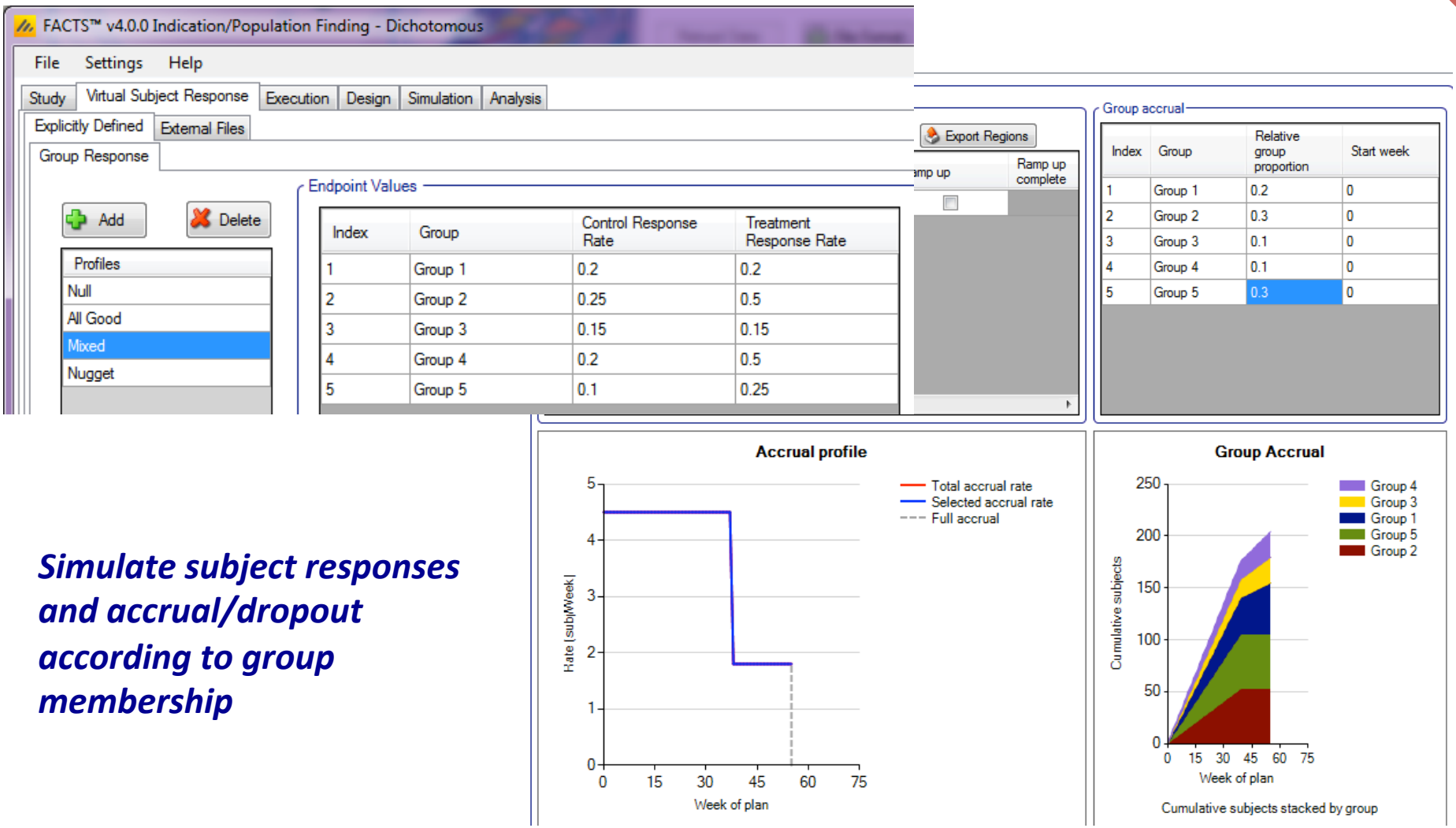
***Ability to combine multiple rules***



# AIPF/Enrichment Designs

- Adaptive Indication and Population Finder
- Given a set of populations, where is the treatment effective?
- Option of hierarchical borrowing of information across groups to make better decisions (borrows most when appropriate, less when not).
- Dropping of groups for futility or graduating for success
- Much current interest in this design within oncology
  - part (not all) of I-SPY 2

# AIPF Virtual Subjects




***Simulate subject responses and accrual/dropout according to group membership***

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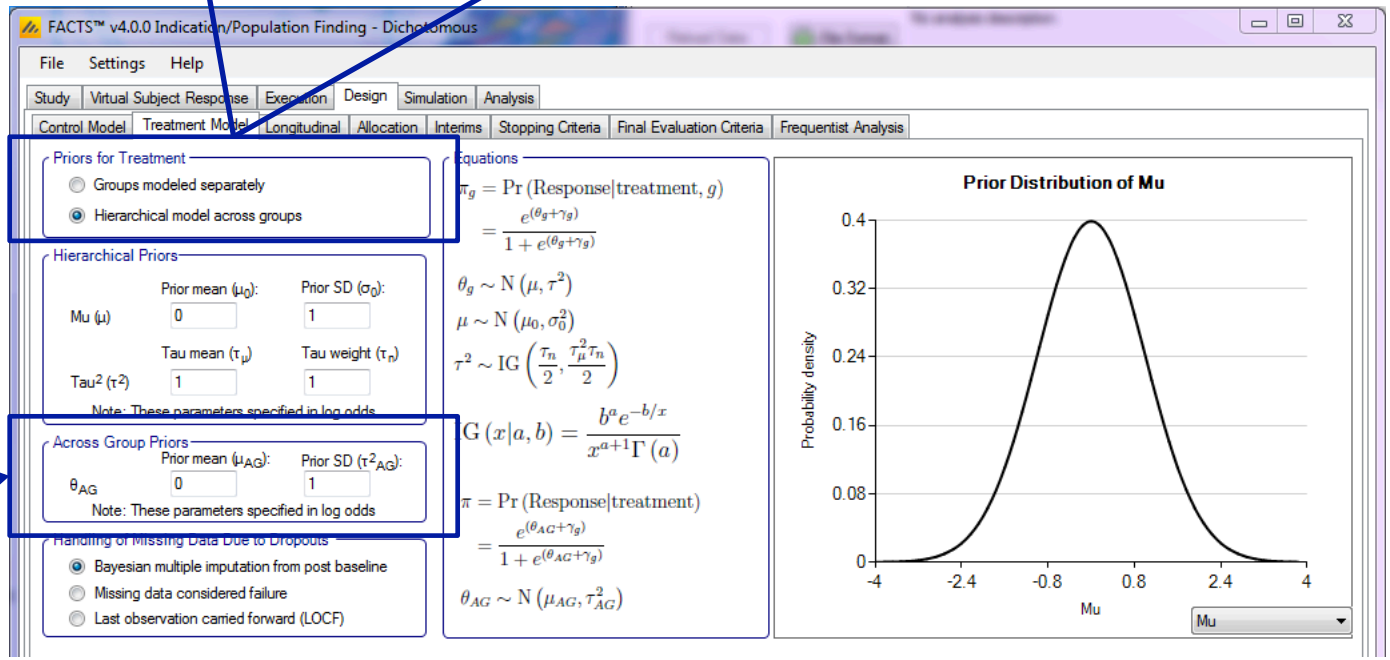
# AIPF Statistical Models

***Separate model for each group*** ***OR*** ***Hierarchical model across groups***

- ***Estimate of treatment effect borrows information from other groups***
- ***Compromise between separate models and pooled analysis***




***Stratified analysis – common treatment effect, but control rate may differ among groups***

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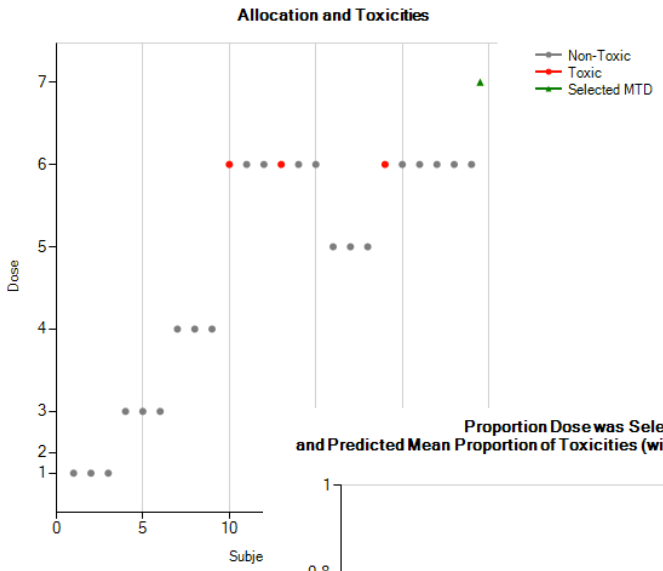
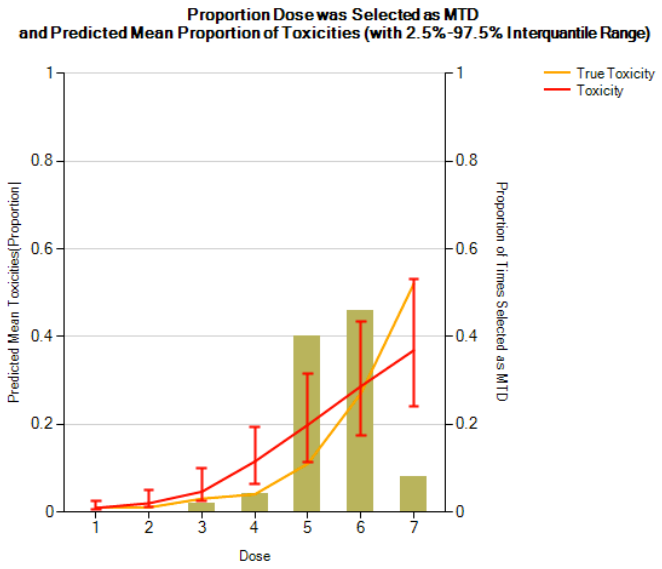
# Dose Escalation

- Continual Reassessment Methods (CRM) with 1- and 2-parameter models for the dose-toxicity curve
- Options for overdose control
- Joint modeling of toxicity and efficacy
- Escalation in two related populations
- Dichotomous or ordinal endpoint
- Flexible rules for controlling escalation
- Simulation of traditional 3+3 design for comparison

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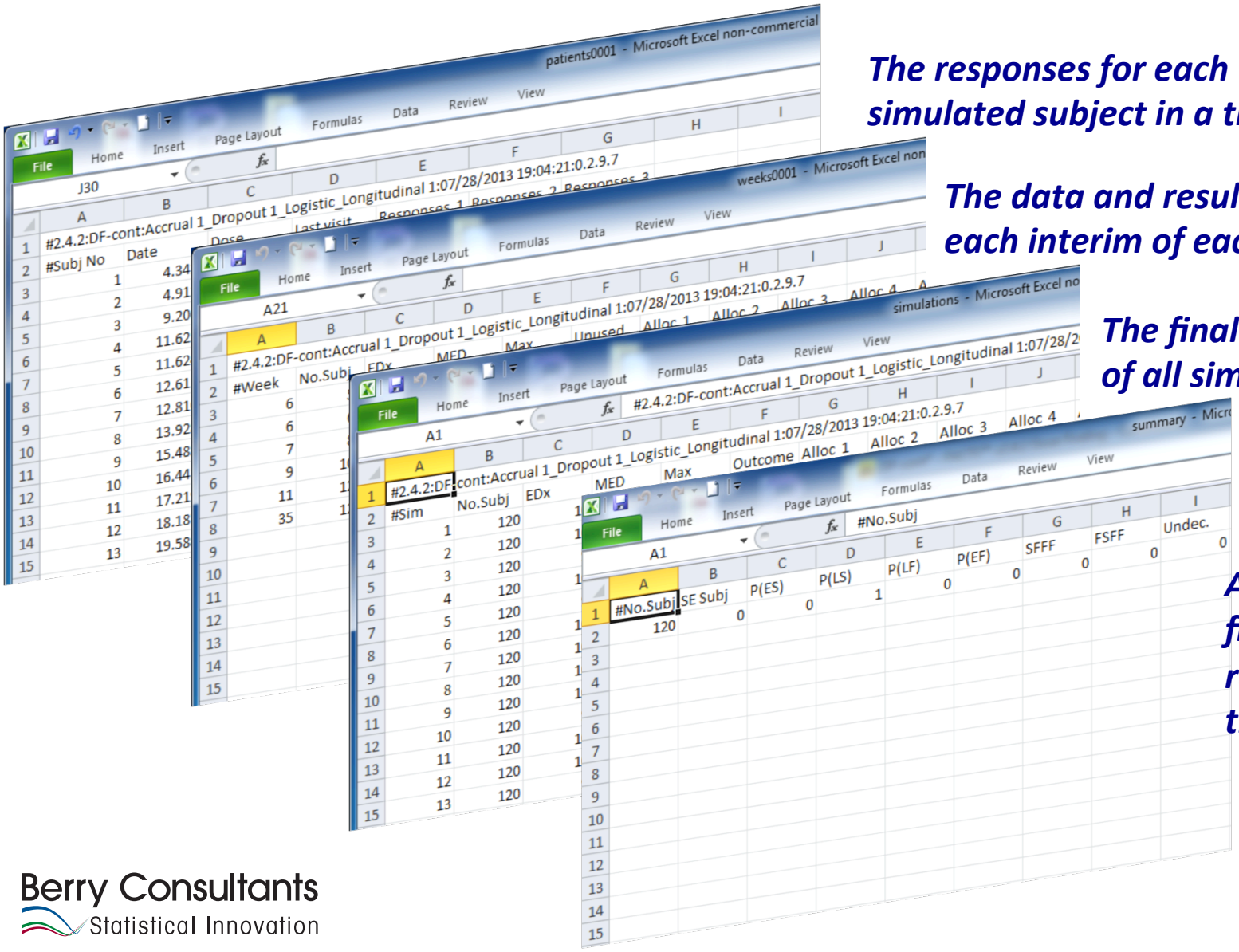
# Extensive Output Files




***The responses for each simulated subject in a trial***

***The data and results at each interim of each trial***

***The final data and results of all simulated trials***

***Average of the final data and results across all trials***

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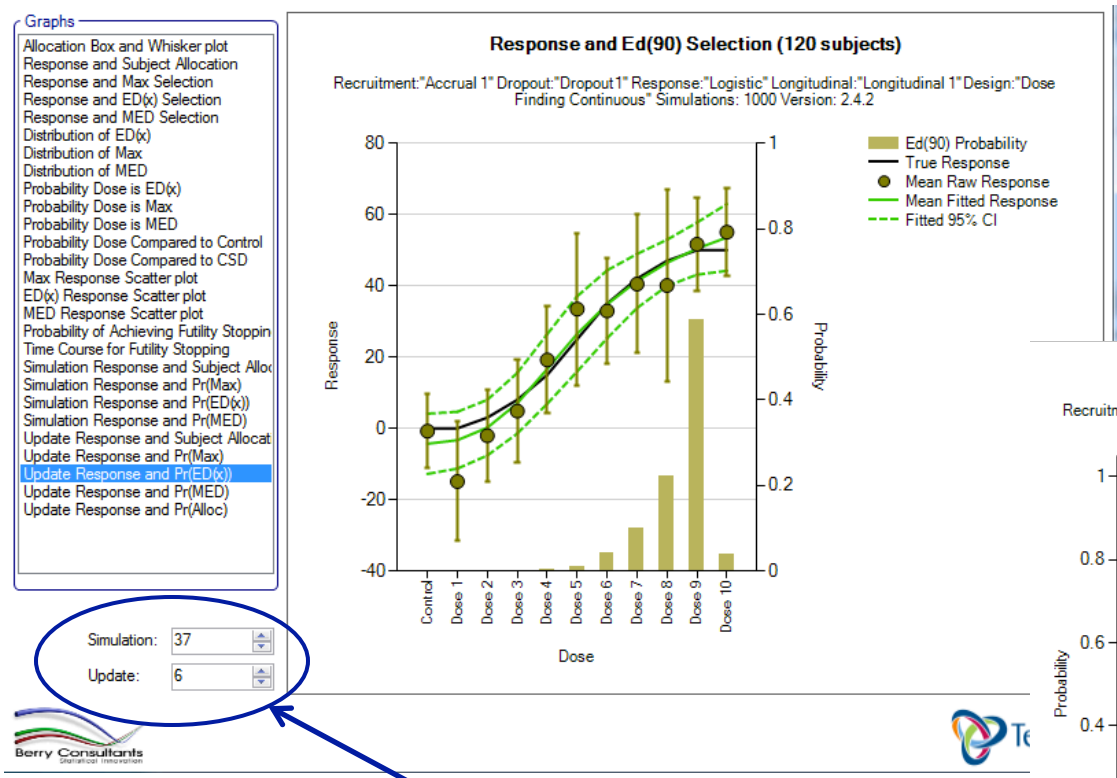
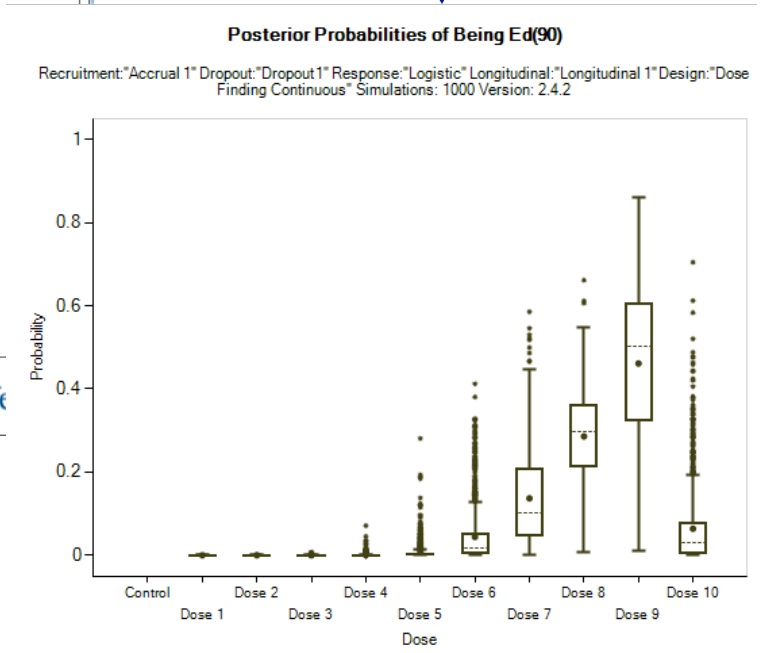
# Built-in Graphics




***Allows quick review of simulation summaries***




***Walk through each interim of a single simulated trial***

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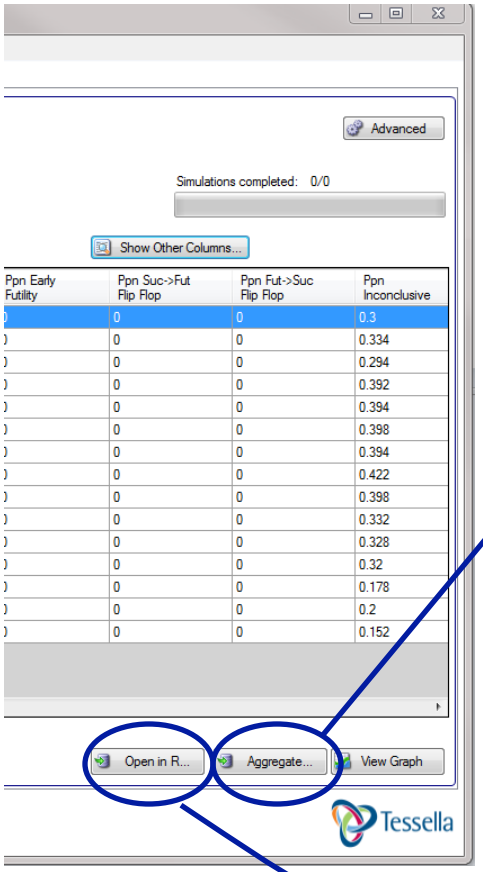
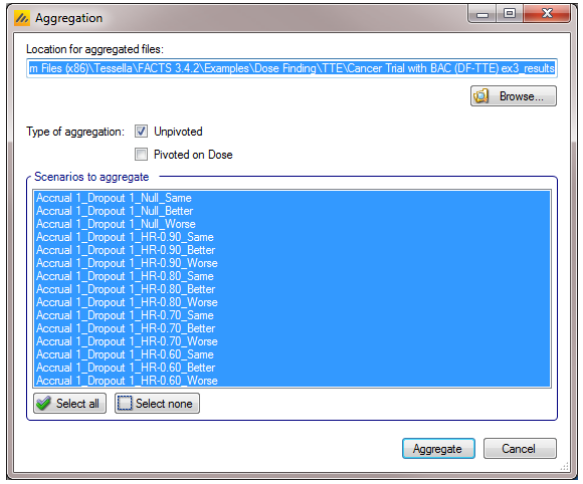
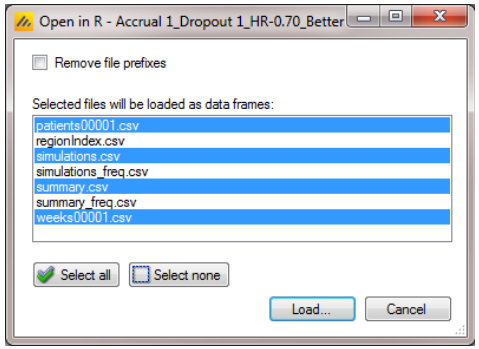
# Support for post-processing results




***Aggregate results from selected scenarios***




***Open in R (individual scenario or aggregated results loaded into data frames) for additional post-processing and customization of output***

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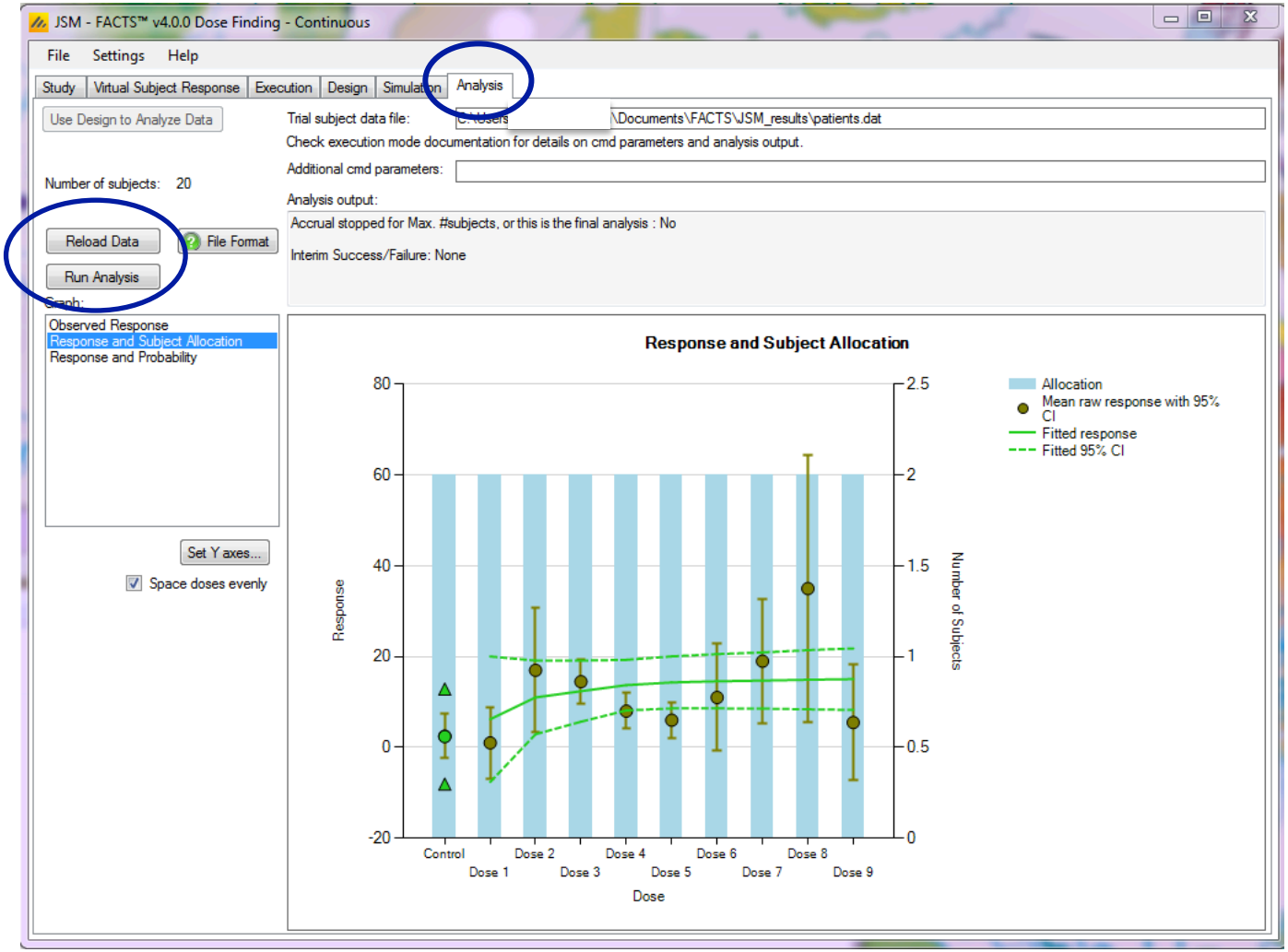
# Analysis Tab

***Analysis tab to run hypothetical interim analyses within FACTS GUI***

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# Benefits of FACTS

- FACTS changes the economics of simulating clinical trials
  - Not an expensive, time-consuming exercise only undertaken by specialized statistical programmers
  - Not limited only to complicated trials
  - Incredibly fast simulations, keeping projects on schedule

- FACTS makes simulation-based trial design possible for all biostatisticians and all clinical trials!