

FACETS



Fixed and Adaptive Clinical Trial Simulator

Berry Consultants
 Statistical Innovation

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 an hour (no programming) and do not require extensive testing, debugging and fixing....

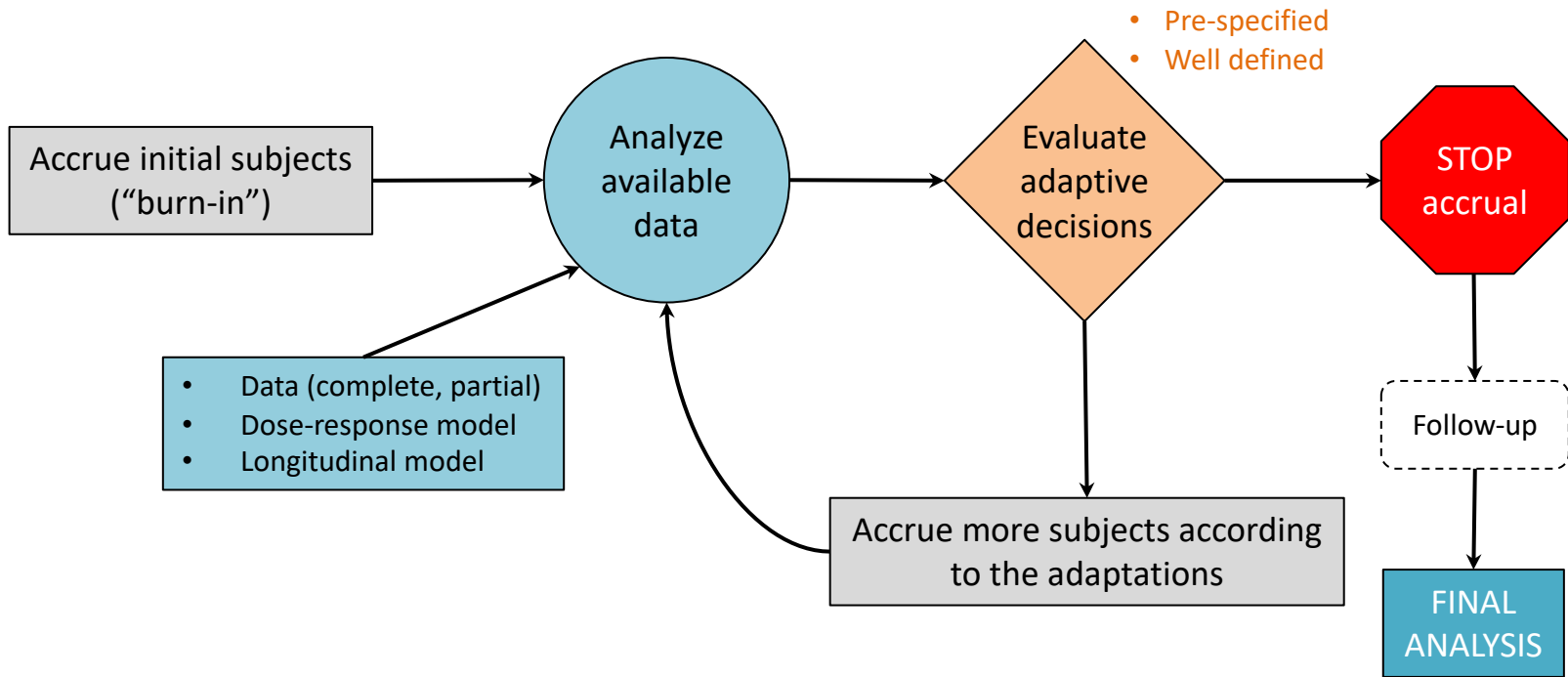
About FACTS

- 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

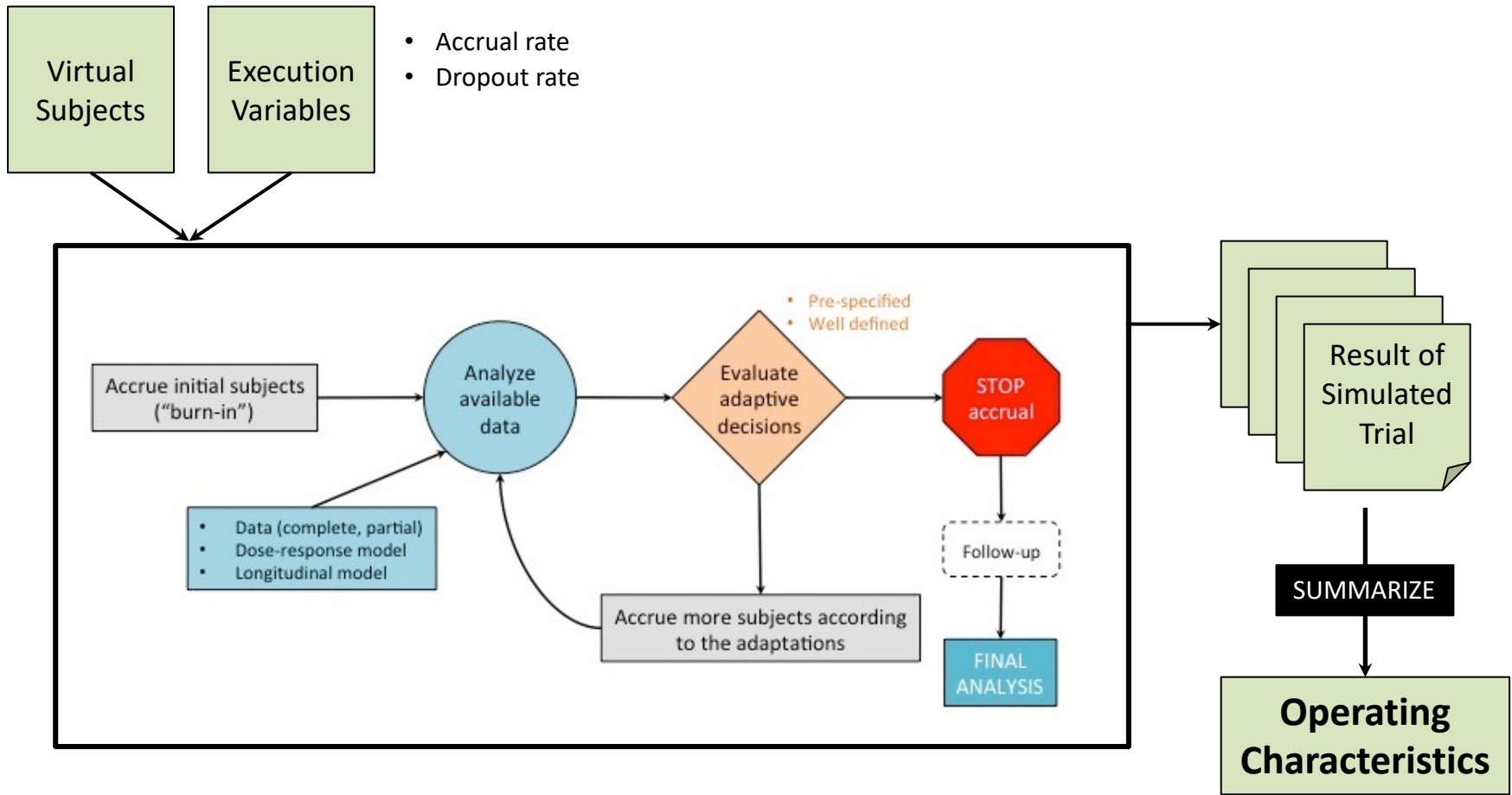
- Allow information that accumulates during the trial to modify key design parameters according to *pre-specified* and *well-defined* rules
- Adaptable components may include:
 - treatment arms (dose, frequency, duration, etc)
 - allocation to the different arms
 - the patient population
 - the sample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

“Scenarios”



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!

FACTS

SIMULATING TRIALS IN FACTS

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...

FACTS™ v5.6 Core Design - Continuous

File Settings Help

Study Virtual Subject Response Execution Quantities of Interest Design Simulation Analysis

Study Info Treatment Arms

Design Options

Adaptive Non-Adaptive

Enable frequentist analysis

Use longitudinal modeling

Include simulation of baseline Response is:

Change from baseline

Final endpoint value

Study Information

Recruit subjects Sequentially In cohorts

Maximum number of subjects:

First cohort size:

Subsequent cohort size:

Maximum number of cohorts:

Time to recruit each cohort (wks):

Maximum trial duration (wks):

Response:

Higher response is subject improvement

Lower response is subject improvement

Trial type:

Superiority

Non-inferiority

Schedule of Post-Baseline Visits

Set Visits Explicitly

Week

Auto-Generate Visits

Number

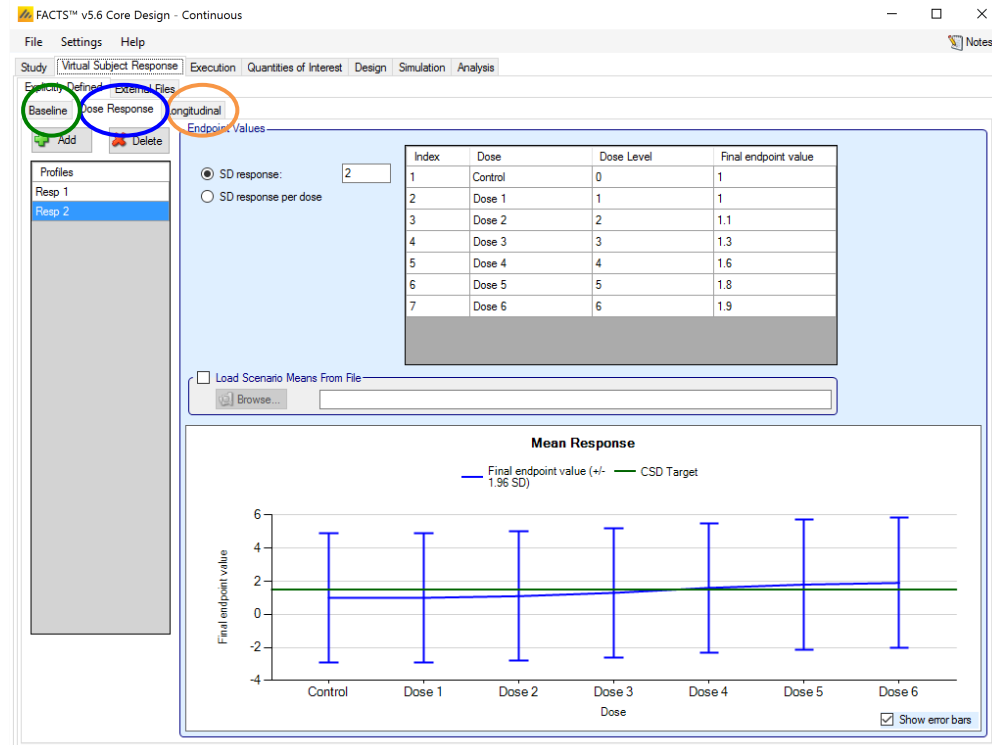
Start

Spacing

Index (t)	Visit Name	Week
1	Visit 1	4
2	Visit 2	8
3	Visit 3	12
4	Visit 4	16

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

The screenshot shows the 'Accrual' configuration window in the FACTS software. The window title is 'FACTS™ v5.6 Core Design - Continuous'. The menu bar includes 'File', 'Settings', and 'Help'. The main menu includes 'Study', 'Virtual Subject Response', 'Execution', 'Quantities of Interest', 'Design', 'Simulation', and 'Analysis'. The 'Accrual' tab is active, showing a table with columns: 'Region Name', 'Peak Accrual Rate (People per Week)', 'Start Accrual Date (Week)', 'Ramp Up', 'Ramp Up Complete (Week)', 'Ramp Down', 'Start Ramp Down (Week)', and 'Ramp Down Complete (Week)'. The table contains three rows for Region 1, Region 2, and Region 3. Region 1 has a peak rate of 4, starts at week 0, ramps up by week 3, and has a ramp down checkbox. Region 2 has a peak rate of 2, starts at week 4, ramps up by week 7, and has a ramp down checkbox. Region 3 has a peak rate of 3, starts at week 8, ramps up by week 11, and has a ramp down checkbox. Below the table is a line graph titled 'Accrual profile' showing 'Rate (subj/Week)' on the y-axis (0 to 10) and 'Week of plan' on the x-axis (0 to 50). The graph shows three lines: 'Total accrual rate' (red), 'Selected accrual rate' (blue), and 'Full accrual' (dashed grey). The total accrual rate starts at 0, ramps up to 4 by week 3, then to 6 by week 7, and finally to 9 by week 11, remaining constant until week 38. The selected accrual rate starts at 0, ramps up to 3 by week 11, and remains constant until week 38. The full accrual rate is a vertical dashed line at week 38.

Region Name	Peak Accrual Rate (People per Week)	Start Accrual Date (Week)	Ramp Up	Ramp Up Complete (Week)	Ramp Down	Start Ramp Down (Week)	Ramp Down Complete (Week)
Region 1	4	0	<input checked="" type="checkbox"/>	3	<input type="checkbox"/>		
Region 2	2	4	<input checked="" type="checkbox"/>	7	<input type="checkbox"/>		
Region 3	3	8	<input checked="" type="checkbox"/>	11	<input type="checkbox"/>		

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

FACTS™ v5.6 Core Design - Continuous

File Settings Help

Study Virtual Subject Response Execution Quantities of Interest Design Simulation Analysis

Calculate for each dose—

Posterior Probabilities	
Pr($\theta_d - \theta_{(Control)} > 0.5$)	X
Pr($\theta_d > \theta_{(Control)}$)	X
Pr($\theta_d - \theta_{(Control)} > 0.25$)	X
Add...	

Predictive Probabilities	
Pr(Succ. Future Trial): N=250; Sup. $\alpha=0.025$; $\delta=0$	X
Add...	

p-values (Trt. vs Control)	
p-value; BOCF: Bonferonni	X
Add...	

Probability of being Target	
Pr(Max)	X
Pr(MED relative to Control: Delta=0.5)	X
Pr(EDq relative to Control: Quantile=0.9)	X
Add...	

Decision Quantities (Scalars)	
Add...	

Standard Evaluation Variables

Restore Default QOIs

Clinically significant difference (CSD):

Default QOIs compare to:

Absolute response

Control

Quantities of Interest

Use defined criteria for selecting arm

User defined decision criteria: test this probability at this dose

FACTS™ v5.6 Core Design - Continuous

File Settings Help

Study Virtual Subject Response Execution Quantities of Interest Design Simulation Analysis

Calculate for each dose—

Posterior Probabilities

Pr($\theta_d - \theta_{(Control)} > 0.5$)	X
Pr($\theta_d > \theta_{(Control)}$)	X
Pr($\theta_d - \theta_{(Control)} > 0.25$)	X
Add...	

Predictive Probabilities

Pr(Succ. Future Trial): N=250; Sup. $\alpha=0.025$; $\delta=0$	X
Add...	

p-values (Trt. vs Control)

p-value; BOCF: Bonferonni	X
Add...	

Standard Evaluation Variables

Restore Default QOIs

Clinically significant difference (CSD):

Default QOIs compare to:

Absolute response

Control

Probability of being Target

Pr(Max)	X
Pr(MED relative to Control: Delta=0.5)	X
Pr(EDq relative to Control: Quantile=0.9)	X
Add...	

Decision Quantities (Scalars)

Add...	
--------	--

Dose-Response Models

Multiple options for modeling the dose-response curve

Baseline Adjustment

FACTS™ v5.6 Core Design - Continuous

File Settings Help

Study Virtual Subject Response Execution Quantities of Interest Design Simulation Analysis

Dose Response Frequentist Analysis Longitudinal Allocation Interims Success/Futility Criteria

Model: Sigmoidal

Model Parameters

Parameter	Prior mean λ_i	Prior SD λ_i
Param a_1 (#=1):	0	10
Param a_2 (#=2):	0	10
Param a_3 (#=3):	5	5
Param a_4 (#=4):	1	5

Equations for Selected Model Type

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

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

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

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

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

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

Prior Distribution of a_3

Graph Type: a_3

Model Control Separately

Fixed Prior

Hierarchical Prior

Active Comparator

Fixed Prior

Hierarchical Prior

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

Error Parameters

Sigma prior mean (σ_μ): 10

Sigma prior weight (σ_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

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

Hierarchical Prior for Control

Priors for hierarchical model

Prior trial data

FACTS™ v5.6 Core Design - Continuous

File Settings Help

Study Virtual Subject Response Execution Quantities of Interest Design Simulation Analysis

Dose Response Hierarchical Priors Frequentist Analysis Longitudinal Allocation Interims Success/Futility Criteria

Control

Equations

$$\theta_{0t} \sim N(\mu_{0t}, \tau_{0t}^2)$$

$$\mu_{0t} \sim N(\mu_0, \sigma_0^2)$$

$$\tau_{0t}^2 \sim \text{IG}(a_0, b_0)$$

Prior Distribution of Tau

Probability density

Tau

Model Parameters

Prior mean μ_0 Prior SD σ_0

Prior mean mean (τ_μ) Prior mean weight (τ_π)

Tau² (τ_{0t}^2):

Study Parameters

Name	Num subj	Response	SD of response
Study 1	25	0.11	2.1
Study 2	30	-0.06	1.78

Longitudinal Models

The screenshot shows the FACTS v5.6 Core Design - Continuous software interface. The 'Model' dropdown is set to 'Linear regression'. The 'Model Instances' section has five radio button options: 'Single model for all arms' (selected), 'Model control separately', 'Model comparator separately', 'Model control and comparator separately', and 'Model all arms separately'. The 'Model Priors' section has three radio button options: 'Same prior across all visits' (selected), 'Specify priors per visit', and 'Specify priors per model instance and visit'. The 'Equations' section contains the following mathematical expressions:

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

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

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

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

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

(These equations apply separately to each model instance)

Below the equations, there are input fields for prior parameters: α prior mean (α_μ): 0, α prior SD (α_σ): 10, β prior mean (β_μ): 0.75, β prior SD (β_σ): 1, Prior lambda mean (λ_μ): 0.5, and Prior lambda weight (λ_n): 1. A graph titled 'Prior Distribution of Alpha' shows a normal distribution curve centered at 0 with a peak density of 0.04. The x-axis is labeled 'Alpha' and ranges from -40 to 40. The y-axis is labeled 'Probability density' and ranges from 0 to 0.04. A dropdown menu labeled 'Alpha' is visible below the graph.

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

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

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*

FACTS™ v5.6 Core Design - Time to Event

File Settings Help

Study Virtual Subject Response Execution Quantities of Interest Design Simulation Analysis

Hazard Model Dose Response Hazardist Analysis Allocation Interims Success/Futility Criteria

Hazard Model

- Use piecewise exponential model
- Use Cox proportional hazard model

Control

Enable hierarchical data modeling for control arm

Segment Breakpoint: 9 weeks

Index	Segment
1	0 - 4
2	4 - 8
3	8 - ∞

Fixed Priors For Control Arm

$T \sim PE(\lambda_1 \dots \lambda_k, c_1 \dots c_{k-1})$ events per week

$\lambda_s \sim \text{Gamma}\left(n_s, \frac{n_s}{\mu_s}\right)$

Index	Segment	prior mean (μ)	prior weight (n)
1	0 - 4	0.0035	2
2	4 - 8	0.007	2
3	8 - ∞	0.0105	2

Prior Distribution of Segment Lambda

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

Study | Virtual Subject Response | Execution | Design | Tests | Si

Predictor Model | Hazard Model | Dose Response | Allocation | Stc

Dose Response | Relationship to Endpoint

Priors for Lambda

Index	Dose	Prior mean of (μ)	Prior weight (n)
1	Control	1	1
2	Dose 1	1	1
3	Dose 2	1	1

Priors for Beta

Priors for β : Mean (m) SD (s)

Equations

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

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

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

Include Predictor

Predictor endpoint type:

Continuous

Dichotomous

Time to event

Response

Higher response is subject improvement

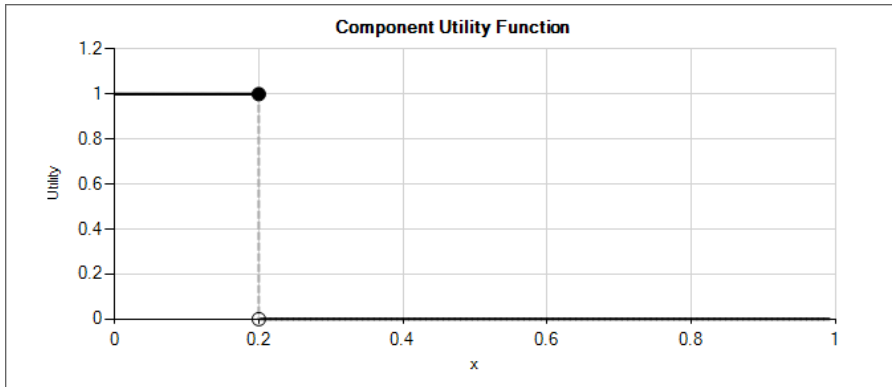
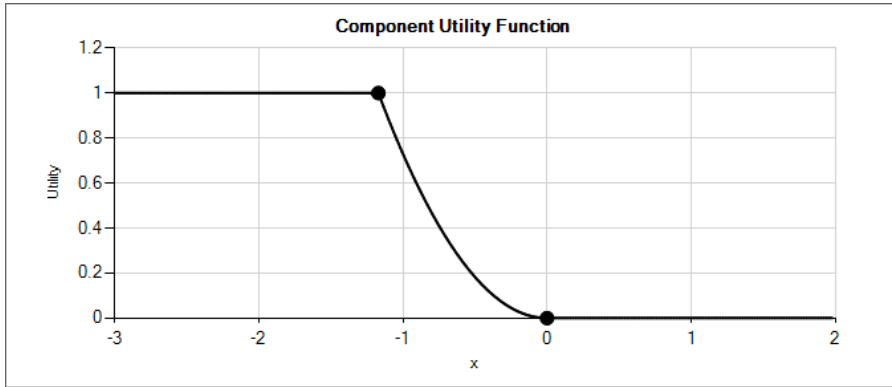
Lower response is subject improvement

Time when predictor is observed (wks):

Predictor CSD (delta):

Primary endpoint is censoring for intermediate predictor

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 enrolled, number of events, by timing, by number of subjects complete.

FACTS™ v5.6 Core Design - Time to Event

File Settings Help

Study Virtual Subject Response Execution Quantities of Interest Design Simulation Analysis

Predictor Model Hazard Model Dose Response Frequentist Analysis Allocation Interims Success/Futility Criteria

Interim Analysis Frequency

Subject Information Defined By:

Subjects Enrolled

Complete Predictor Data

Opportunity to Complete Predictor

Events

Specify Interims By:

Time - every: 2 weeks

First interim at: 100 subjects (predictor)

Information - at:

Interim	Predictor (complete)	
1	100	X
2	200	X
3	300	X

Subject Follow-up Options

Continue follow-up if study stopped for success

Continue follow-up if study stopped for futility

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

FACTS™ v5.3 Core Design - Time to Event

File Settings Help

Study Virtual Subject Response Execution Quantities of Interest Design Simulation Analysis

Hazard Model Dose Response Frequentist Analysis Allocation Interims Success/Utility Criteria

Fixed Allocation
 Arm Dropping
 Adaptive Allocation
 Legacy Adaptation

Index	Dose	Allocation Ratio	Fix Alloc.	Post First Interim 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"/>	

If control allocation is not fixed, it will seek to match that to best dose arm. Check documentation for details.
 Pre interim block size is the sum of allocation ratios.

Post first interim block size:

Slots in block that will be allocated adaptively:

Adaptive Allocation Targets

Add...

Allocation probability set to zero for values less than:

Raise allocation to power (γ):

Target Dose or Static Weight: $W_d = \text{QOI value for dose } d$

Probability: $V_d = W_d^\gamma$

Information: $V_d = \left(\frac{W_d \text{Var}(\theta_d)}{n_d + 1} \right)^{\gamma/2}$

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

FACTS™ v5.6 Core Design - Time to Event

File Settings Help

Study Virtual Subject Response Execution Quantities of Interest Design Simulation Analysis

Predictor Model Hazard Model Dose Response Frequentist Analysis Allocation Interims Success/Futility Criteria

Create

Create new interim criteria at interim: Create

Interim 1 Final Evaluation

Copy From: Final Evaluation

These criteria will apply at all intervening interims until the next interim for which criteria are defined.

Futility Criteria

QOI	
Pr(HR_d - 1 > -0.1); d=Greatest Pr(MED relative to Control: Delta=0.2) < 0.1	X
Add...	

Combine criteria using: AND OR

Minimum Information Required (all must be met)

Minimum number of Predictor Completers before trial can stop for futility: 150

Evaluation Dose	Minimum Number of Predictor Completers
Add...	

Success Criteria

QOI	
Pr(HR_d - 1 > -0.1); d=Greatest Pr(MED relative to Control: Delta=0.2) > 0.8	X
Pr(MED relative to Control: Delta=0.2); d=Max probability over all doses > 0.6	X
Add...	

Combine criteria using: AND OR

Minimum Information Required (all must be met)

Minimum number of Predictor Completers before trial can stop for success: 200

Evaluation Dose	Minimum Number of Predictor Completers
Greatest Pr(MED relative to Control: Delt...	50 X
Add...	

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

Ability to combine multiple rules

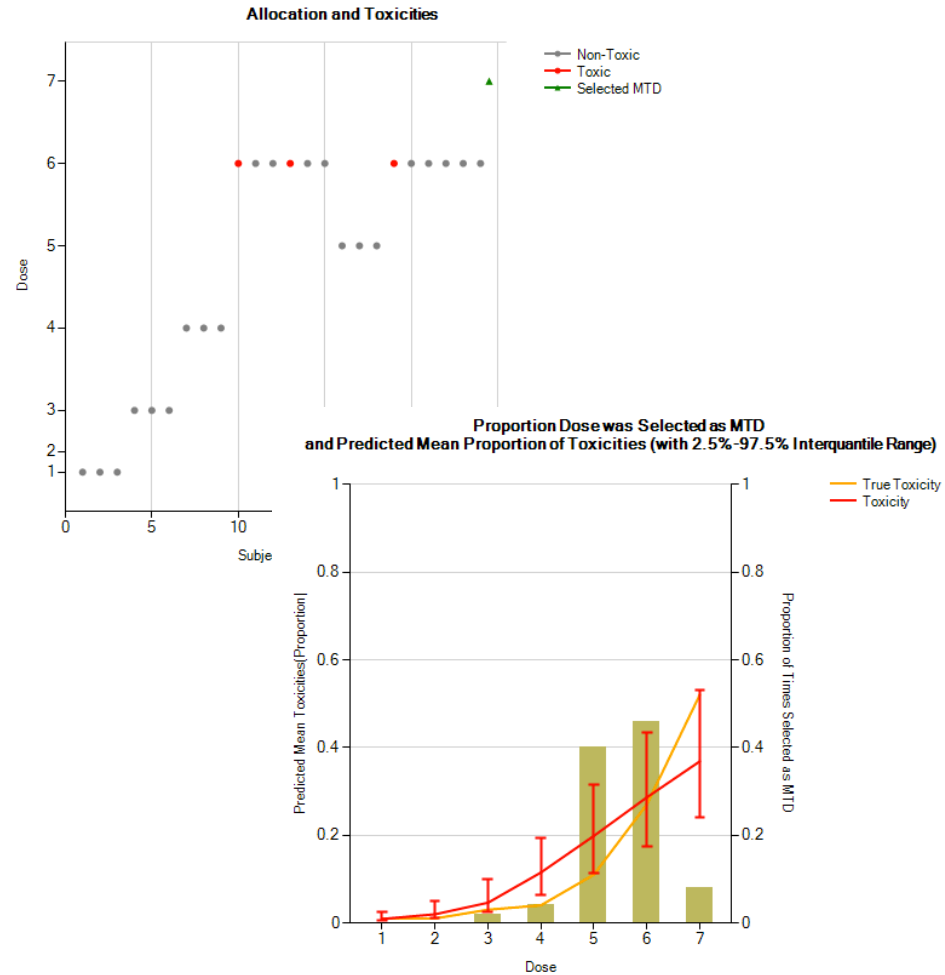
Minimum requirements for number of subjects enrolled or complete (or number of events for TTE).

Can be overall or on a specific arm.

FACTS DOSE ESCALATION DESIGNS

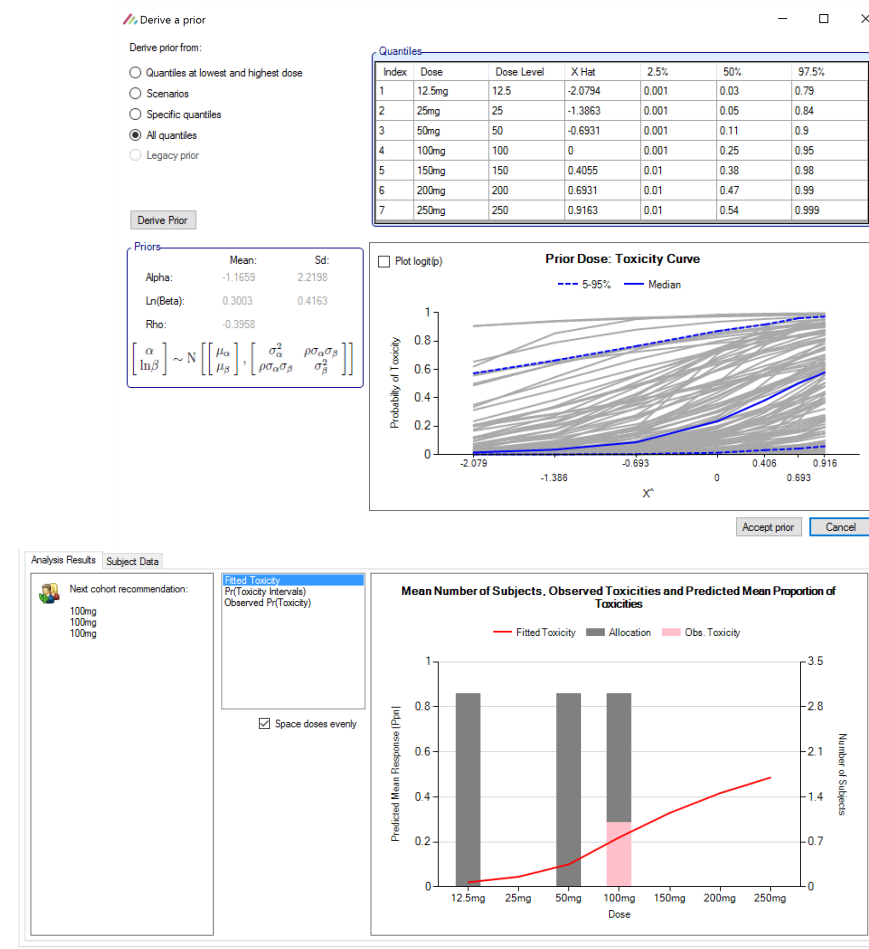
Dose Escalation

- 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



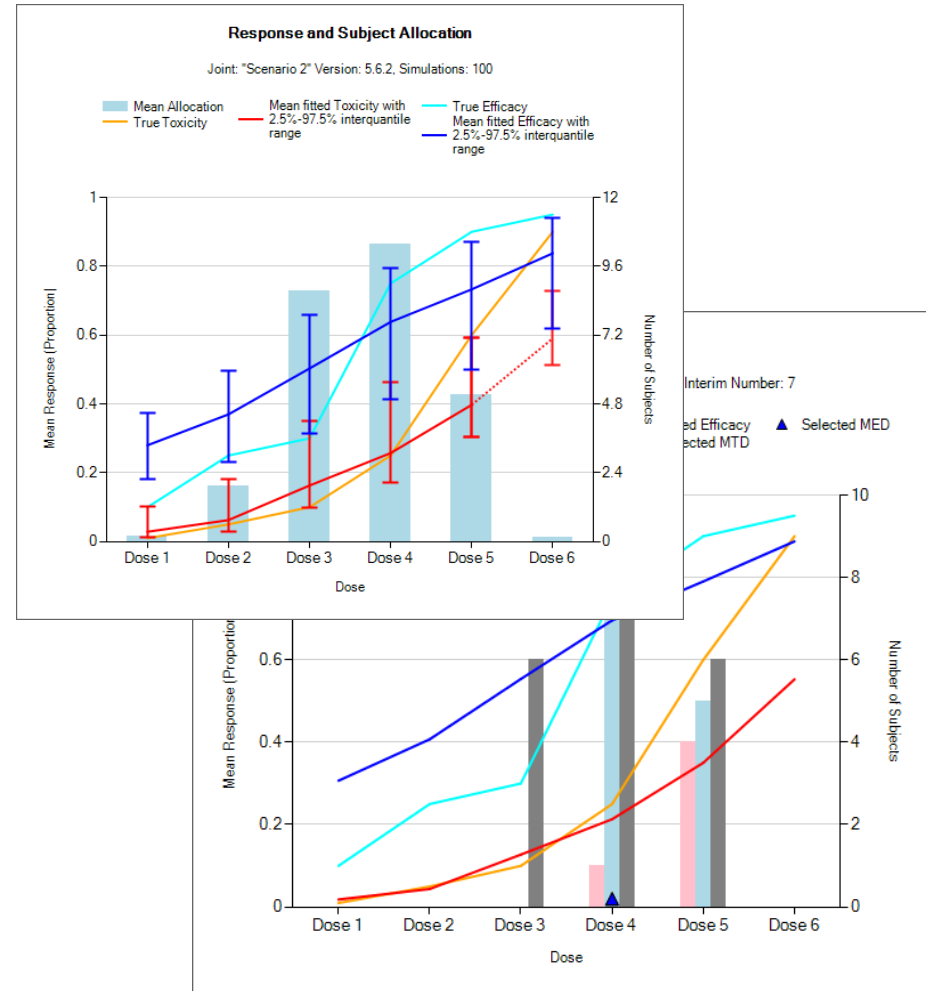
Toxicity Bands & Overdose Control

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



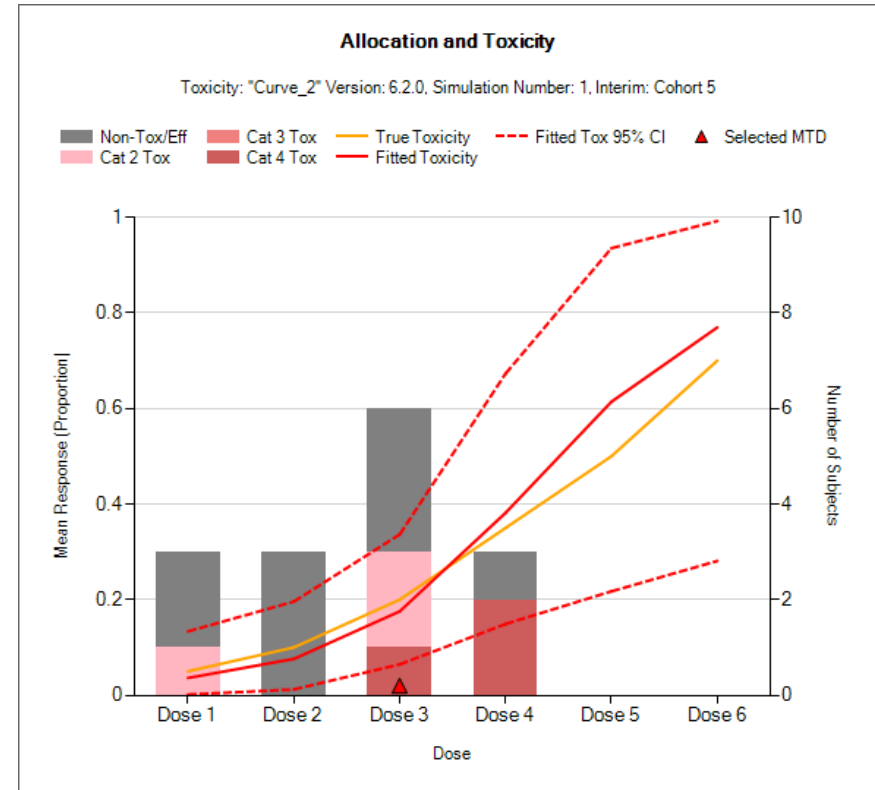
Bivariate CRM: Efficacy & Toxicity

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



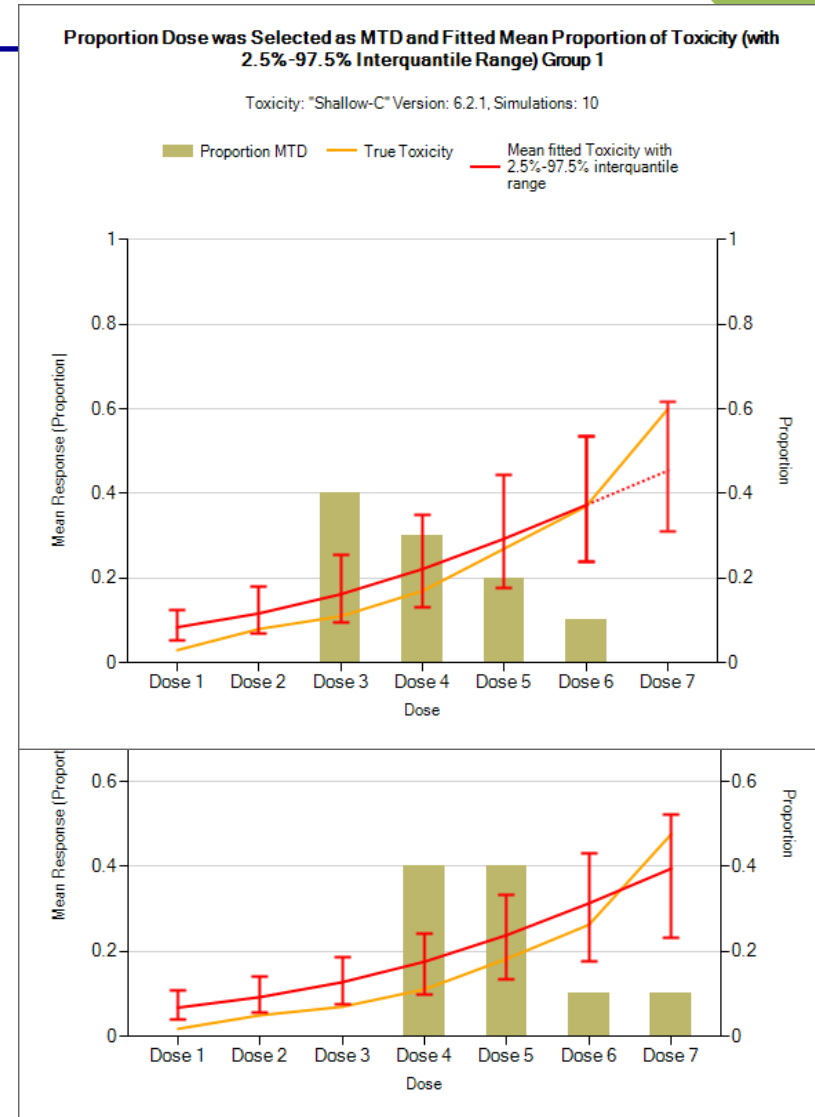
Ordinal CRM

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



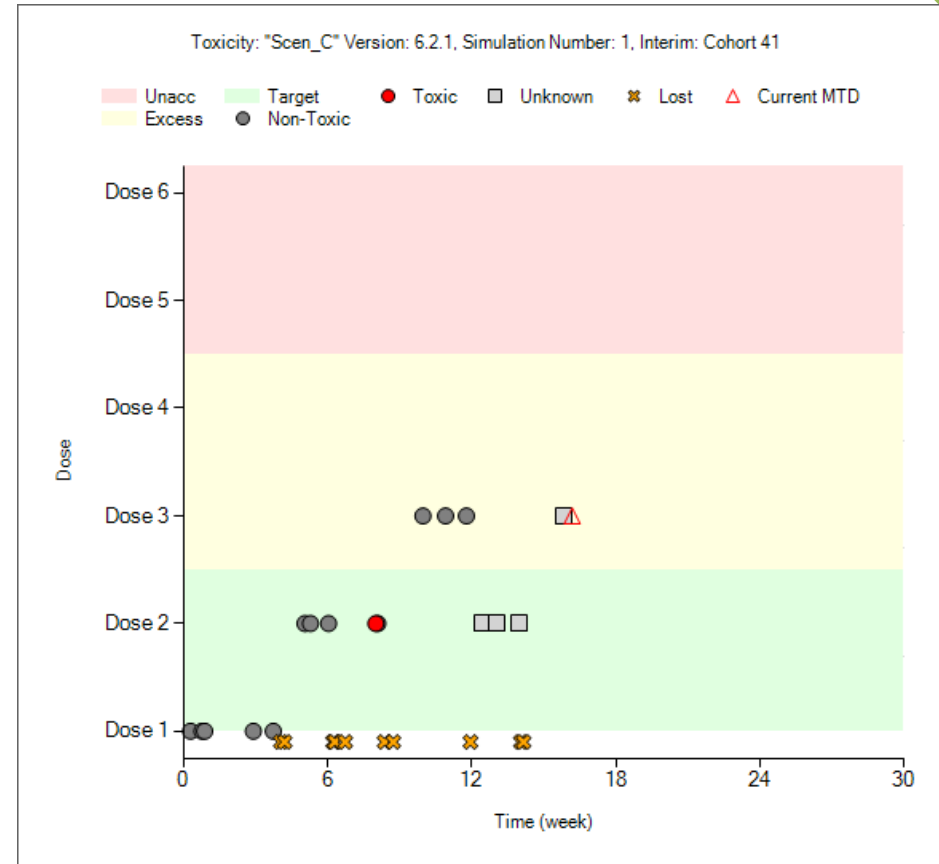
2 Groups

- 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 $\alpha_2 < \alpha_1$



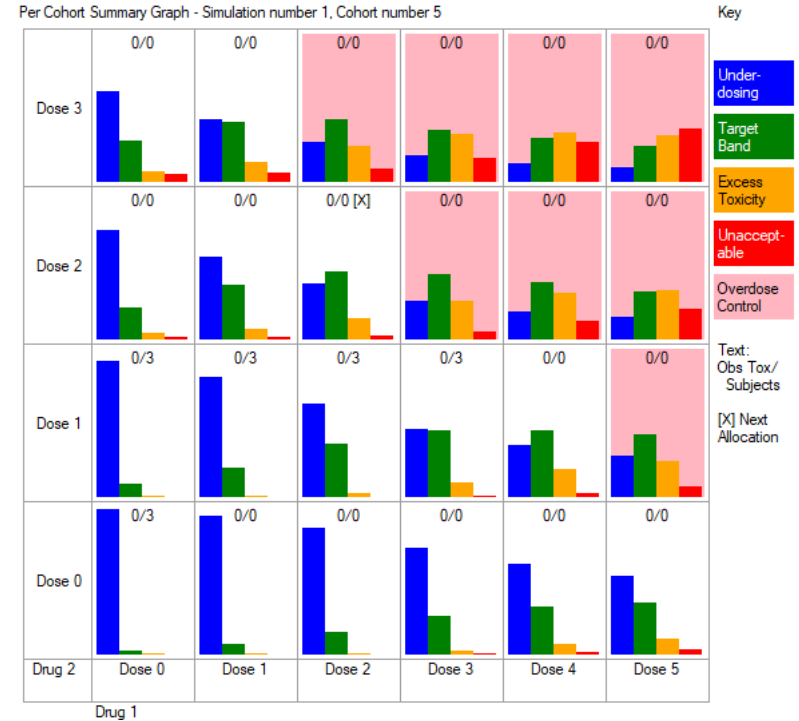
Cohort or Open Enrolment

- 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

aipfhiercap - FACTS™ v5.6 Enrichment Design - Dichotomous

File Settings Help

Study Virtual Subject Response Execution Design Simulation Analysis

Explicitly Defined External Files

Group Response

+ Add - Delete

Endpoint Values

Index	Group	Control Response Rate	Treatment Response Rate
1	Group 1	0.2	0.2
2	Group 2	0.25	0.25
3	Group 3	0.15	0.15
4	Group 4	0.3	0.3
5	Group 5	0.2	0.2

Profiles

- null
- allgood
- mixedgood
- slight
- great
- nugget3
- various

Enrichment Design - Dichotomous

Execution Design Simulation Analysis

Accrual

Regions

+ Add - Remove Import Regions Export Regions

Name	Peak rate	Start date	Ramp up	Ramp up complete
Region 1	5	0	<input type="checkbox"/>	

Group accrual

Index	Group	Relative group proportion	Start week
1	Group 1	0.1	0
2	Group 2	0.2	0
3	Group 3	0.1	0
4	Group 4	0.3	0
5	Group 5	0.3	0

Accrual profile

— Total accrual rate — Selected accrual rate - - - Full accrual

Rate (subj/Week)

Week of plan

Group Accrual

Cumulative subjects

Week of plan

Cumulative subjects stacked by group

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

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'*

The screenshot shows the FACTS software interface for an enrichment design. The 'Priors for Treatment' section has 'Hierarchical model across groups' selected. The 'Hierarchical Priors' section shows parameters for μ (mean 0, SD 10) and τ^2 (mean 0.25, weight 1). The 'Across Group Priors' section shows parameters for θ_{AG} (mean 0, SD 10). The 'Handling of Missing Data Due to Dropouts' section has 'Bayesian multiple imputation from post baseline' selected.

The 'Equations' section displays the following mathematical models:

$$\pi_g = \Pr(\text{Response}|\text{treatment}, g) = \frac{e^{\theta_g + \gamma_g}}{1 + e^{\theta_g + \gamma_g}}$$

$$\theta_g \sim N(\mu, \tau^2)$$

$$\mu \sim N(\mu_0, \sigma_0^2)$$

$$\tau^2 \sim \text{IG}\left(\frac{\tau_n}{2}, \frac{\tau_n^2}{2}\right)$$

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

$$\pi = \Pr(\text{Response}|\text{treatment}) = \frac{e^{\theta_{AG} + \gamma_g}}{1 + e^{\theta_{AG} + \gamma_g}}$$

$$\theta_{AG} \sim N(\mu_{AG}, \tau_{AG}^2)$$

The 'Prior Distribution of Mu' plot shows a normal distribution with a mean of 0 and a standard deviation of 10. The x-axis is labeled 'Mu' and ranges from -40 to 40. The y-axis is labeled 'Probability density' and ranges from 0 to 0.04.

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

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

test6-intpred-fixed - FACTS™ v6.2 Staged Core Design - Time to Event

File Settings Help

Study Virtual Subject Response Execution Quantities of Interest Stage 1 Design Transition Stage 2 Design Simulation Analysis

Predictor Model Hazard Model Dose Response Frequentist Analysis Allocation Interims Success/Futility/Graduation Criteria

Create

Create new interim criteria at interim: Create

Interim 1 Final Evaluation

Copy From: Final Evaluation

These criteria will apply at all intervening interims until the next interim for which criteria are defined.

Futility Criteria (No go to Stage 2)

QOI

Pr(HR_d < 1); d=Greatest Pr(Max) < 0.15

Add...

Combine criteria using: AND OR

Minimum Information Required (all must be met)

Min Events to stop for futility:

Evaluation Dose	Min Events
Add...	

Graduation to Stage 2 Criteria

QOI

Pr(HR_d < 1); d=Greatest Pr(Max) > 0.99

Add...

Combine criteria using: AND OR

Minimum Information Required (all must be met)

Min Events to graduate:

Evaluation Dose	Min Events
Add...	

Success Criteria (No go to Stage 2)

QOI

Pr(HR_d < 1); d=Greatest Pr(Max) > 0.99

Add...

Combine criteria using: AND OR

Minimum Information Required (all must be met)

Min Events to stop for success:

Evaluation Dose	Min Events
Add...	

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

The screenshot shows the 'Dose Selection' tab in the FACTS v6.2 Staged Core Design software. The 'Dose Selection Method' is set to 'Standard Selection Logic'. The 'Keep Control and/or Additional Comparator in Stage 2' options are checked for 'Control' and 'AC'. The 'Individual Dose Decisions' section is expanded, showing the following rules in order of priority:

- Individual Dose Decisions
- Keep Dose 4
- Target Dose Decisions
- None
- All Dose Decisions

Sort Priority: Keep highest Pr(HR_d < 1)
Minimum to keep: 1, Maximum to keep: 2 - out of 4 possible doses

Notes:

- Decisions are applied in the following priority (highest to lowest):
 - Individual Dose Decisions
 - Target Dose Decisions
 - All Dose Decisions
- Once applied, decisions cannot be reversed - i.e. higher priority decisions take precedence over lower priority ones.

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

The screenshot shows the 'test6-intpred-fixed-tmp* - FACTS™ v6.2 Staged Core Design - Time to Event' window. The 'Dose Selection Method' is set to 'Representative Arm Logic'. The 'Group Builder' panel shows two groups, Group A and Group B, each containing four doses. Dose 1 and Dose 4 are highlighted in yellow. A blue arrow points from the text on the right to these highlighted doses. The 'Representative Arm Decisions' panel shows the 'Method' set to 'Keep one group' and the 'Group Representative' set to 'Pr(Max)'. The 'QOI' is 'Pr(HR_d - 1 < -0.5)' and the 'Priority' is 'Greatest'.

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

test6-intpred-fixed-tmp* - FACTS™ v6.2 Staged Core Design - Time to Event

File Settings Help

Study Virtual Subject Response Execution Quantities of Interest Stage 1 Design Transition Stage 2 Design Simulation Analysis

Dose Selection Data Inclusion

In Stage 2 analysis, Stage 1 data is:

- not used
- included in full
- included where the subjects are on arms that are kept in Stage 2
- included in full and pooled with the one Stage 2 treatment arm Note: this is only available when keeping exactly one Stage 1 arm

Min and Max Decision QOIs and Target QOIs are selectable from:

- only arms selected for Stage 2
- all arms

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

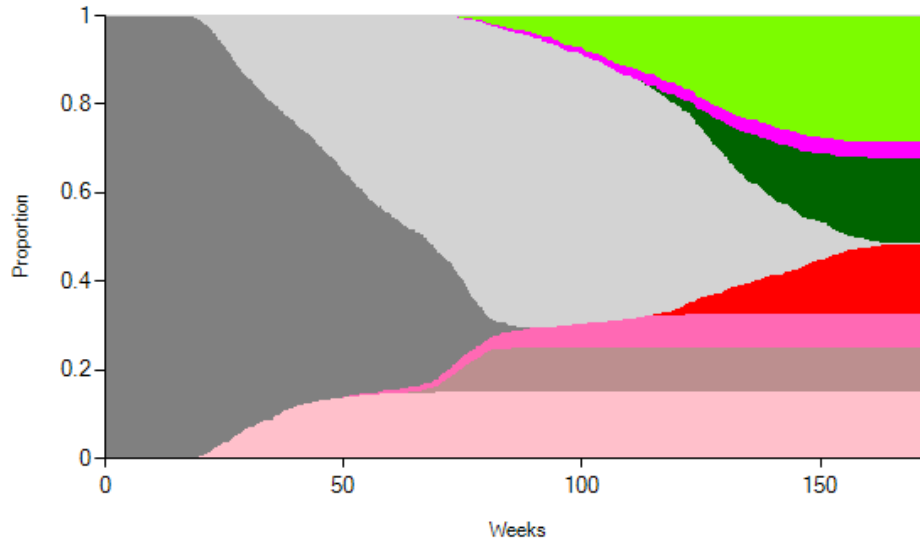
From 'None' to 'All' with several options in between.

2 Separate Trials, or 2 stage trials

Cumulative Proportion of Outcomes Over Time/Subjects

Recruitment: "Accrual 1" Dropout: "Dropout 1" , Dose Response: "AsPredict" , Control Hazard Rates: "CHaz 1" , Predictor: "Alt" , Version: 6.2.1, Simulations: 1000

- Stopped early for success Stage 2
- Success to futility flipflop S2
- Stopped late for success Stage 2
- In stage 2 / Inconclusive
- In stage 1
- Stopped late for futility Stage 2
- Stopped early for futility Stage 2
- Stopped late for futility Stage 1
- Stopped early for futility Stage 1



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

FACTS™ v7.0 Platform Trial Design - Continuous

File Settings Help

Trial Virtual Response Accrual Quantities of Interest Design Simulation

Trial Info Trial Arms

Design Options

- Enable adaptive features
- Use longitudinal modeling
- Include simulation of baseline

Response is:

- Change from baseline
- Final endpoint value

Trial Information

- Max enrollment time (wks) 500
- Max number of participants 300
- Max successful treatments 2
- Max participants per treatment: 100
- Max concurrent treatments: 4

Response: Higher response is improvement
 Lower response is improvement

Schedule of Post-Baseline Visits

Time to Final Endpoint (weeks): 8

Classification of Simulated Treatments

We would want a treatment to be a success if treatment effect > 2

We would want a treatment to be a failure if treatment effect < 1

Treatments expected to be a success are referred to as Good.
Treatments expected to be a failure are referred to as Unacceptable.
Treatments that fall in between are referred to as Mediocre.

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

Ealry stop - FACTS™ v7.0 Platform Trial Design - Continuous

File Settings Help

Trial Virtual Response Accrual Quantities of Interest Design Simulation

Trial Info Trial Arms

Definition Arrivals

Add Delete

Profiles

Arrival 1

Treatment Arrival Values

Index	Treatment	Earliest Possible Arrival (wks)	Latest Possible Arrival (wks)	Withdrawn If Not Used Within (wks)
1	Treatment 1	0	0	0
2	Treatment 2	0	0	0
3	Treatment 3	26	52	26
4	Treatment 4	52	78	26
5	Treatment 5	78	104	26
6	Treatment 6	104	130	26
7	Treatment 7	130	156	26
8	Treatment 8	156	182	26
9	Treatment 9	182	208	26
10	Treatment 10	208	234	26

<- Create one or more profiles that define when treatments enter the trial. For each treatment...

'Earliest possible arrival' defines the first week in the trial the treatment may be available.

'Latest possible arrival' defines an uncertainty about that date, the treatment will arrive with uniform probability across the interval between these times.

'Withdrawn if not used within' is the maximum number of weeks the treatment will wait to be able to enter after arrival.

Note: At least one treatment should start a time 0.

Note: A treatment cannot enter the trial if there are already 'Max concurrent treatments'.

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 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

The screenshot shows the 'Treatment Sampled Mean Response/Effect' configuration window in the FACTS v7.0 Platform Trial Design software. The window is titled 'Ealry stop - FACTS™ v7.0 Platform Trial Design - Continuous'. It has a menu bar with 'File', 'Settings', and 'Help'. Below the menu bar are tabs for 'Trial', 'Virtual Response', 'Accrual', 'Quantities of Interest', 'Design', and 'Simulation'. The 'Simulation' tab is active, and within it, the 'Treatment Distribution' sub-tab is selected. On the left, there is a 'Profiles' list with 'Dist 1' selected. The main area contains the following settings:

- Response Effect Size
- Prob effect size is 0:
- Distribution type:
- Mean: SD:
- Minimum: Maximum:

A note at the bottom states: 'Note: The Beta distribution is rescaled to have the specified mean and standard deviation, and to be between the minimum and maximum bounds.' A blue arrow points from the 'Beta' dropdown menu to the text in the second callout box.

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

File Settings Help

Trial Virtual Response Accrual Quantities of Interest Design Simulation

Control Response Treatment Response Allocation Trial Updates Success/Futility Criteria

Fixed Allocation Adaptive Allocation

Allocation Options

Constant proportion allocated to control

Allocation to control per sub-block:

Allocation to treatments per sub-block:

Sub-block size per treatment:

Note: the randomization block will be made up of a sub-block for each active treatment

Allocation dependent on number of treatments

Randomization Ratio and Blocking

No. of Current Treatments	Allocation to each Treatment	Allocation to Control	Block Size
1	1	1	2
2	1	1	3
3	1	1	4
4	1	1	5

Note: Treatment dropping criteria are specified on the Success/Futility Tab

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

Allocation Options

Constant proportion allocated to control

Allocation to control per sub-block:

Allocation to treatments per sub-block:

Sub-block size per treatment:

Note: the randomization block will be made up of a sub-block for each active treatment

Allocation dependent on number of treatments

Randomization Ratio and Blocking

No. of Current Treatments	Allocation to each Treatment	Allocation to Control	Block Size
1	1	1	2
2	1	1	3
3	1	1	4
4	1	1	5

Note: Treatment dropping criteria are specified on the Success/Futility Tab



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.

Allocation: response adaptive

Ealry stop* - FACTS™ v7.0 Platform Trial Design - Continuous

File Settings Help

Trial Virtual Response Accrual Quantities of Interest Design Simulation

Control Response Treatment Response Allocation Trial Updates Success/Futility Criteria

Fixed Allocation
 Adaptive Allocation

Allocation Options

Constant proportion allocated to control
 Allocation to control per sub-block:
 Allocation to treatments per sub-block:
 Sub-block size per treatment:
 Note: the randomization block will be made up of a sub-block for each active treatment

Allocation dependent on number of treatments
 Ratio of Control to Adaptively Allocated Slots

No. of Current Treatments	Slots Allocated Adaptively to Treatments	Allocation to Control	Block Size
1	1	1	2
2	2	1	3
3	3	1	4
4	4	1	5

Note: Initial allocation during burn-in up to first interim allocates slots between treatments equally. But treatments getting fixed allocation get 1/T of the adaptively allocated slots where T is number of current treatments.

Fixed Allocation Period

Number of subjects allocated to new treatment before being included in adaptive randomization:

Adaptive Allocation Targets

Adaptive Allocation Targets	
Pr(Max), Probability Weight=2	X
Static, Probability Weight=1	X
Add..	

Allocation probability set to zero for values less than:

Raise allocation to power (γ):

Target Dose or Static Weight: $W_d = \text{QOI value for dose } d$

Probability: $V_d = W_d^2$

Information: $V_d = \left(\frac{W_d \text{Var}(\theta_d)}{n_d + 1} \right)^{\gamma/2}$

Static Weights

Dose	Ratio
Control	
Treatment 1	1
Treatment 2	1
Treatment 3	1
Treatment 4	1
Treatment 5	1

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

Early stop* - FACTS™ v7.0 Platform Trial Design - Continuous

File Settings Help

Trial Virtual Response Accrual Quantities of Interest Design Simulation

Control Response Treatment Response Allocation Trial Updates Success/Futility Criteria

Fixed Allocation
 Adaptive Allocation

Allocation Options

Constant proportion allocated to control
 Allocation to control per sub-block:
 Allocation to treatments per sub-block:
 Sub-block size per treatment:
 Note: the randomization block will be made up of a sub-block for each active treatment

Allocation dependent on number of treatments
 Ratio of Control to Adaptively Allocated Slots

No. of Current Treatments	Slots Allocated Adaptively to Treatments	Allocation to Control	Block Size
1	1	1	2
2	2	1	3
3	3	1	4
4	4	1	5

Note: Initial allocation during burn-in up to first interim allocates slots between treatments equally. But treatments getting fixed allocation get 1/T of the adaptively allocated slots where T is number of current treatments.

Fixed Allocation Period

Number of subjects allocated to new treatment before being included in adaptive randomization:

Adaptive Allocation Targets

Adaptive Allocation Targets	
Pr(Max), Probability Weight=2	X
Static, Probability Weight=1	X
Add...	

Allocation probability set to zero for values less than:

Raise allocation to power (γ):

Target Dose or Static Weight: $W_d = \text{QOI value for dose } d$

Probability: $V_d = W_d^2$

Information: $V_d = \left(\frac{W_d \text{Var}(\theta_d)}{n_d + 1} \right)^{\gamma/2}$

Static Weights

Dose	Ratio
Control	
Treatment 1	1
Treatment 2	1
Treatment 3	1
Treatment 4	1
Treatment 5	1

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

Ealry stop* - FACTS™ v7.0 Platform Trial Design - Continuous

File Settings Help

Trial Virtual Response Accrual Quantities of Interest Design Simulation

Control Response Treatment Response Allocation Trial Updates Success/Futility Criteria

Update Frequency

Participant Information Defined By:

Participants Enrolled

Complete Data at Specified Visit

Opportunity to Complete at Specified Visit

Updates occur whenever a treatment milestone is met

Updates occur on a regular schedule

Treatments may enter trial between updates

First update specified by:

Time at 4 weeks

Information at 90 participants 1 visit

Subsequent updates specified by:

Time every 8 weeks

Information every 100 participants 1 visit

Note: a treatment's final analysis is carried out as soon as its final follow-up is complete

Participant Follow-up Options

Continue follow-up if treatment stopped for success

Continue follow-up if treatment stopped for futility

Note: stopping early for futility doesn't stop follow-up of controls

Treatment Milestones

Evaluate milestone criteria at each update after milestone reached

Evaluate milestone criteria only when milestone first reached

Note: only the latest milestone criteria will be evaluated if more than one milestone is achieved between updates

Add

Milestone	Visit	Participants (opportunity)	
1	1	30	X
2	1	40	X
3	1	50	X

'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

The screenshot displays the 'Success/Futility Criteria' tab in the FACTS v7.0 Platform Trial Design software. The interface includes a menu bar (File, Settings, Help), a toolbar with tabs for Trial, Virtual Response, Accrual, Quantities of Interest, Design, and Simulation. Below the toolbar, there are sections for 'Create' (with a 'Create new criteria at milestone' dropdown set to '3' and a 'Copy From' dropdown set to 'All Treatments'), 'Milestone' selection (Milestone 1, Milestone 2, Milestone 3, Final Evaluation), and two main panels for 'Futility Criteria' and 'Success Criteria'. Both panels show a 'QOI' (Quantity of Interest) with a formula: $\text{Pr}(\text{Succ. Future Trial}): N=132; \text{Sup. } \alpha=0.025; \delta=0 < 0.1$ for Futility and $\delta=0 > 0.95$ for Success. Each panel also has an 'Add...' button and a 'Combine criteria using' section with radio buttons for AND and OR. Two blue arrows point from the text on the right to the 'QOI' fields in both panels.

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

Simulation

Run Configuration

Number of simulations: 100

Parallelization packet size: 100

Subject Simulation Parameters:

Random seed: 3500

Start at simulation: 1

MCMC Settings

Results Output:

Number of "Weeks" files to output: 100

Number of "Patients" files to output: 1

Run Simulations:

Locally On Grid

Simulations completed: 200/200

Simulate Cancel

Results Options

View Graph Open in R... Design Report...

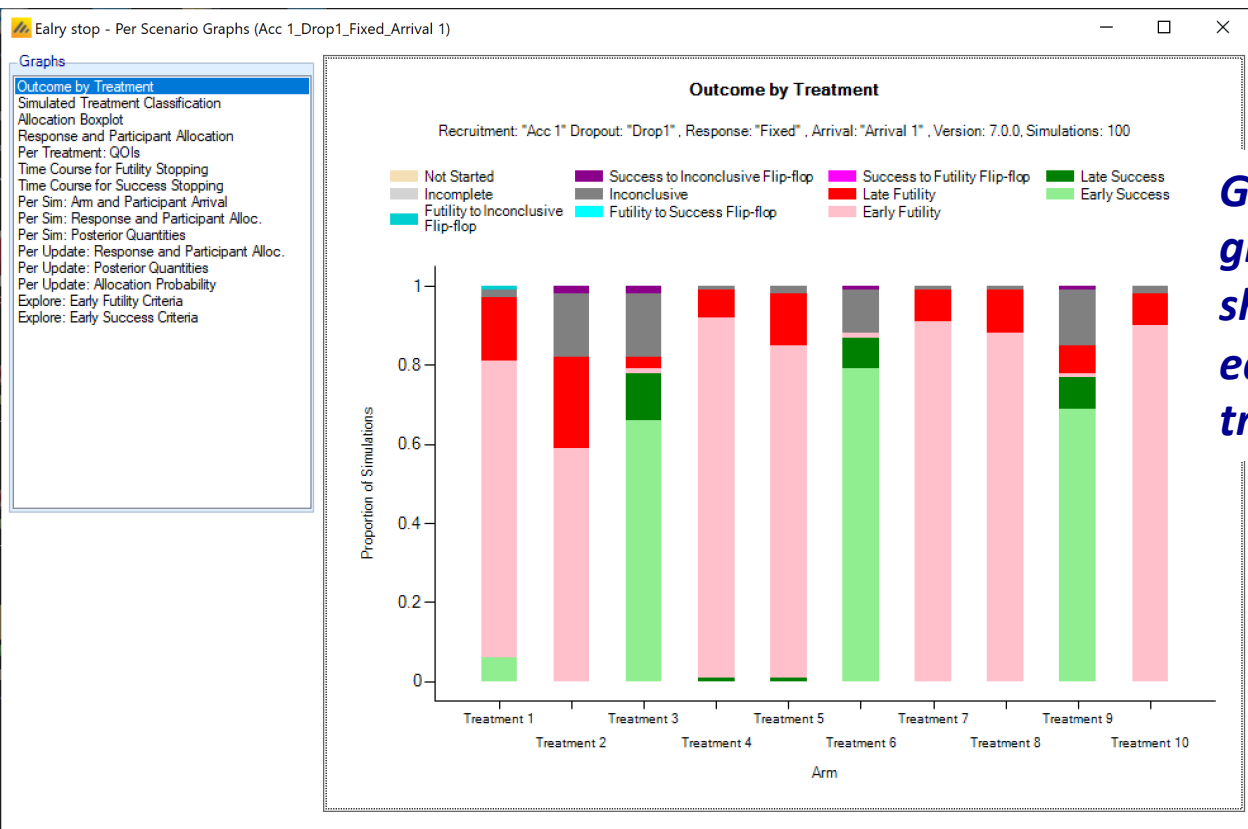
Show Other Columns... Aggregate...

Select All	Settings	Status	Scenario	Ppn Successes Treatment Good	Ppn Futilities Treatment Good	Ppn Inconclusives Treatment Good	Ppn Successes
<input type="checkbox"/>		Compl...	Acc 1_Drop 1_Fixed...	0.8067	0.0433	0.15	0.0114
<input type="checkbox"/>		Compl...	Acc 1_Drop 1_Samp...	0.8814	0.0192	0.0994	0.0031

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

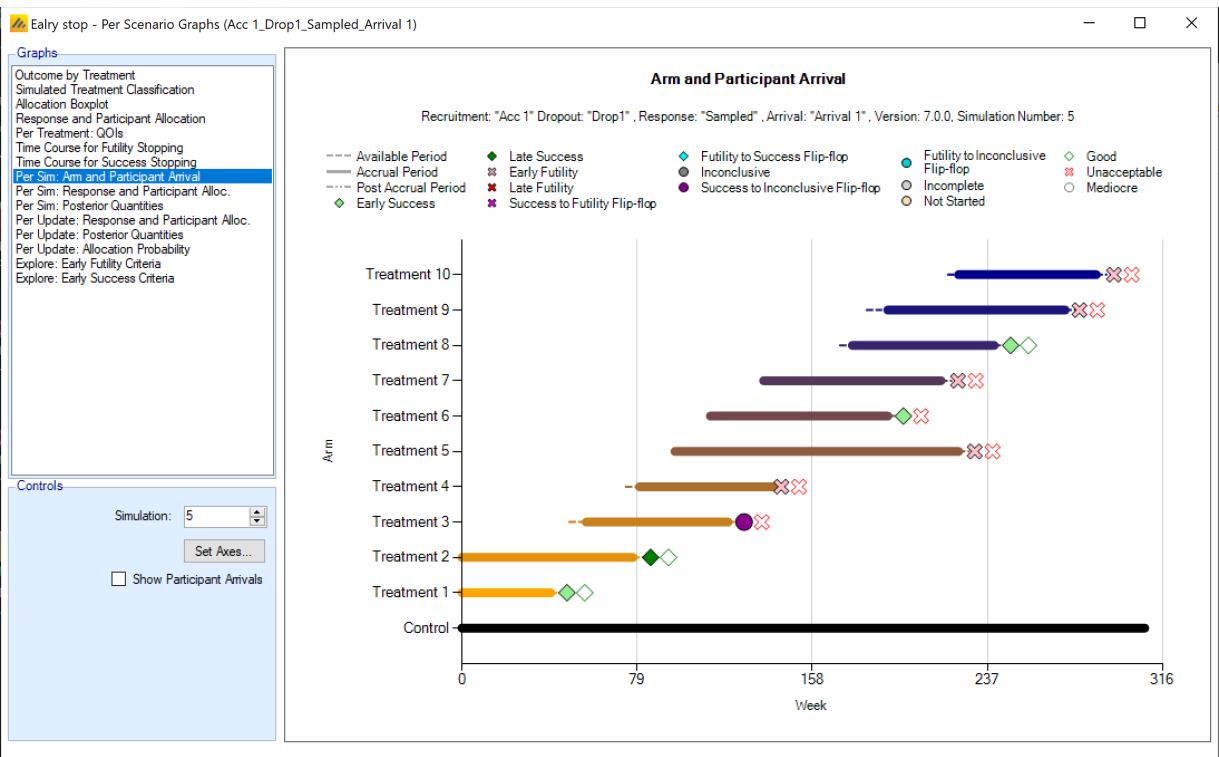
Reported results include the proportion of Good / Mediocre / Unacceptable treatments that are Successful / Inconclusive / or Futile.

Graphs



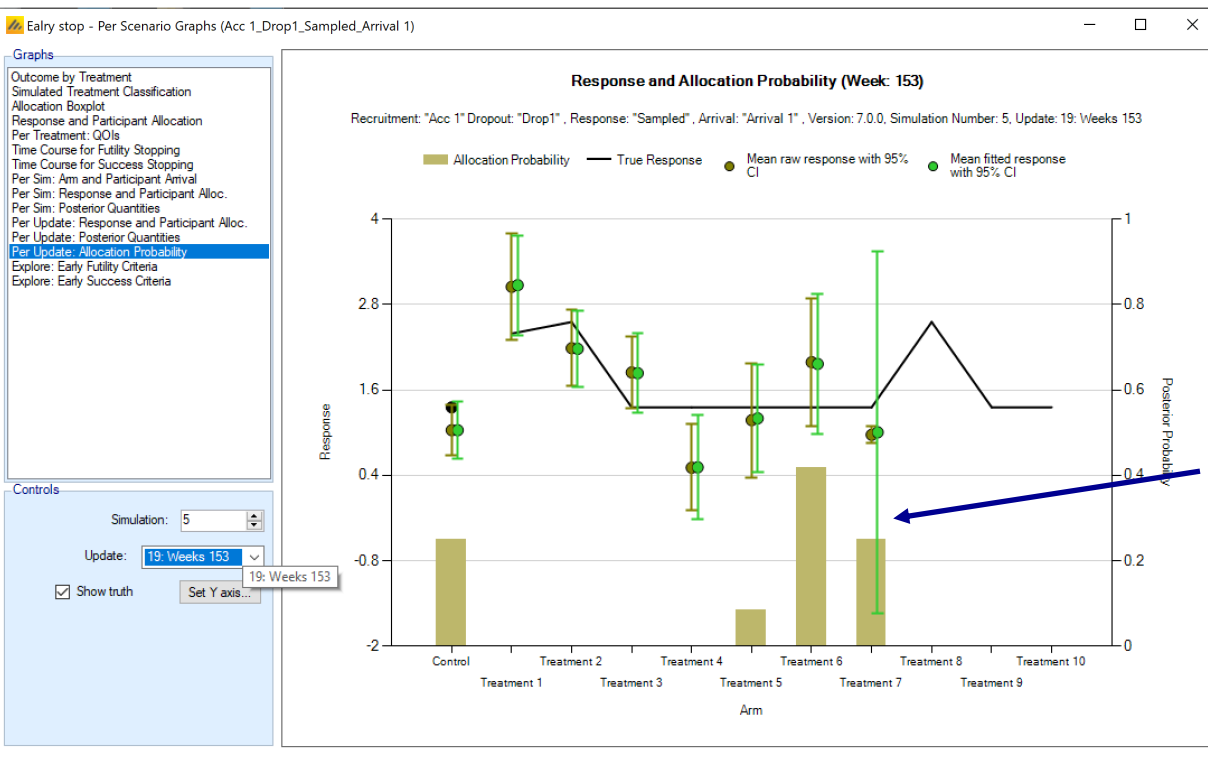
Graphs include summary graphs, here for instance showing the proportion of each type of outcome for each treatment.

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

The screenshot displays the 'Single Endpoint Utility' software interface. The 'Simulation' tab is active, showing configuration options for the number of simulations (1000), parallelization packet size (25), random seed (3500), and start at simulation (1). The 'Results Output' section shows options for the number of 'Weeks' files to output (100), 'Subject' files to output (1), and 'Frequentist' weeks files to output (1). The 'Run Simulations' section shows a progress bar and a 'Simulations completed: 2100/4000' indicator. The 'Results Options' section includes buttons for 'View Graph', 'Open in R...', 'Show Other Columns...', and 'Aggregate...'. Below the configuration panels is a table of simulation results.

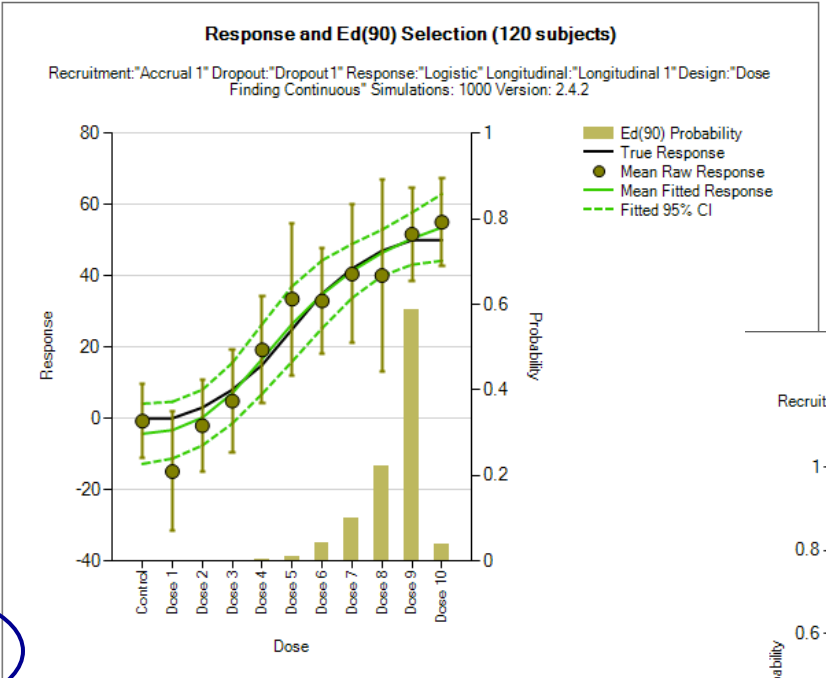
Select All	Settings	Status	Scenario	Num Sims	Mean Subj.	Ppn Early Success	Ppn Late Success	Ppn Late Futility
<input type="checkbox"/>		Completed (07/26/2016 20:29:07)	Accrual_1_Dropout_1_Composite 1	1000	100	0	0.394	0
<input type="checkbox"/>		Completed (07/26/2016 20:31:20)	Accrual_1_Dropout_1_Composite 2	1000	100	0	0.888	0
<input checked="" type="checkbox"/>		Running (07/26/2016 20:31:12)	Accrual_1_Dropout_1_Composite 3					
<input checked="" type="checkbox"/>		No Results	Accrual_1_Dropout_1_Composite 4					

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

- 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 Alloc
- Simulation Response and Pr(Max)
- Simulation Response and Pr(ED(x))
- Simulation Response and Pr(MED)
- Update Response and Subject Allocat
- Update Response and Pr(Max)
- Update Response and Pr(ED(x))
- Update Response and Pr(MED)
- Update Response and Pr(Alloc)

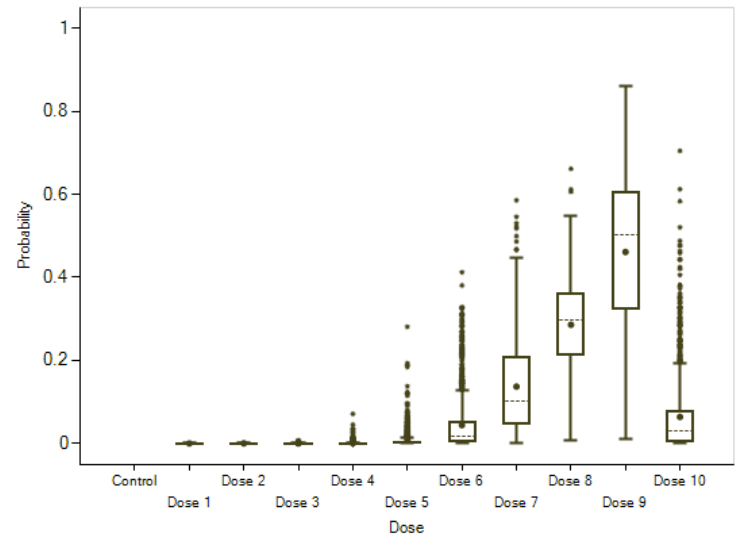


Allows quick review of simulation summaries



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

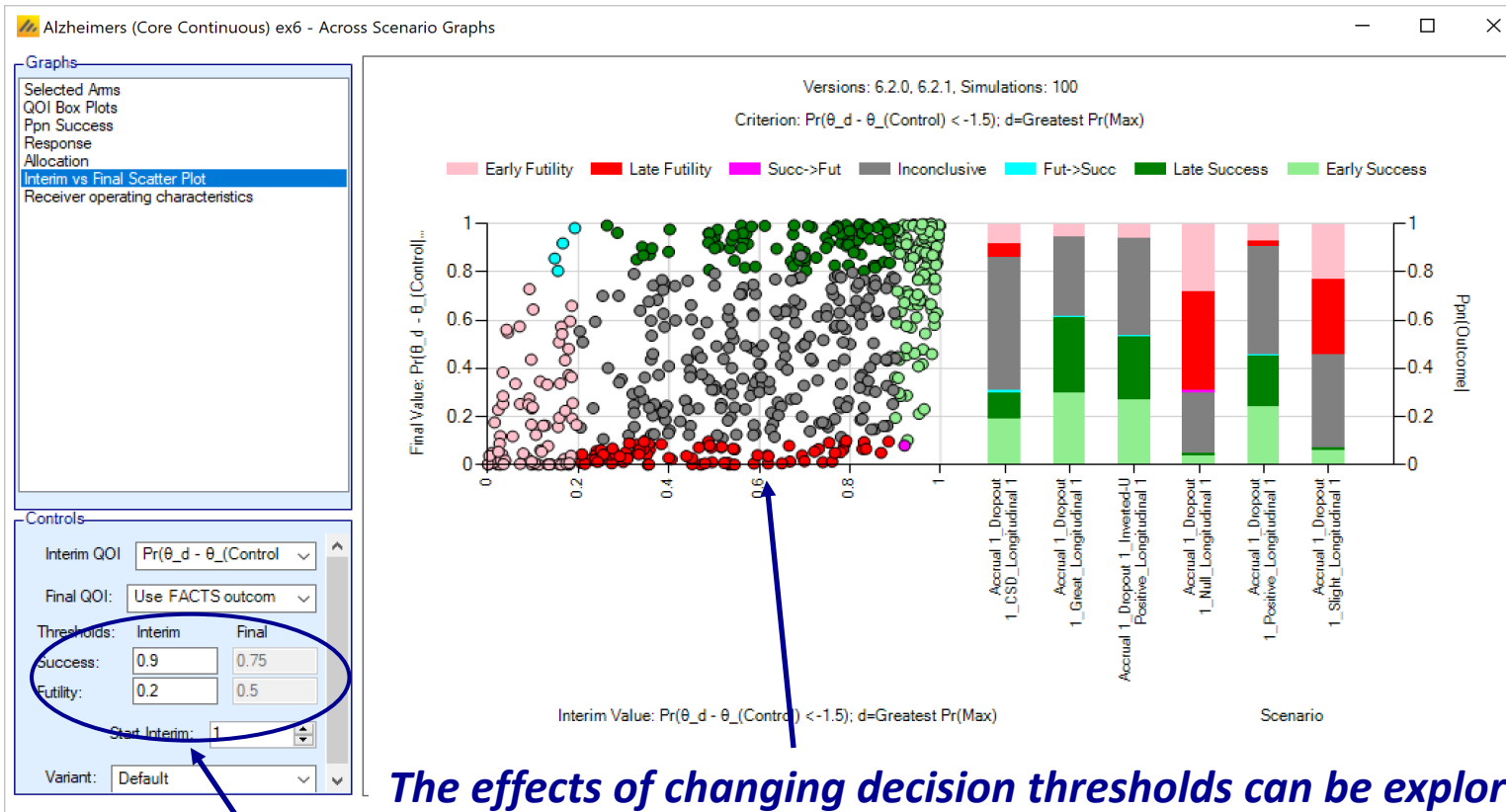


Simulation: 37
Update: 6

Walk through each interim of a single simulated trial



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

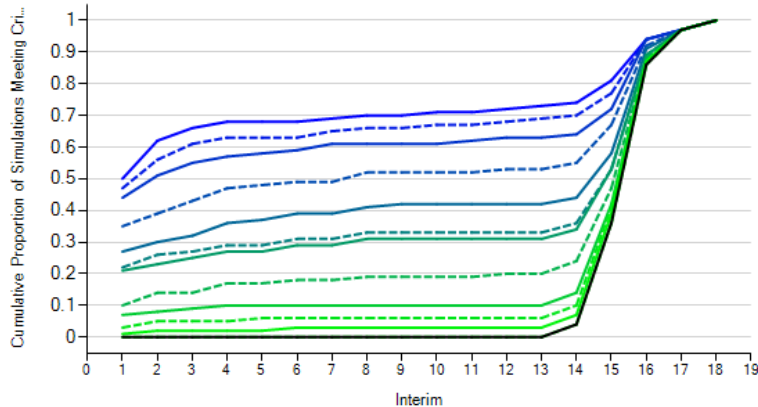
Built-in Graphics to explore the design

Cumulative Proportion of Simulations Satisfying Success Criterion by Interim

Recruitment: "Accrual 1" Dropout: "Dropout 1", Response: "Null", Longitudinal: "Longitudinal 1", : "Var1",
Version: 6.2.1, Simulations: 250

Criterion: $\Pr(\text{Succ. Future Trial})$; $N=250$; Sup. $\alpha=0.025$; $\delta=0$ @ $\Pr(\text{Max})$

— >0.5 - - - >0.65 - - - >0.75 - - - >0.85 - - - >0.95 - - - >0.99
 - - - >0.55 — >0.7 — >0.8 — >0.9 — >0.98 — Existing stopping rules
 — >0.6

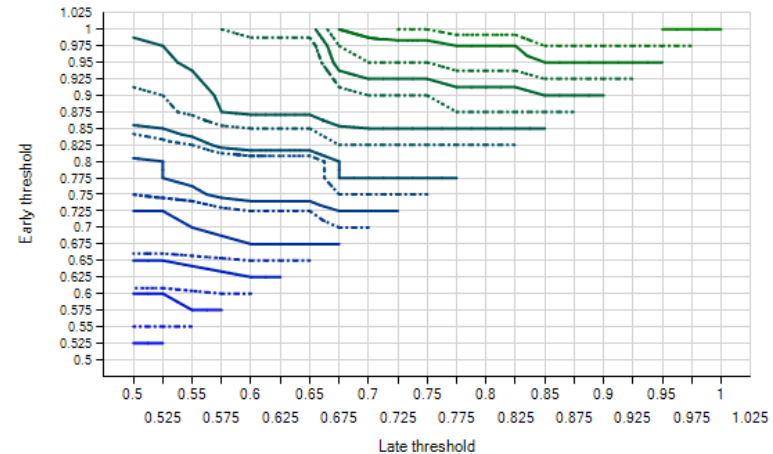


NB Graph based on the 100 simulations for which "weeks" files were output
Warning: Graph based on data in which early stopping was enabled

Proportion of Simulations Reaching Success for Early/Late Criterion Thresholds

Recruitment: "Accrual 1" Dropout: "Dropout 1", Response: "Null", Longitudinal: "Longitudinal 1", : "Var1",
Version: 6.2.1, Simulations: 250

— 0.73 ····· 0.63 — 0.46 ····· 0.33 ····· 0.25 ····· 0.12 ····· 0.08 ····· 0.04
 ····· 0.7 — 0.56 ····· 0.42 — 0.31 — 0.2 — 0.1 — 0.06 — 0
 — 0.65 ····· 0.53 — 0.39

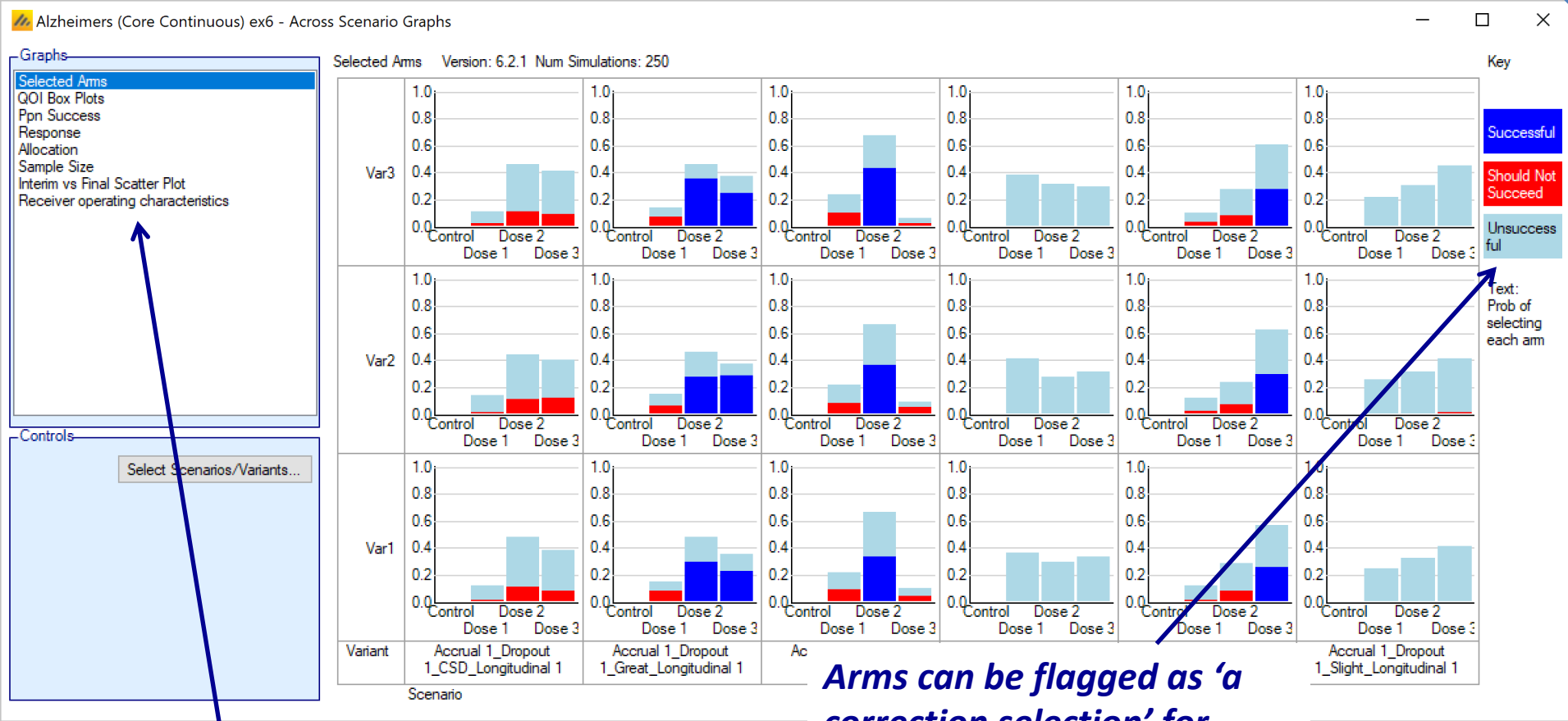


NB Graph based on the 100 simulations for which "weeks" files were output

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

Built-in Graphics to compare design variants



Arms can be flagged as 'a correction selection' for each scenario.

Allowing a design's ability to 'select a good dose' to be summarized

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

Analysis Tab

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

Load data file

Alzheimers (Core Continuous) ex1 - FACTS™ v6.1 Core Design - Continuous

File Settings Help

Study Virtual Subject Response Execution Quantities of Interest Design Simulation **Analysis**

Analysis Parameters

Run Analysis

Monte Carlo Settings

Length of burn in: 2500

Number of samples: 5000

Random Seed: 3500

Generate MCMC file

Do interim analysis number: 1

Do final analysis

Current week: 0

Edit command line parameters

n 0 -interim 1 -current-week 0

Reset

See execution mode documentation for details on cmd parameters and analysis output.

Analysis Results Subject Data

Trial subject data file: Z:\FACTS\test\FACTS 6.1 Testing\Core Examples\Alzheimers (Core Continuous) ex1_results\patients.dat

File Format

Number of subjects: 254

Subject ID	Region ID	Date	Dose index	Last Visit#	Dropout	Baseline	Visit 1
1	1	0.579982	4	1	0	-9999	-5.48283
2	1	3.17844	2	1	0	-9999	-4.71724
3	1	3.29212	1	1	0	-9999	0.975542
4	1	3.43428	3	1	0	-9999	-3.31307
#5	1	6.10413	4	0	1	-9999	-9999
6	1	6.60441	2	1	0	-9999	-1.58081
7	1	7.48359	1	1	0	-9999	-0.404461
8	1	8.44285	3	1	0	-9999	-10.5515
9	1	9.1451	2	1	0	-9999	-7.24464
10	1	9.78853	3	1	0	-9999	-13.3134
11	1	10.7048	4	1	0	-9999	-8.5091
12	1	11.113	1	1	0	-9999	6.91323
#13	1	12.2168	4	0	1	-9999	-9999

Delete Row

Reload Data

Save

Analysis Tab

Run analysis

Check results

The screenshot displays the 'Analysis' tab in the FACTS software. The 'Analysis Parameters' section includes a 'Run Analysis' button, which is circled in blue. Below it are 'Monte Carlo Settings' with input fields for 'Length of burn in' (2500), 'Number of samples' (5000), and 'Random Seed' (3500). There are also radio buttons for 'Do interim analysis number' (set to 1) and 'Do final analysis', and a 'Current week' field (set to 0). At the bottom, there is an 'Edit command line parameters' section with a text box containing 'n 0 -interim 1 -current-week 0' and a 'Reset' button. The 'Analysis Results' section shows a message: 'No interim stopping criteria have been met'. A legend on the right lists 'Observed Response', 'Response and Subject Allocation', 'Response and Probability', and 'Response and Pr(Allocation)'. The 'Quantity' is set to 'Pr(MED relative)' and 'Space doses evenly' is checked. The main chart, titled 'Response and Pr(MED relative to Control: Delta=-1.5) Probability', is a dual-axis plot. The x-axis is 'Dose' with categories Control, Dose 1, Dose 2, and Dose 3. The left y-axis is 'Response' (ranging from -6 to 2) and the right y-axis is 'Posterior Probability' (ranging from 0 to 1). The legend indicates: a blue bar for 'Pr(MED relative to Control: Delta=-1.5) Probability', a black dot for 'Mean raw response with 95% CI', and a red dot for 'Mean fitted response with 95% CI'. The chart shows that as the dose increases, the response decreases and the posterior probability increases.

Dose	Pr(MED relative to Control: Delta=-1.5) Probability	Mean raw response with 95% CI	Mean fitted response with 95% CI
Control	~0.4	~0.3	~0.35
Dose 1	~0.4	~-2.5	~-2.5
Dose 2	~-4.5	~-3.5	~-3.5
Dose 3	~-5.5	~-2.5	~0.5

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

The image displays four overlapping Excel spreadsheets representing different stages of clinical trial data analysis:

- Top Spreadsheet:** Shows subject-level responses over time. Columns include #2.4.2:DF-cont:Accrual 1_Dropout 1_Logistic_Longitudinal 1:07/28/2013 19:04:21:0.2.9.7, #Subj No, and Date. Data points range from 4.34 to 19.58.
- Second Spreadsheet:** Shows interim data with columns for #Week, No.Subj, EDx, MED, Max, Unused, Alloc 1, Alloc 2, Alloc 3, and Alloc 4. Data points range from 6 to 35.
- Third Spreadsheet:** Shows final data for all simulated trials with columns for #Sim, No.Subj, EDx, MED, Max, Outcome, Alloc 1, Alloc 2, Alloc 3, and Alloc 4. Data points range from 1 to 15.
- Bottom Spreadsheet:** Shows summary statistics with columns for #No.Subj, SE Subj, P(ES), P(LS), P(LF), P(EF), SFFF, FSFF, and Undec. Data points range from 0 to 1.

Support for post-processing results

Aggregate results from selected scenarios

Advanced

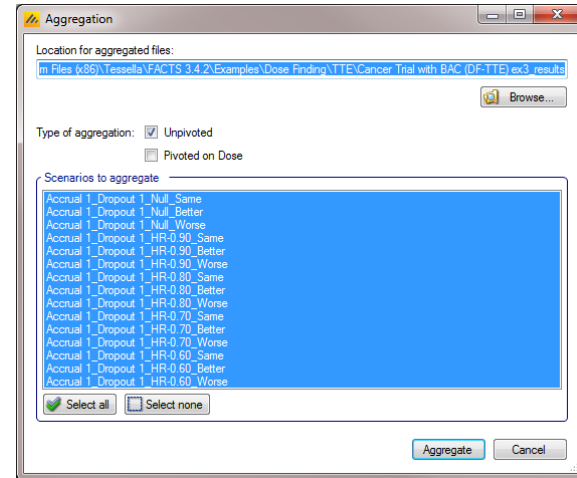
Simulations completed: 0/0

Show Other Columns...

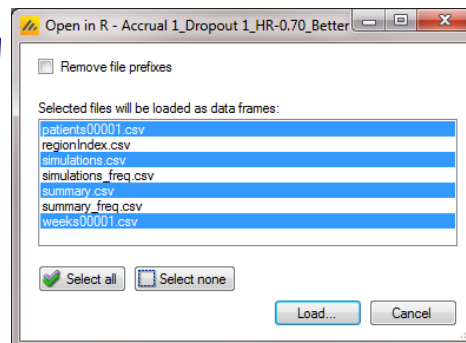
Ppn Early Futility	Ppn Suc->Fut Flip Flop	Ppn Fut->Suc Flip Flop	Ppn Inconclusive
0	0	0	0.3
0	0	0	0.334
0	0	0	0.294
0	0	0	0.392
0	0	0	0.394
0	0	0	0.398
0	0	0	0.394
0	0	0	0.422
0	0	0	0.398
0	0	0	0.332
0	0	0	0.328
0	0	0	0.32
0	0	0	0.178
0	0	0	0.2
0	0	0	0.152

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



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!