



Clinical Trial Technologies:

## Optimizing Drug Development

**Clinical trials are expensive and all too frequently fail. The pharmaceutical industry needs to find a better way to manage and execute trials. This better way requires modelling, simulation and active trial management. Tessella has an integrated set of consultancy services and solutions to help in all these areas.**

The success rates for drugs in clinical development are declining – the success rate for a drug entering Phase I and progressing to actual launch fell by 23% between 2001 and 2006. Meanwhile the time taken to develop drugs has increased – the average time taken for a drug entering Phase I clinical trials to completing Phase III increased by 1.2 years to 7 years between 2000 and 2004.

Clearly the pharmaceutical industry needs to find a better way of managing and running trials.

Firstly, the pharmaceutical industry needs to incorporate modelling and trial simulation to better understand the likely outcome of the trial across a range of situations. Secondly the industry needs a way of running trials that maximizes the information obtained from each patient and optimizes the drug development decisions.

Evidence has demonstrated that companies save millions of dollars through adaptive trials by stopping failing trials quickly, and reducing the development program cost by combining two phases (1/2a, 2a/2b and 2b/3) in a single trial.

Implementing adaptive trials is a challenge, and poses a number of issues in what is already a complex operation; we need to be able to:

- Design, simulate and evaluate adaptive trials easily and quickly
- Run large numbers of simulations efficiently to optimize and ensure the robustness of the trial design
- Assess the impact of the design on supply requirements and simulate and evaluate different supply plans
- Easily and reliably translate the simulated design into a trial execution engine
- Gather and process response data quickly and reliably
- Review, manage and implement trial adaptations quickly and reliably.
- Access knowledgeable resources to help overcome the operational challenges of 'going adaptive'



## Simulation

Unlike the relatively fixed menu of conventional designs, the range of adaptive designs is vast, frequently offering a unique design per trial. When the design of a trial is 'against the clock', the time it might take to design a specifically tailored design can be a significant disincentive to considering a tailored design. We need to know quickly whether a design is worth considering and to do this we need to be able to simulate the trial and compare it to the conventional design.

If an adaptive design is potentially superior to a conventional design, more simulations are required to estimate how well it will perform over the full range of likely scenarios. These scenarios cover such things as how the subjects respond to the treatment, how this is reflected in the observed responses, how quickly subjects are recruited and how likely subjects are to dropout.

From the simulation results, it is possible to estimate the likely duration of the trial, number of subjects recruited, and accuracy of the decision-making under each scenario. For instance, if the treatments show no difference from the control, how many subjects are likely to be recruited before the trial can be reliably stopped for futility can be estimated. Conversely, where the treatment has an effect different from the control, how well can this be determined and how well can the treatment with the best response profile be identified?

Examining many simulations has traditionally meant developing and validating complex software (when frequently there is insufficient time or internal resources). To address this problem we have produced, in collaboration with Berry Consultants, leading adaptive trial designers, the Tessella and Berry Consultants FACTS™ (Fixed and Adaptive Clinical Trial Simulator). FACTS supports a range of fixed and adaptive designs including design engines for CRM (Continuous Re-assessment Method) first-in-man trials, and for Bayesian Dose Finding Designs. There is an active development program producing further design engines.

A consistent user interface allows biostatisticians to configure designs from a wide range of options including

- Target of the trial
- Model to fit to response data
- Model to fit to longitudinal data
- Degree and nature of the adaptation
- Criteria for stopping the trial early
- Criteria for evaluating the success of the compound at the end of the trial

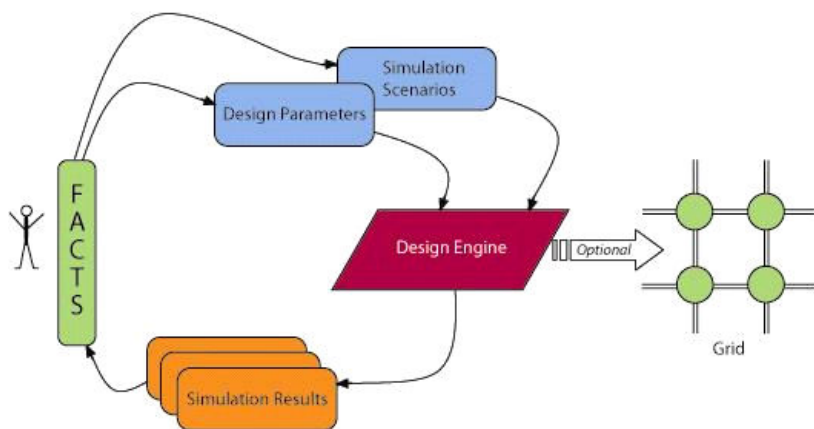
It is easy to start with a design with no response model fitting, no longitudinal model fitting, no adaptation and no early stopping. This allows designs to be built up incrementally to see if the additional complexity delivers any improvement in the expected operating characteristics of the trial.

## Supply Forecasting

The supplies in a clinical trial can be a significant contributor to its cost or a constraint on its design. Having insufficient supply, or having it in the wrong location, can seriously compromise a trial's outcome. Trial supply plans are often approximate and usually very conservative. The significant cost of supply can cause the logistics group to be very wary of supporting innovative trial designs.

The properties of a proposed clinical trial supply plan such as overage, number of shipments and number of stock-outs can only be assessed with any accuracy by simulating the mechanics of the trial. The model needs to include:

- 'locations' such as the central warehouse or pharmacy, regional depots and clinical sites where the subjects are recruited
- manufacturing and packing plans
- packaging and shipping arrangements
- sites with different start dates,



**Tessella FACTS system**



recruitment rates and re-supply plans

- subject screening, randomization, follow-up visits, and drop-outs
- treatment arm randomization schemes and treatment regimes

The Tessella SFT™ (Supply Forecasting Tool) supports simulating clinical trial supplies during planning so that logistics teams can forecast drug supply needs and costs. It allows teams to plan optimal production and delivery schedules, explore the possible consequences on supply and cost of different recruitment rates or delivery times, and consider different packaging options.

Forecasting can also be used during trial execution.

### Fixed & Adaptive Trial Execution System

When we want to run an adaptive design because we've simulated it and it has been shown to be significantly better than the conventional design, we want to be able to take the software that has been running the simulations and deploy it on a trial simply and reliably. We believe in the well established engineering principle of 'test what you fly and fly what you test', so our design engines have been built so that exactly the same software that was used in simulation can be deployed to perform the analysis for the adaptation during the actual trial.

The use of the adaptive software during the trial to create the adaptation recommendation and accompanying reports should be as automated as possible. This makes the process quick, efficient, repeatable, validatable and scalable.

To this end we have designed Tessella FATES™ (Fixed and Adaptive Trial Execution System) as a production environment to support hosting adaptive algorithms as the trial runs. FATES is a production environment into which a design engine and its parameter file can be dropped. It then manages the receipt of response data and the running of the design engine for the duration of the trial. It processes the design engine output to create the inputs to the randomization system and reports for the Data Monitoring Committee and the supply team.

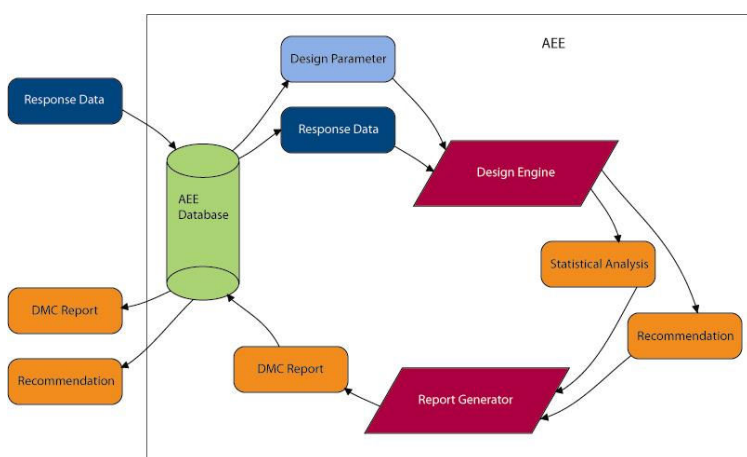
Components of FATES have been used at Tessella to support a number of Bayesian adaptive dose finding studies, integrating remotely with various EDC systems and IVRS providers. This proven technology is available to organizations who wish to scale up their capabilities to host adaptive trials.

### The Tessella EDC-Lite™

Adaptive clinical trials typically only adapt based on the key endpoint data collected in a trial, which is a small subset of the full data collected from each patient. Sometimes the time taken for the data to be entered at the sites and then cleaned in the EDC system may significantly delay the availability of that response data to the adaptive algorithm.

In a number of trials where this was the case, Tessella has provided a second, lightweight data capture system to be run alongside the main EDC system, into which just the key endpoint data was entered. The EDC-Lite has been developed quickly for each trial, using a data collection mechanism appropriate to the trial such as fax, email, phone or SMS text. By designing it to be convenient for the person reporting the response, we typically deliver data to FATES the same day it is collected. Results from real trials have demonstrated that the parallel EDC-Lite not only produces real-time data, but that it can also act as a second validation tool to the primary CRF database by regularly reconciling the two. The error rates in the EDC-Lite data have also been shown to be lower than those in the cleaned data in the primary EDC system.

Ultimately EDC-Lite not only increases the data available for adaptation, it actually increases the quality of the final data as well.



Tessella FATES system



## In Summary

Tessella's Clinical Trial Technologies and Services address the unique needs of Adaptive Clinical Trials, allowing the advantages of faster and better-informed decision making in drug development to be fully realized:

- ☑ **Design, simulate and evaluate adaptive trials easily and quickly**

Using the FACTS user interface and flexible Design Engines, trial designers can evaluate adaptive 'Learn Trial' designs using response modelling, longitudinal modelling, adaptation and decision making using Bayesian posterior probabilities.

- ☑ **Efficiently run large numbers of simulations to optimize and determine the Design robustness**

Using the FACTS 'grid adapter', simulations can be easily offloaded onto compute grids using standard grid management software such as Condor or Sun Grid

- ☑ **Assess the impact of the adaptive design on supply requirements, and simulate and evaluate different supply plans**

Using SFT, supply plans can be simulated over a range of scenarios. SFT can be used to estimate likely numbers of packs that will need to be shipped, when subsequent batches need to be available, likely overage, and mid-trial re-estimation.

- ☑ **Easily and reliably translate the simulated design into implementation**

Transfer the Design Engine from FACTS along with a selected set of parameters from a simulated design to FATES and you have an environment ready to automatically process the adaptive rules whenever response data is supplied.

- ☑ **Gather and process response data quickly and reliably**

Where an EDC cannot be used, or the EDC cannot supply the required response data quickly, Tessella's 'EDC-Lite' technology can provide a quickly configured system to capture the key response data, selecting the most appropriate media from a range of technologies such as phone, fax form, email, SMS text and internet.

- ☑ **Review, manage and implement adaptation quickly and reliably**

From FATES, automatic reports are produced for the Data Management Committee and Supply Team. Clear adaptation recommendations and new randomization lists, where required, are also produced.

- ☑ **Access knowledgeable resources to help overcome the operational challenges of 'going adaptive'**

Tessella and Berry Consultants have significant experience in designing, implementing and hosting Adaptive Designs. This enables us to provide a unique Consultancy service to help identify process changes and suitable drug candidates to ensure success from the first trial onwards.

### For more information about Tessella's Clinical Trial Technologies:

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### For background information on Tessella:

please see our website [www.tessella.com](http://www.tessella.com)

### For background information on Berry Consultants:

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