



**Fixed and Adaptive Clinical Trial Simulator**

**Berry Consultants**  
 Statistical Innovation

# What is FACTS?

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- 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

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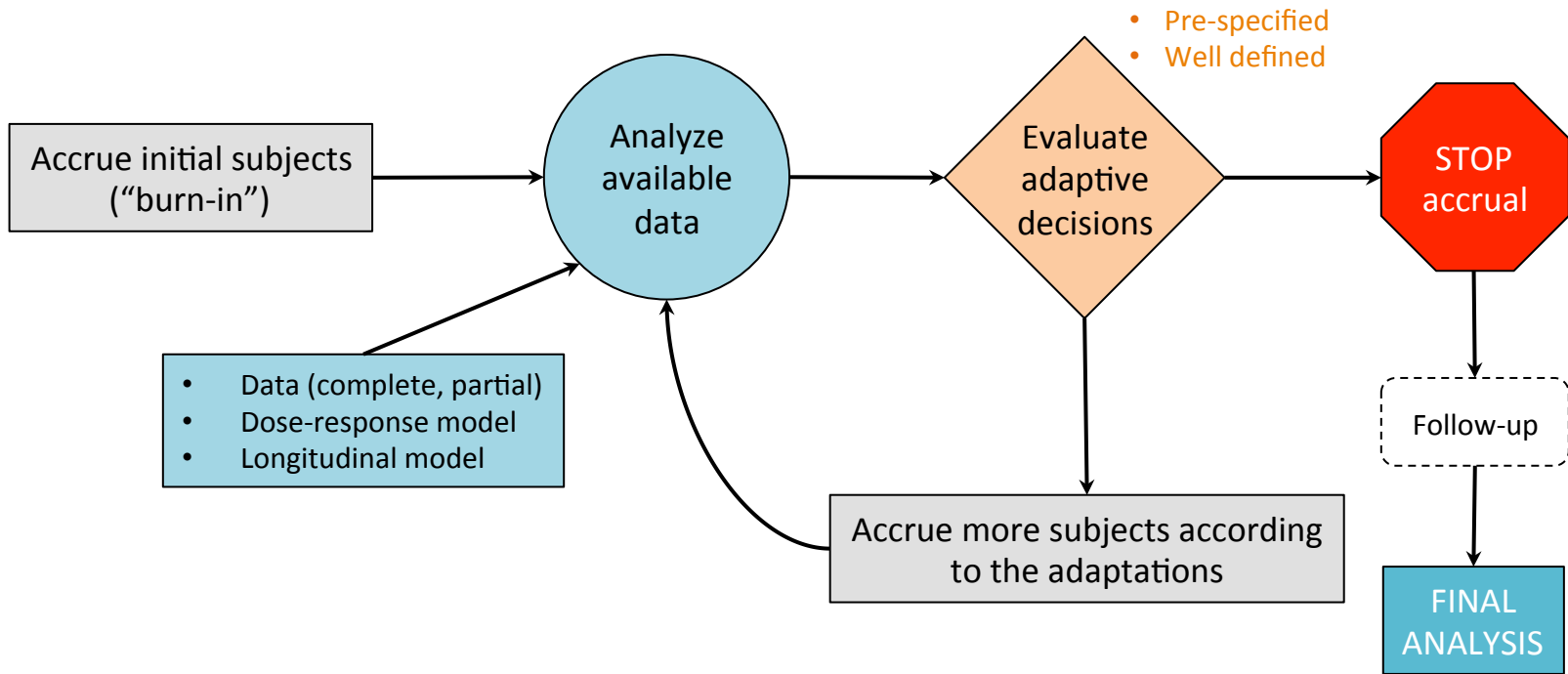
- FACTS has modules (“design engines”) to simulate:
  - ***Dose Escalation trials*** (phase 1 and phase 2a)
    - dichotomous or ordinal endpoints
  - ***Dose Finding trials***
    - continuous, dichotomous, time-to-event endpoints
    - multiple endpoints (up to 4 continuous/dichotomous)
  - ***Enrichment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

# Adaptive Designs

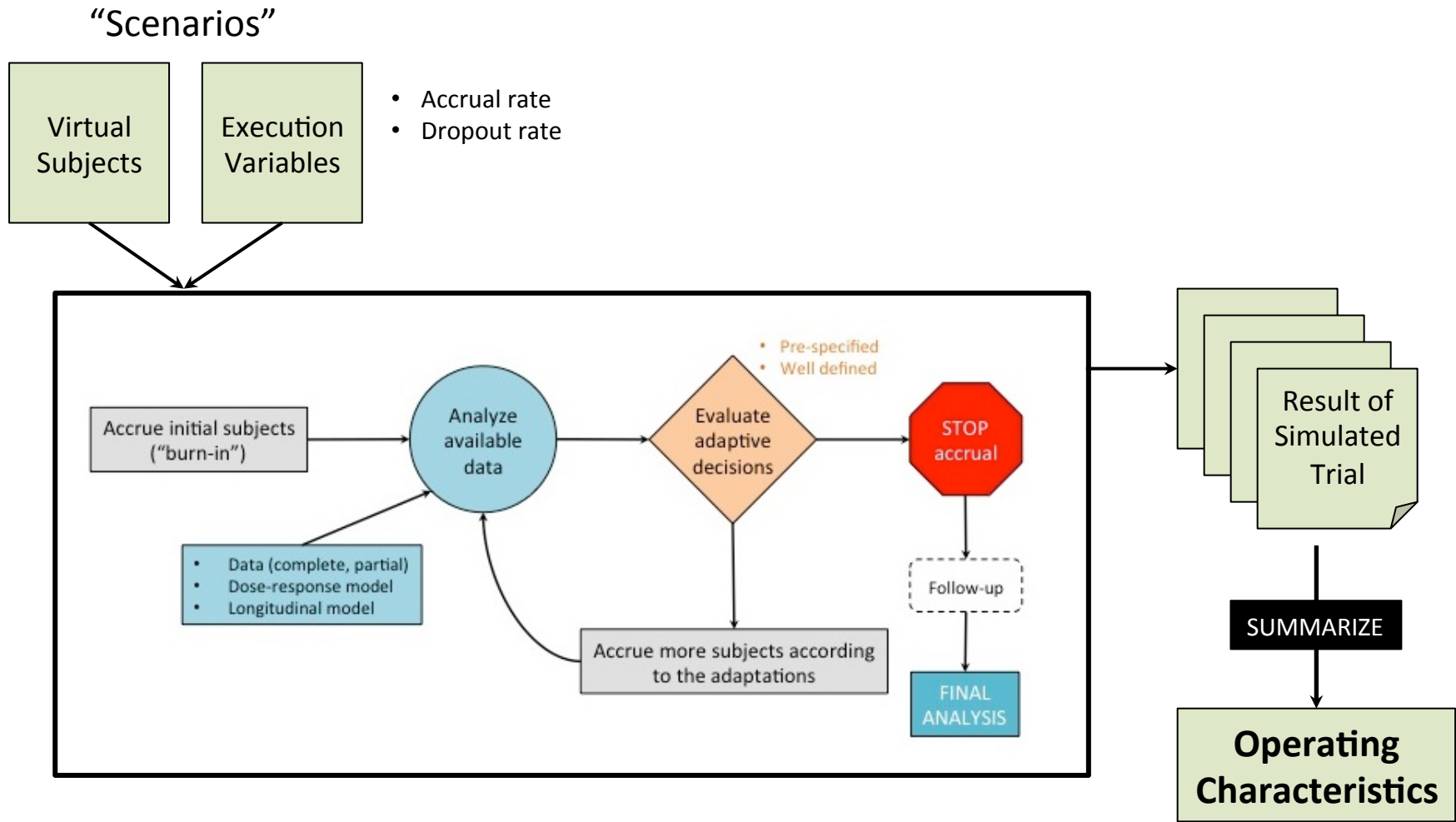
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- Allow information that accumulates during the trial to modify key design parameters according to *pre-specified* and *well-defined* rules
- Adaptable components may include:
  - treatment arms (dose, frequency, duration, etc)
  - allocation to the 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?

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- 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**



# Specifying Design Features

*Adaptive vs. Fixed*

*Maximum Sample Size*

*Superiority vs. Non-inferiority*

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

*Visit Structure*

*etc...*

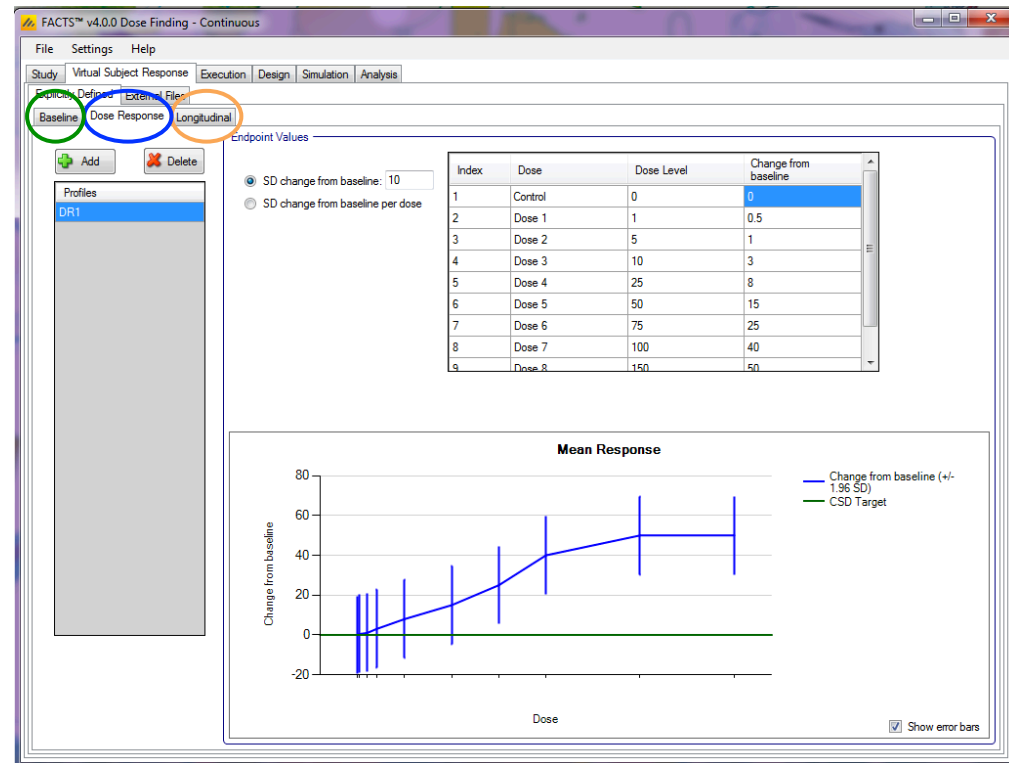
The screenshot displays the FACTS v4.0.0 Dose Finding - Continuous software interface. The main window is titled "FACTS™ v4.0.0 Dose Finding - Continuous" and features a menu bar with "File", "Settings", and "Help". Below the menu bar are tabs for "Study", "Virtual Subject Response", "Execution", "Design", "Simulation", and "Analysis". The "Design" tab is currently selected, and within it, the "Study Info" sub-tab is active.

The interface is divided into several panels:

- Design Options:** Includes radio buttons for "Adaptive" (selected) and "Non-Adaptive". Checkboxes for "Use longitudinal modeling" and "Include simulation of baseline" are both checked. Under "Response is:", "Change from baseline" is selected over "Final endpoint value".
- Evaluation Variables:** Includes input fields for "Effective dose quantile (ED<sub>01</sub>)" (0.9) and "Clinically significant difference (CSD)" (5). Radio buttons for "Absolute response" and "Response relative to control" are present, with "Response relative to control" selected. A checkbox for "Phase III criteria:" is also visible. Below it, "Trial type is:" has "Superiority" selected over "Non-inferiority". Input fields for "Subjects per arm:" (250), "One-sided alpha: α" (0.025), and "Supersuperiority margin:" (0) are also present.
- Study Information:** Includes radio buttons for "Recruit subjects" (Sequentially selected) and "In cohorts". Input fields for "Maximum number of subjects:" (300), "First cohort size:" (20), "Subsequent cohort size:" (5), "Maximum number of cohorts:" (50), "Time to recruit each cohort (wks):" (0), and "Maximum trial duration (wks):" (600) are shown. Under "Response:", "Higher response is subject improvement" is selected over "Lower response is subject improvement". Under "Trial type:", "Superiority" is selected over "Non-inferiority".
- Schedule of Post-Baseline Visits:** Includes buttons for "Delete visit" and "Clear all visits". Radio buttons for "Set Visits Explicitly" (selected) and "Auto-Generate Visits" are present. Under "Set Visits Explicitly", "Week No." is set to 13, and an "Add" button is visible. Under "Auto-Generate Visits", input fields for "Number" (4), "Start" (1), and "Spacing" (1) are shown, along with a "Generate" button. A table with 3 columns (Index (t), Visit Name, Week) and 4 rows (1-4) is displayed, showing visits at weeks 3, 6, 9, and 12.

# 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

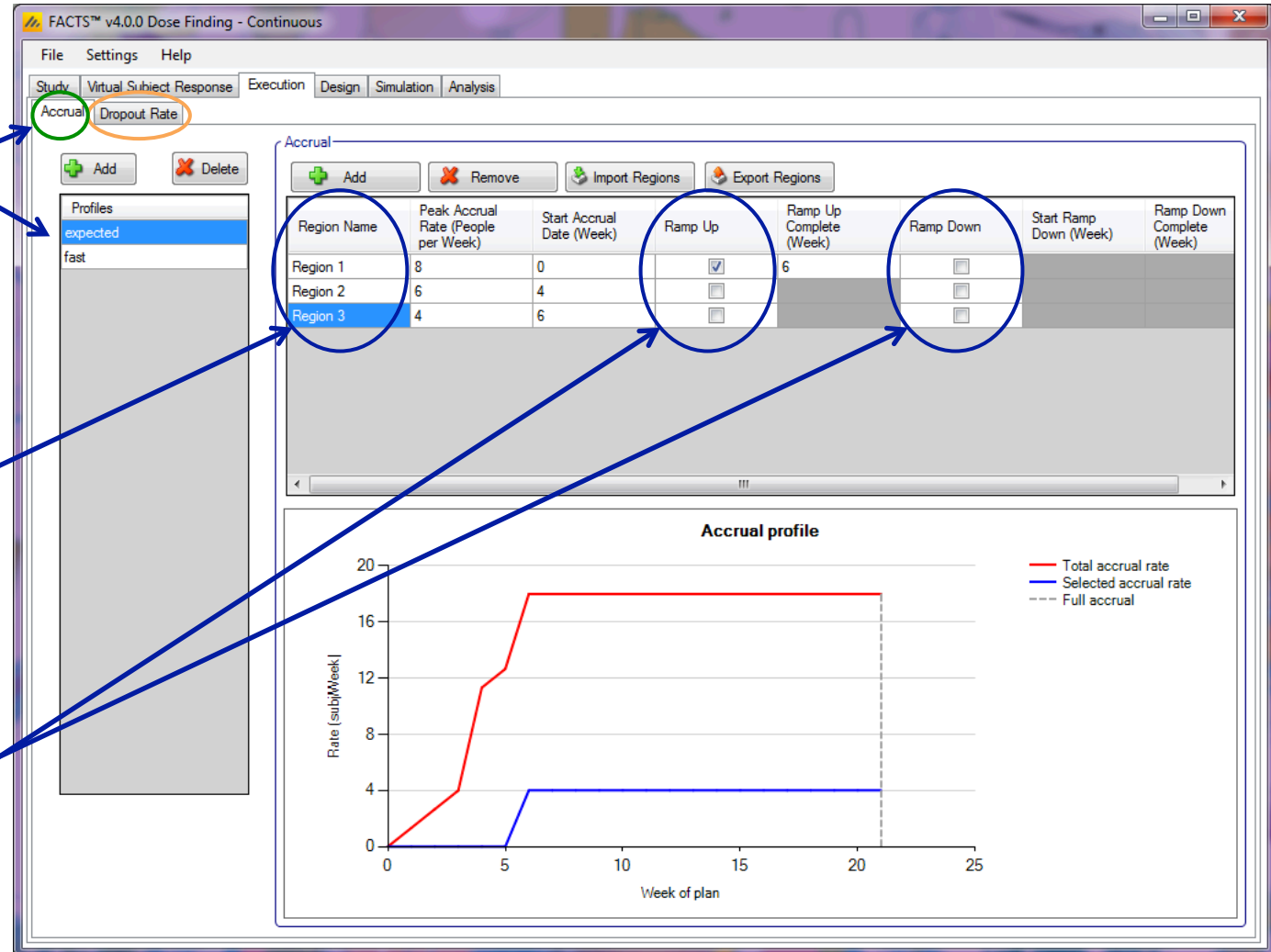


# Simulating Accrual and Dropout

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



# Dose-Response Models

*Multiple options for modeling the dose-response curve*

*Hierarchical borrowing of historical control data*

FACTS™ v4.0.0 Dose Finding - Continuous

File Settings Help

Study Virtual Subject Response Execution Design Simulation Analysis

Dose Response Longitudinal Allocation Interims Stopping Criteria Final Evaluation Criteria Frequentist Analysis

Model: Sigmoidal

Model Parameters:

- Simple NDLM
- Monotonic NDLM
- Second Order NDLM
- 3-Parameter Logistic
- Hierarchical Logistic
- Sigmoidal
- U-shaped Model
- Plateau Model
- Independent Dose Model
- Legacy 2nd Order NDLM

Param a<sub>1</sub> (i=1): 0

Param a<sub>2</sub> (i=2): 50

Param a<sub>3</sub> (i=3): 5

Param a<sub>4</sub> (i=4): 2

Equations for Selected Model Type

$$Y \sim N(\theta_d, \sigma^2)$$

$$\theta_d \sim a_1 + \frac{(a_2 - a_1) v_d^{a_4}}{v_d^{a_4} + a_3^{a_4}}$$

$$a_i \sim N(\Lambda_i, \lambda_i^2) \text{ for } i = \{1, 2\}$$

$$a_i \sim N^+(\Lambda_i, \lambda_i^2) \text{ for } i = \{3, 4\}$$

$$\sigma^2 \sim \text{IG}\left(\frac{\sigma_n}{2}, \frac{\sigma_\mu^2 \sigma_n}{2}\right)$$

$$\text{IG}(x|a, b) = \frac{b^a e^{-b/x}}{x^{a+1} \Gamma(a)}$$

Prior Distribution of a<sub>3</sub>

Set Additional Comparator Priors

Prior mean  $\mu_{AC}$  Prior SD  $\tau_{AC}$

Comparator: 0 100

Equation:  $\theta_{AC} \sim N(\mu_{AC}, \tau_{AC}^2)$

Error Parameters

Sigma prior mean ( $\sigma_\mu$ ) 10

Sigma prior weight ( $\sigma_n$ ) 1

Handling of Missing Data Due to Dropouts

- ☒ Bayesian multiple imputation from post baseline
- ☐ Baseline observation carried forward (BOCF)
- ☐ Last observation carried forward (LOCF)

☐ Use Baseline Adjusted Model

Prior mean  $\mu_{0d}$  Prior SD  $v_{0d}$

Beta: 0 1

Equation:  $\beta \sim N(m_\beta, s_\beta^2)$

☒ Model Control Separately

☐ Fixed Prior ☒ Historical Prior

Prior mean  $\mu_0$  Prior SD  $\sigma$

Mu ( $\mu$ ): 1 10

Prior mean mean ( $\tau_\mu$ ) Prior mean weight ( $\tau_n$ )

Tau<sup>2</sup> ( $\tau^2$ ): 1 0.5

+ Add Study - Delete Study

Name	Num subj	Response	SD of response
Study 1	1	0.5	10
Study 2	1	0	8

# Longitudinal Models

FACTS™ v4.0.0 Dose Finding - Continuous

File Settings Help

Study Virtual Subject Response Execution Design Simulation Analysis

Dose Response Longitudinal Allocation Interims Stopping Criteria Final Evaluation Criteria Frequentist Analysis

Model: Linear regression

Model Priors

Model 1: Linear regression

☒ Last observed carried forward  
☐ Sir Time course hierarchical  
☐ Kernel density  
☐ McITP  
☐ Model comparator separately  
☐ Model control and comparator separately  
☐ Model all arms separately

Model Priors

☒ Same priors across all visits  
☐ Specify priors per visit  
☐ Specify priors per model instance and visit

Equations

$$Y_t | y_{it} \sim N(\alpha_t + \beta_t y_{it}, \lambda_t^2)$$

$$\alpha_t \sim N(\alpha_\mu, \alpha_\sigma^2)$$

$$\beta_t \sim N(\beta_\mu, \beta_\sigma^2)$$

$$\lambda_t^2 \sim \text{IG}\left(\frac{\lambda_n}{2}, \frac{\lambda_\mu^2 \lambda_n}{2}\right)$$

$$\text{IG}(x|a, b) = \frac{b^a e^{-b/x}}{x^{a+1} \Gamma(a)}$$

(These equations apply separately to each model instance)

$\alpha$  prior mean ( $\alpha_\mu$ ): 0  
 $\alpha$  prior SD ( $\alpha_\sigma$ ): 10  
 $\beta$  prior mean ( $\beta_\mu$ ): 0.75  
 $\beta$  prior SD ( $\beta_\sigma$ ): 1  
 Prior lambda mean ( $\lambda_\mu$ ): 0.5  
 Prior lambda weight ( $\lambda_n$ ): 1

Prior Distribution of Alpha

Alpha

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

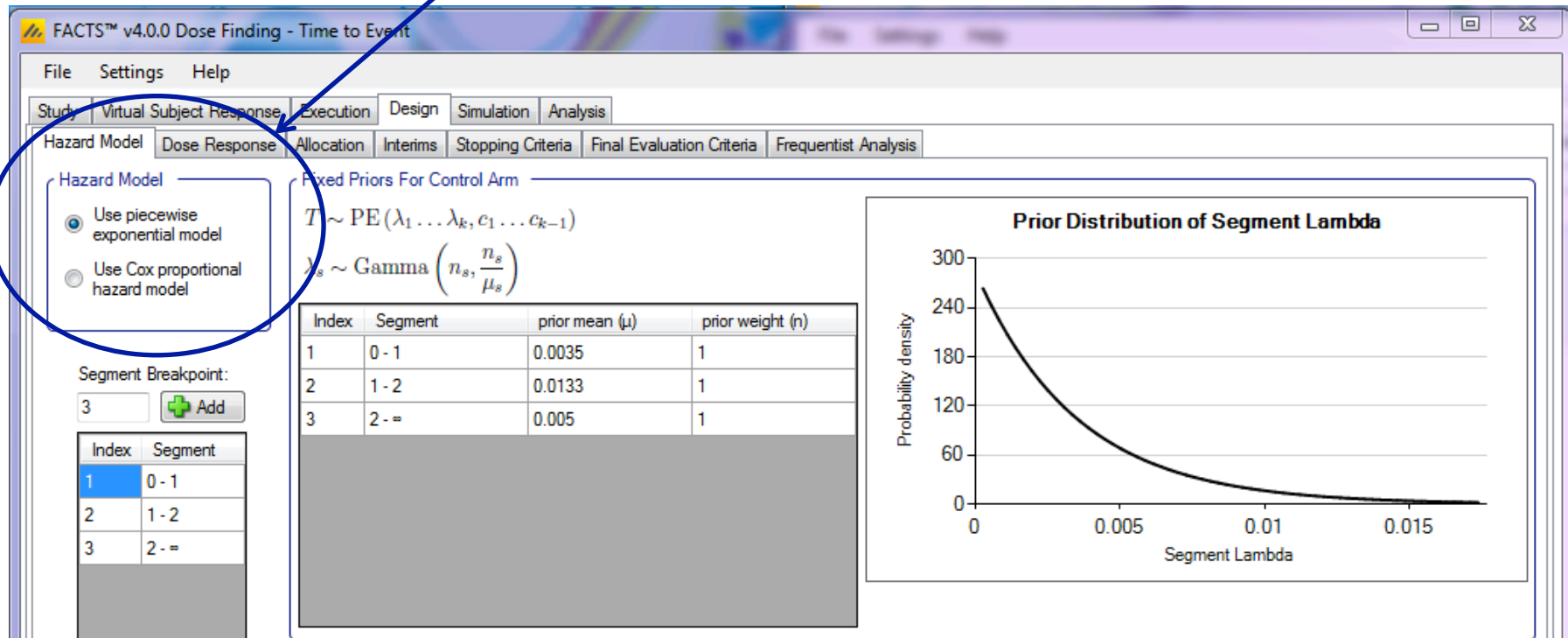
*Create a dichotomous endpoint from continuous based on a threshold*

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

- ☒ Enable Special Longitudinal Options
- ☐ Endpoint is dichotomized continuous-valued response  
 Y greater than 0 indicates response
- ☒ Use restricted Markov model  
 Subject in stable state at final visit counted as:  
☐ Response ☒ Failure

# 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

☒ Include Predictor

Predictor endpoint type:

☒ Continuous

☐ Dichotomous

☐ Time to event

Response

☒ Higher response is subject improvement

☐ Lower response is subject improvement

Time when predictor is observed (wks):

Predictor CSD (delta):

☐ Primary endpoint is censoring for intermediate predictor

Study Virtual Subject Response Execution Design Tests Statistics

Predictor Model Hazard Model Dose Response Allocation Stopping Rules

Dose Response Relationship to Endpoint

Priors for Lambda

Index	Dose	Prior mean of ( $\mu$ )	Prior weight (n)
1	Control	1	1
2	Dose 1	1	1
3	Dose 2	1	1

Priors for Beta

Priors for  $\beta$ :

Mean (m)  SD (s)

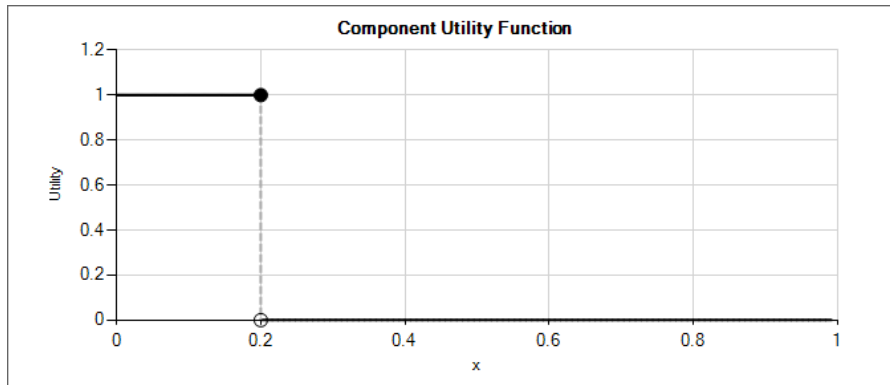
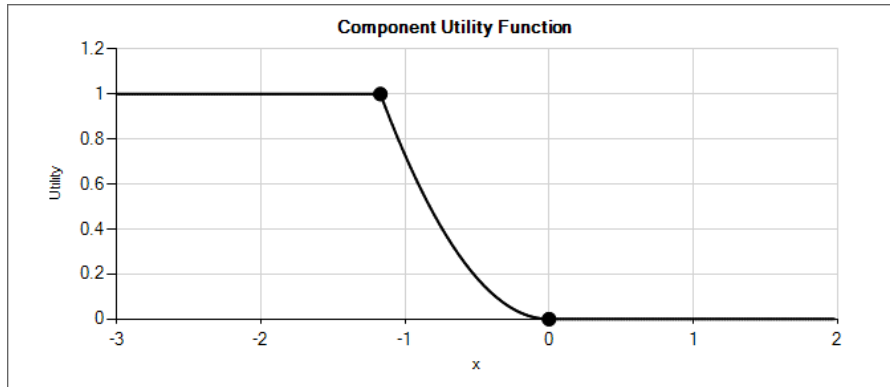
Equations

$$T \sim \exp(\lambda_d \exp(Z\beta))$$

$$\lambda_d \sim \text{Gamma}\left(n_d, \frac{n_d}{\mu_d}\right)$$

$$\beta \sim N(m, s^2)$$

# Utility Functions: Multiple Endpoint



*Specify utility (weight)  
functions for each endpoint*

*Combine utilities either  
additively or multiplicatively*

Component Utility Combination Method

- ☐ Add Utilities  
 $U(x, y) = U(x) + U(y)$
- ☒ Multiply Utilities  
 $U(x, y) = U(x) U(y)$

*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*

The screenshot displays the 'FACTS™ v4.0.0 Dose Finding - Continuous' software window. The 'Interims' tab is selected, showing the 'Interim analysis frequency' section. The 'Interims every' radio button is selected, with a value of '2' weeks and 'Interims start at subject: 50'. The 'Specify interims by subjects accrued' radio button is also visible. Below these are buttons for 'Delete interim' and 'Clear all interims'. The 'Interim value' is set to '10', with an 'Add' button. The 'Autogenerate' section includes 'Number' (4), 'Start' (10), 'Spacing' (10), and a 'Generate' button. A list box titled 'Interims' is empty. The 'Post Accrual Actions' section has three checkboxes: 'Continue followup if study stopped for success' (checked), 'Continue followup if study stopped for futility' (unchecked), and 'Discontinue interim analysis beyond full accrual' (unchecked). Blue arrows point from the text annotations to the 'Interims every' radio button, the 'Continue followup if study stopped for success' checkbox, and the 'Discontinue interim analysis beyond full accrual' checkbox.

FACTS™ v4.0.0 Dose Finding - Continuous

File Settings Help

Study Virtual Subject Response Execution Design Simulation Analysis

Dose Response Longitudinal Allocation Interims Stopping Criteria Final Evaluation

Interim analysis frequency

☒ Interims every 2 weeks  
Interims start at subject: 50

☐ Specify interims by subjects accrued

Delete interim Clear all interims

Interim value: 10  
Add

Autogenerate:

Number 4  
Start 10  
Spacing 10  
Generate

Interims

Post Accrual Actions

☒ Continue followup if study stopped for success  
☐ Continue followup if study stopped for futility  
☐ Discontinue interim analysis beyond full accrual

# Adaptations

## Response adaptive randomization

FACTS™ v4.0.0 Dose Finding - Continuous

File Settings Help

Study Virtual Subject Response Execution Design Simulation Analysis

Dose Response Longitudinal Allocation Interims Stopping Criteria Final Evaluation Criteria Frequentist Analysis

☒ Adaptive Allocation ☐ Arm Dropping ☐ Fixed Allocation ☐ Legacy Adaptation

Index	Dose	Burn-in	Fix Alloc.	Post Burn-in Alloc. per Block
1	Control	5	<input type="checkbox"/>	
2	Dose 1	5	<input type="checkbox"/>	
3	Dose 2	5	<input type="checkbox"/>	
4	Dose 3	5	<input type="checkbox"/>	
5	Dose 4	5	<input type="checkbox"/>	
6	Dose 5	5	<input type="checkbox"/>	

If control allocation is not fixed, it will seek to match that to best dose arm.  
Check documentation for details.

Block size:

Slots in block that will be allocated adaptively:

Allocation probability set to zero for values less than:

**Adaptive Allocation Targets**

Relative weight:

Weight for:

Maximum Response: ☐ Probability ☐ Information

Effective Dose Quantile: ☐ Probability ☐ Information

Minimum Effective Dose: ☐ Probability ☐ Information

Raise allocation to power ( $\gamma$ ):

Probability:  $V_d^* = [Pr(d = d^*)]^\gamma$  Information:  $V_d^* = \left[ \frac{Pr(d = d^*) Var(\theta_d)}{n_d + 1} \right]^{\gamma/2}$

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

☐ Forced arm selection

Interim for forced arm selection: (1=end of burnin)

Number of treatment arms to retain:

Retain arms with highest:

- ☐ Pr(EDx)
- ☒ Pr(Max)
- ☐ Pr(MED)
- ☐ Pr(S Phase III)
- ☐ Pr( $\theta_d > \theta_0$ )
- ☐ Pr( $P_d - P_0 > CSD$ )

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

# 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*

The screenshot displays the FACTS v4.0.0 Dose Finding - Continuous software interface. The 'Stopping Criteria' tab is active, showing two main sections: 'Enable Futility Stopping Criteria' and 'Enable Success Stopping Criteria'. Both sections have a 'Minimum Information Required (all must be met)' section with input fields for 'Minimum subjects before study can stop for futility/success', 'Minimum subjects on EDx', 'Minimum subjects on MED', and 'Minimum subjects on Max'. Below these are 'Only one enabled criterion must be met for study to stop' and 'All enabled criteria must be met for study to stop' sections, each with a list of criteria and their corresponding thresholds. The 'Evaluation variables' section includes 'Effective dose quantile', 'Clinically significant difference (CSD)', and 'Phase III criteria'. The 'Minimum subjects' section has radio buttons for 'In terms of enrollment' and 'In terms of completers'.

**Enable Futility Stopping Criteria**

Minimum Information Required (all must be met)

Minimum subjects before study can stop for futility: 20

Minimum subjects on EDx: 0

Minimum subjects on Max: 0

Only one enabled criterion must be met for study to stop

☐ Pr ( S Phase III ) < 0.1 for dose d<sub>EDx</sub>

☐ Pr ( S Phase III ) < 0.15 for dose d<sub>max</sub>

☐ Pr( $\theta_d > \theta_0$ ) < 0.05 for dose d<sub>EDx</sub>

☒ Pr( $\theta_d > \theta_0$ ) < 0.05 for dose d<sub>max</sub>

☐ Pr( $\theta_d - \theta_0 > \text{CSD}$ ) < 0.5 for dose d<sub>EDx</sub>

☐ Pr( $\theta_d - \theta_0 > \text{CSD}$ ) < 0.5 for dose d<sub>max</sub>

☐ Pr( $\theta_d > \theta_{AC}$ ) < 0.1 for dose d<sub>EDx</sub>

☐ Pr( $\theta_d > \theta_{AC}$ ) < 0.1 for dose d<sub>max</sub>

**Evaluation variables**

Effective dose quantile: 0.9

Clinically significant difference (CSD): 0

**Phase III criteria**

Subjects per arm: 250

Limit of one-sided  $\alpha$ : 0.025

Supersuperiority margin: 0

**Minimum subjects**

☒ In terms of enrollment ☐ In terms of completers

**Enable Success Stopping Criteria**

Minimum Information Required (all must be met)

Minimum subjects before study can stop for success: 100

Minimum subjects on EDx: 0

Minimum subjects on MED: 0

Minimum subjects on Max: 25

All enabled criteria must be met for study to stop

☐ Pr ( EDx ) > 0.7 for dose d<sub>EDx</sub>

☐ Pr ( Max ) > 0.7 for dose d<sub>max</sub>

☐ Pr ( MED ) > 0.7 for dose d<sub>med</sub>

☐ Pr ( S Phase III ) > 0.9 for dose d<sub>EDx</sub>

☐ Pr ( S Phase III ) > 0.9 for dose d<sub>max</sub>

☐ Pr( $\theta_d > \theta_0$ ) > 0.9 for dose d<sub>EDx</sub>

☒ Pr( $\theta_d > \theta_0$ ) > 0.975 for dose d<sub>max</sub>

☐ Pr( $\theta_d - \theta_0 > \text{CSD}$ ) > 0.9 for dose d<sub>EDx</sub>

☐ Pr( $\theta_d - \theta_0 > \text{CSD}$ ) > 0.9 for dose d<sub>max</sub>

☐ Pr( $\theta_d > \theta_{AC}$ ) > 0.8 for dose d<sub>EDx</sub>

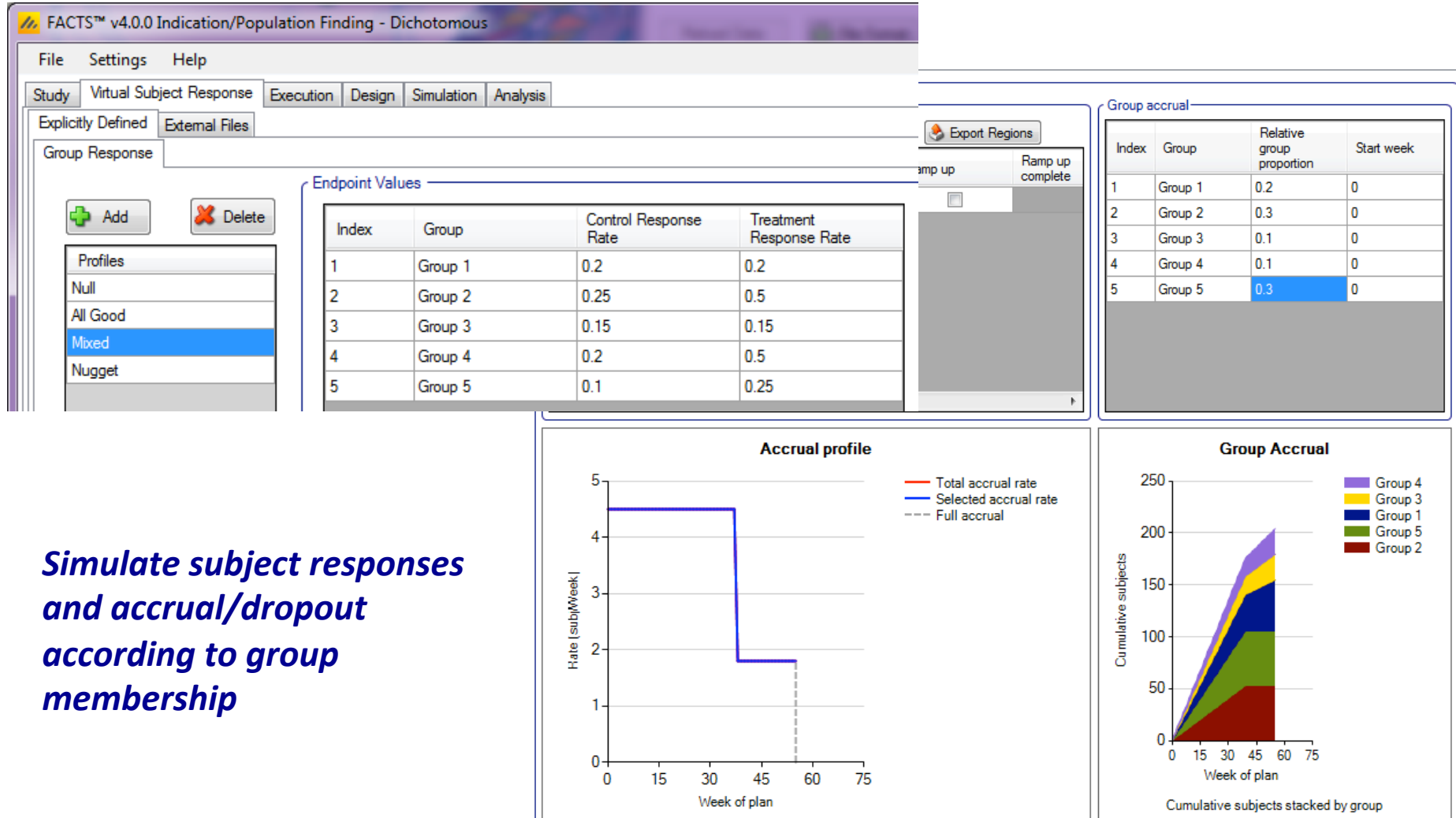
☐ Pr( $\theta_d > \theta_{AC}$ ) > 0.8 for dose d<sub>max</sub>

# AIPF/Enrichment Designs

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- Adpative 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



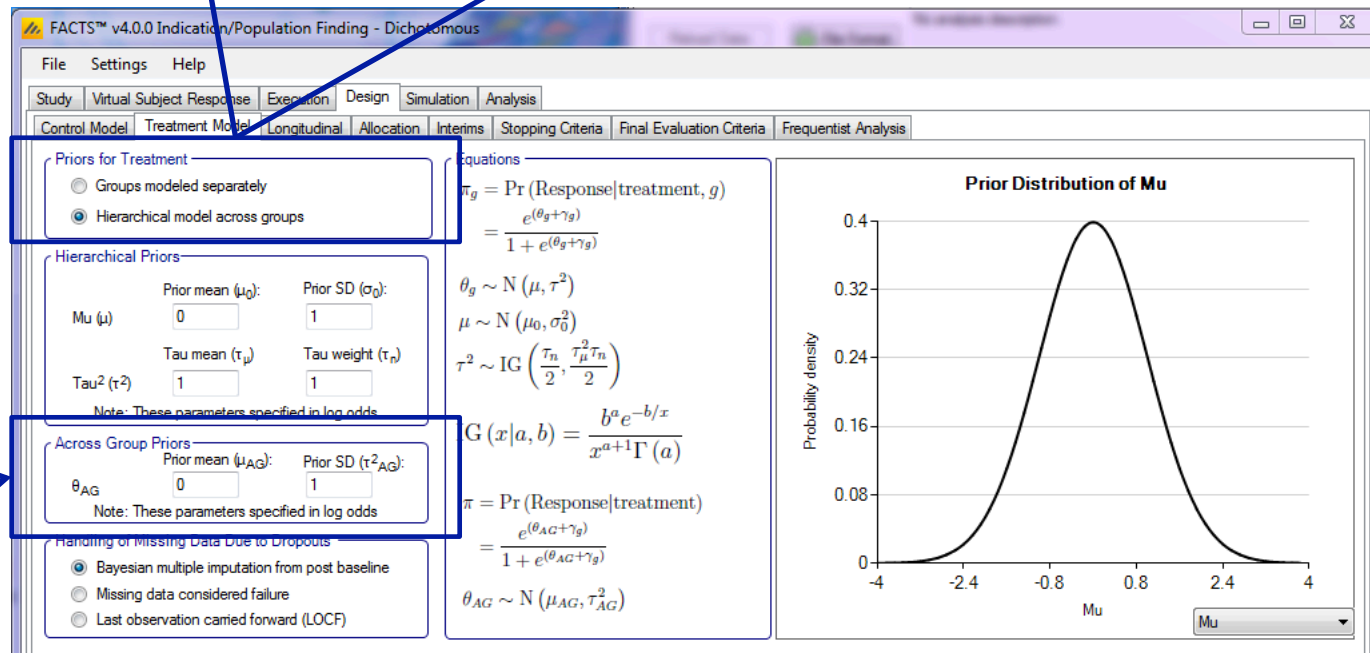
# AIPF Statistical Models

*Separate model for each group*

*OR*

*Hierarchical model across groups*

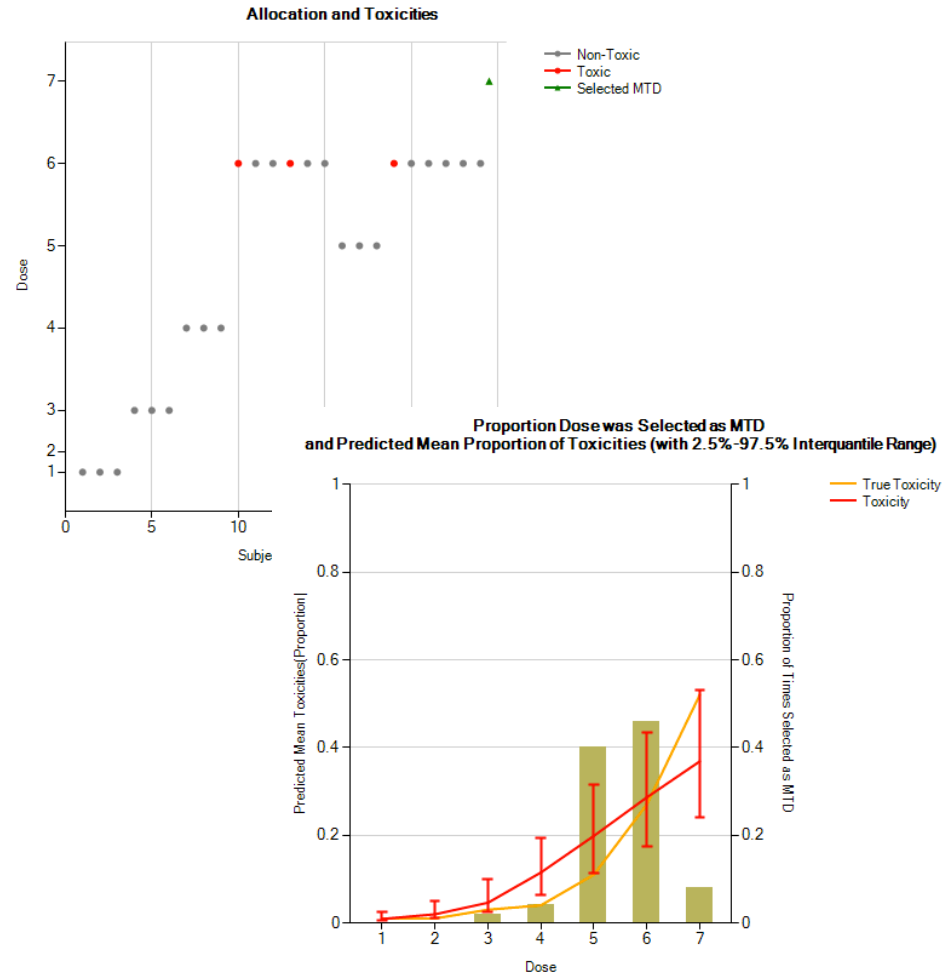
- *Estimate of treatment effect borrows information from other groups*
- *Compromise between separate models and pooled analysis*



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

# 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



# 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*

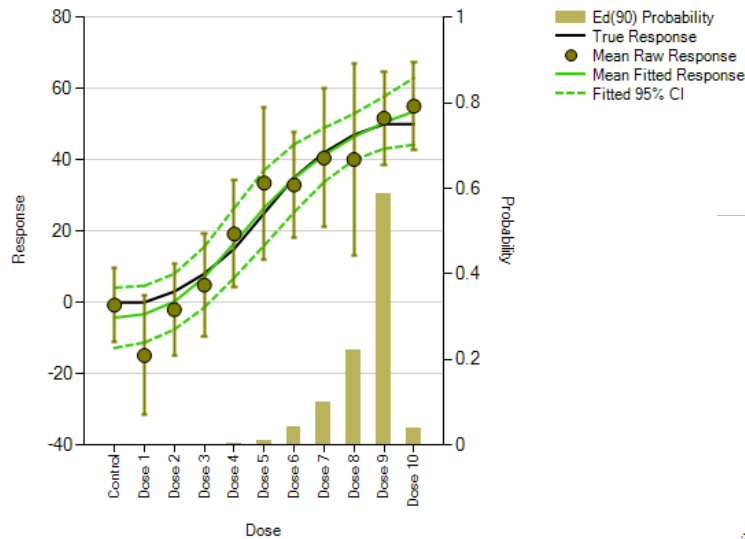


# Built-in Graphics

## Graphs

Allocation Box and Whisker plot  
 Response and Subject Allocation  
 Response and Max Selection  
 Response and ED(x) Selection  
 Response and MED Selection  
 Distribution of ED(x)  
 Distribution of Max  
 Distribution of MED  
 Probability Dose is ED(x)  
 Probability Dose is Max  
 Probability Dose is MED  
 Probability Dose Compared to Control  
 Probability Dose Compared to CSD  
 Max Response Scatter plot  
 ED(x) Response Scatter plot  
 MED Response Scatter plot  
 Probability of Achieving Futility Stopping  
 Time Course for Futility Stopping  
 Simulation Response and Subject Allocation  
 Simulation Response and Pr(Max)  
 Simulation Response and Pr(ED(x))  
 Simulation Response and Pr(MED)  
 Update Response and Subject Allocation  
 Update Response and Pr(Max)  
 Update Response and Pr(ED(x))  
 Update Response and Pr(MED)  
 Update Response and Pr(Alloc)

**Response and Ed(90) Selection (120 subjects)**  
 Recruitment: "Accrual 1" Dropout: "Dropout 1" Response: "Logistic" Longitudinal: "Longitudinal 1" Design: "Dose Finding Continuous" Simulations: 1000 Version: 2.4.2

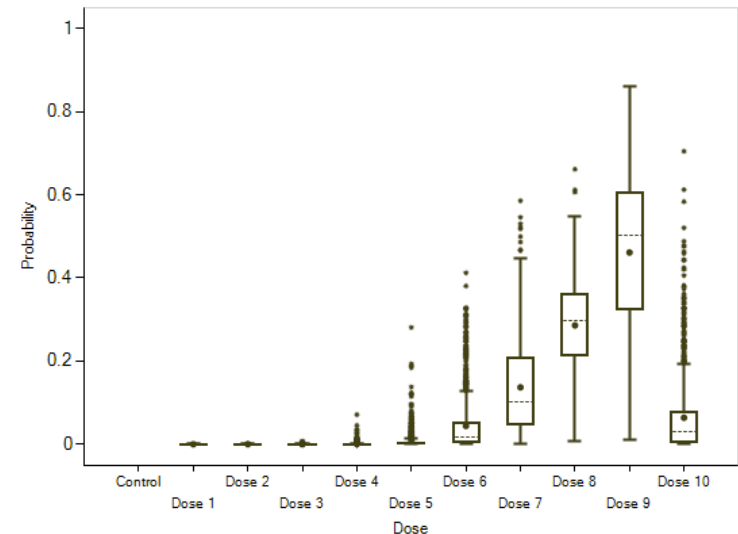


*Allows quick review of simulation summaries*



**Posterior Probabilities of Being Ed(90)**

Recruitment: "Accrual 1" Dropout: "Dropout 1" Response: "Logistic" Longitudinal: "Longitudinal 1" Design: "Dose Finding Continuous" Simulations: 1000 Version: 2.4.2



*Walk through each interim of a single simulated trial*

# Support for post-processing results

*Aggregate results from selected scenarios*

Advanced

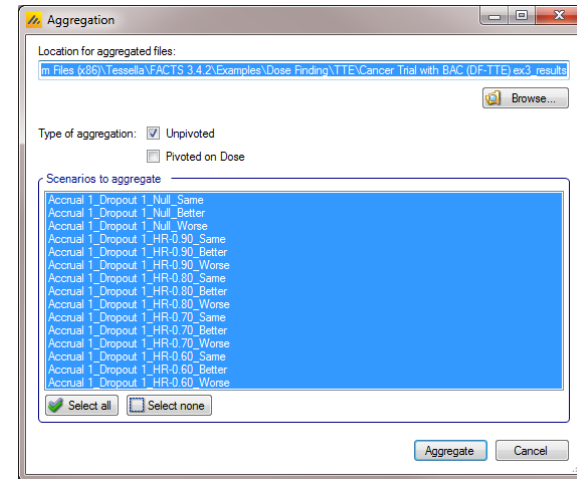
Simulations completed: 0/0

Show Other Columns...

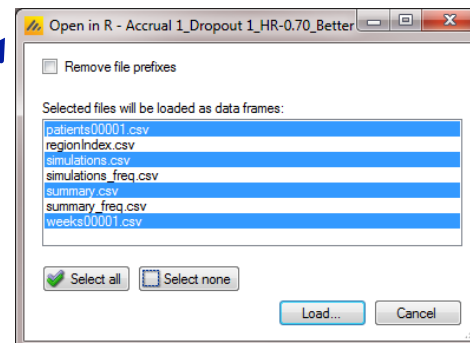
Ppn Early Futility	Ppn Suc->Fut Flip Flop	Ppn Fut->Suc Flip Flop	Ppn Inconclusive
0	0	0	0.3
0	0	0	0.334
0	0	0	0.294
0	0	0	0.392
0	0	0	0.394
0	0	0	0.398
0	0	0	0.394
0	0	0	0.422
0	0	0	0.398
0	0	0	0.332
0	0	0	0.328
0	0	0	0.32
0	0	0	0.178
0	0	0	0.2
0	0	0	0.152

Open in R... Aggregate... View Graph

Tessella

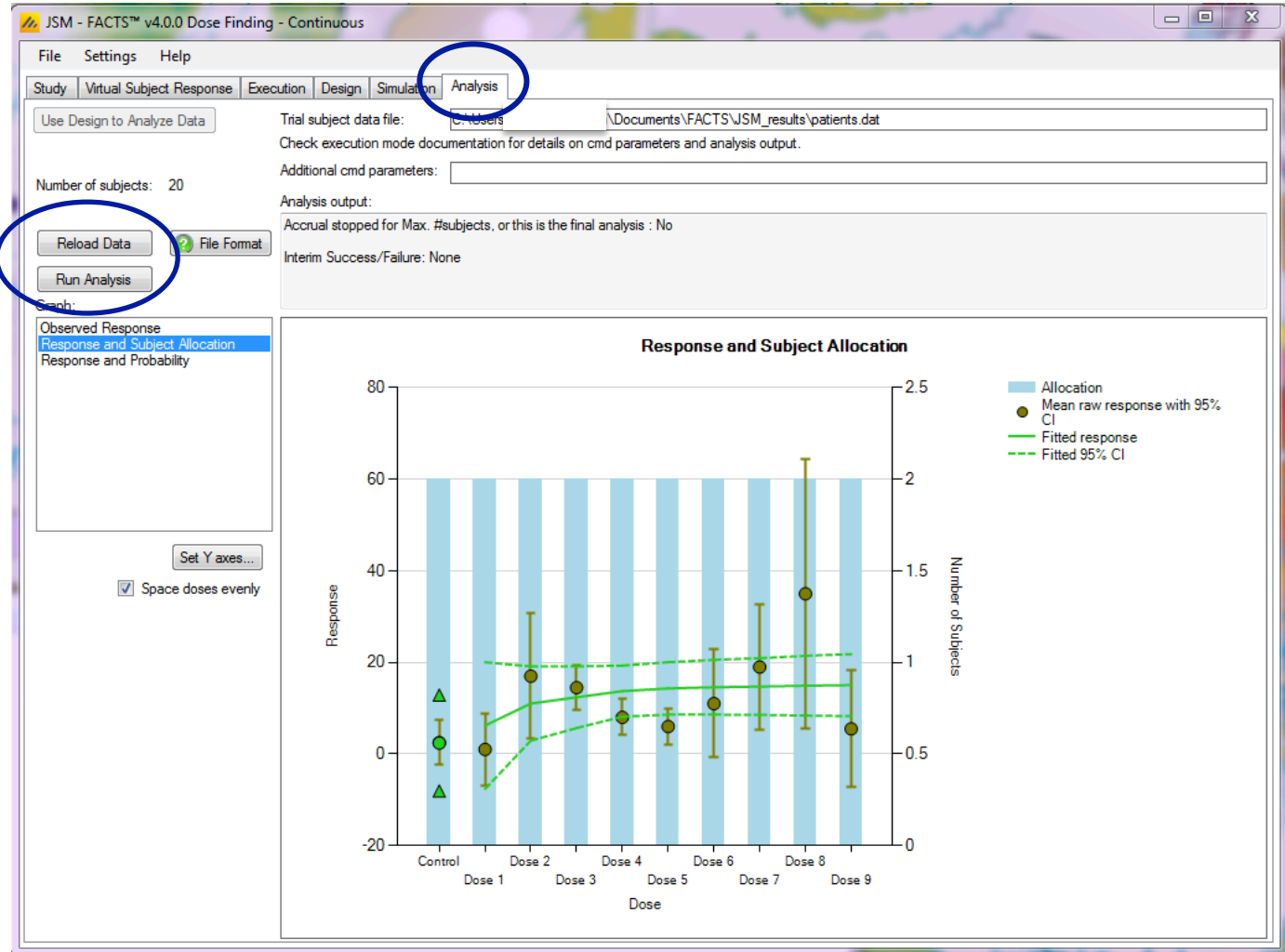


*Open in R (individual scenario or aggregated results loaded into data frames) for additional post-processing and customization of output*



# Analysis Tab

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



# Benefits of FACTS

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- 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!