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 C++ a compiled low-level language – it runs simulations ***very FAST***!
- Designs can be specified in under and hour (no programming) and do not require extensive testing, debugging and fixing….

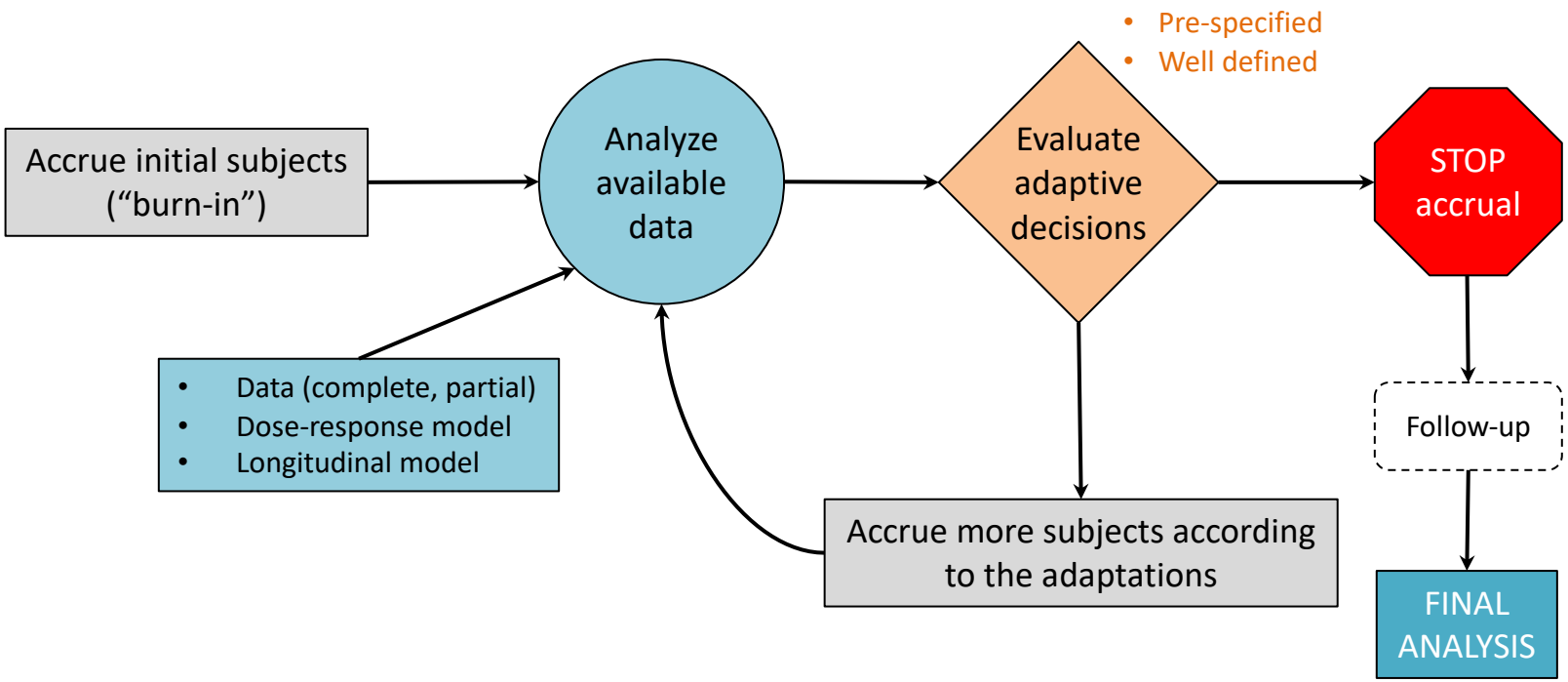
About FACTS

- FACTS has modules ("design engines") to simulate:
  - ***Dose Escalation trials***
    - Dichotomous or ordinal endpoints, efficacy and safety, multiple 'groups', open enrolment, "fine grained" dose levels, 2 drugs & escalation in 2D
  - ***Treatment Comparison trials***
    - Continuous, dichotomous, time-to-event endpoints
    - Multiple endpoints (up to 4 continuous/dichotomous)
    - A single trial or consecutive trials
    - Seamless IIa/IIb or seamless II/III
  - ***Enrichment trials***
    - Testing multiple sub-groups or multiple indications
    - Continuous, dichotomous, time-to-event endpoints
    - Separate decision making group by group
    - Hierarchical and clustered modelling
  - ***Platform trials***
    - Testing multiple treatments against a common control over time
    - Treatments come and go, may 'wait' to enter
    - Final and early stopping per treatment, different allocation strategies
    - Continuous or dichotomous endpoints

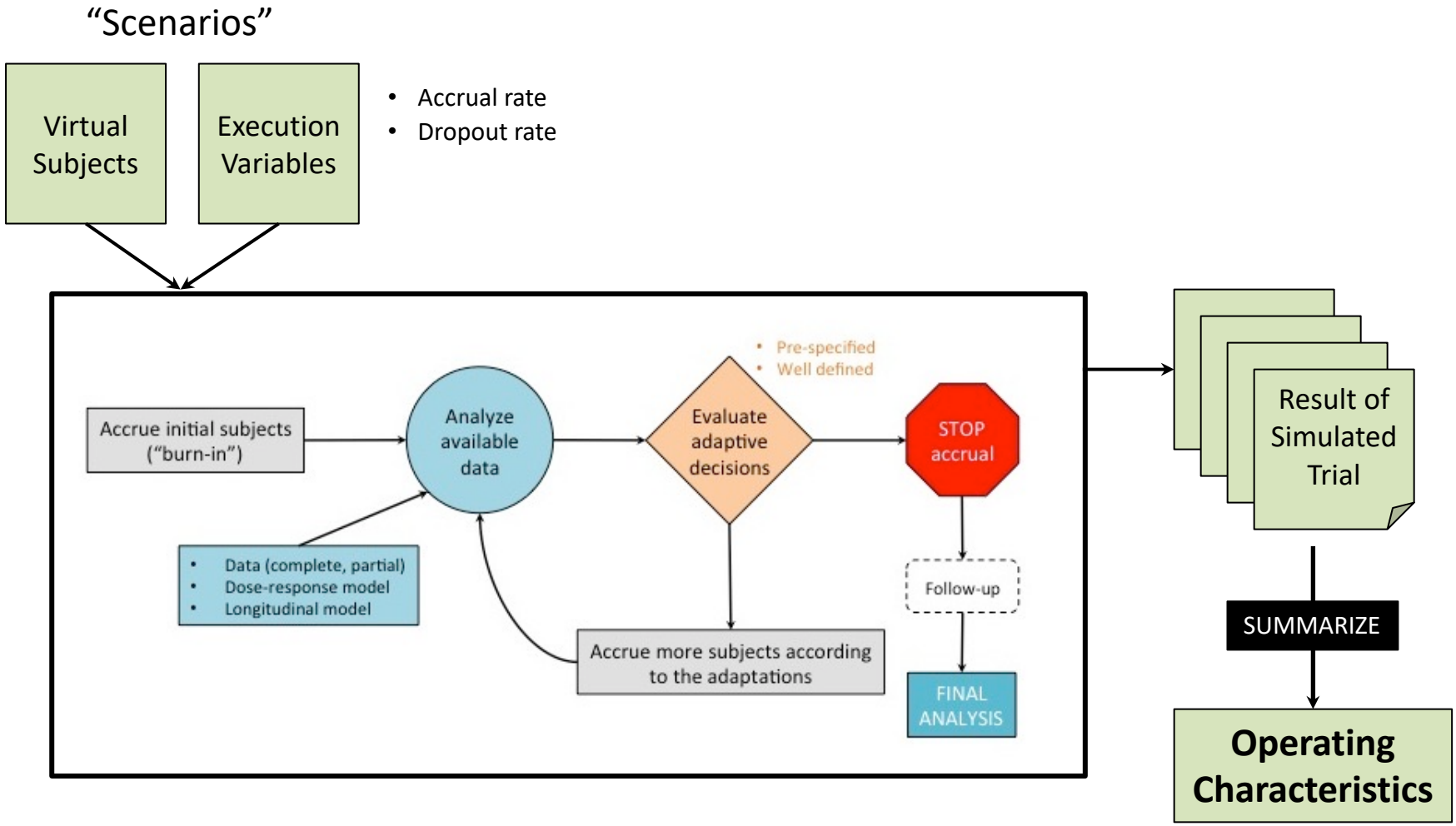
Adaptive Designs

- 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
  - Minimize the 'time to decision'

The Adaptive Process



Simulating Clinical Trials



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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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FACTS IS …

- A Clinical Trial Simulator
- It does not design the trial for you (yet!)
- You pick the features, set the parameters and choose the scenarios to simulate
- FACTS performs the simulations and produces the simulation results
- You choose which operating characteristics to prioritize in judging the performance of the design
- You create alternative designs in FACTS and simulate them too and then compare results and choose between the competing designs
- You can re-analyze the results yourself post simulation

Classes of trial design currently supported FACTS

Core:	Trials that test the effectiveness of one or more treatments in a population
Dose Escalation:	Cancer type Phase I trials where a dose is increased up to some tolerable limit of toxicity
Enrichment Designs:	Trials that test a treatment in multiple subgroups or multiple similar indications (e.g. Basket trials)
Staged Designs:	The simulation of two consecutive FACTS Core trials (possibly seamless), the results of the first feeding into the second
Platform Trials:	Trials that run for a long time testing multiple treatments against a common control arm, with treatments leaving and new treatments entering the trial over time

FACTS CORE

Specifying Design Features

Adaptive vs. Fixed

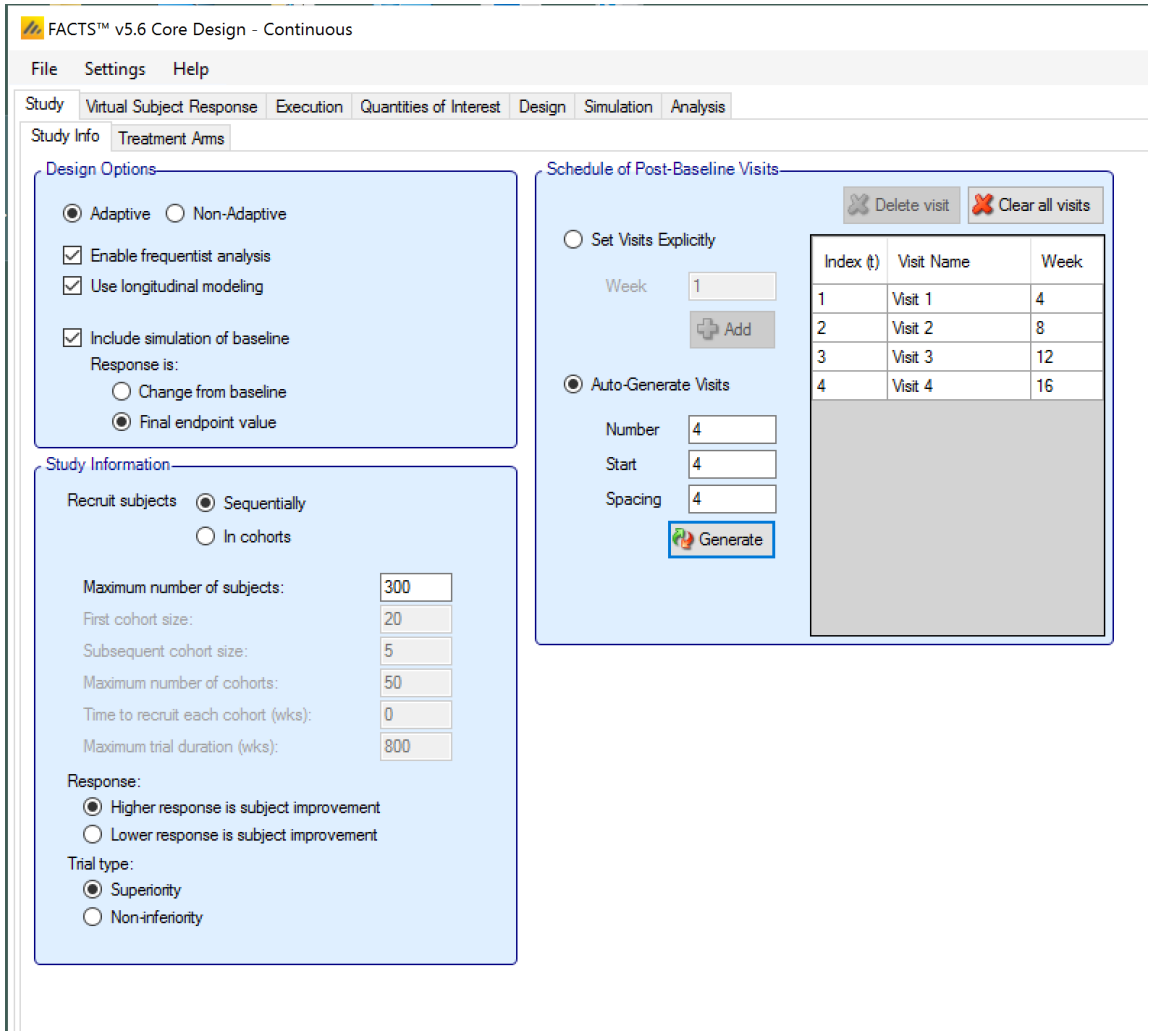
Maximum Sample Size

Superiority vs. Non-inferiority

or Super-superiority by defining a margin (CSD)

Visit Structure

etc…



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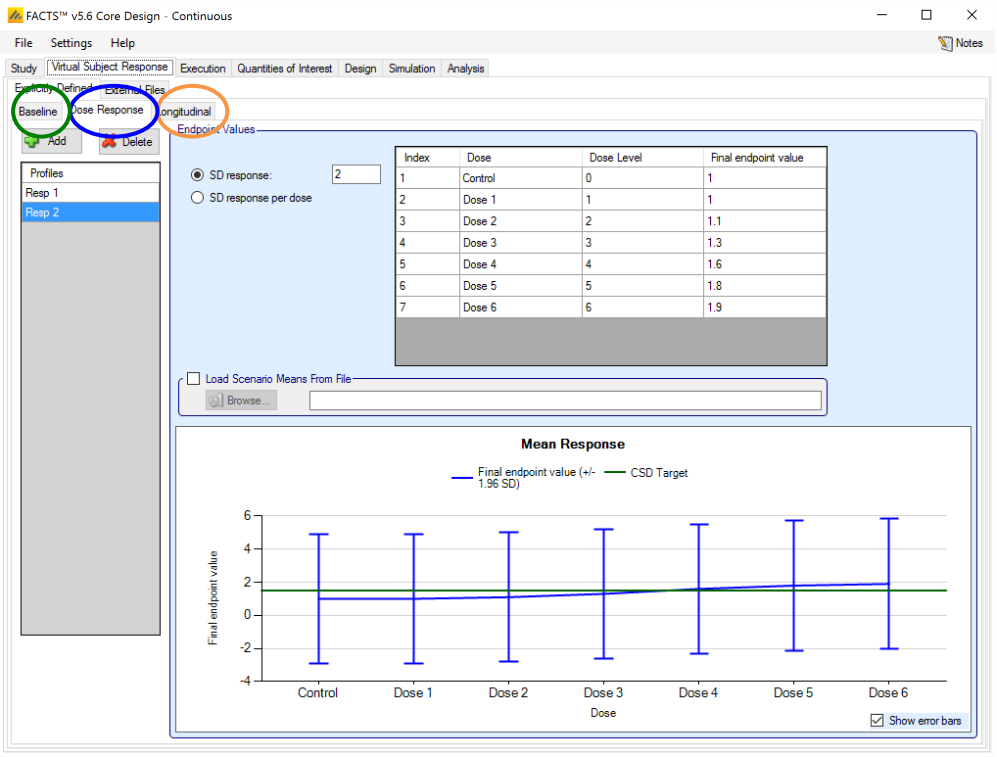
Simulating "Virtual Subjects"

- 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



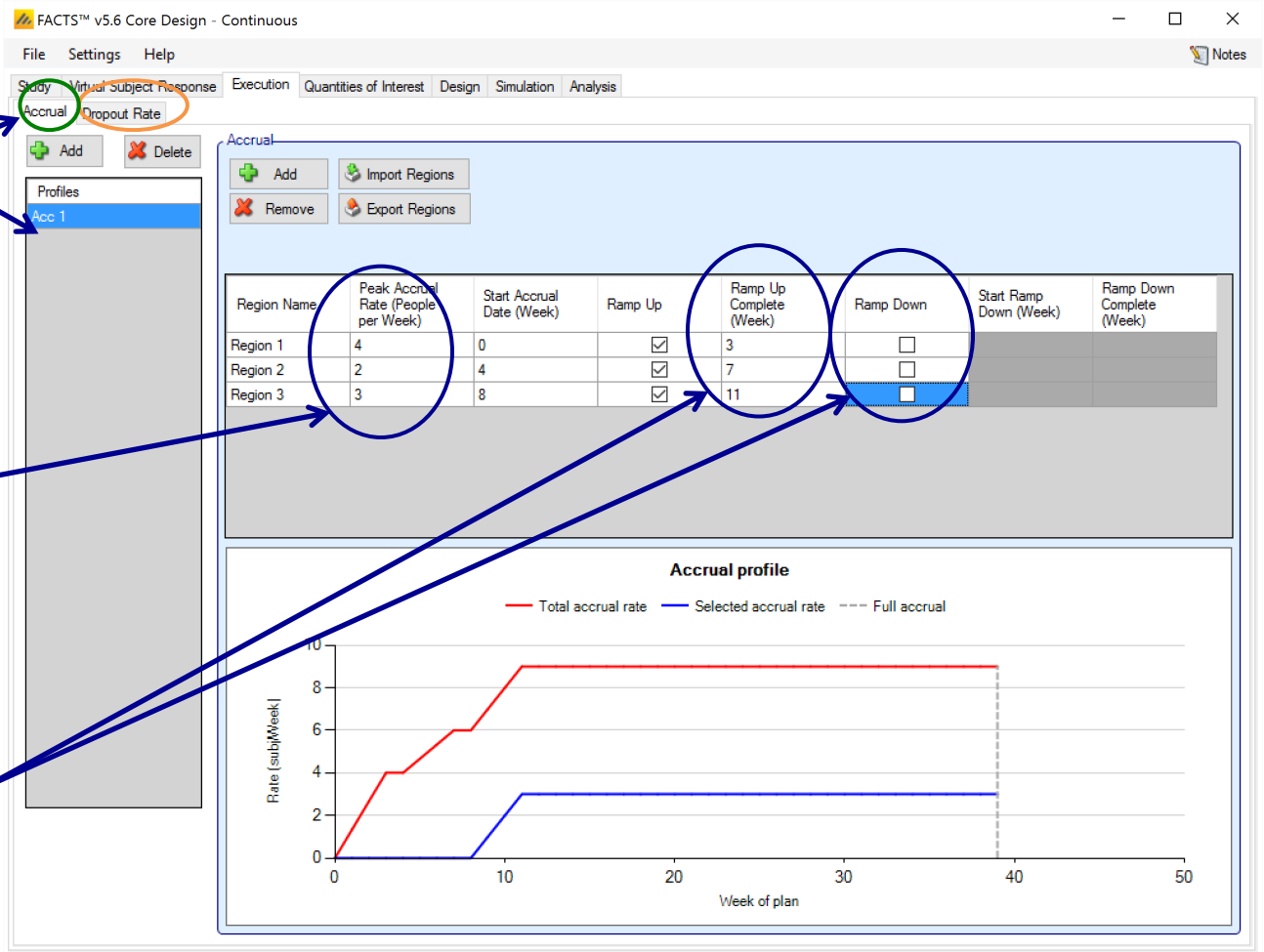
- Keeps track of how much data would be available at each interim analysis

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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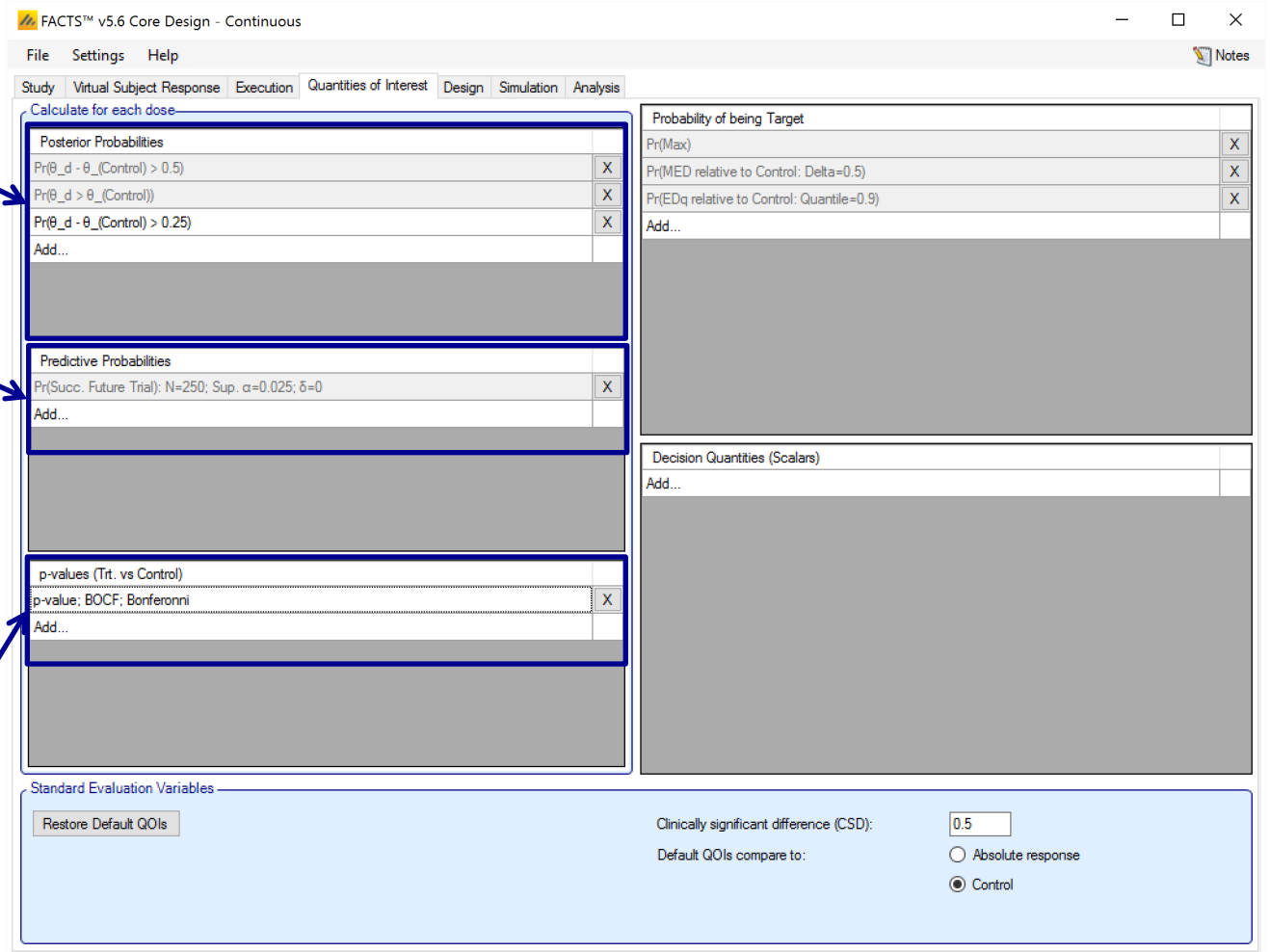
Quantities of Interest

Use defined posterior probabilities of comparisons

User defined Predictive probabilities of future success:

- ***A future trial***
- ***The current trial if accrual stops now***
- ***The current trial at complete accrual***

User selected P-values



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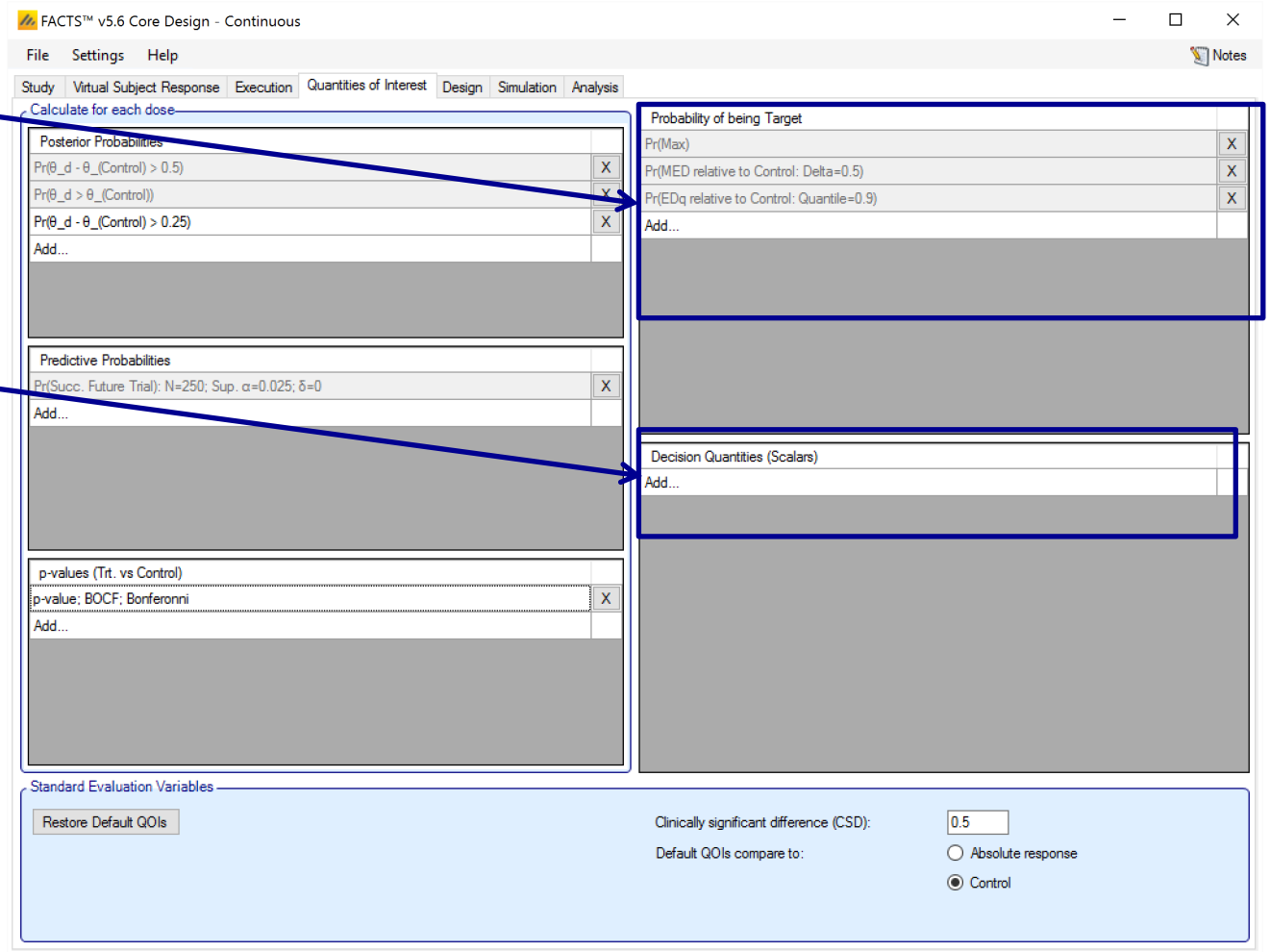
Quantities of Interest

Use defined criteria for selecting arm

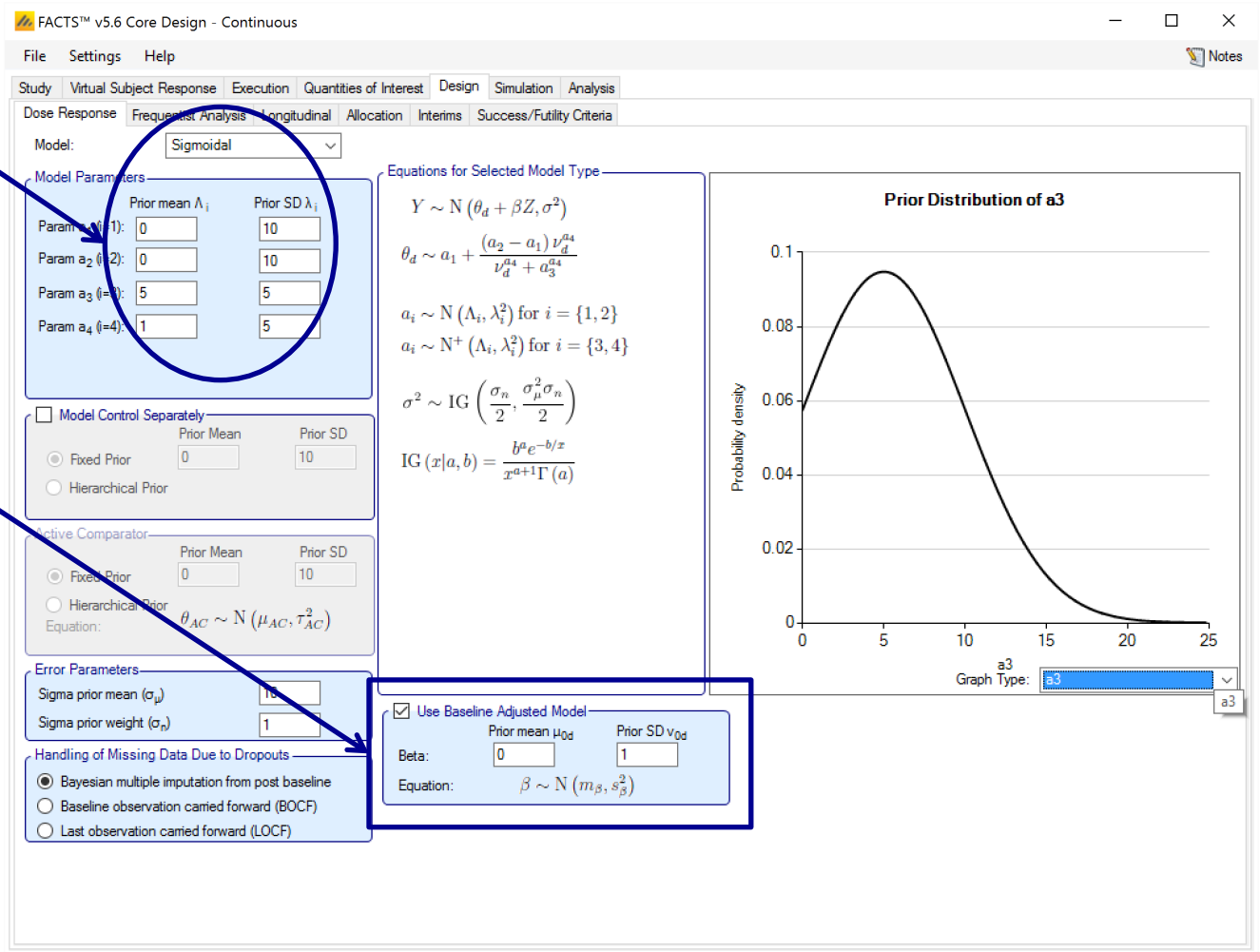
User defined decision criteria: test this probability at this dose



Dose-Response Models

Multiple options for modeling the dose-response curve

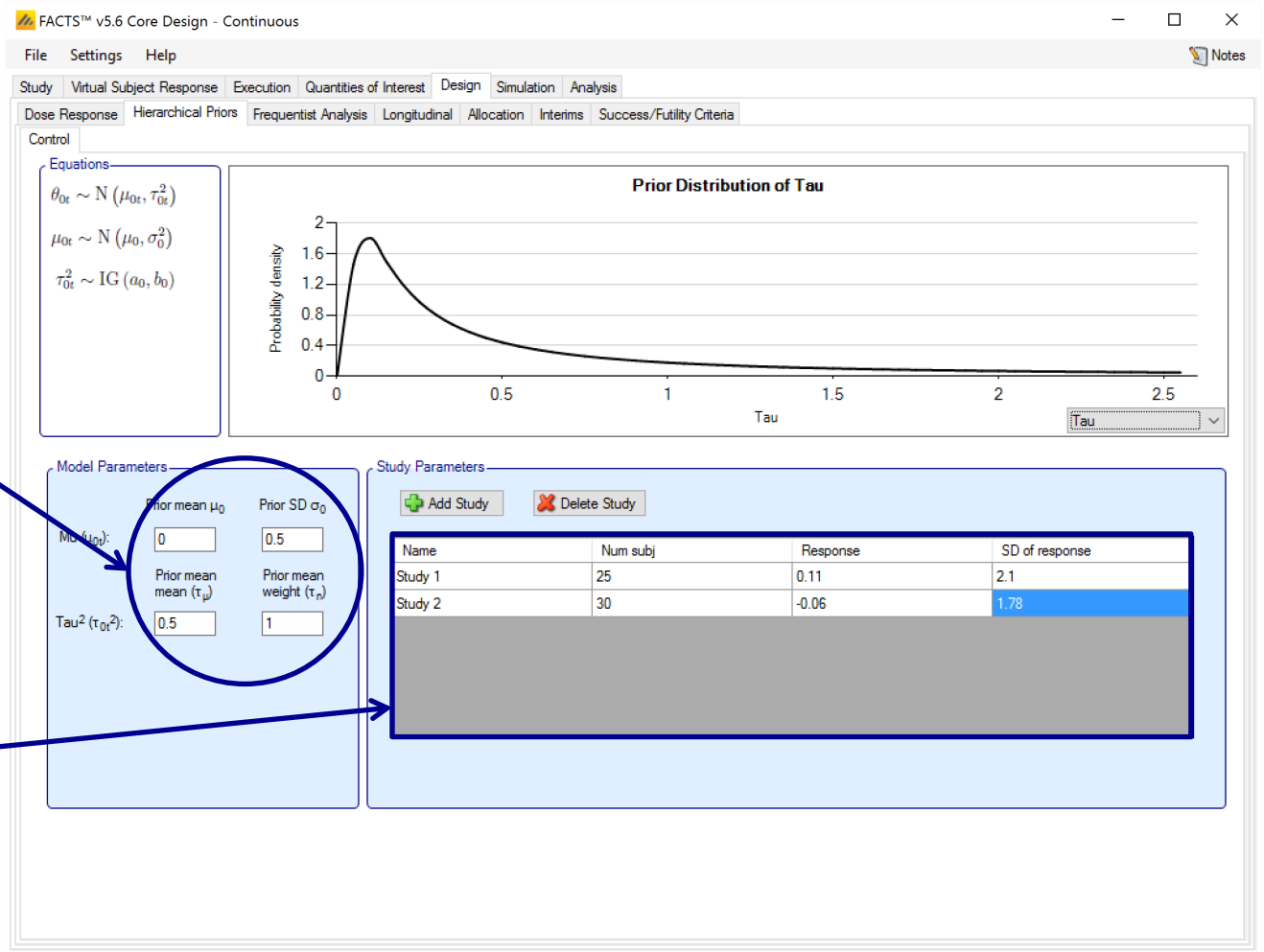
Baseline Adjustment



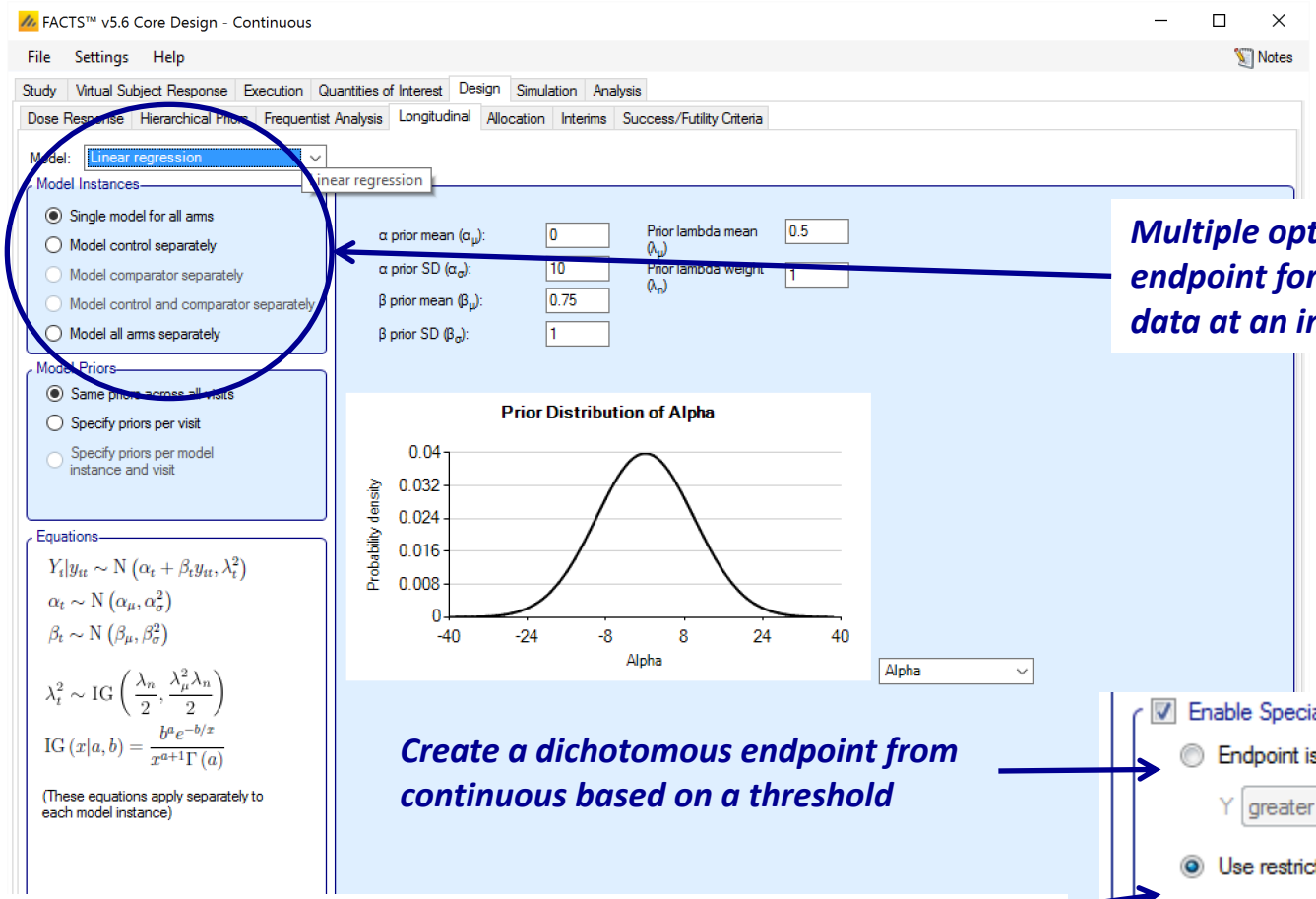
Hierarchical Prior for Control

Priors for hierarchical model

Prior trial data

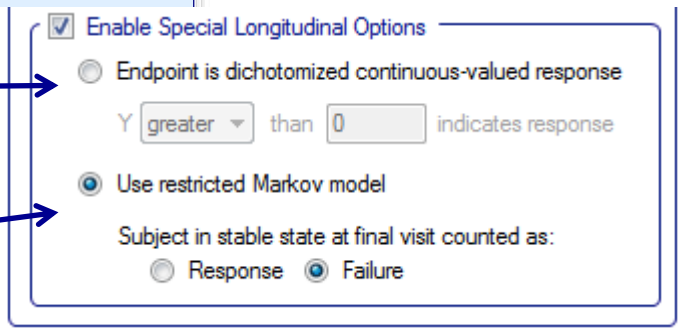


Longitudinal Models



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

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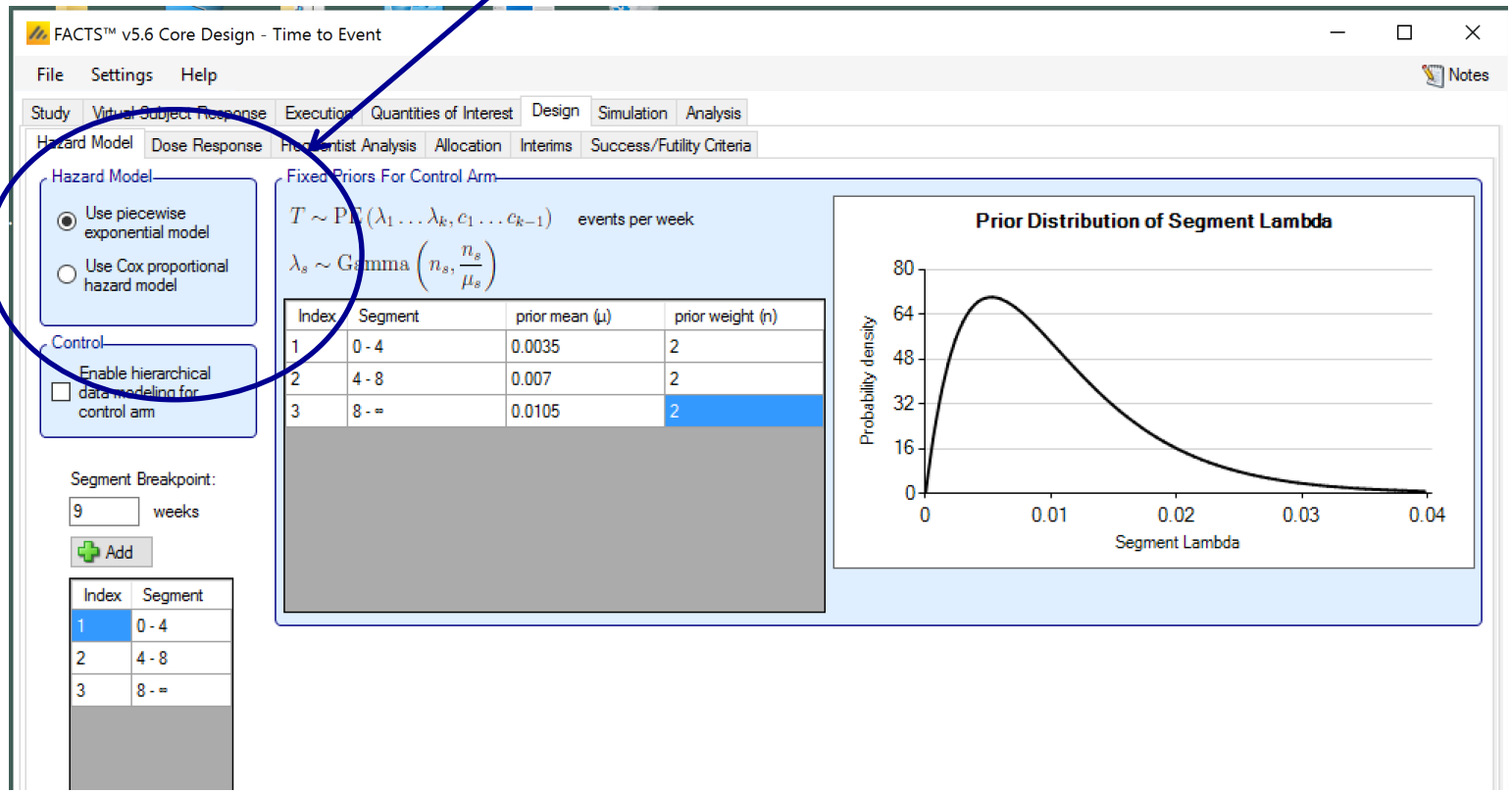
Time-to-Event (TTE) Models

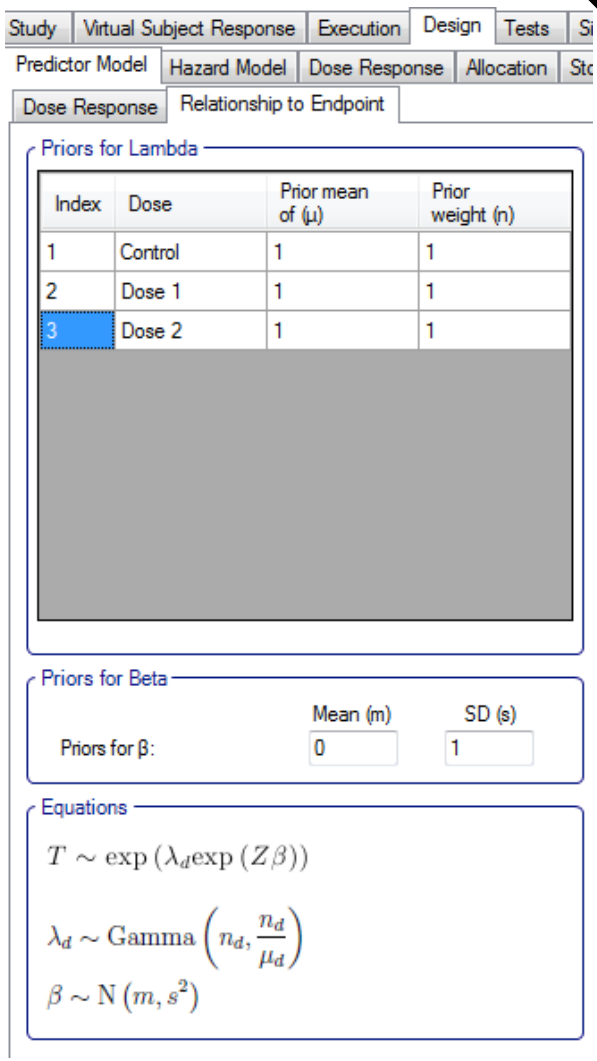
Piecewise-exponential
or
Cox proportional hazard

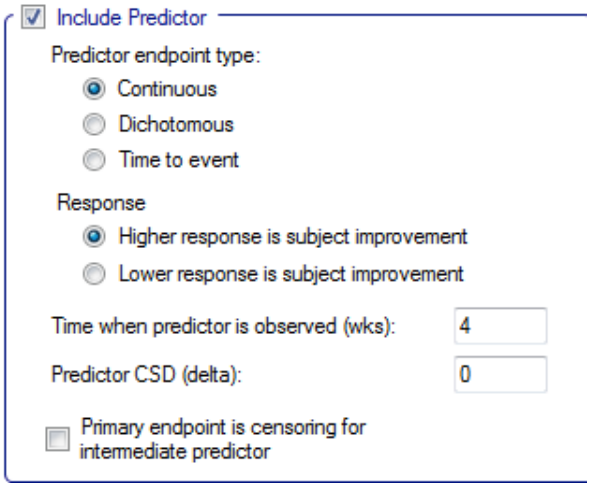


Early Predictors for TTE

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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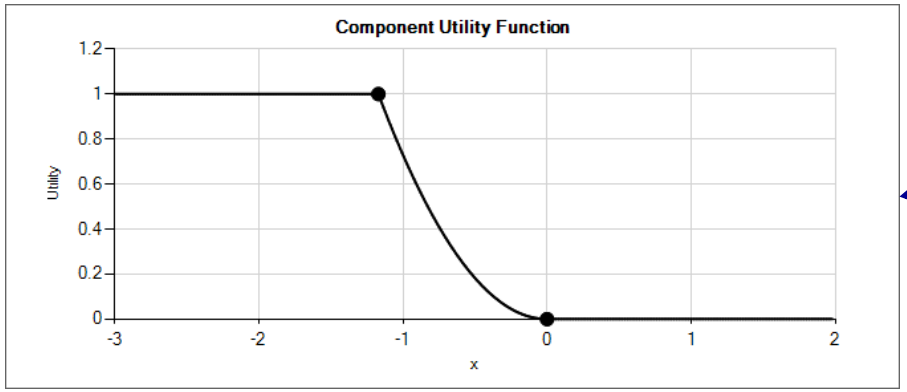
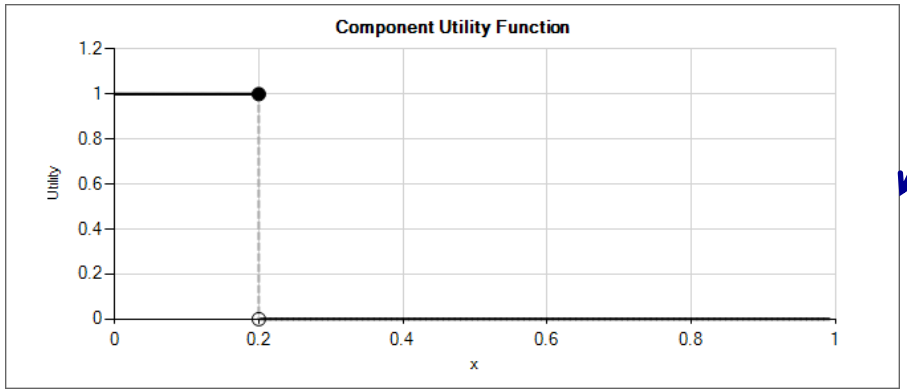
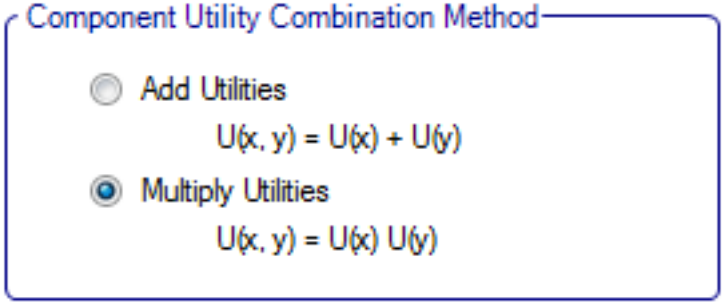
Utility Functions: Multiple Endpoint





Specify utility (weight) functions for each endpoint

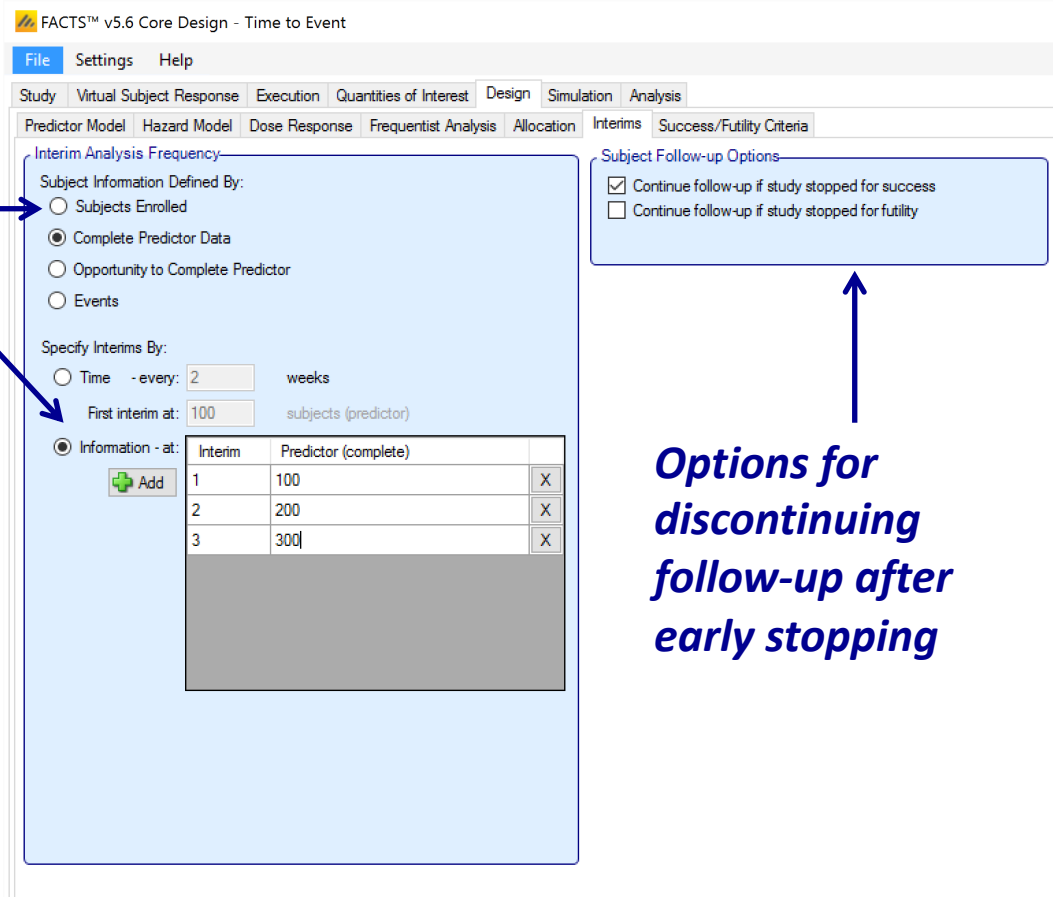
Combine utilities either additively or multiplicatively



Adaptations and evaluation criteria are based on the estimated utility

Timing/Frequency of Interims

Specify frequency based on number enrolled, number of events, by timing, by number of subjects complete.



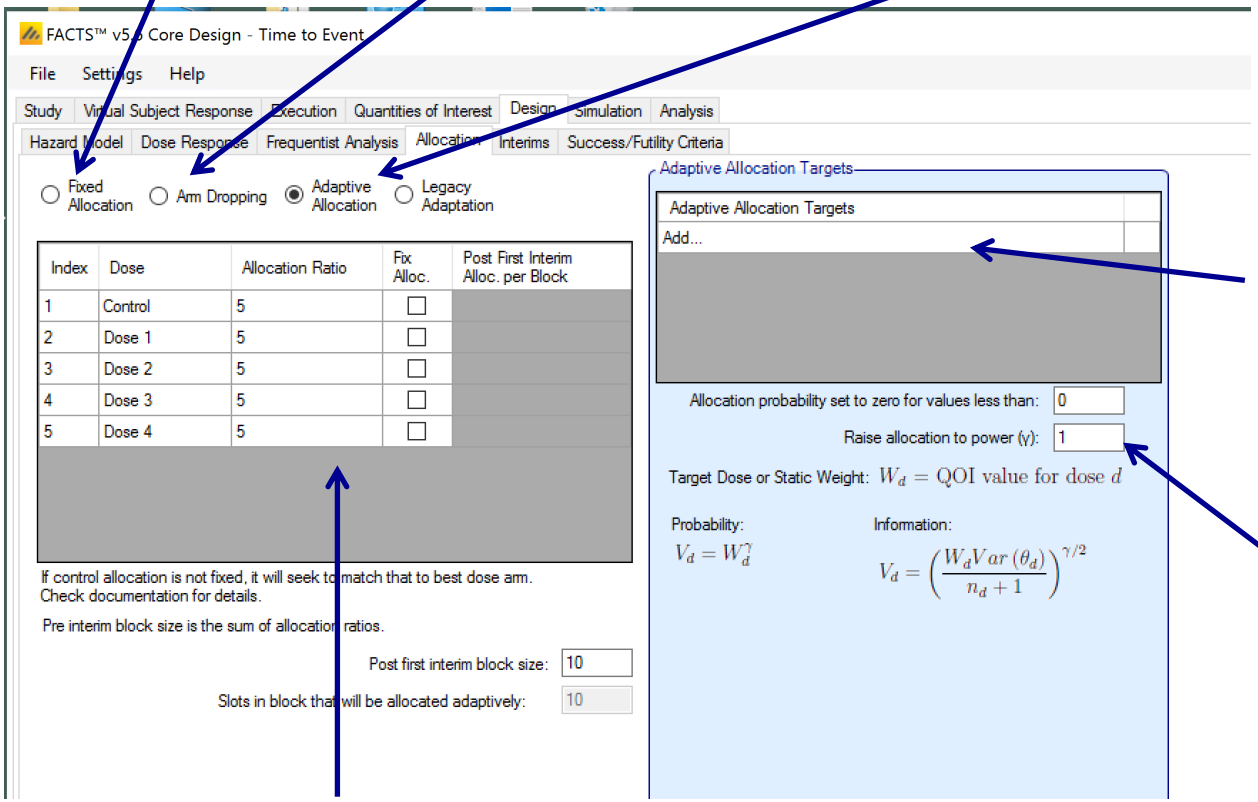
Options for discontinuing follow-up after early stopping

"Subjects complete", can be:

- ***Complete up to a particular visit,***
- ***Complete on a particular endpoint***
- ***Those who actually completed,***
- ***Or those who could have completed (but may have dropped out).***

Adaptations

Fixed allocation ***Arm dropping*** ***Response adaptive randomization***



Combine targets for dose response adaptive randomization (RAR)

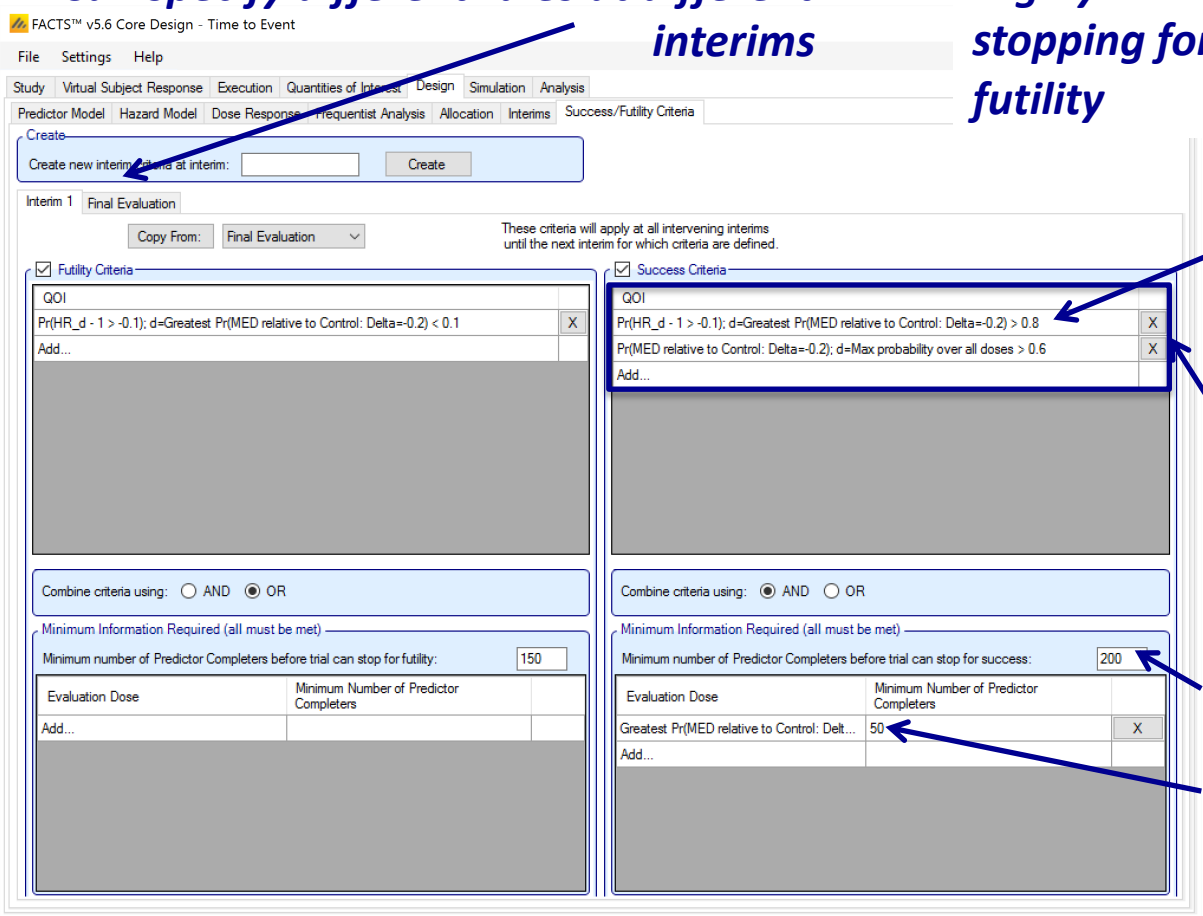
Control how moderate or aggressive the adaptation is

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

Early Stopping Rules

Can specify different rules at different interims

Highly customizable early stopping for success and/or futility



Rules use defined "Quantity of Interest", at a target, beating a threshold.

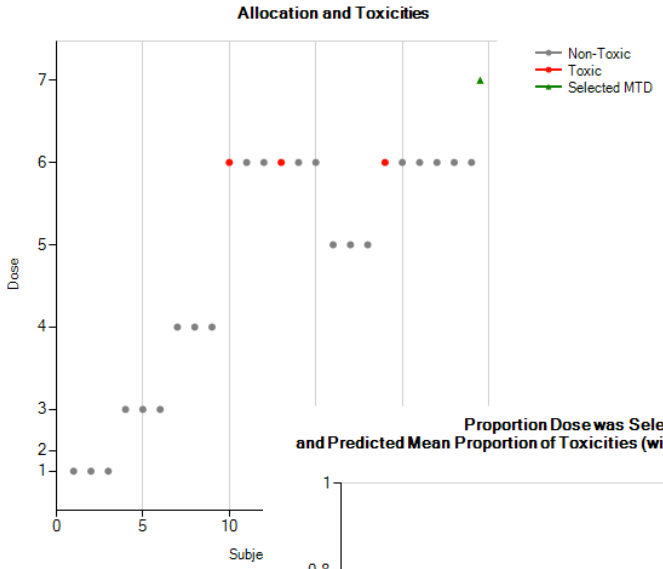
Ability to combine multiple rules

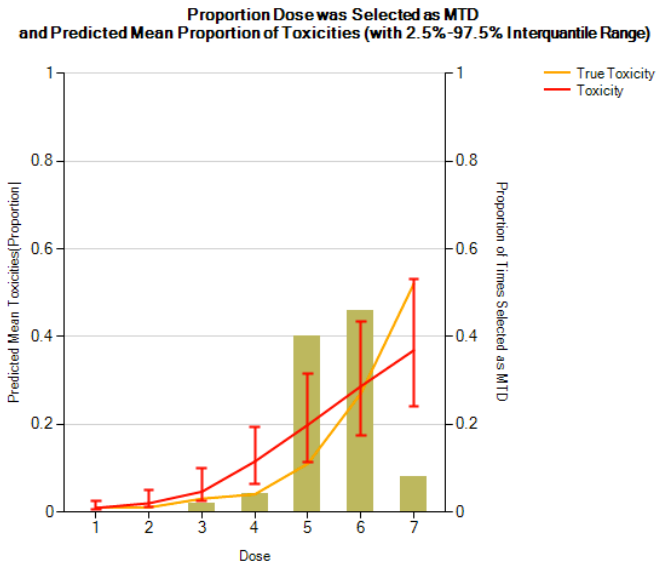
Minimum requirements for number of subjects enrolled or complete (or number of events for TTE).
Can be overall or on a specific arm.

FACTS DOSE ESCALATION DESIGNS

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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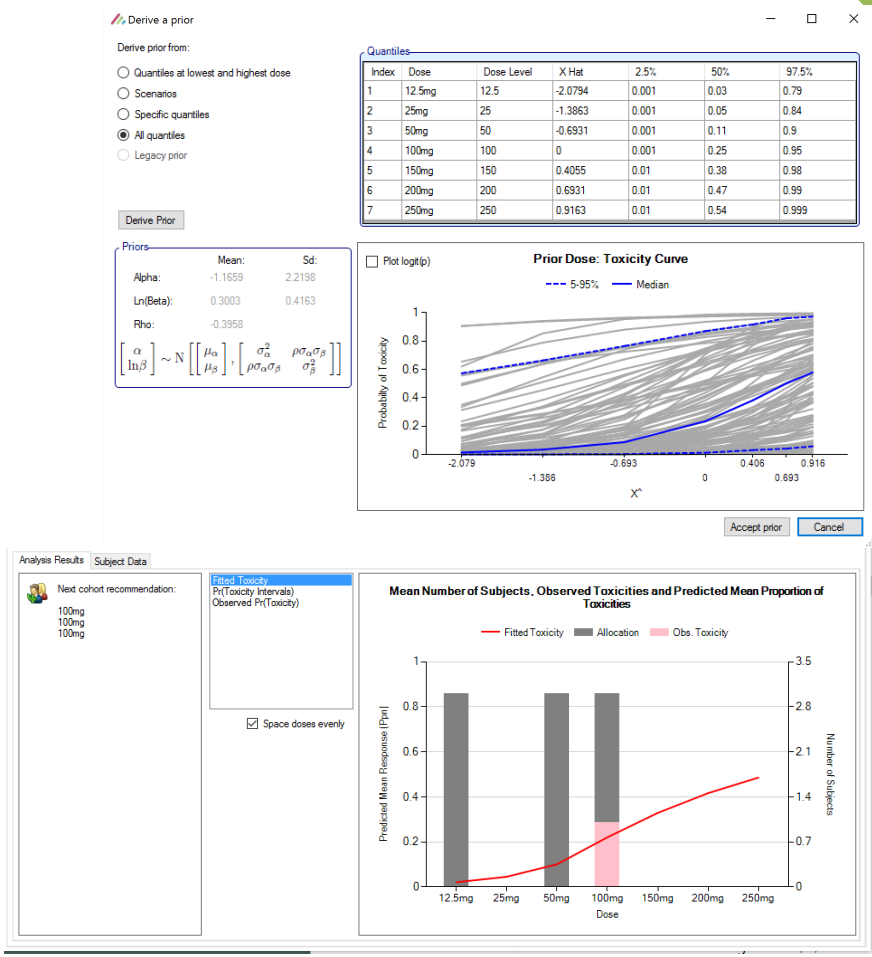
Toxicity Bands & Overdose Control

- Novartis CRM method
- Support for deriving prior
- Copious extensions
  - Continuous enrolment
  - Fine grain dose selection
  - “Look ahead” stopping rules
- Support for trial implementation



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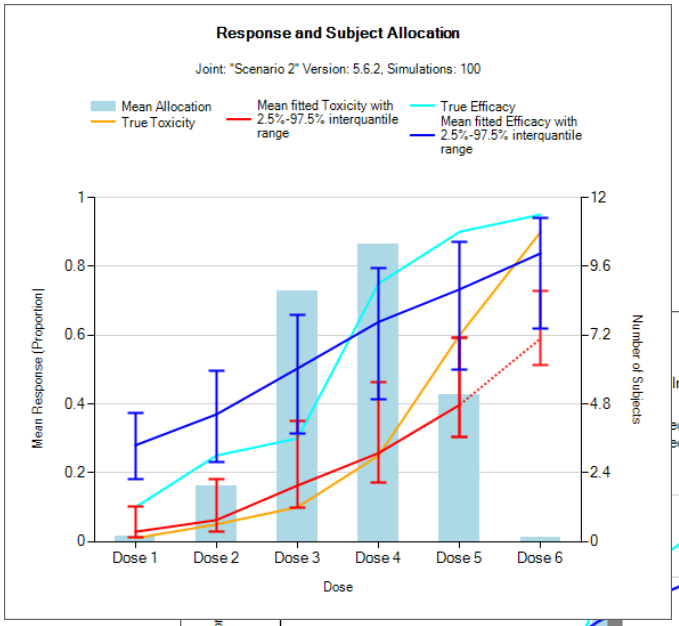
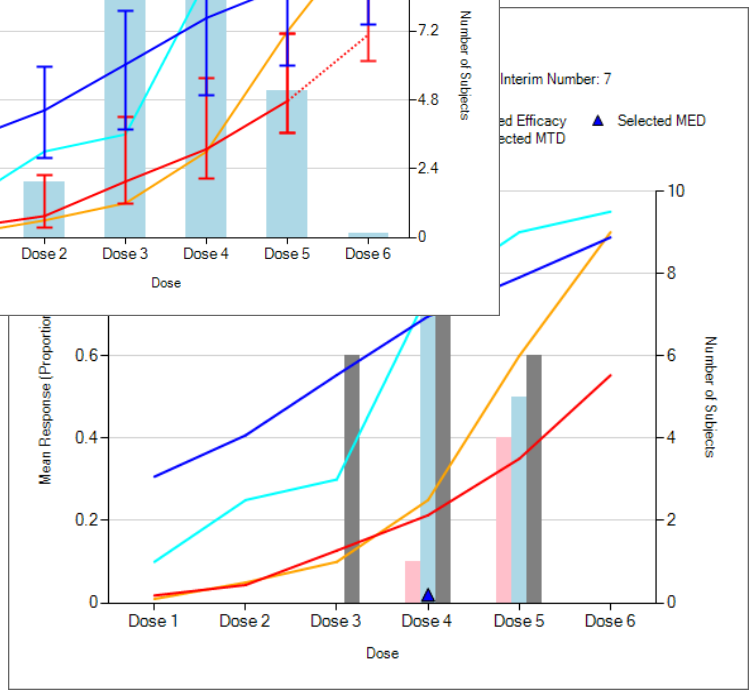
Bivariate CRM: Efficacy & Toxicity

- bCRM
- Estimate Toxicity and Efficacy
- Target “Optimal Dose”





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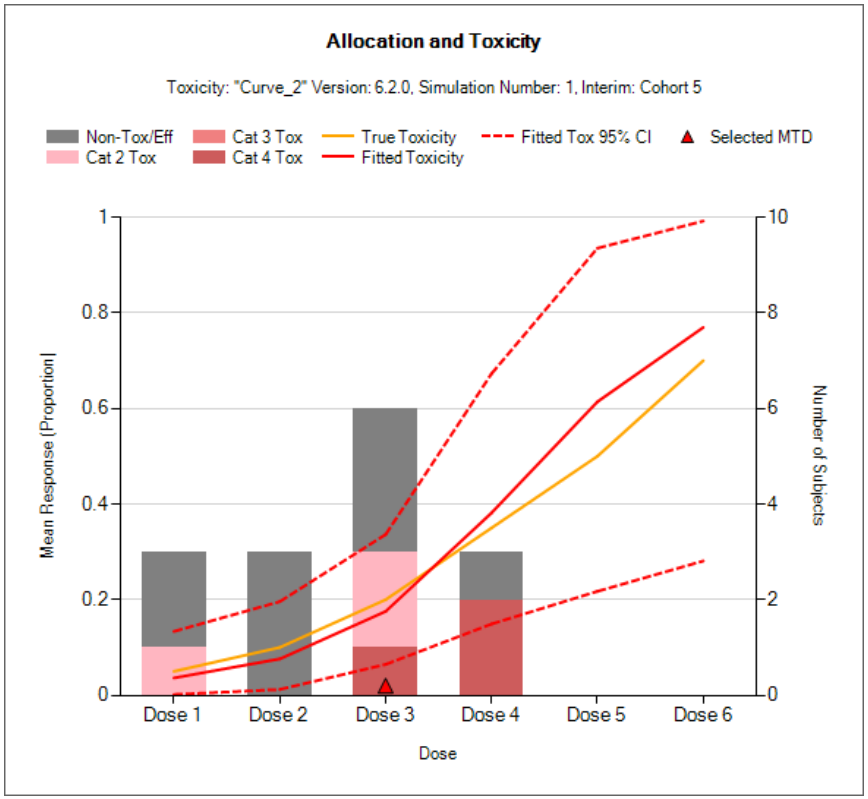
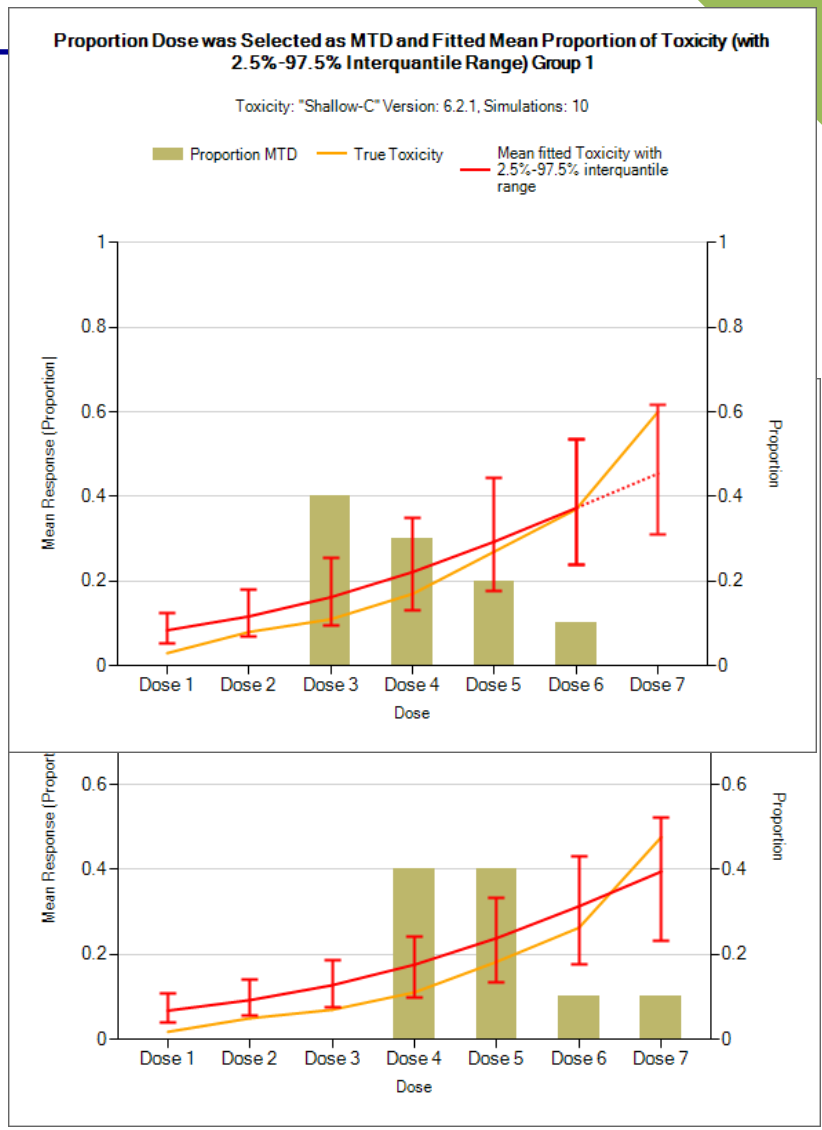
Ordinal CRM

- CRM with 3 or 4 categories of toxicity
- Separate logits for each category
  - Common slope
  - Independent alpha's constrained $\alpha_2 > \alpha_3 > \alpha_4$



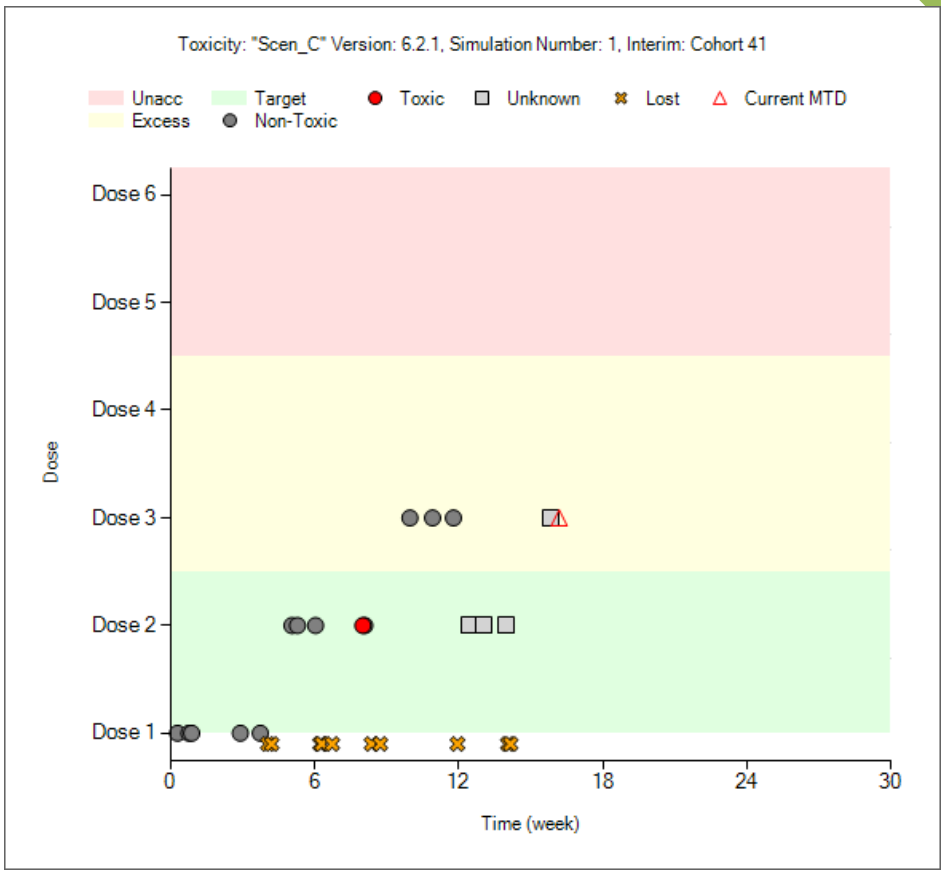
2 Groups

- 2 parallel CRMs – e.g. in 2 treatment regimes, or 2 populations such as adult and child.
- Separate logits for each category
  - Optionally with a common slope
  - Independent alpha's optionally constrained $\alpha_2 > \alpha_1$ or $\alpha_2 < \alpha_1$



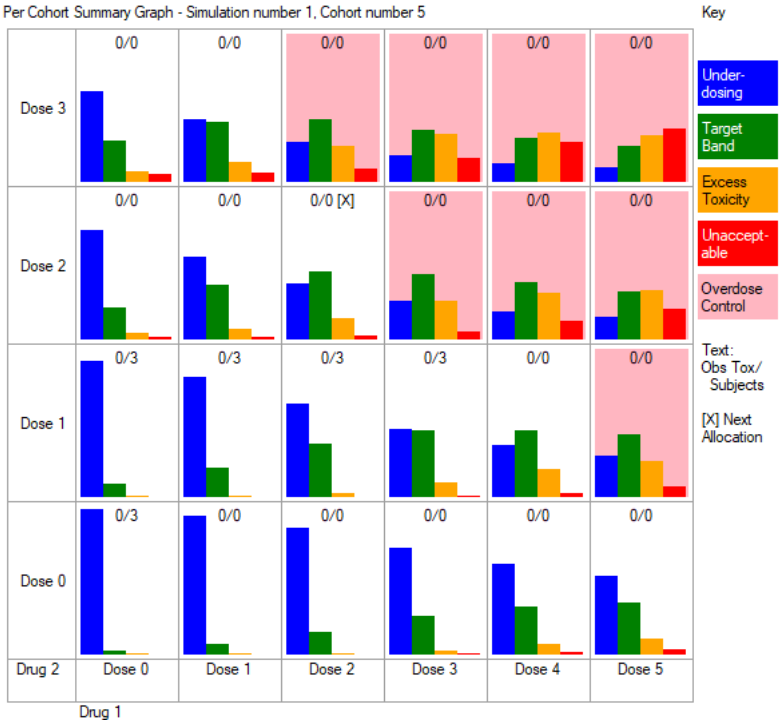
Cohort or Open Enrolment

- Recruitment can be by cohort or ‘open enrolment’ with a ‘maximum # incomplete
- All these features efficacy, open enrolment, ordinal toxicity, 2 groups, etc. can be combined (from FACTS 6.2 onwards).



2D-CRM – Dose Escalation in 2D

- 2 combined Bayesian Logistic Models, plus interaction term
- Toxicity band targeting & over dose control
- Multiple escalation strategies
- Ability to augment model prior with ‘prior pseudo subjects’ data



FACTS ENRICHMENT DESIGNS

Enrichment Designs (ED)

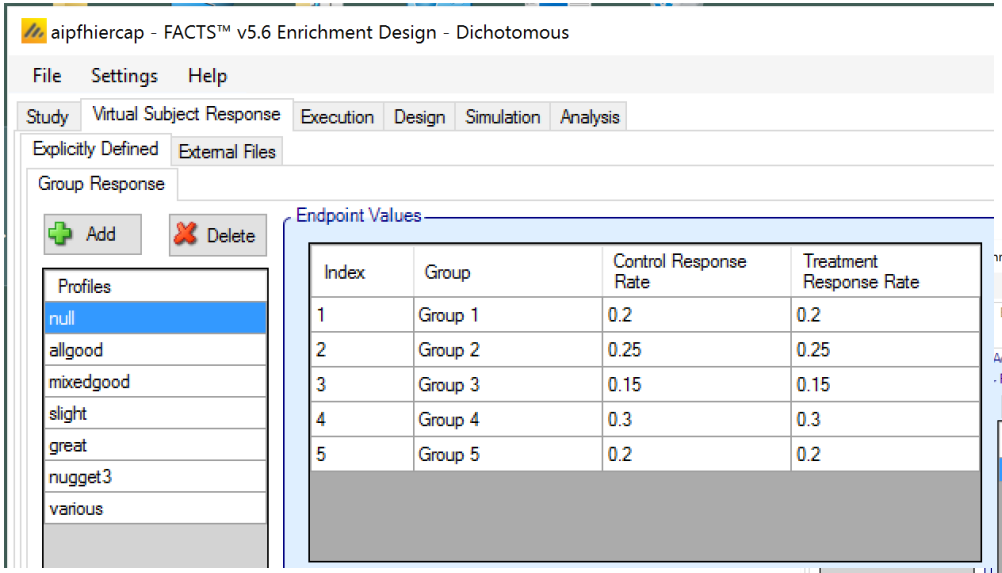
- Given a set of populations, where is the treatment effective?
- Or testing a treatment across a range of indications, can easier to study indications help us on harder ones?

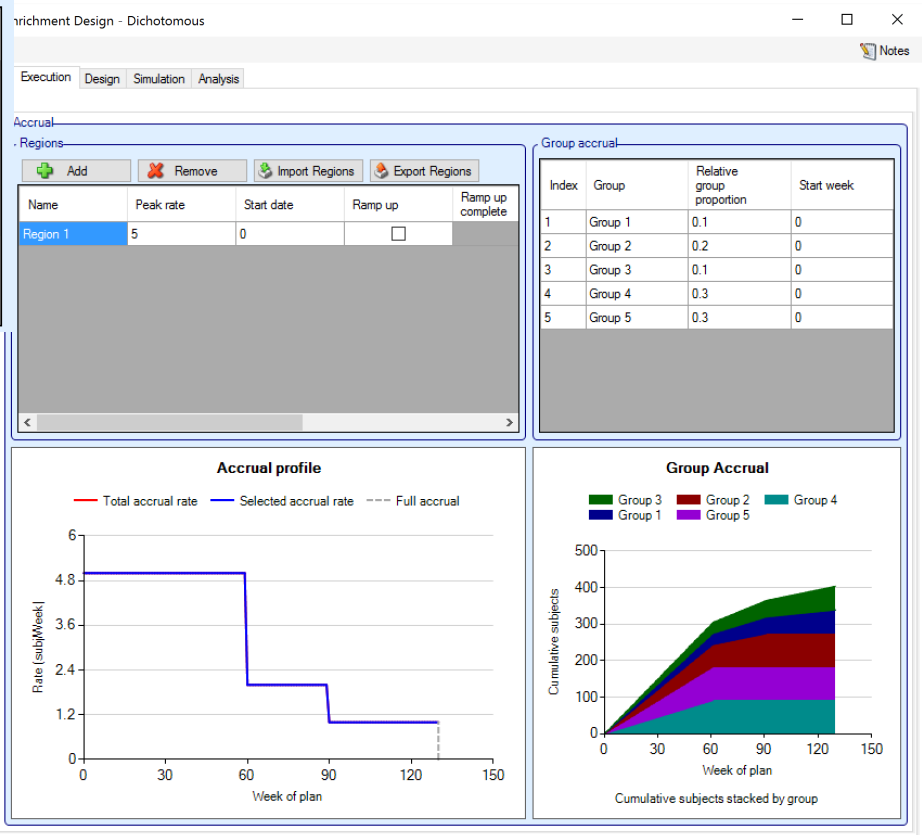
- Option of hierarchical borrowing of information across groups to make better decisions (borrows most when appropriate, less when not).

- Dropping of groups for futility or graduating for success

- Much current interest in this design within oncology
  - part (not all) of I-SPY 2

Virtual Subjects





Simulate subject responses and accrual/dropout according to group membership

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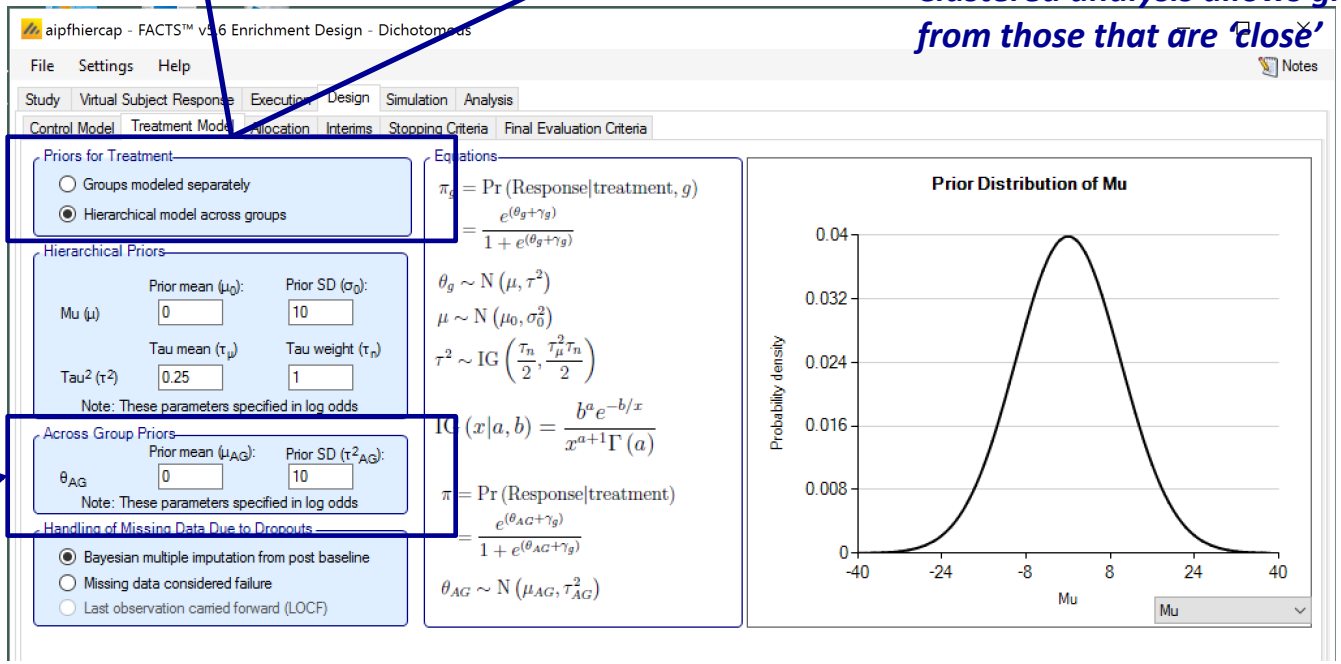
ED Statistical Models

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***
- ***Clustered analysis allows groups to borrow from those that are 'close'***



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

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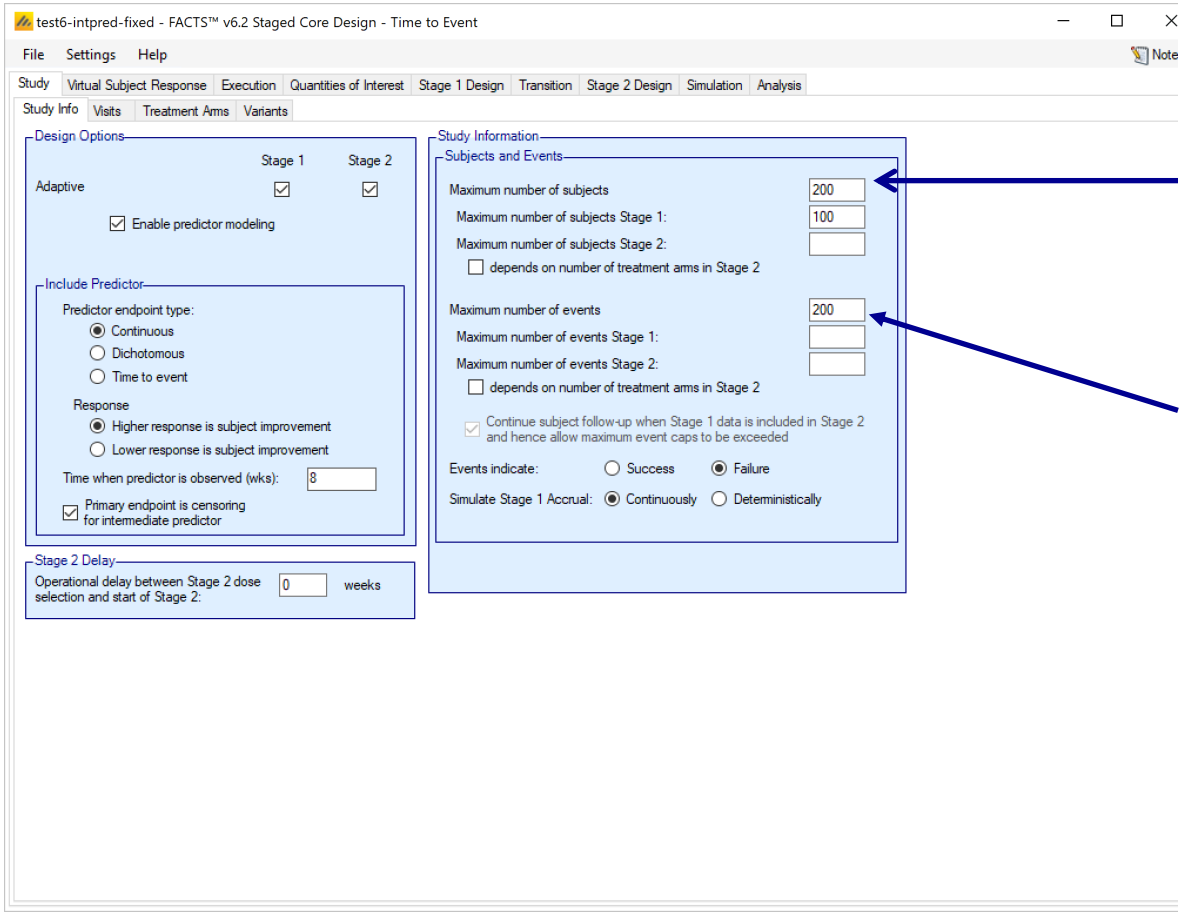
FACTS STAGED DESIGNS

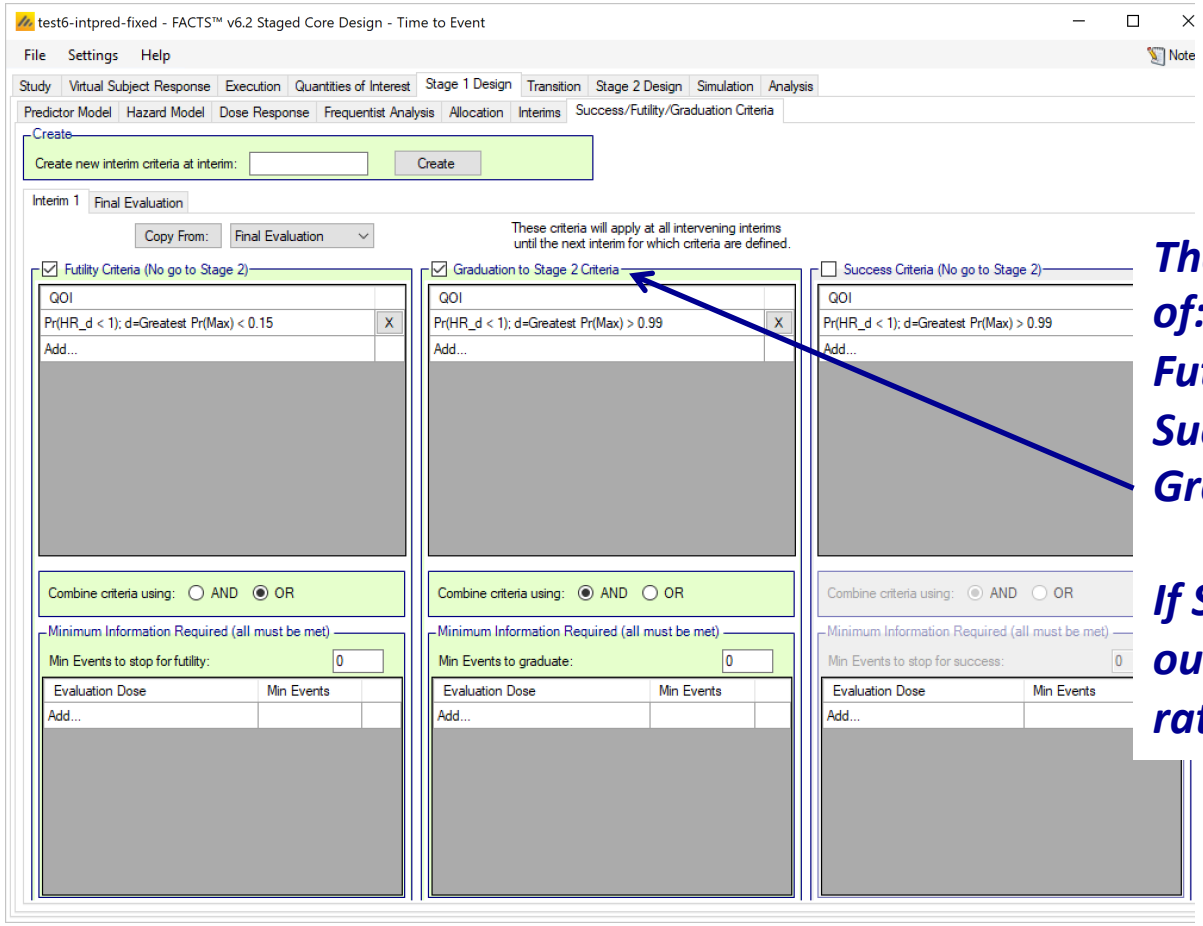
2 Separate Trials, or 2 stage trials



Ability to set max overall size for both stages and/or max size for one or both stages.

With a TTE endpoint, size can be set for both maximum number of subjects and maximum number of events

2 Separate Trials, or 2 stage trials



The outcome of Stage 1 is now one of:

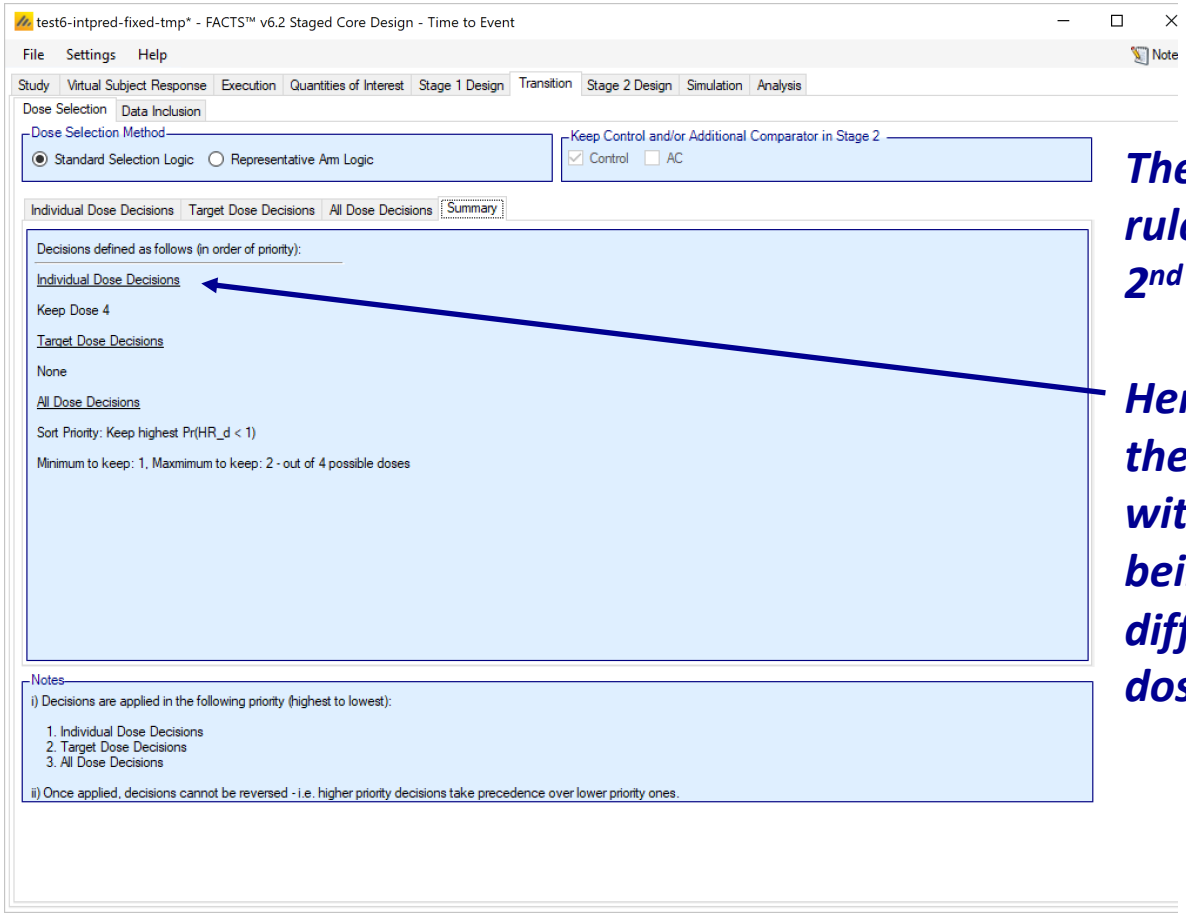
Futility: don't run the second stage

Success: don't run the second stage

Graduation: run the second stage

If Stage 1 is adaptive, these outcomes can also be decided 'early' rather than at the end of the stage.

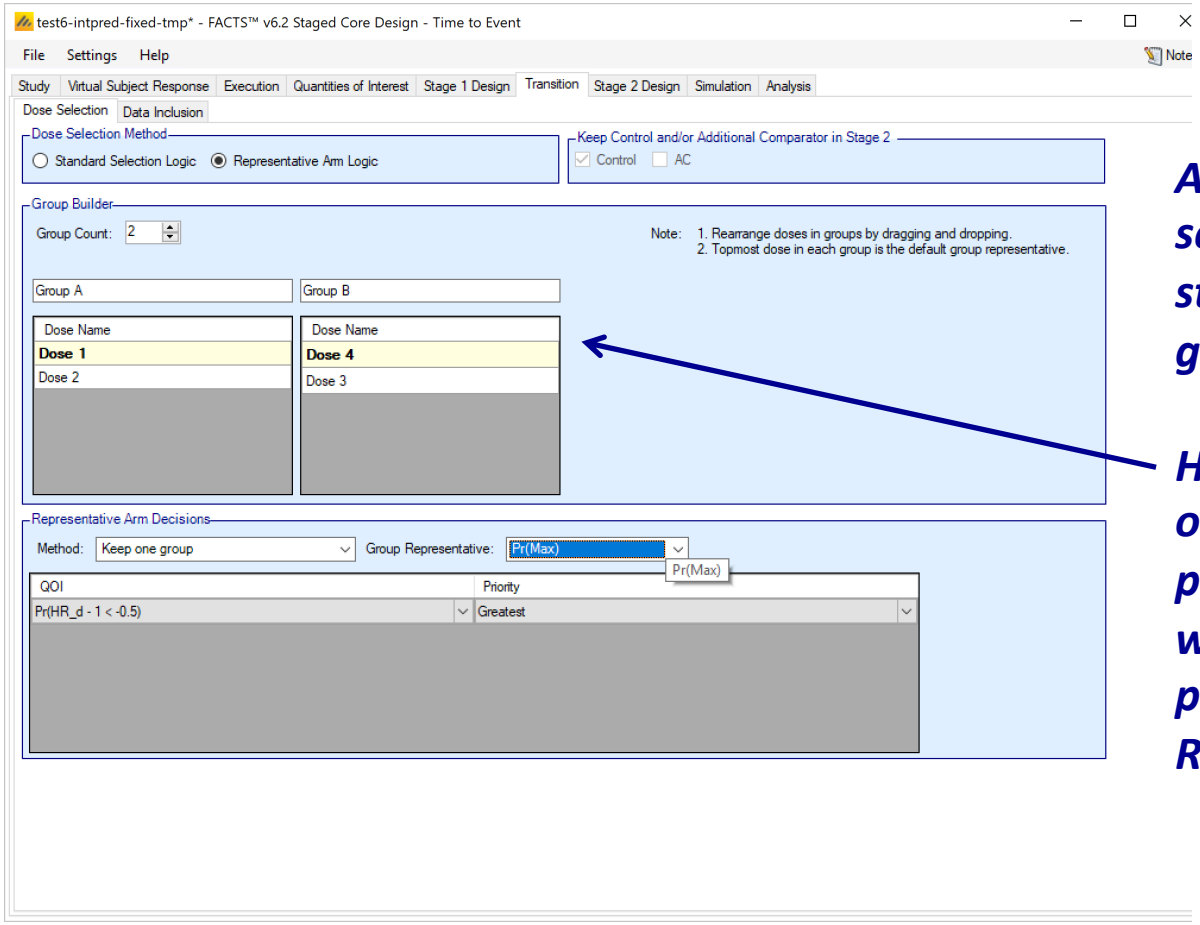
2 Separate Trials, or 2 stage trials



There are flexible arm selection rules for which arms to take to the 2nd Stage

Here for example: 'take Control, the maximum dose, and the dose with the maximum probability of being better than control (if different from the maximum dose)'.

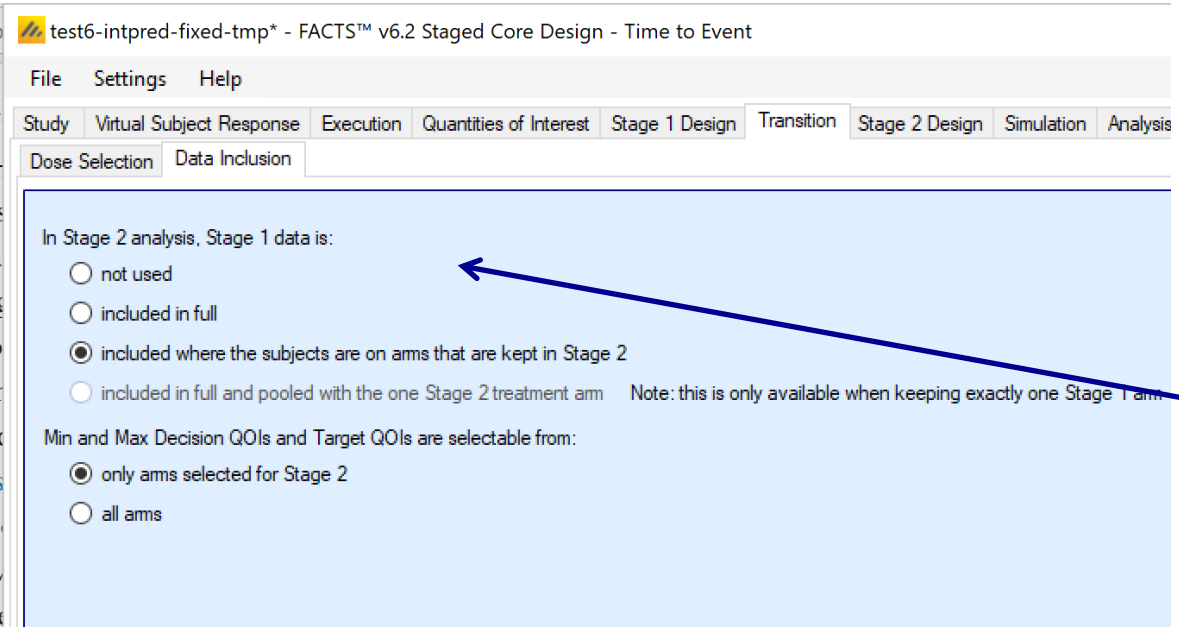
2 Separate Trials, or 2 stage trials



Alternatively arms can be selected for using in the second stage by first dividing them into groups.

Here we take either Arms 1 & 2, or Arms 3 & 4 based on the best performing arm of either pair – which has the highest probability of having a Hazard Ratio of < 0.5.

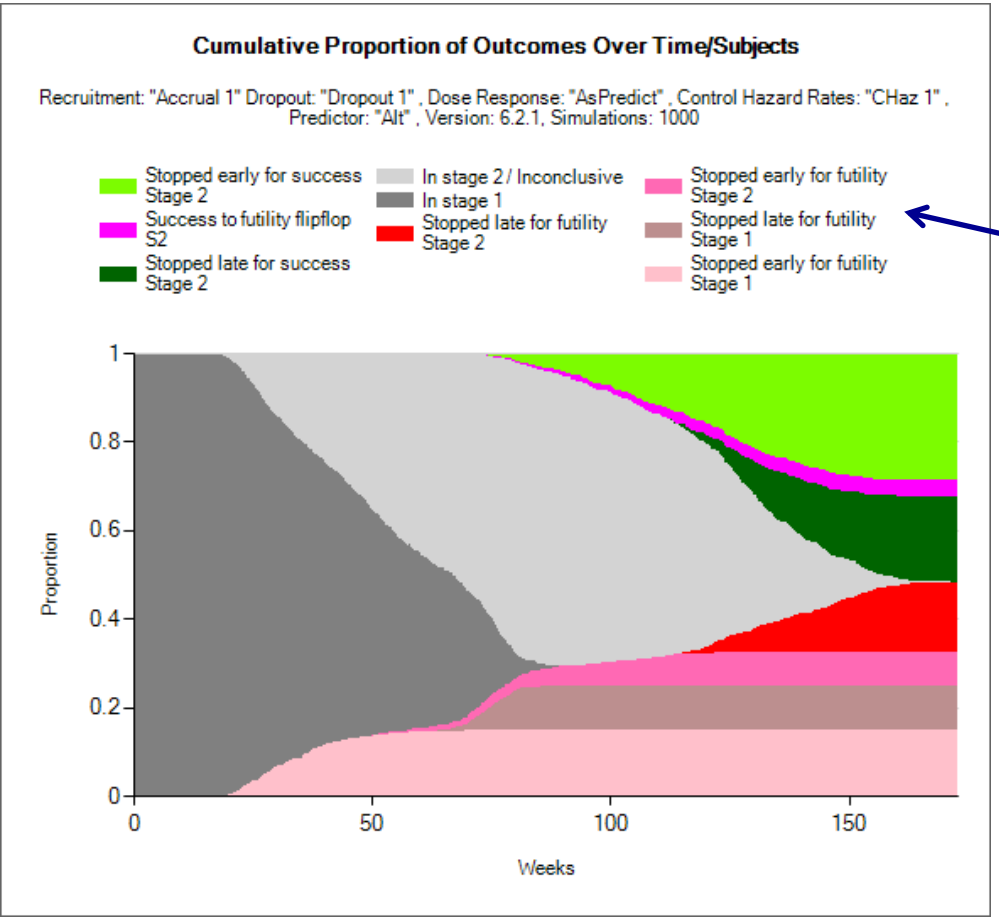
2 Separate Trials, or 2 stage trials



There are multiple options on whether and which first Stage data can be included in the second Stage analysis.

From 'None' to 'All' with several options in between.

2 Separate Trials, or 2 stage trials



There are copious results with details and summaries of:

Stage 1

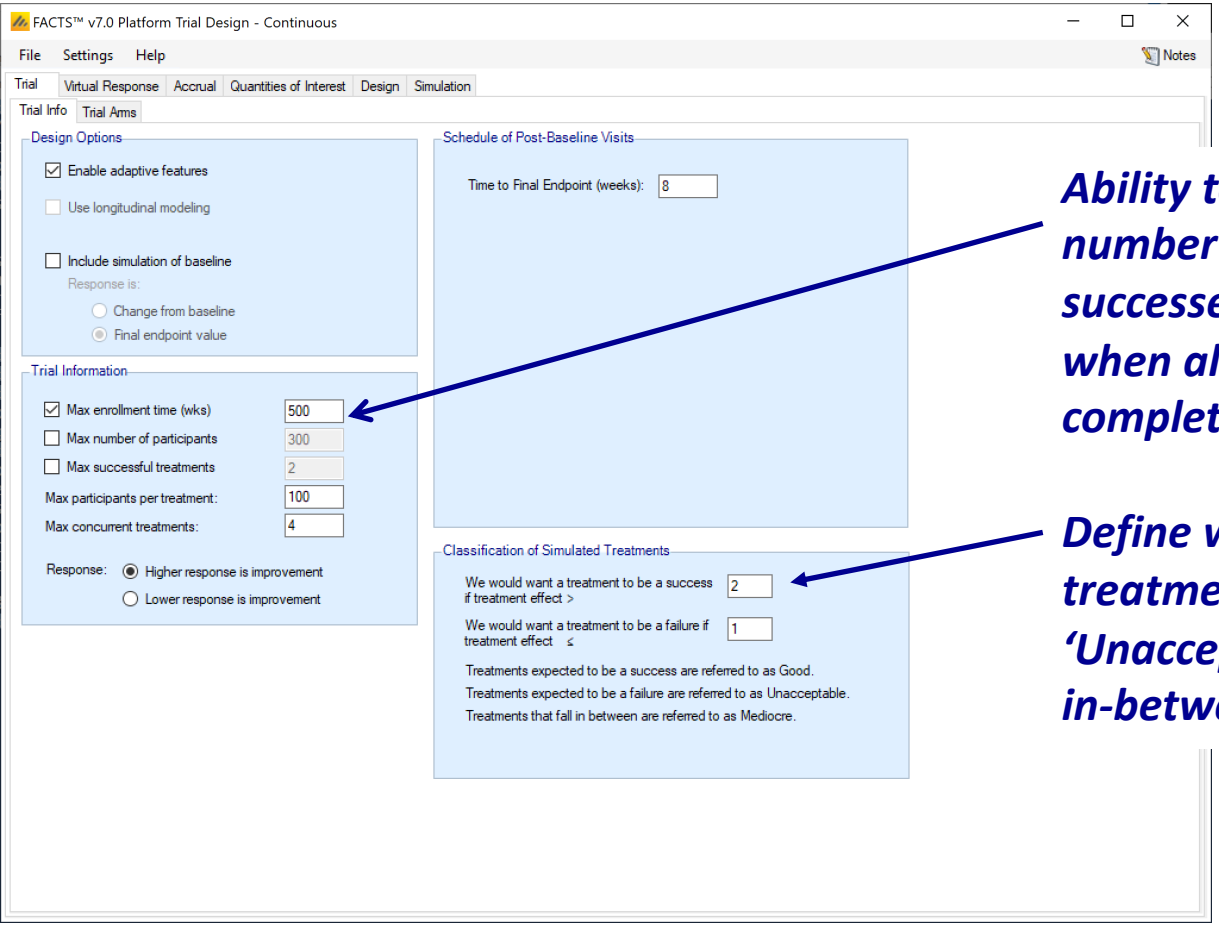
The treatment selection at the end of Stage 1

Stage 2

Overall

FACTS PLATFORM TRIALS

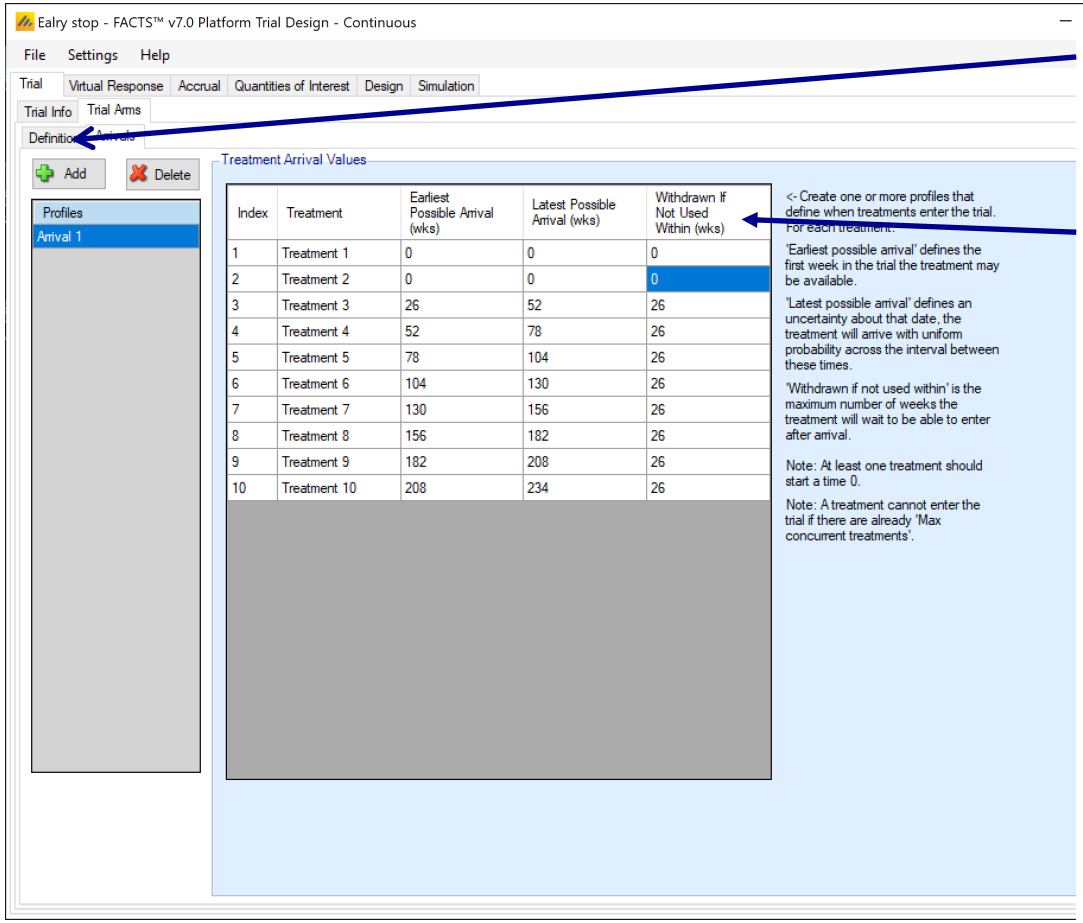
Multiple Stopping Criteria



Ability to set limit of simulation by time, number of trial participants, number of successes. Simulation will always end when all the defined treatments have completed.

Define what counts as a 'Good' treatment and what counts as an 'Unacceptable' treatment. Treatments in-between are labelled 'Mediocre'.

Many Treatments Over Time



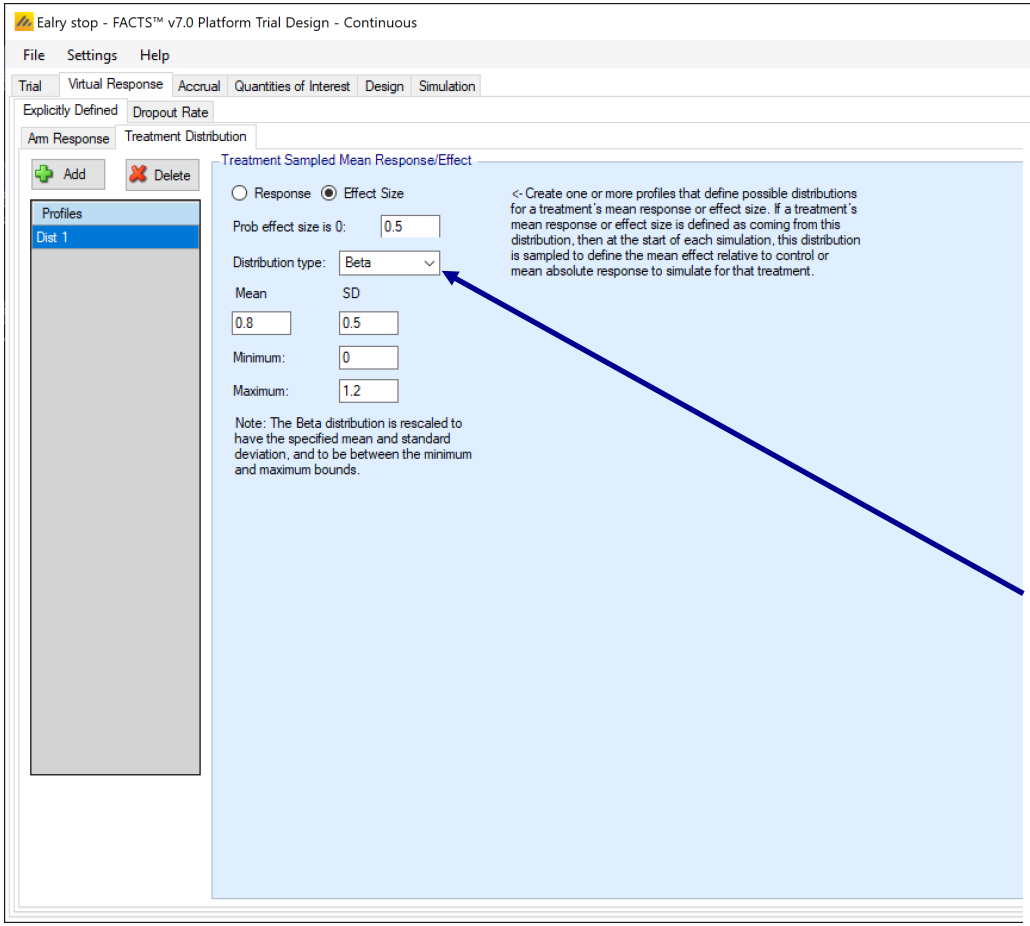
Define the treatments that can be simulated on the previous tab.

Then for each treatment define the window when it could be available, and how long it it would be prepared to wait to enter the trial.

Treatment arrival is simulated as a random process with the arrival time sampled uniformly between their 'first and last' date.

Treatments might not enter immediately they arrive, there can be a 'max concurrent treatments' limit, and entry can be restricted to 'updates'.

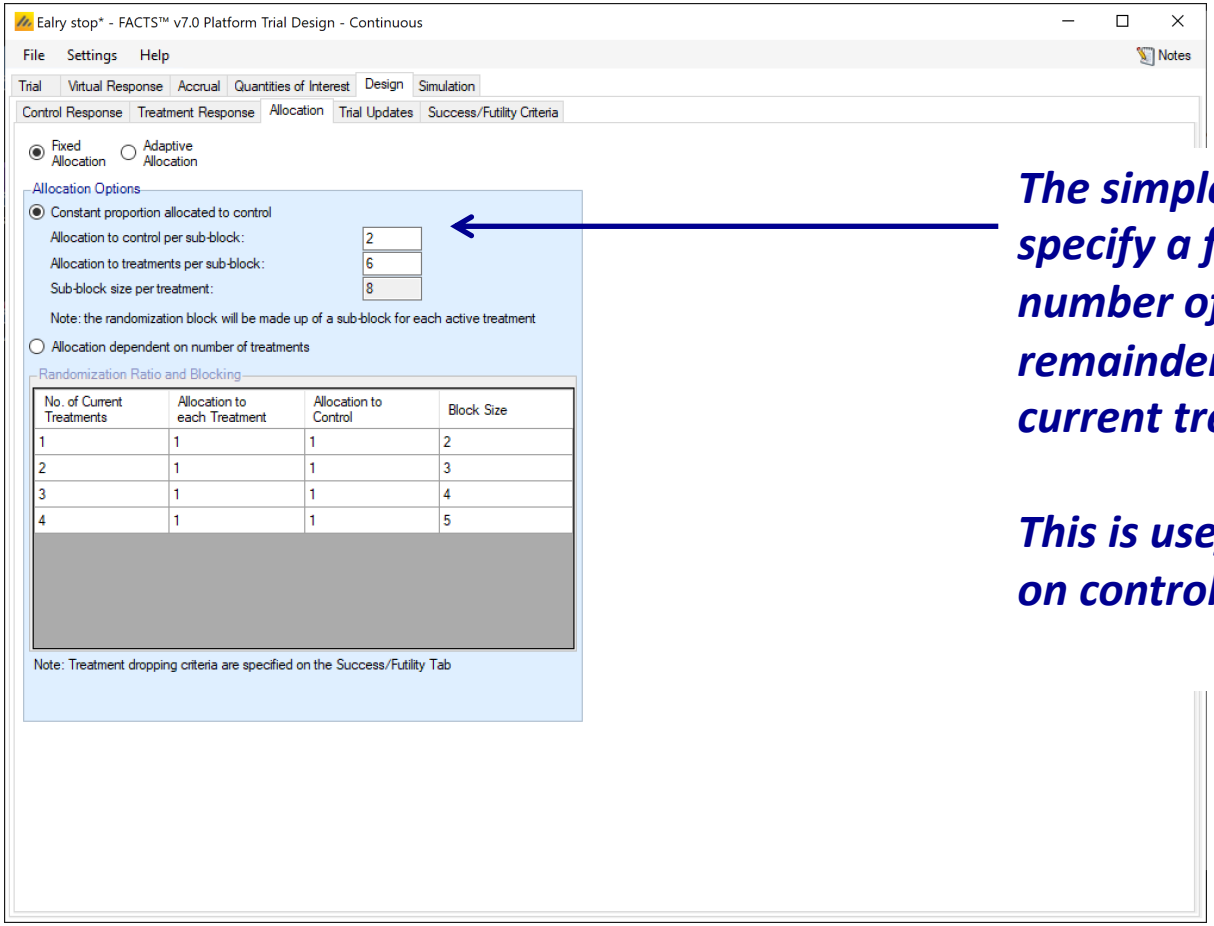
Simulated Response can be sampled



A treatment's simulated response can be specified as a fixed value (absolute or relative to control) or it can be specified as being sampled from a distribution at the start of each simulation.

Here we define such possible distribution, it can be absolute or relative to control, it can include a probability of no effect, the distribution can be Normal, Truncated Normal or Beta. With Mean, SD and limits defined.

Allocation: fixed proportion to control

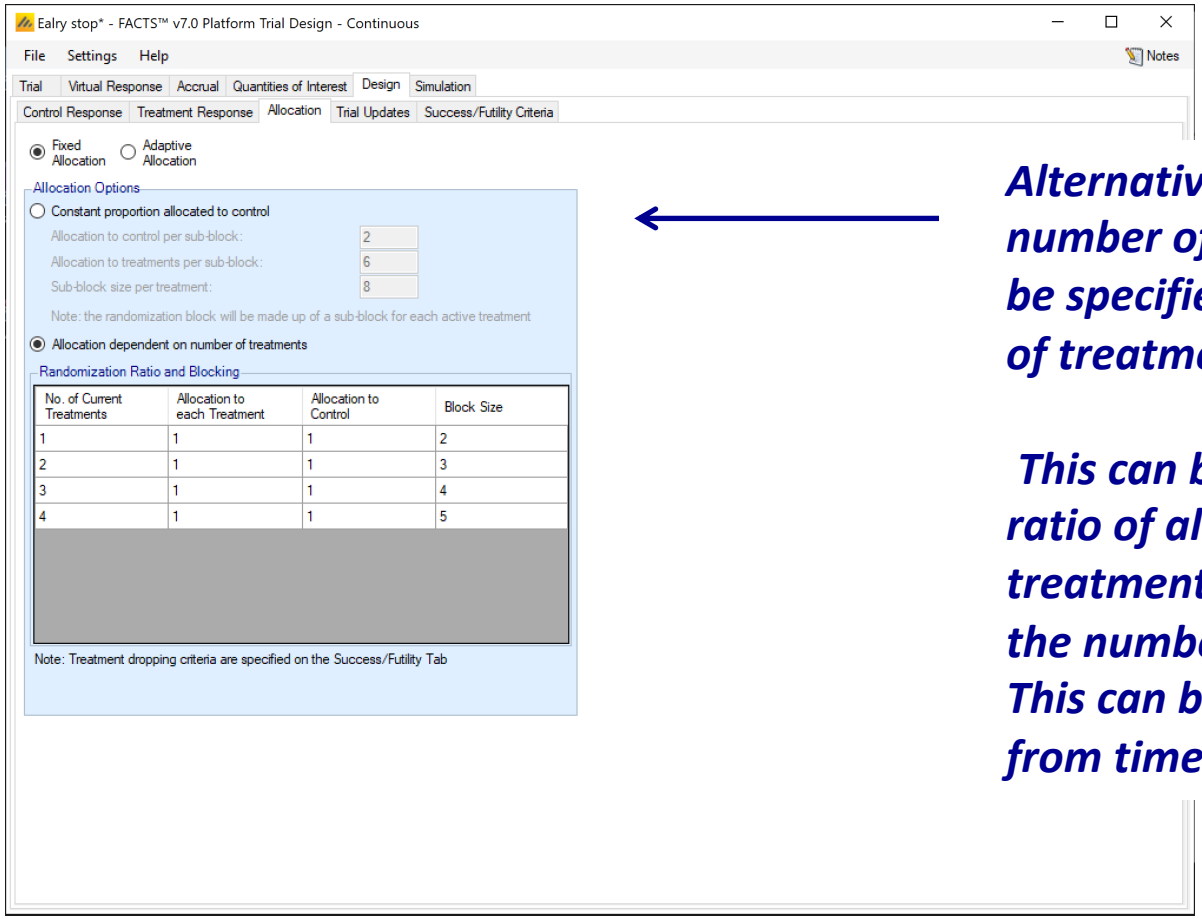


The simplest allocation option is to specify a fixed block size, with a fixed number of slots allocated to control, the remainder being divided between the current treatments in the trial.

This is useful if a guaranteed proportion on control is required.

Allocation: ratios dependent on the number of treatments

Platform



Alternatively the block size and the number of slots allocated to control can be specified dependent on the number of treatments currently in the trial.

This can be used to ensure a constant ratio of allocation between any treatment and control independent on the number of treatments in the trial. This can be used to avoid bias arising from time trends.

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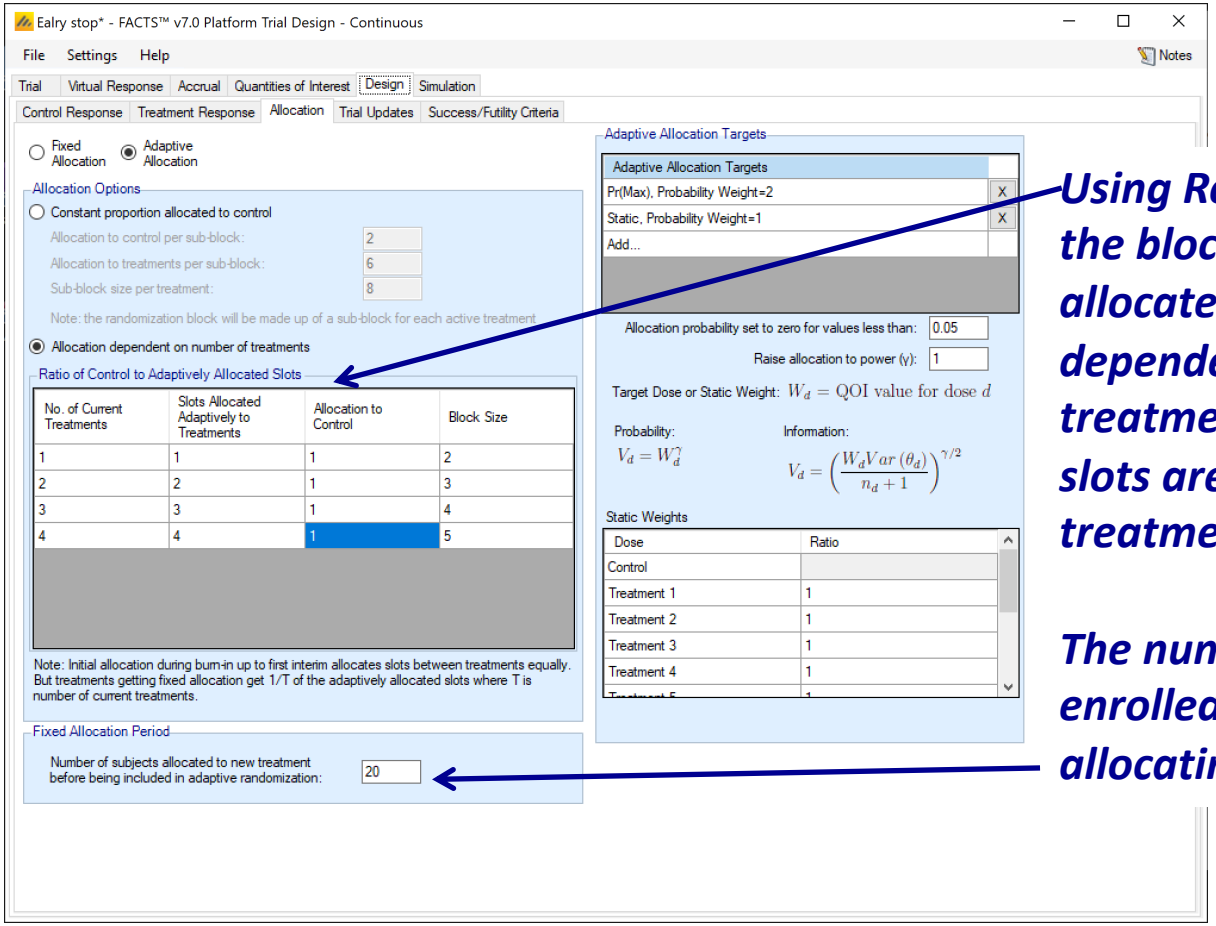
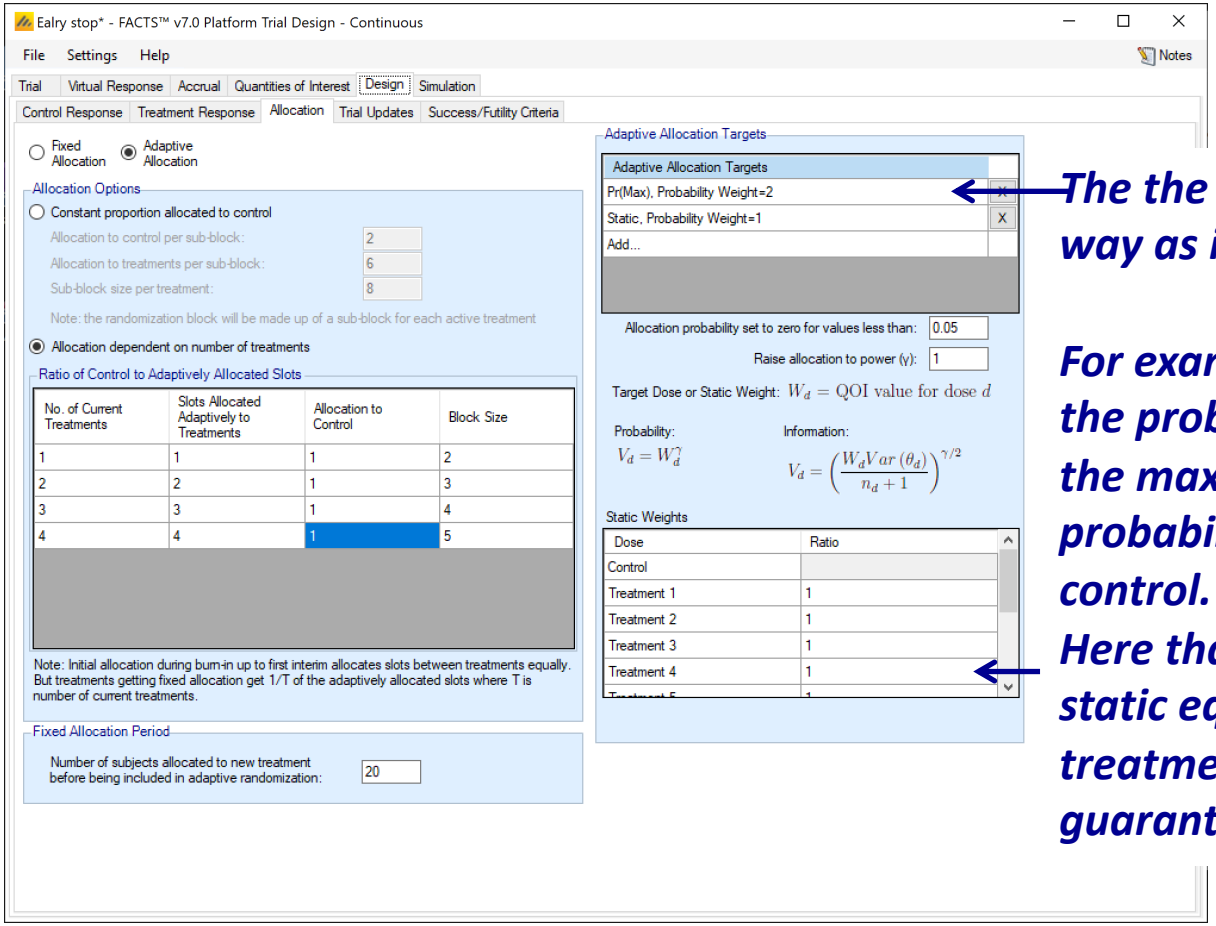
Allocation: response adaptive



Using Response Adaptive Allocation the block size and number of slots allocated to control is specified dependent on the number of treatments in the trial - the remaining slots are divided between the treatments.

The number of participants to be enrolled to a treatment before allocating to it adaptively is specified.

Allocation: response adaptive: 2

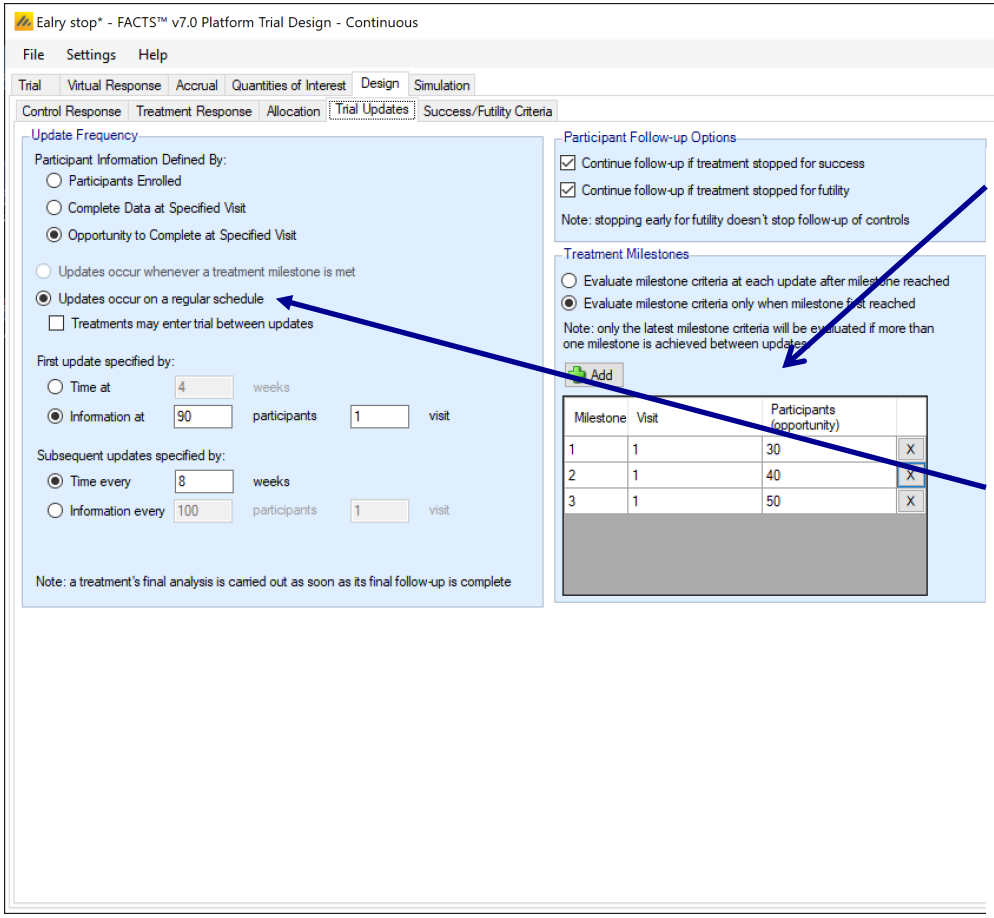


The the RAR is specified, the same way as in FACTS Core.

For example it can be on the basis of the probability that the treatment has the maximum response, or the probability that its better than control.

Here that has been combined 2:1 with static equal allocation to all treatments, so every treatment has a guaranteed minimum allocation rate.

Updates and Milestones

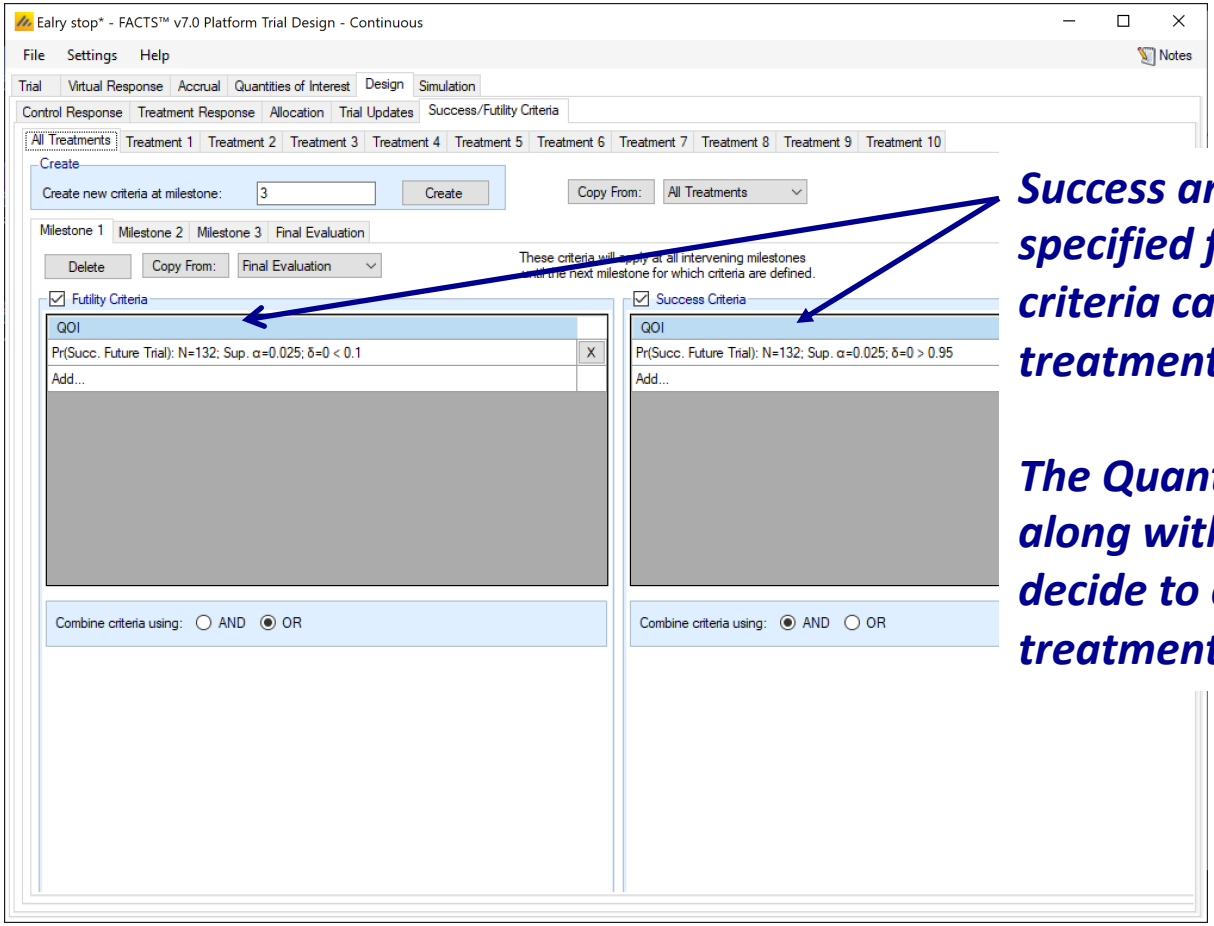


'Milestones' are specified that apply to every treatment, when they are reached early stopping criteria are tested for that treatment.

Interims can be specified to occur whenever a treatment reaches a milestone, or (as is more often the case in practice) to occur on a regular schedule with milestones being evaluated if they've been reached.

The entry of new treatments into the trial can be limited to updates.

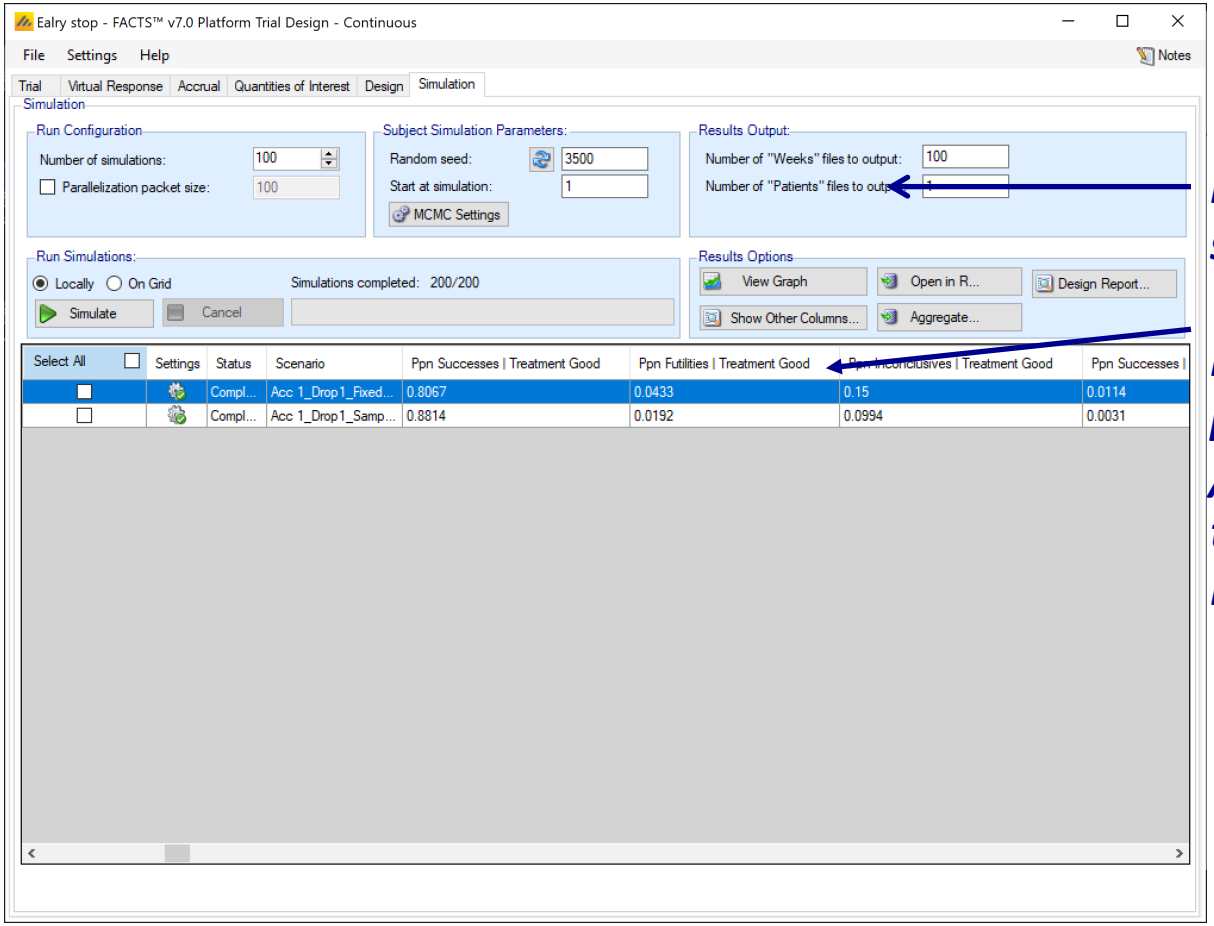
Success / Futility Criteria



Success and Futility criteria can be specified for each Milestone. Additional criteria can be specified for specific treatments.

The Quantity to evaluate is specified along with the threshold for the test to decide to declare Success/Futility for the treatment.

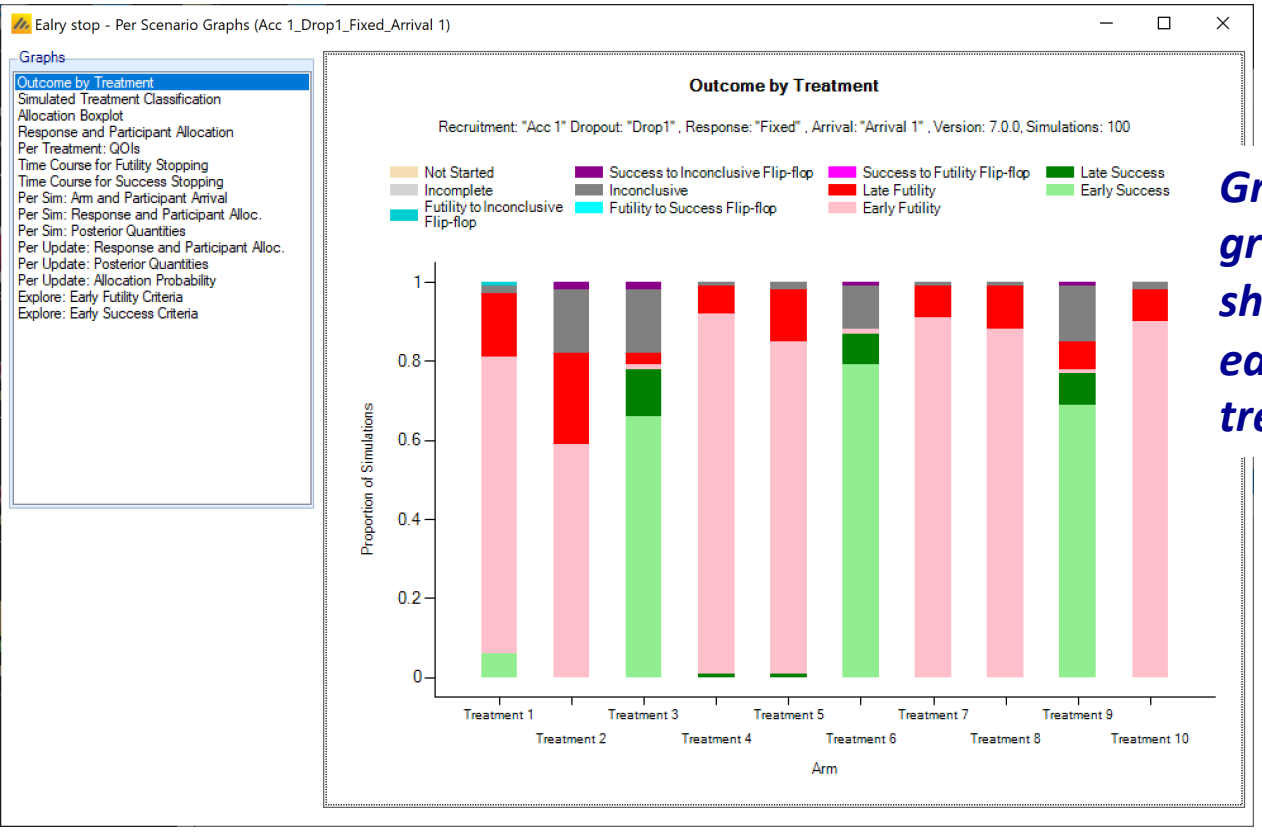
Simulation



Running simulations is the same as in the rest of FACTS.

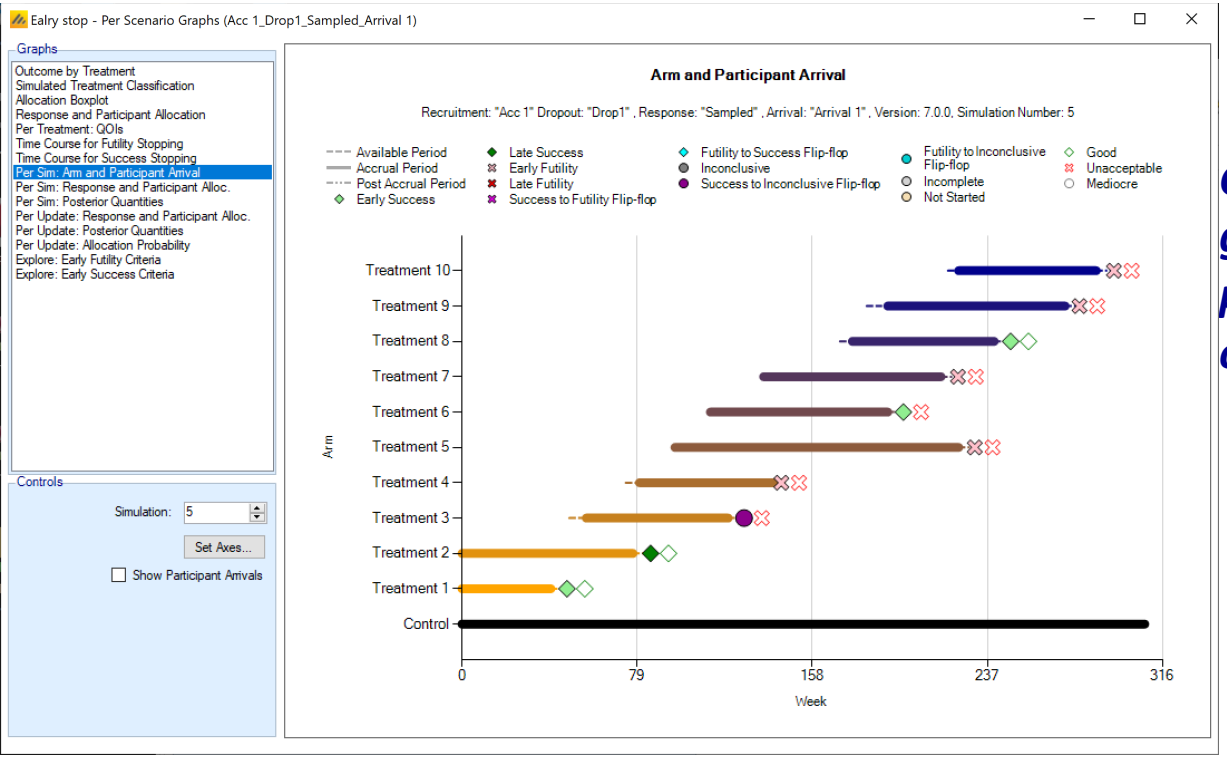
Reported results include the proportion of Good / Mediocre / Unacceptable treatments that are Successful / Inconclusive / or Futile.

Graphs



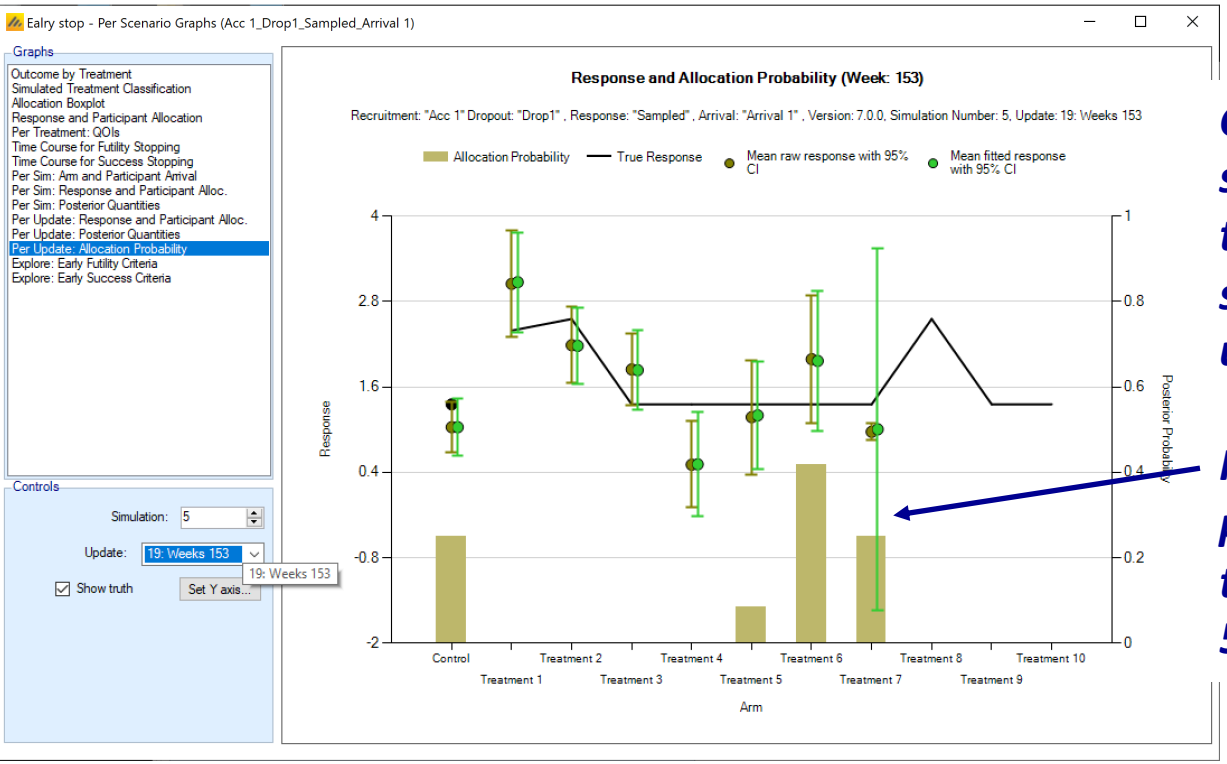
Graphs include summary graphs, here for instance showing the proportion of each type of outcome for each treatment.

Graphs



Graphs include per-simulation graphs that show how a particular simulation played out.

Graphs



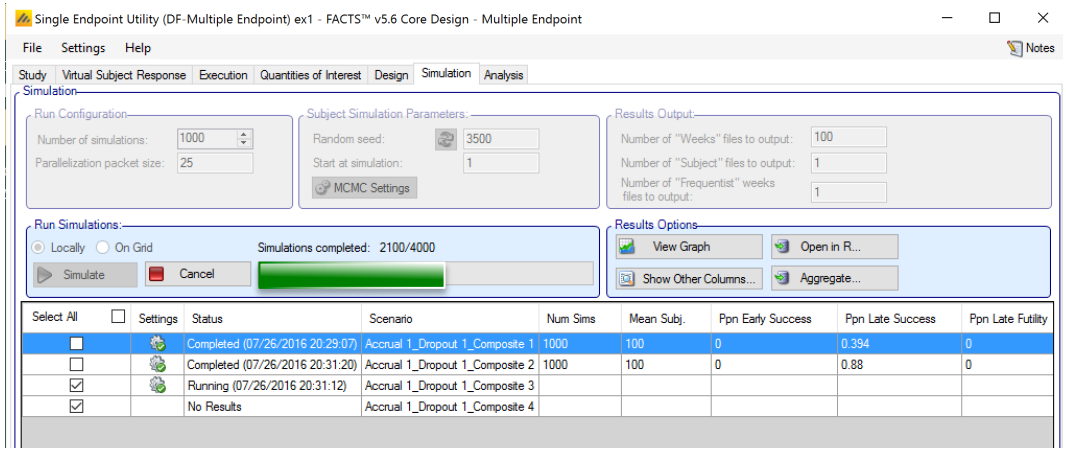
Graphs include per-update per simulation graphs that show the state of a particular simulation at a particular update.

Here we show the allocation probabilities at the point when treatment 7 joined treatments 5 & 6.

FACTS GENERAL FEATURES

FACTS is *fast*

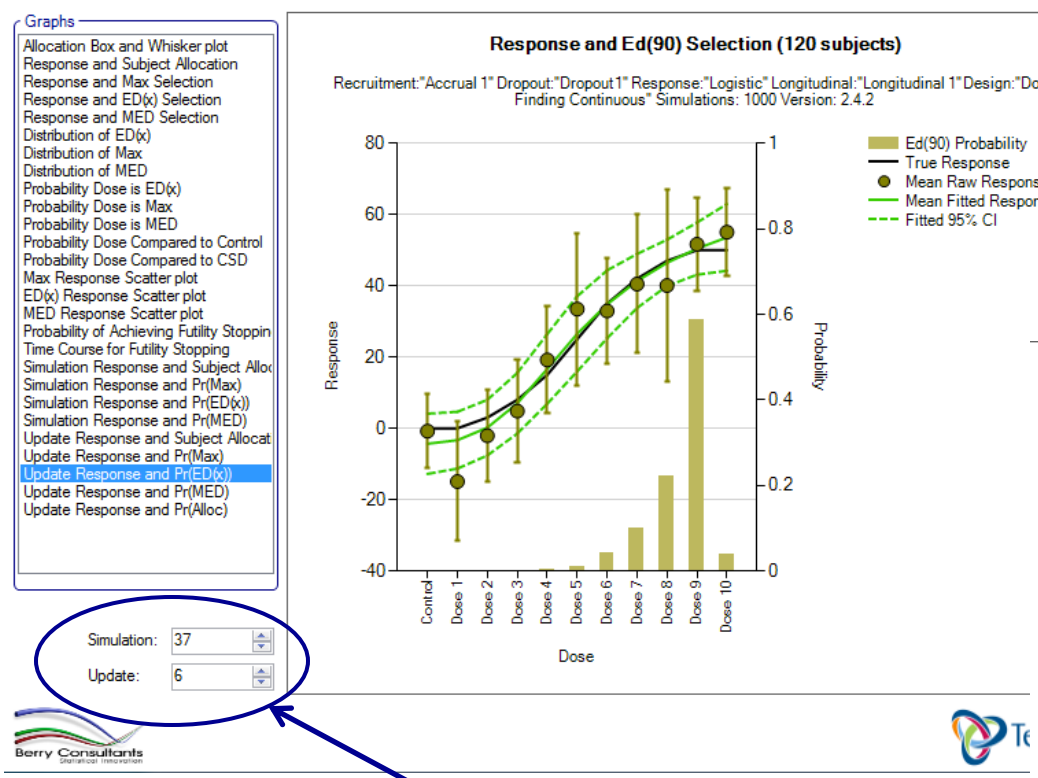
- All simulators written in C++ and use the latest Intel numerical library
- 100s or 1000s of simulated trials a minute
- Simulations divided over the available processing cores
  - Drop FACTS onto a 32 core server and get 32 simulations run in parallel with no additional work
  - 4 parallel threads on the typical laptop
- Integration with compute grid available



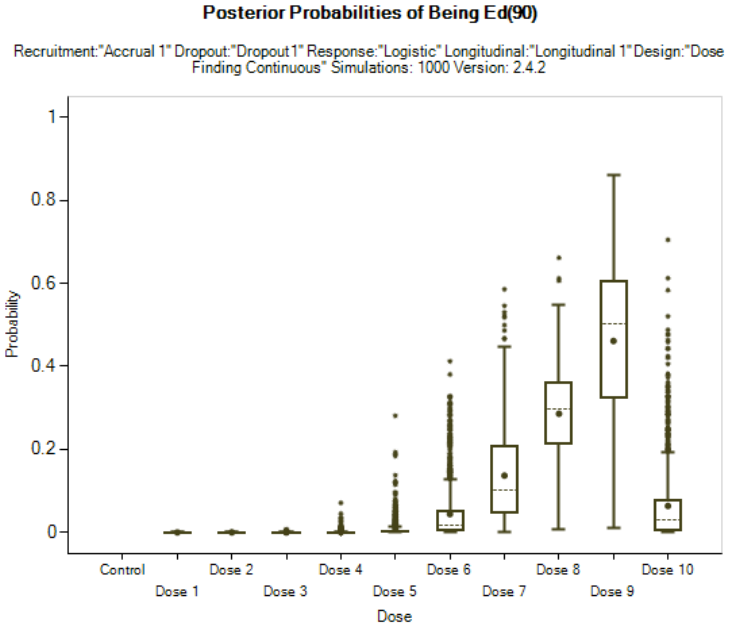
Options intermix

- For a particular design engine all options can be intermixed:
  - Study type
  - How subjects responses simulated
  - Accrual patterns
  - Dropout rates
  - Analysis models
  - Longitudinal models
  - Fixed or Adaptive
  - Interims – number and timing
  - Early stopping
  - Adaptation

Built-in Graphics



Allows quick review of simulation summaries



Walk through each interim of a single simulated trial

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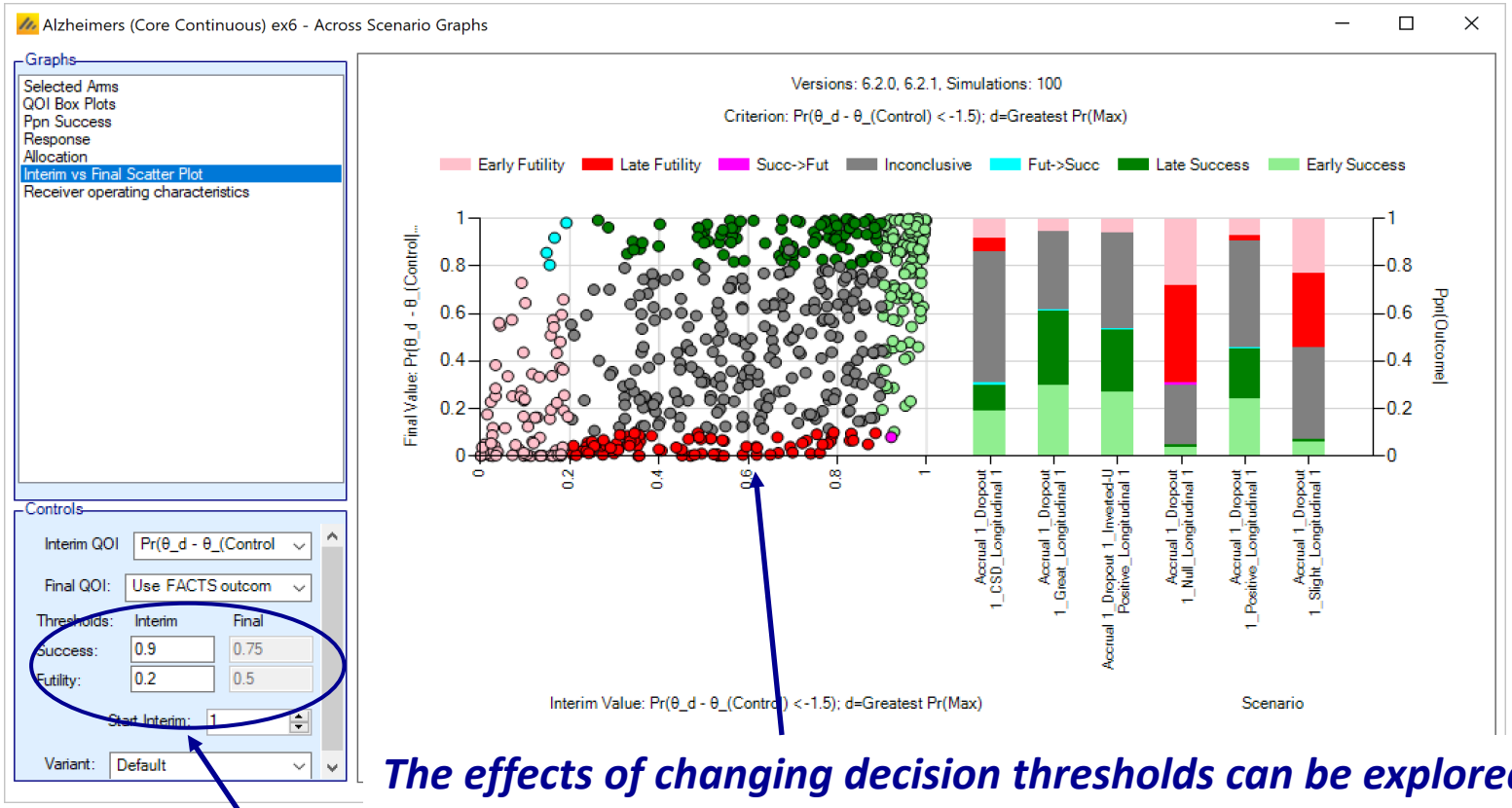
Built-in Graphics to explore the design

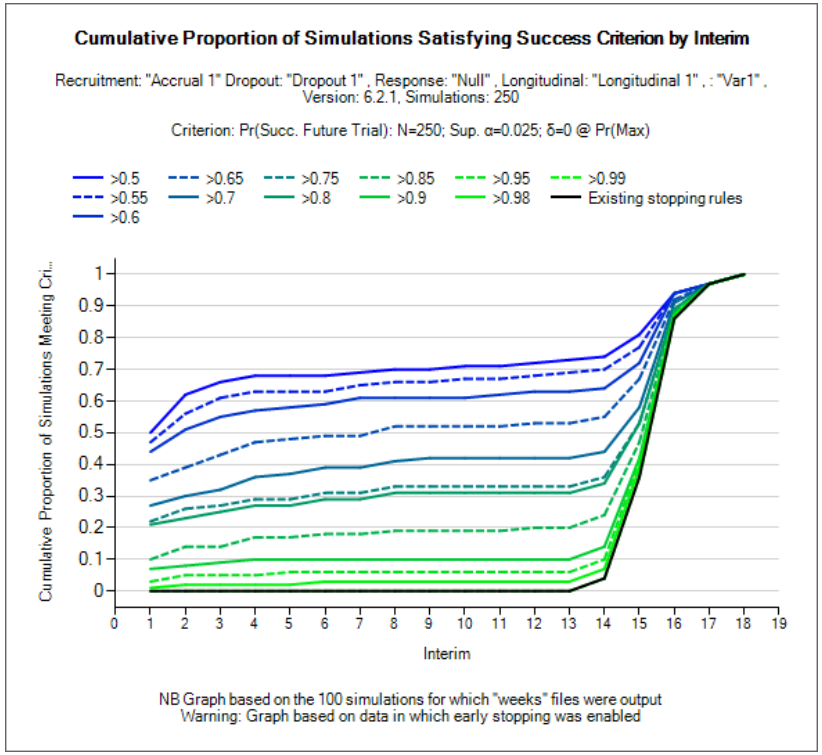


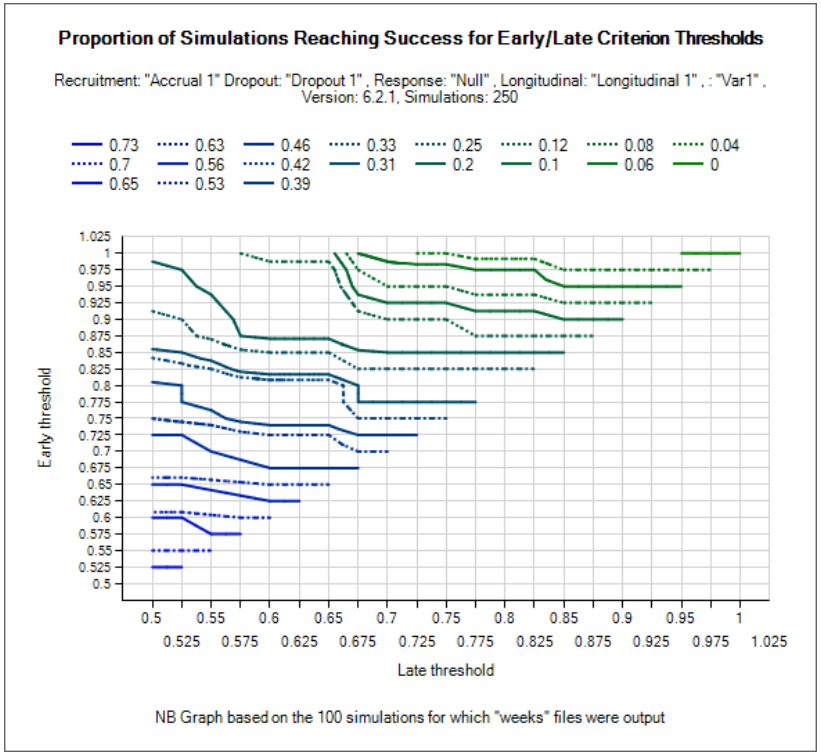
The effects of changing decision thresholds can be explored without having to re-run simulations.

Here we see a plot of all simulations by final response vs response at a selected interim and the outcome of the simulation.

We can change the thresholds and have the graph re-plotted

Built-in Graphics to explore the design





The effects of changing decision thresholds can be explored without having to re-run simulations.

Here we see the cumulative proportion of simulations that would have stopped for success in the Null scenario at different decision thresholds, and contours of equal proportion of success for different combinations of interim and final success threshold

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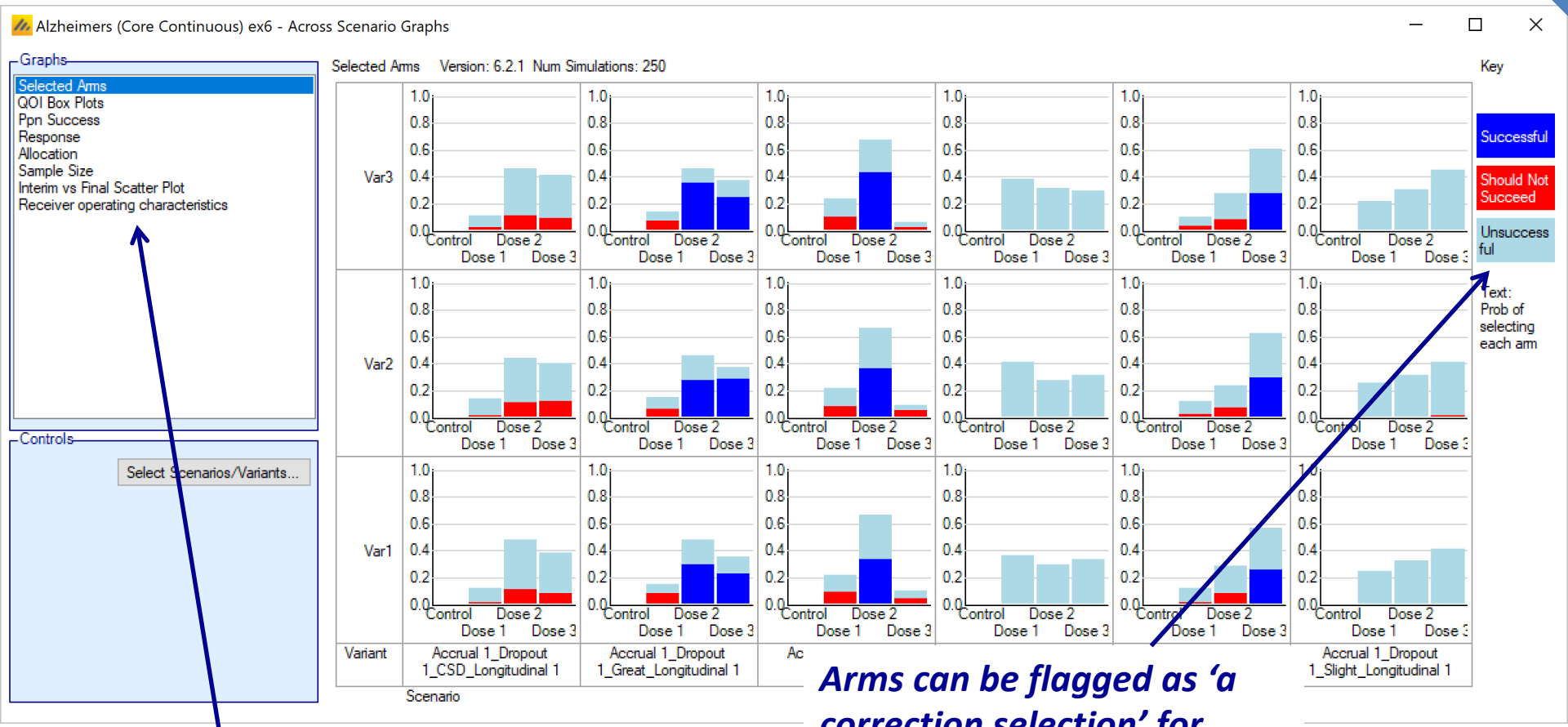
Built-in Graphics to compare design variants



Graphs that compare the results of different design variants over all scenarios

Arms can be flagged as 'a correction selection' for each scenario.
Allowing a design's ability to 'select a good dose' to be summarized

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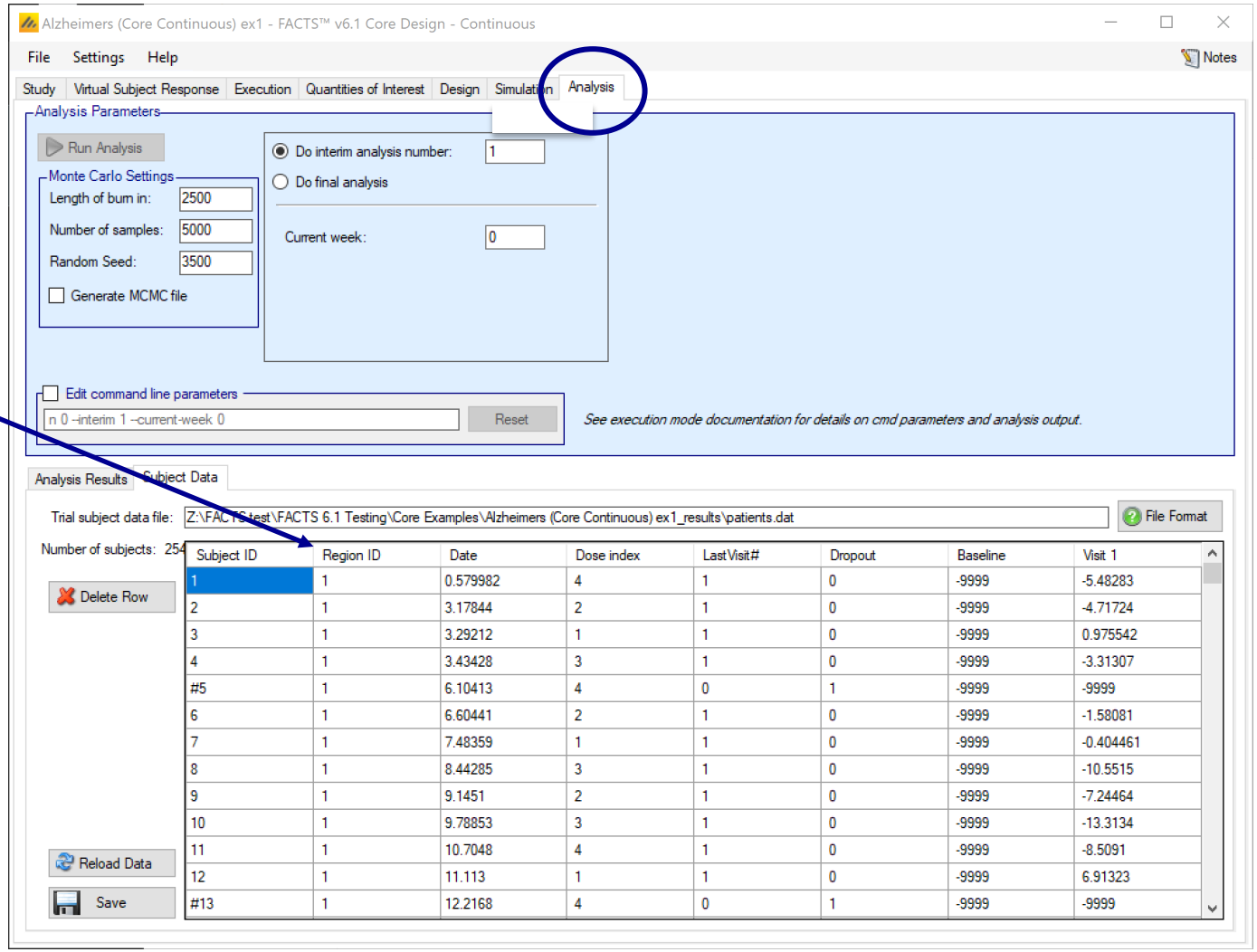
Analysis Tab

Analysis tab to run hypothetical or actual interim analyses within FACTS GUI

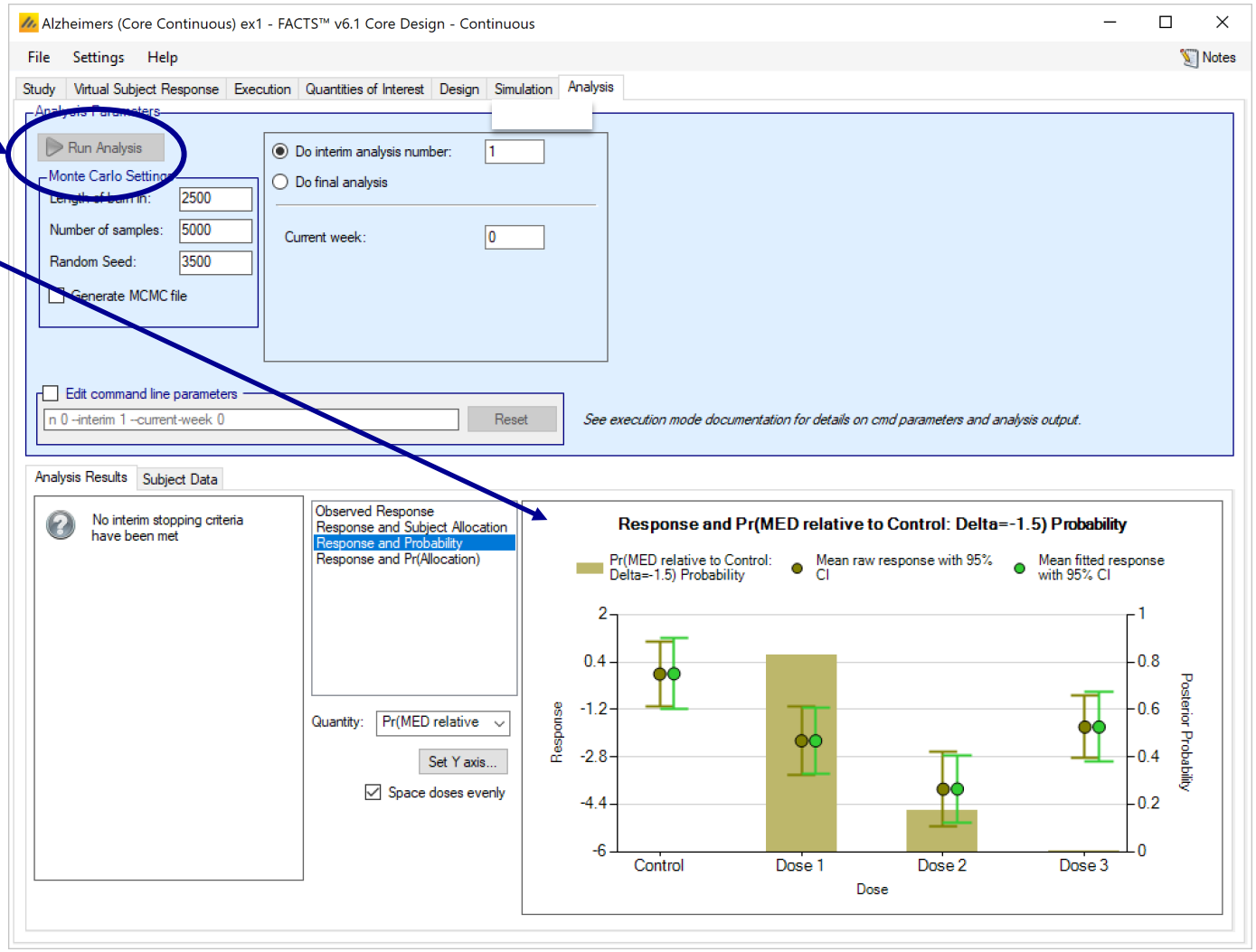
Load data file



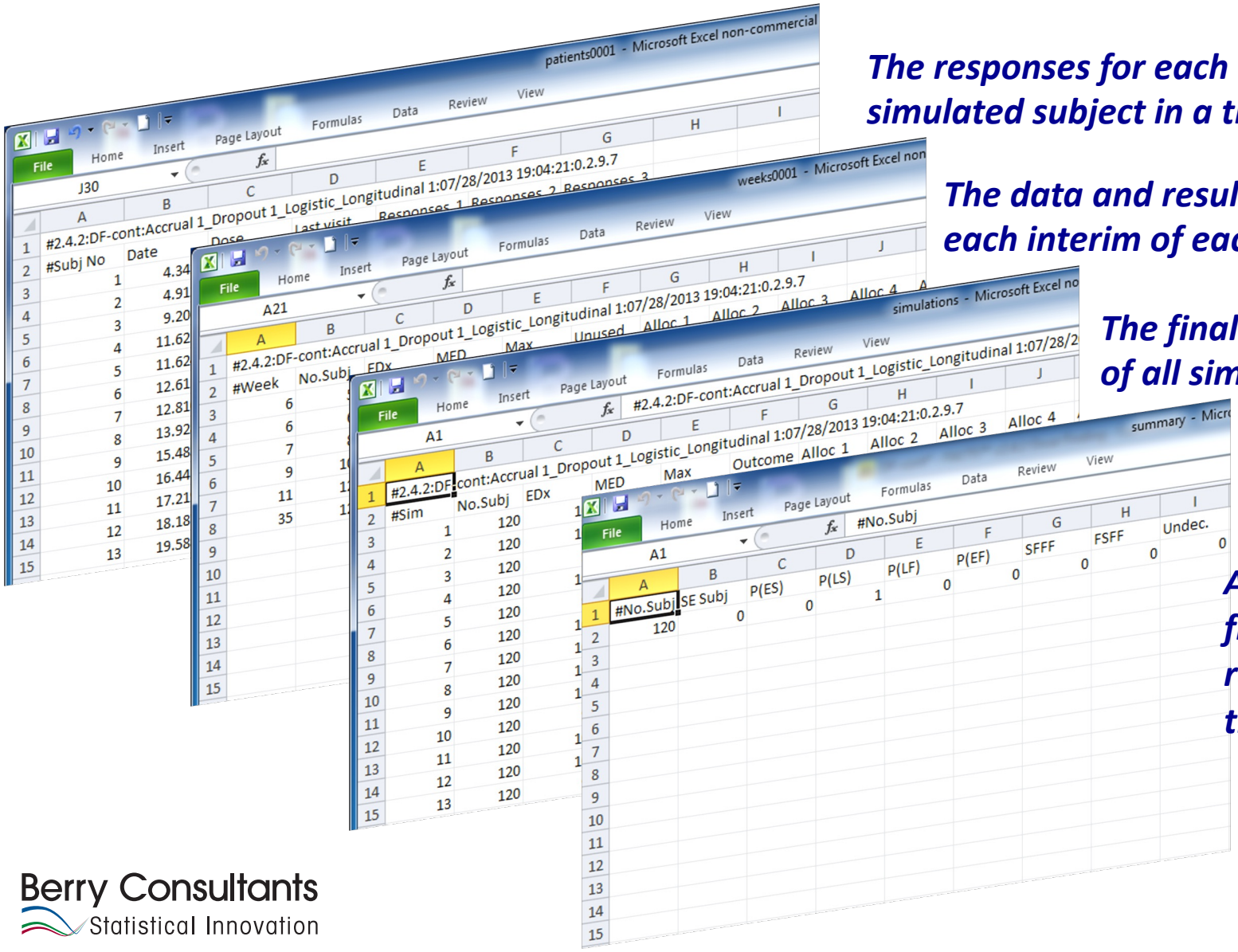
Analysis Tab

Run analysis

Check results



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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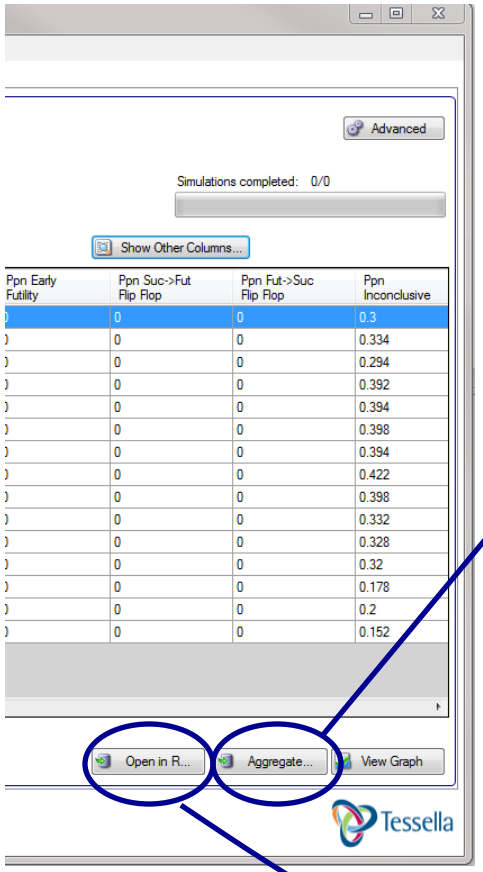
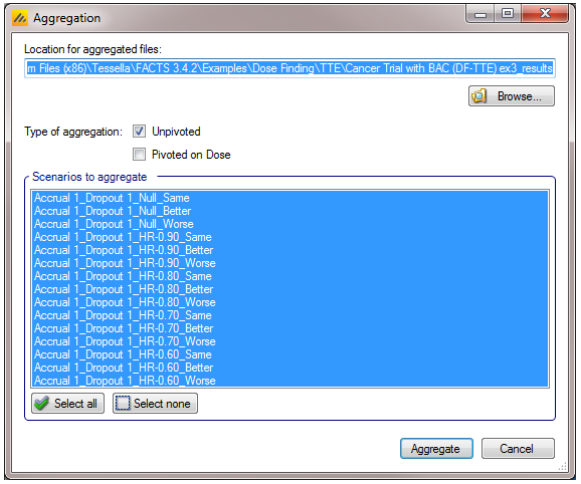
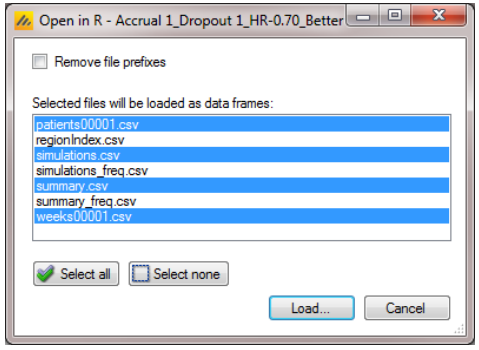
Support for post-processing results



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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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!