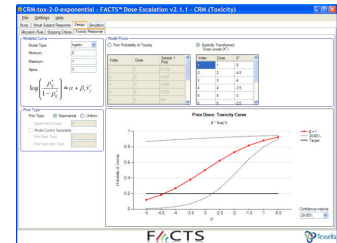


# F<sub>ACTS</sub>

Tessella and Berry Consultants

## Fixed and Adaptive Clinical Trial Simulator v2



**FACTS™** is a software system that helps clinical teams optimize their trial design. It does this by providing a suite of programs that allow most common phase 1 and phase 2 trial types to be defined and then simulated. It incorporates many of the current leading edge trial design innovations as options so that their potential benefits for the trial under consideration can be easily assessed.

Innovations such as dose response modeling, Bayesian analysis, longitudinal modeling and response-adaptive features can all be incorporated in designs. These features are selected and configured via the clear, consistent and easy-to-use graphical interface; no programming is required by the user. Once the design has been created the system runs simulations of the design using user-defined scenarios for the underlying drug performance, recruitment profiles, dropout rates etc. Summaries of the results of the simulated trials are presented so that the user can easily understand and evaluate the impact of his or her design choices and compare the performance of alternative designs.

### Trial Simulators

The trial simulators (“design engines”) are all tightly coded in high performance numerical programming languages and run far faster

than designs created within statistical programming environments can run. For many designs 1,000 trials can be simulated in a few minutes on a modern laptop (even an extreme case – a design using 10 interims per trial and the most compute intensive model, the kernel density longitudinal model – FACTS can run 1,000 trial simulations in just over an hour).

FACTS includes design engines for phase 1 dose escalation studies, including Continuous Reassessment Method (CRM) designs with variants for ordinal outcomes, modeling two populations and looking at efficacy outcomes alone or along with toxicity.

FACTS also has design engines for phase 2a / 2b dose finding studies supporting trials where the primary endpoint is continuous, dichotomous, or time-to-event, and a further design engine for studies using two endpoints that can be either continuous or dichotomous.

The dose finding design engines allow the user to include design options such as dose response modeling, longitudinal modeling, interim analysis and adaptive decisions such as early stopping, arm dropping and adaptive randomization.

The two-endpoint design engine allows the user to specify utility transformations of each end point and how they are then combined to produce an overall utility score. Decision making can be based on the utility function or the primary endpoint. This allows designs that combine efficacy and toxicity endpoints, efficacy endpoints or early biomarker and final efficacy endpoints.

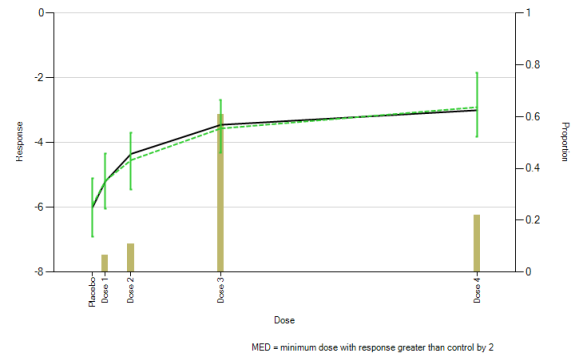
### Detailed Simulation

FACTS™ gives detailed control of the simulated data that is fed to the design as trials are simulated – the overall dose response, patterns of longitudinal responses, recruitment rates and dropout rates can all be specified. The ease with which these can be specified and the management by the GUI of the different scenarios resulting from the combinations of simulation profiles allow designs to be specified, simulated, and analyzed in hours rather than days.

In addition to simulation of subject responses within FACTS, it is possible to load into FACTS a database of externally simulated subject responses, allowing the clinical team almost complete control of the simulated patient population. A significant benefit of this is that it allows the clinical team a meaningful and well defined way of interacting with PK-PD modelers.

### Use on Fixed Trials

Even without using the innovative trial design features within FACTS, it can deliver better



insight into the proposed trial design than current, primarily sample size driven, methods. FACTS makes it easy to explore the impact of unequal drop-out and the use of LOCF on the expected type 1 error and power. It also makes it easy to explore other key operating characteristics such as the probability of correctly determining the minimum effective dose, ED90 or dose with the maximum response. As well as Bayesian modeling during the trial and of the final data, FACTS includes frequentist analysis of the final data, calculating p-value and confidence intervals using Bonferroni and Dunnett's adjustments and a trend test.

### A Platform for the Future

As well as a summary of the results of simulated trials, FACTS provides full access to all the simulation results including the final analysis of each simulated trial, every interim analysis of each simulated trial and all the simulated subjects and their responses within each trial.

For designing adaptive trials, FACTS offers an unparalleled access to adaptive design ideas, all based on adaptive designs that have actually been run, and linked to a simulator that accurately reproduces the timing of events and data availability in the simulated trial.