Berry Consultants

FACTS

FACTS Development Team

# FACTS: Fixed and Adaptive Clinical Trial Simulator

Computer Software Version 7.0
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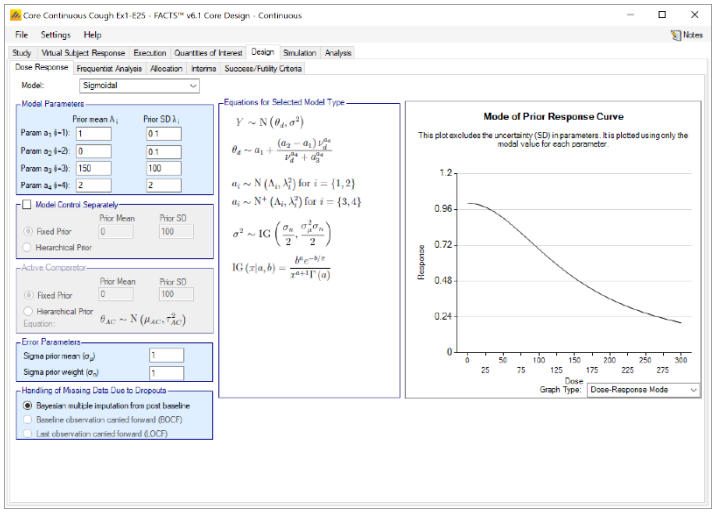
**Abstract.** Berry Consultants' Fixed and Adaptive Clinical Trial Simulator (FACTS) software is the most powerful, versatile, and fastest simulation tool on the market today for advanced clinical trial design. This document provides a summary of the key capabilities and features within FACTS Version 7.0.

## Introduction to FACTS

FACTS V1.0 was released in 2008 and has grown in capability ever since then. FACTS was not the first clinical trial simulator the developers had worked on; they already been writing clinical trial simulators for 8 years before starting on FACTS and FACTS is built on that experience.

One of the difficulties in developing a software for a general-purpose clinical trial simulator is the extra-ordinary diversity of features required for different trials. Any attempt to build a single simulator seems to be doomed to failure either because it lacks too many critical features or it has so many features that it becomes hard to use, unreliable, and difficult to extend. Alternatively building many different simulators, each for a different trial type, tends to lead to simulators that are too specific to a particular design. Whilst the resulting simulator is simple to use, it is too likely to lack critical features that your design needs. Also, unless the many simulators are scrupulously maintained, they are likely to diverge which will make it difficult to compare their results to determine which is best.

FACTS solves these problems by being built as a set of specific simulation engines, each of which spans a whole class of trial designs. Each class of design is aimed at answering a very different clinical question and thus any divergence in the engines is unlikely to be an issue. The result of this is that for any particular type of trial all the options in FACTS are available and can be separately enabled or disabled. This allows trial designs to start simple and then introduce different options one at a time – allowing their individual impact to be assessed. This makes FACTS a great platform for experimenting with and learning about different possible statistical approaches such as dose response models, longitudinal




FACTS Development Team (2023 04). FACTS: Fixed and Adaptive Clinical Trial Simulator. Computer Software Version 7.0, Berry Consultants LLC, Austin, TX. https://www.berryconsultants.com/software/facts/.

modelling, Bayesian augmentation of the Control data, hierarchical modelling of response across subgroups and response adaptive randomization.

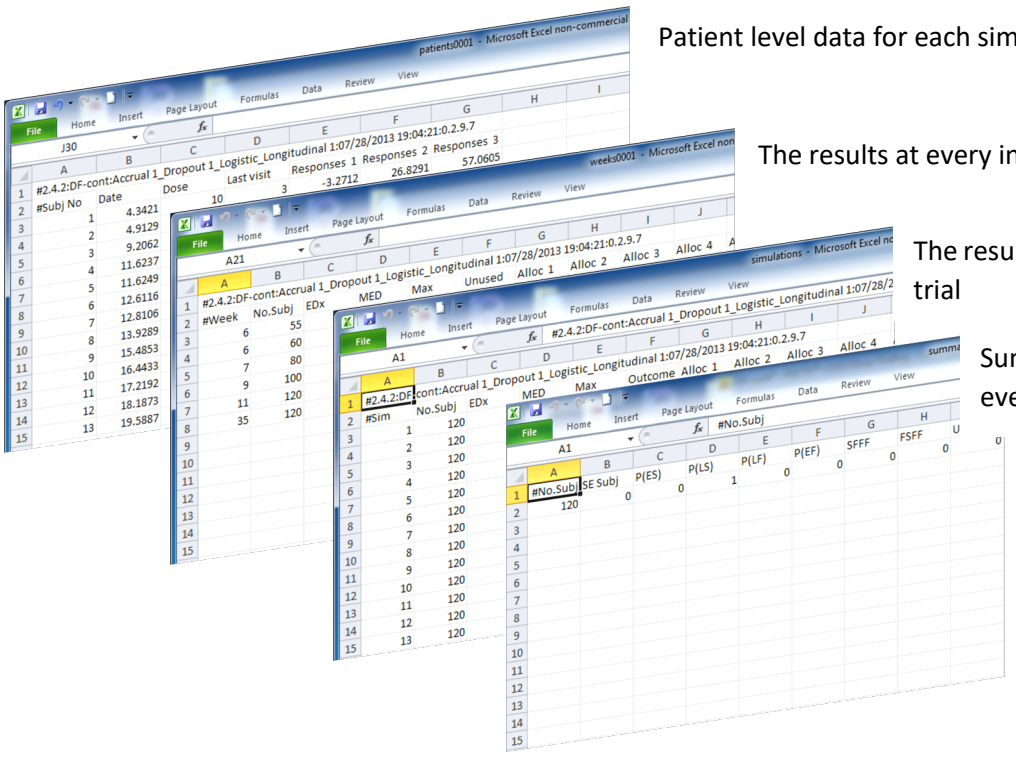
## Technology

- ✓ FACTS comprises a GUI and simulation engines.
- ✓ The GUI runs on all Windows platforms, using the .NET Framework.
- ✓ The simulation engines are pre-compiled and validated C++ command line executables that can run on Windows or Linux, providing the fastest clinical trial simulation engine available (by orders of magnitude!). The simulation engines can be run entirely via the GUI, there is no need to interact with them directly.
- ✓ Any simulated trial is easily executed using the same simulation engine to analyze the trial data, that was used to design the trial.
- ✓ Self-contained ability to parallelize simulations across the number of available processor cores.
- ✓ Full ability to connect to a HPC grid and run simulated trials in parallel on your or other grids (e.g. AWS)
- ✓ All supported by users guides, comprehensive specifications, numerous examples, and tutorials.

## Inter-operation with R

FACTS can simulate subject response by sampling from a file of virtual patients. This means that the user can create sampled responses from any distribution and with any correlation between endpoints or across visits.

The simulation engines create easy to use .csv files summarizing the data from all the simulated trials at different levels (interims, trials, and summaries of scenarios). These results can be easily imported into R for additional post-processing of the results. This makes it very straightforward to do additional post-processing to perform analysis unique to a particular problem.



Patient level data for each simulated trial

The results at every interim

The results for every trial

Summary for every scenario

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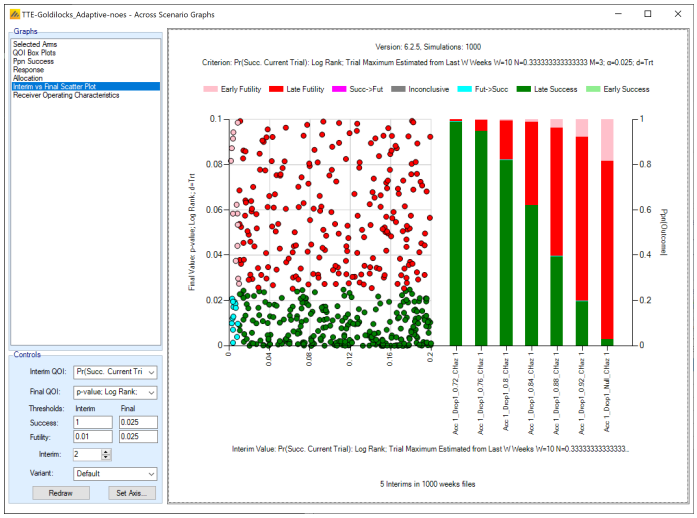
## Key Capabilities of FACTS

- ✓ A common user interface for all the simulation engines making it easier to learn and use FACTS.
- ✓ The simulation engines are all pre-compiled C++ programs taking all their inputs from a parameter file generated by the FACTS user interface. Making them far faster than simulators written in R.
- ✓ The simulation engines are all validated by a comprehensive, multi-faceted testing strategy.
- ✓ The FACTS GUI automatically exploits the multi-core, multi-threading architecture of any computer its run on when running the simulations.
- ✓ The simulation engines can produce comprehensive output in easy to read 'csv' files for checking or further analysis.
- ✓ The GUI can generate a "Design Report", a MS Word document, describing the trial designed and simulated in FACTS.
- ✓ The simulation engines (directly or via the user interface) all support analysis of a provided dataset so they can be used to perform the analysis of any trial that has been designed in FACTS.
- ✓ A range of graphs are built into the user interface to allow the simulation results to be readily visualized.




# Features of Simulation Engines in FACTS 7.0

**FACTS CORE** is the engine for simulating trials where one or more treatment arms are being tested, either to show the treatment is effective (a phase 3 trial) or to select from the treatments 'the best' (however that should be defined) (a phase 2 trial):

- ✓ Available for Continuous, Dichotomous, Multiple Endpoint, and Time-to-Event endpoints (including an option to have a secondary early outcome 'predictor' endpoint in Time-to-Event).
- ✓ Decisions based on Bayesian posterior probabilities, Bayesian predictive probabilities (including the predicted probability of success of the current trial) or p-values.
- ✓ Treatment arm selection using Max response, EDq (e,g, ED90) or minimum effective dose (relative to a specified clinically significant difference).
- ✓ Analysis using pairwise comparison or dose response models: NDLM, 2nd order NDLM, linear, linear hierarchical, hierarchical, logistic, logistic hierarchical, sigmoid, plateau and inverted-U.
- ✓ To define multiple "quantities of interest" to be calculated from the analyses.

- ✓ Longitudinal modelling of patient responses over time and the option to impute patient outcomes for missing data.
- ✓ To define interim schedules on different criteria and adaptions to occur at the interims: early stopping, arm dropping and response adaptive randomization.

**FACTS STAGED DESIGNS** is the engine for simulating two separate consecutive trials (such phase 2, followed by a phase 3), a seamless trial with two stages (such as seamless phase 2/3), or a trial with a major decision point in it (such as a seamless phase 2a/2b or a phase 3 that starts with multiple arms and has a decision point at which just one arm is selected for completion):

- ✓ Available for Continuous, Dichotomous, Multiple Endpoint, and Time-to-Event endpoints (including an option to have a secondary early outcome 'predictor' endpoint in Time-to-Event).
- ✓ All features of FACTS Core are available for simulating each stage.
- ✓ In stage 1, the predictive probability of success in stage 2 can be calculated.
- ✓ Stage 1 and stage 2 can be simulated as disjoint or seamless.
- ✓ Multiple 'data inclusion' rules are available for how and which data in stage 1 can be used in stage 2, if any.
- ✓ Comprehensive dose selection rules are provided for defining the decision as to which arms are to be included in stage 2.

**FACTS ENRICHMENT DESIGNS** is the engine for simulating trials where a single treatment is tested in different patient subgroups or different (but similar) disease indications to determine which subgroups should be included in the phase 3 target population, or which indications should be tested in phase 3 trials:

- ✓ Available for Continuous, Dichotomous, and Time-to-Event endpoints.
- ✓ The treatment can be compared to a control arm or to an objective absolute rate.
- ✓ Groups can be analyzed separately and jointly, with independent and hierarchical models available.
- ✓ Longitudinal modelling of patient responses over time and the option to impute patient outcomes for missing data.
- ✓ To define interim schedules on different criteria and adaptions to occur at the interims: early stopping of the whole trial or individual groups.

**FACTS PLATFORM TRIALS** is the engine for simulating trials where many treatments are tested, with treatments entering and leaving the trial over time, to determine which treatments should be taken forward for testing in phase 3 trials:

- ✓ Available for Continuous and Dichotomous endpoints.
- ✓ Multiple options to define 'how long' to simulate for: max time, subjects, treatments, number of successes.
- ✓ Treatment arrival over time simulated, with 'windows' of when the treatment might become available to enter the trial and how long the treatment might wait to enter.
- ✓ Treatments' response to be simulated can be specified (as response or treatment effect relative to control) or sampled from a distribution.

- ✓ Allocation options include: fixed proportion to control, allocation ratios dependent on the number of treatments and response adaptive randomization.
- ✓ Decisions based on Bayesian posterior probabilities, Bayesian predictive probabilities or p-values. Analysis comparing to the whole control arm.
- ✓ Global success and futility criteria can be supplemented with additional per-treatment criteria.

**FACTS DOSE ESCALATION DESIGNS** is the engine for simulating Oncology phase 1 trials, where successively higher doses of a novel drug are tested to determine the maximum tolerable dose that can be taken forward for further development, or the therapeutic range of doses from the minimum efficacious to the highest tolerable:

- ✓ Simple non-model based designs: 3+3 and mTPI.
- ✓ Bayesian Logistic Regression ("N-CRM") with many options:
    - Overdose control,
    - Target and MTD or a toxicity band,
    - Tools to derive the prior for the model parameters,
    - The ability to include prior data,
    - The ability to model a second population of subjects,
    - The ability to simulate an 'open-enrolment' design, with backfilling to lower doses
    - Optionally model ordinal toxicity
    - Optionally model efficacy as well as toxicity
- ✓ Separate implementations of the original CRM, CRM with ordinal toxicity, CRM with two groups and CRM with toxicity and efficacy.

## Contact

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