Berry Consultants
Statistical Innovation

FACTS

FACTS Capabilities

Fixed and Adaptive Clinical Trial Simulation (FACTS) software is the most powerful, versatile, and fastest simulation tool on the market today for advanced clinical trial design. This document provides a summary of some of the key capabilities and features within FACTS.

Dose-Finding:

- Engines for dose-finding with endpoints that are continuous, dichotomous, time-to-event (TTE), and multiple endpoints (up to 4).

- Trial Types: Superiority trials, super-superiority (as defined by a superiority margin), non-inferiority, utility (weighting) of multiple endpoints, best therapeutic doses over efficacy and safety.

- Dose-Response Models: NDLMs, sigmoid (EMAX), logistic, hierarchical logistic, plateau model, inverted-U. Specification of Bayesian priors, and ability to use historical data for the Control arm.

- Longitudinal Modeling: Models incorporating repeated measures, linear regression, kernel density estimates, beta-binomials, support for continuous endpoints that are dichotomized based on a threshold, time-to-failure for dichotomous, time-to-event with piecewise exponentials or Bayesian Cox modeling. Ability to model early predictors (continuous, dichotomous, TTE) for TTE endpoints. Various options for handling incomplete/lost-to-follow-up subjects: LOCF, BOCF, imputed failure or success.

- Adaptations: Arm-dropping with option for forced arm-dropping, adaptive randomization, arm blocking. Flexibility for burn-in period. Early stopping for success or futility. Interims by number of subjects enrolled, number of subjects complete, time-intervals, or number of events (for TTE). Interims can be conducted during and after full accrual. Options for discontinuing follow-up after early stopping.

- Virtual Subject Simulation: Flexible simulation methods for correlated results across visits, variation by visit and by arm. Complete flexibility to simulate from models different from analysis models. Ability to import virtual subject files for sampling with replacement.

- Simulating Execution: Full flexibility to simulate complex accrual rates (Poisson process random accrual) over regions and sites. Cohort accrual. Ability to simulate complex drop-out scenarios.

- Graphics and Output: Summary plots for each interim for every simulated trial. Extensive output (.csv files) of all analyses: summarized across trials, final result of each trial, each interim of each trial, and the simulated patient-level data for a trial. Explore full frequentist or Bayesian summaries, time, patients, interims, etc. Facility to output MCMC samples for diagnostics. Full graphical presentation of operating characteristics and simulated trials. Ability to port simulation results to R.

- Trial Execution: Executable program provided for running trials. Creates randomization lists (allows for block specification). Analysis tab to run hypothetical interim analyses within FACTS GUI.

Enrichment-Designs:

- Engines for simulating treatment effects by population characteristics. Allows indication and population finding, and enrichment designs. Available for continuous, dichotomous, and time-to-event endpoints.

- Trial Types: Superiority trials, super-superiority (as defined by a superiority margin), non-inferiority, success and failure by patient groups. Enrichment designs (dropping of less successful groups).

- Group Models: Ability to model the different groups using independent models (optionally borrowing from historical data on the control arm) or Bayesian hierarchical modeling,

- Longitudinal Modeling: Models incorporating repeated measures, linear regression, kernel density estimates, beta-binomials, support for continuous endpoints that are dichotomized based on a threshold, time-to-failure for dichotomous, time-to-event with piecewise exponentials or Bayesian Cox modeling. Various options for handling incomplete/lost-to-follow-up subjects: LOCF, BOCF, imputed failure or success.

- Adaptations: Dropping groups for futility or graduating for success. Separate modeling and decisions/conclusions for groups as well as for the overall population. Interims defined by number of subjects enrolled, number of subjects complete, time-intervals, or number of events (for TTE).

- Virtual Subject Simulation: Ability to simulate differences across population groups. Flexible simulation methods for correlated results across visits, variation by visit and by arm. Complete flexibility to simulate from models different from analysis models. Ability to import virtual subject files for sampling with replacement.

- Simulating Execution: Ability to simulate different accrual rates for each group, variation over time in group's accrual rates. Full flexibility to simulate complex accrual rates (Poisson process random accrual) over regions and sites. Ability to simulate complex drop-out scenarios.

- Graphics and Output: Summary plots for each interim for every simulated trial. Extensive output (.csv files) of all analyses: summarized across trials, final result of each trial, each interim of each trial, and the simulated patient-level data for a trial. Explore full frequentist or Bayesian summaries, time, patients, interims, etc. Facility to output MCMC samples for diagnostics. Full graphical presentation of operating characteristics and simulated trials. Ability to port simulation results to R.

- Trial Execution: Executable program provided for running trials. Creates randomization lists (allows for block specification). Analysis tab to run hypothetical interim analyses within FACTS GUI.

Dose-Escalation:

- Ability to simulate trial designs where dose escalation takes place based on observations of tolerability and/or efficacy observations. A range of designs from simple (3+3) to complex continual reassessment methods.

- Trial Types: Dose escalation to maximum tolerated dose (MTD) based on binary toxicity outcomes. Dose escalation to MTD based on ordinal toxicity outcomes. Dose escalation to MTD and MED based on a joint model for toxicity and efficacy.

- Dose-Response Models: one-parameter logistic, power, and hyperbolic tangent; two-parameter logistic; proportional odds model for ordinal outcomes. Bivariate model for toxicity and efficacy.

- Dose Range: Explicitly define individual dose levels or a continuous dose range. Option to include a control arm.

- Escalation: Ability to specify the size of a cohort, with option for a small-cohort run-in stage. Specify limits on escalation (e.g. maximum increment from one cohort to the next, possibly different in different parts of the dose range). Prevent escalation to doses with high probability of overdose. Early stopping rules.

- Virtual Subject Simulation: Simulate subjects by explicitly defining the toxicity and/or efficacy rate per dose, or simulate from a parametric model. Ability to import virtual subject files for sampling with replacement.

- Target Dose Definitions: Define the MTD by a single quartile of the toxicity curve (e.g. 25%) or by a toxicity interval (e.g. 16-25%).

- Graphics and Output: Summary plots for each interim for every simulated trial. Extensive output (.csv files) of all analyses: summarized across trials, final result of each trial, each interim of each trial, and the simulated patient-level data for a trial. Explore full frequentist or Bayesian summaries, time, patients, interims, etc. Facility to output MCMC samples for diagnostics. Full graphical presentation of operating characteristics and simulated trials. Ability to port simulation results to R.

- Trial Execution: Executable program provided for running trials. Creates randomization lists (allows for block specification). Analysis tab to run hypothetical interim analyses within FACTS GUI.

Technology:

- Runs on all Windows platforms using the .NET environment

- Simulates trials with pre-compiled C++ engines, providing the fastest clinical trial simulation engine available (by orders of magnitude!)

- Creates easy to use .csv files from all simulated trials for very easy processing of unique needs. Stores interims, trials, and summaries of trials.

- Allows importing of results to R for easy customizing of results

- Any simulated trial is easily executed using the identical engine used to simulate the trial.

- Self-contained ability to parallelize simulations to optimize the number of processors

- Full ability to connect to a grid and run simulated trials in parallel on your or other grids (e.g. Amazon)

All supported by users guides, comprehensive specifications, numerous examples and tutorials.

For more information, see www.berryconsultants.com or contact us at: info@berryconsultants.com