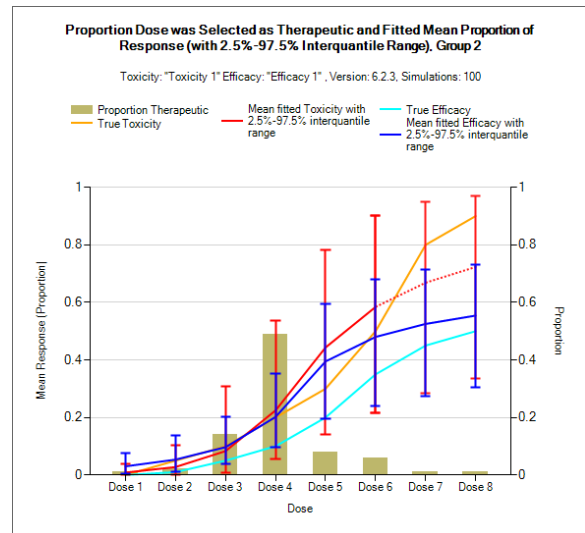# The Release of FACTS 6.2

To: FACTS Licensees
From: Berry Consultants
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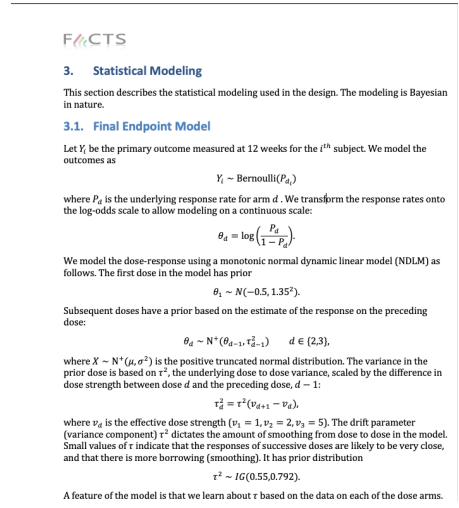
Introducing FACTS 6.2

Berry Consultants is delighted to announce that FACTS 6.2 is ready for release!

Building on FACTS 6.1, FACTS 6.2 adds new features to "FACTS N-CRM", the ability to generate a "Design Report" from FACTS Core designs and extending the ability to compute predictive probabilities to FACTS Core TTE and FACTS Staged TTE.

- FACTS N-CRM extensions. FACTS has had versions of the CRM with an efficacy endpoint, ordinal toxicity endpoint and 2 groups since its inception. But these were in separate engines and used the old CRM model for analysis. We have now added all these features as options to the N-CRM so they can be used with the 2 parameter Bayesian Logistic Regression model, targeting toxicity bands and the option to use overdose control. These features cannot only now but used with this better methodology, but can be used in combination with each other, and in combination with the other advanced features that were already included in the FACTS DE N-CRM simulator such as, run ins, stopping rules, escalation rules, fine grain dosing and open enrolment.

- FACTS Design Report. In FACTS Core there is now the ability to generate a "Design Report" as a MS Word file that describes the design and simulation results. The file is not intended as the final article but as something where the bulk of the straightforward text (and equations) have been provided and should just require polishing, particularly with the details of the indication and trial setting that FACTS is inevitably unaware of.

- FACTS 6.2 completes the implementation of predictive probabilities. Predictive probabilities in the current trial with a TTE endpoint are considerably more complex than predictive probabilities in the other endpoints. For the other endpoints the expected about of information after full enrolment and full follow-up is known, for time-to-event it can depend on multiple things such as accrual rate and the expected number of events so a degree of simulation within the simulation is required.

FACTS 6.2 is fully backwards compatible with FACTS 6.1, 6 and 5 – it can load and run all your FACTS 6 and FACTS 5 designs – and then use new FACTS 6.2 features with those designs.

You can have FACTS 6.2 and FACTS 6.1 installed on the same machine, so it's easy to have a transition period as you move to the new version.

Key New Features

FACTS Dose Escalation, the N-CRM (also known as Bayesian Logistic Regression) now has options for:
- An ordinal toxicity endpoint
- To simulate a trial across 2 groups (e.g. Adults and Pediatrics)
- An additional binary Efficacy endpoint
- These options can be combined with each other and all the other N-CRM options.

FACTS Core TTE
- The ability to compute the predictive probability of success at the full enrollment of the current trial.

FACTS Staged Design TTE
- The ability to compute the predictive probability of success
  - in Stage 1 at full enrollment
  - of Stage 2 (whilst in Stage 1)
  - in Stage 2 at full enrollment (whilst in Stage 2).

The following appears as an inset document excerpt:

FACTS

3. Statistical Modeling

This section describes the statistical modeling used in the design. The modeling is Bayesian in nature.

3.1. Final Endpoint Model

Let Y_i be the primary outcome measured at 12 weeks for the ith subject. We model the outcomes as

$$Y_i \sim \text{Bernoulli}(P_{d_i})$$

where P_d is the underlying response rate for arm d. We transform the response rates onto the log-odds scale to allow modeling on a continuous scale:

$$\theta_d = \log\left(\frac{P_d}{1 - P_d}\right).$$

We model the dose-response using a monotonic normal dynamic linear model (NDLM) as follows. The first dose in the model has prior

$$\theta_1 \sim N(-0.5, 1.35^2).$$

Subsequent doses have a prior based on the estimate of the response on the preceding dose:

$$\theta_d \sim N^+(\theta_{d-1}, \tau_{d-1}^2) \qquad d \in \{2,3\},$$

where $X \sim N^+(\mu, \sigma^2)$ is the positive truncated normal distribution. The variance in the prior dose is based on τ^2, the underlying dose to dose variance, scaled by the difference in dose strength between dose d and the preceding dose, $d-1$:

$$\tau_d^2 = \tau^2(v_{d+1} - v_d),$$

where v_d is the effective dose strength ($v_1 = 1, v_2 = 2, v_3 = 5$). The drift parameter (variance component) τ^2 dictates the amount of smoothing from dose to dose in the model. Small values of τ indicate that the responses of successive doses are likely to be very close, and that there is more borrowing (smoothing). It has prior distribution

$$\tau^2 \sim IG(0.55, 0.792).$$

A feature of the model is that we learn about τ based on the data on each of the dose arms.