Business Benefits of using FACTS for the Modelling and Simulation of Clinical Trial Designs

Being able to simulate a clinical trial while designing it gives the biostatistician considerable advantages, it is easier to: take into account knowledge from models and existing data (for example from pre-clinical, early clinical or published studies), interact with clinical operations and communicate with the clinical team, and to consider and evaluate more complex trial designs. Berry Consultant's vision to create more efficient and ethical clinical trials has produced software called FACTS, the "Fixed and Adaptive Clinical Trial Simulator".

FACTS

FACTS currently has modules ("design engines") for Dose Escalation trials (phase 1 and phase 2a) with dichotomous endpoints and for Dose Finding trials with continuous, dichotomous, time-to-event and multiple endpoints.

FACTS has simple but powerful built-in facilities for simulating interim and final patient responses, patient dropouts, and patient accrual. It has a range of facilities for simulating simple and complex designs, with almost unlimited power to combine different options. If interim decisions are included in the design, FACTS carefully simulates exactly how much information would be available at the time of the interim analysis. Highly detailed simulation results are available for analysis, including: the data and results of each individual trial, the data and results at each interim of each trial, and even the responses for each simulated subject in each trial. It is also possible to limit the results that are output to just the level of detail required.

The FACTS "design engines" that perform the simulations are implemented in Fortran and C++. There is no programming required to use them, and they run simulations many times faster than is possible for simulators written using statistical programming tools such as SAS, R or WinBUGS. The tool does not lessen the statistical skill and insight required to create the designs, but it does mean the statistician does not have to also be a literate programmer. It also means they can create the design in a matter of minutes, not days. Additionally, since FACTS is validated, the statistician does not have to worry about possible errors in the simulator which greatly reduces risk and effort.

FACTS changes the economics of simulating trial designs. Instead of being an expensive time consuming exercise that could only be undertaken by specialist statistical programmers, simulation-based trial design is now something that can be done routinely by all biostatisticians. Instead of being a specialist technique that is only deployed on trials that are innately difficult, it can be used on all trials.

Better Understanding of even Simple Designs

The traditional use of simple analytical techniques to determine trial size and power has a tendency to cause certain complexities to be ignored, in particular the impact of subjects dropping-out and where the use of a normal distribution is a poor approximation for the distribution of subject responses. These can seriously undermine the actual power of the design if not properly taken into account. Unbalanced rates of drop-out across different treatment arms can even undermine the control of the type-1 error.

Secondly, simple analytical techniques give primacy to control of type-1 error (falsely claiming success), type-2 error (failing to correctly claim success) and sample size. Whilst this is appropriate in a phase 3, confirmatory setting, these should be of secondary concern in pre-confirmatory, "learn-phase" trials. Instead the focus of learn-phase trials should be to optimize the decision-making in the drug development program. If after a phase 2 trial, a company correctly determines the drug is effective, but selects the wrong dose to take forward to phase 3, it will incur the cost of *both* a type-1 error *and* a type-2 error. It both incurs

the cost of a futile subsequent phase 3 trial *and* loses a potentially successful compound. Conventional trial design does not try to analyse or manage this risk, which we could christen a “type-3 error”.

Furthermore, in modern drug development there are many important operating characteristics of a trial that it is useful to be able to estimate, such as: its ability to determine safety as well as efficacy, select the right dose, select the right patient sub-groups, compare the study drug against an active comparator, and estimate the dose response model. It very quickly becomes impossible to calculate a design’s abilities to achieve these objectives, but they are easy to estimate from simulations. Once simulations are being used, almost any operating characteristic can be studied.

Better use of PK-PD Modelling & Translational Medicine

In addition to using the built-in simulation machinery, FACTS can use PK-PD simulated subject responses. This allows arbitrarily complex models of subject response to be used and faithfully represented in the simulation of the trial design.

Currently, largely because of the lack of trial design tools, the complexity and richness of PK-PD, drug and disease models stay trapped in the PK-PD and translational medicine groups. Meanwhile, the trial design is performed using simple mean values derived from these models, losing the uncertainty in those means along the way. Alternatively the PK-PD or translational medicine groups try to simulate trial designs and are limited to only the simplest types of design.

By being able to drive trial design simulations using PK-PD distributions of response, correlation between responses at early and late visits, and the correlation between different endpoints, not only is the work of these groups fully utilized, but the interface between them and the trial designer is clear and precise, creating a clear and efficient workflow.

Better Communication

In order to optimize a trial design it is necessary for the trial’s designer to take into account the pre-existing knowledge, the operational constraints, and the clinical development context. Unfortunately this information lies in groups with different specializations and different vocabularies—the trial designer’s principal vocabulary will be statistical and difficult for the other groups to understand fully.

The use of simulation means that groups can see the consequences of the design directly and in concrete terms through looking at both the expected average operating characteristics and at the design’s behaviour in individual simulated trials. They can also request different assumptions to be simulated, have sensitivity analyses performed, and see the results reflected directly in the simulated data. Thus the knowledge of all these specialist groups can be fully incorporated into the design, reducing the chance of mistakes, misunderstandings, and simple oversights.

Companies that have adopted adaptive trial designs for some of their trials have quickly learned of the benefit of accompanying trial simulations to facilitate richer, multi-disciplinary trial design meetings that yield much better informed designs for all trials, adaptive or not.

Trial Design Optimization

These key properties of trial simulation—incorporation of expected outcomes; simulation of operational aspects such as patient accrual, dropouts, and the time to get endpoint data; the ability to provide estimations of the key operating characteristics; and the ability to study concrete examples of the design’s behaviour—allow trial design options to be explored and ranked by the clinical team.

By using credible estimates that use the best information available, the design can be optimized to support the development program. By ensuring that the simulations are performed across a range of scenarios that span the range of possible outcomes in the trial, it can be ensured that the design is robust and that its behaviour is well understood.

Proven Advantages from Advanced Trial Designs

As a proof point, there are 3 distinct features that can in the right circumstances be added to phase 2 trials, which have been seen to give considerable advantages over conventional parallel group designs. These are:

- Dose response modelling to both 'understand the dose response' and to manage the multiplicity of studying a number of doses without losing statistical power or requiring larger sample sizes.
- Interim analyses of the data, particularly to allow early stopping for futility.
- Adaptive randomization.

The principal benefits that can be gained from including these features in a phase 2 trial design are:

- Using multiple interims allows failing trials to be stopped early for futility, saving time, money and resources. In our experience, when the trial fails, an adaptive design saves on average 30% of the time and cost compared to a trial designed with a single interim for futility.
- Testing more doses in phase 2b for the same sample size, type-1 error rate and power as non-adaptive, parallel group phase 2b trials through the use of dose response modelling.
- Adapting the randomization so that more subjects are allocated to the doses most likely to be used in phase 3, yielding more data on those doses at the end of the trial.

Thus adaptive designs used in phase 2, can both save resources and increase the probability of technical success in phase 3.

History of Successful Trial Designs created by Berry Consultants using FACTS

FACTS is used as the primary tool for designing trials by Berry Consultants. The enhanced functionality available in FACTS allows us to use FACTS to formulate a majority of our trial designs. This is getting more and more cost-efficient as CROs and vendors of services related to trial execution and conduct get familiar with handling programs and files from FACTS-designs.

For More Information

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