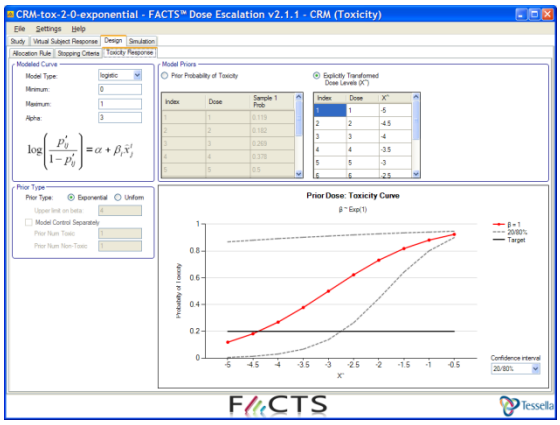
Fixed and Adaptive Clinical Trial Simulator V4

FACTS is a software system that helps clinical teams understand and optimize the design of their clinical trials. It does this by providing a suite of programs that allow most types of phase 1 and phase 2 trials to be defined and simulated. It incorporates many of the current leading edge trial design innovations as options so that their usefulness, or otherwise, for a particular trial can be easily assessed.

Innovations such as dose response modelling, Bayesian analysis, longitudinal modelling and response-adaptive features can all be incorporated in designs. These features are selected and configured via a 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 response to the drug, 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.

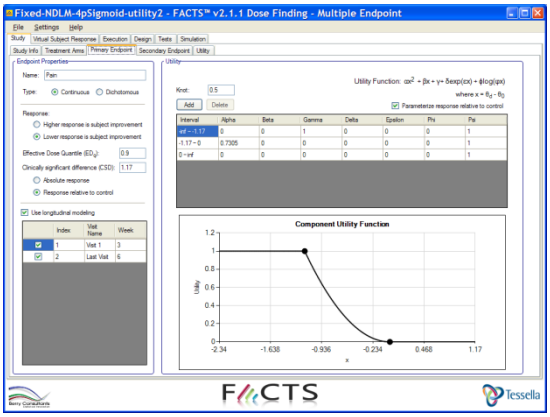
Trial Simulators



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 PC. FACTS has design engines for phase 1 and phase 2 trials.

For phase 1, FACTS includes design engines for Continuous Reassessment Method (CRM) designs with variants for ordinal outcomes, modelling two populations, overdose control, and looking at efficacy outcomes alone or along with toxicity.

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



The dose finding design engines allow the user to include design options such as dose response modelling, longitudinal modelling and interim analysis with adaptive decisions such as early stopping, arm dropping and adaptive randomization. The time-to-event allows for modelling a predictive biomarker or

predictor (continuous, dichotomous or time-to-event values) that is observed prior to the event of interest.

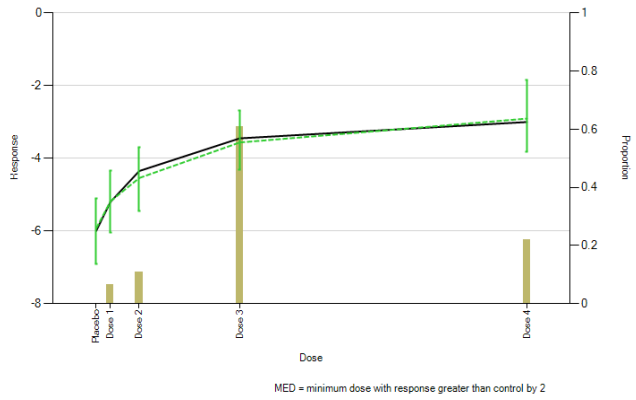
The multiple-endpoint design engine allows the user to specify utility transformations of each end point and how they are then combined to produce an overall utility score. Decision making can be based on the utility function or the primary endpoint. This allows designs that combine efficacy and toxicity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

Detailed Simulation

FACTS allows detailed specification of the simulated data to be sampled and passed to the design as the trials are simulated – properties such as 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 managed using the GUI allows 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 modellers.

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, sample size driven, methods. FACTS makes it easy to explore the impact of unequal drop-out rates on different treatment arms on the expected type 1 error and power. It 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 modelling during the trial and of the final data, FACTS provides 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

The user can specify how much data FACTS writes out, allowing 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. The results are written out into CSV files that are easily loaded into other analysis tools.

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 trial simulator that accurately reproduces the timing of events and data availability in the simulated trial.

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