Berry Consultants
Statistical Innovation

FACTS

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

Being able to simulate a clinical trial whilst designing it, gives the biostatistician considerable advantages. It is easier for him or her to: generate estimates of all the operating characteristics of the proposed trial, take into account knowledge from PK/PD models and existing data, interact with clinical operations, communicate with the clinical team, and to consider and evaluate more complex trial designs.

To further Berry Consultants' aim to create more efficient and more ethical clinical trials, we have produced software to facilitate clinical trial simulation called FACTS, the "Fixed and Adaptive Clinical Trial Simulator".

FACTS™

FACTS currently has the ability to design Dose Escalation trials, Multi-arm treatment testing trials including Dose Finding trials and Confirmatory trials, Enrichment trials testing a treatment in different groups or indications, Seamless Phase 2a/2b designs, Seamless Phase 2/3 designs and Platform Trials.

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 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 of designing a complex trial.

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 Fixed Designs

The traditional use of simple analytical techniques to determine trial size and power causes 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. Traditional tools

for designing Group Sequential trials in addition typically ignore the effect of the time between subject accrual and when their final endpoint data is available.

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.

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. Here the focus should instead 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 incurs both the cost of a futile subsequent phase 3 trial *and* loses a potentially successful compound. That is equivalent to committing *both* a type-1 error *and* a type-2 error, yet 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 overall dose response model. It very quickly becomes impossible to calculate a design’s abilities to achieve these objectives, but they can be estimated 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 files of externally simulated subject responses. This allows arbitrarily complex models of subject response, such as those derived from PK-PD models to be used and faithfully represented in the simulation of the trial design.

Without a trial simulation tool such as FACTS, the complexity and richness of PK-PD, drug and disease models stay trapped in the PK-PD and translational medicine groups. And trials are designed 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, whether the trial is 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

Phase I Designs

It is now widely acknowledged that Bayesian Logistic Regression Model (BLRM) based designs produce superior estimates of the "Maximum Tolerated Dose" compared to the old "3+3" method. Using the model based estimates of the toxicity rates to implement "Overdose Control", the BLRM designs can also be just as safe.

The BLRM design is also easy to extend to allow Phase I design of greater richness and flexibility than was possible with "3+3", or other methods restricted to cohorts.

- Include models of other endpoints such as efficacy or other levels of toxicity, allowing more nuanced dose escalation or expansion cohort decisions.
- Use continuous enrolment (up to a maximum number of enrolled but not complete subjects) to allow faster accrual and earlier escalation / de-escalation decisions.
- Include models of additional treatment groups which could be different treatment regimens or different subject populations (e.g. adults and children) allowing a more efficient single trial rather than two separate ones.
- Include a second drug and escalate in "two dimensions" using increased doses of either drug.

Because FACTS implements both simple and complex designs it is possible to compare the expected performance on a 'level playing field'.

From FACTS 6.2 onwards the BLRM based designs as implemented in a single module with a rich set of options that can be enabled one at a time – allowing their individual merits to be assessed and a design created that combines the options that work best for your trial.

FACTS includes a facility that implements the model analysis on the data as the trial progresses using exactly the model and options that were simulated, making it easy to implement the trial that was designed.

Phase II Designs

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 across the study doses (typically the proportion allocated to the Control arm is kept constant) 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.

Phase 3 Designs

FACTS allows the simulation and design of phase 3 design with a conventional frequentist analysis and p-value, and also the use of Bayesian “Goldilocks” design to support early decision making. In these designs, at pre-planned interims the Bayesian predictive probability of final success is calculated under two assumptions: firstly that the trial will recruit to its maximum sample size, secondly that enrolment will be stopped now and the current population followed up to their final visits and then analysed. The former probability can be used for futility stopping – if the probability of final success drops below a certain threshold (5% for example), then the trial can be stopped now for futility. The latter can be used to decide to stop enrolment if it is above a certain threshold (99% for example) and follow up the currently enrolled subjects in the strong expectation that the final analysis will be a success.

There are three key advantages to this approach compared to a Group Sequential design:

- The calculation of the Bayesian predictive probability can include early information from subjects who have not yet had their final visit (so make use of more information that a conventional Group Sequential analysis). This is of particular benefit in trials with long follow-up periods.
- Because the decision to stop for success is actually a decision to stop enrolling, complete follow-up and then perform an analysis in anticipation of success, the type-1 error inflation is not as great as in a Group Sequential trial, though there is some and the amount by which the final alpha level has to be reduced has to be determined by simulation.
- The decisions to stop early are much more easily justified to the rest of the trial team and the sponsor.

Enrichment Designs

These are trials where there are either multiple patient subgroups of interest or related indications that the treatment can be tested in, in parallel. The FACTS simulators for these types of trials allow early stopping of subgroups or indications for success or futility, allowing resources within the overall trial to

be re-allocated to groups or indications where more data is needed to increase the certainty of the outcome.

FACTS also includes various options for learning between the different groups, whether about the performance on control or about the treatment effect that can considerably increase the power of these trials compared to studying the subgroups or indications separately.

Where a disease has potentially many subgroups, studying each subgroup separately can effectively turn each subgroup into a rare disease, making it very hard to study. This 'Basket Trial' approach and hierarchical modelling can transform the viability of this sort of trial.

Platform Trials

These are trials that can run for a greater time than normal, testing multiple treatments some from the outset and some joining the trial later, possibly after earlier treatments have completed. The efficiency advantages (comparing to a common control arm, just one trial to setup and initiate) more than make up for the greater design effort – as long as there is a sufficient number of treatments that can be tested in the same trial. This form of trial is suited both as a phase 2 screening trial within a pharmaceutical company that has a particularly rich pipeline in a particular disease area, and setup and run outside any single company to research treatments in a neglected area or during a pandemic.

Possible design features that it will be of interest to explore through simulation are:

- What proportion of trial participants to assign to control?
- How aggressive to be in stopping treatments early?
- Whether to use response adaptive randomization to progress treatments with promising early data faster?

These can all help find identify the treatments more likely to be effective, more quickly than using conventional trials.

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 trial conduct get familiar with handling programs and files from FACTS-designs.

For more information

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