Clinical trial simulations using a stroke disease progression model

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Objective

To perform clinical trial simulations to calculate the power to detect a drug effect different from zero, using a disease progression model for NIH stroke scale (NIHSS) [1], and to assess the bias and precision of the drug parameter, under various conditions.

Background

- Combined categorical-continuous models such as the stroke disease progression models [1-3] are of particular use where the data is non-monotonic, which is a typical scenario when analyzing stroke scale data. Maximal use is made of the available information, and even missing observations can be informative. These models may provide significant advantages over current analytical methodology used in the interpretation of the score data routinely collected during stroke trials.

Methods

- To be able to perform clinical trial simulations a drug effect parameter had to be introduced in the NIHSS disease progression model. Due to the structure of the model, several options on where to introduce a drug parameter were available; probability of improvement, probability of max score, probability of dropout, magnitude of improvement and magnitude of decline. In this scenario the effect was only added linearly on the magnitude of improvement.
- The design of the study was a parallel study with four arms; placebo and three active doses. Observations were made at day 0, 7, 30 and 90, and the study size was varied between 15-200 patients per arm.

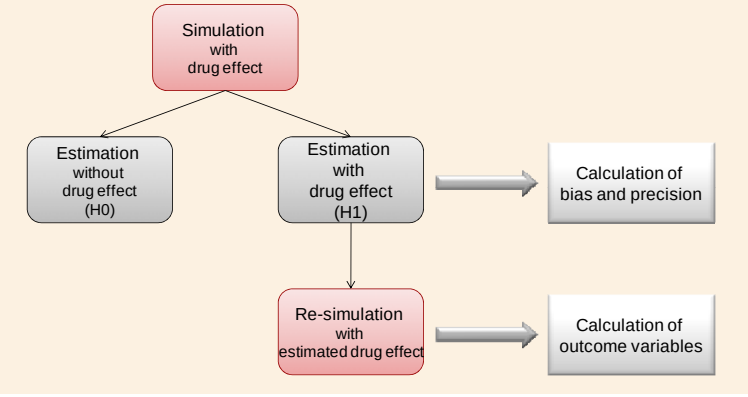

Figure 1. Stochastic Simulation and Estimation (SSE) setup. The process was repeated 500 times.

- The dose-effect relation was calibrated such that a low, medium and high dose level would result in 25%, 33% and 50% increase in fully recovered patients at end of study (the definition of a fully recovered patient was NIHSS<2 [4]), compared to placebo.
- The study power was defined as the power to detect a drug effect, i.e. the possibility to estimate a drug parameter different from zero. The power was calculated based on individual OFV values [5], and used to generate a power curve. This method has the advantage of being faster and does not require a type I error assessment for each study size.
- The parameter bias and precision and the outcome variables was calculated through stochastic simulations and estimations (sse), the process is visually described in figure 1.

Conclusions

- Under the studied conditions, and using the model for hypothesis testing, a minimum of 50 patients per arm was required to reach a study power of 80%.
- The drug parameter was estimated with high precision and a slight negative bias.
- The % fully recovered patients was estimated with high precision and a small bias.
- The results confirm the usefulness of a model based approach in the therapeutic area of stroke.

Results

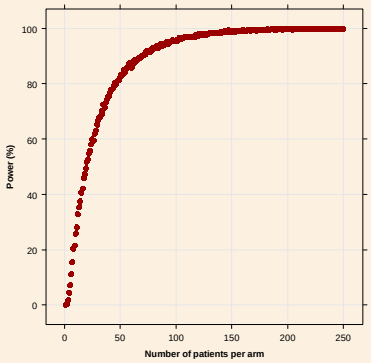

Figure 2. Power curve to detect a drug effect different from zero. The curve is generated via the MCMP metod described by Vong et al [5].

A continuous power curve (figure 2), produced by the MCMP method [5], showed that 50 patients per arm was the minimum for obtaining an 80% statistical power to detect a drug effect different from zero.

The behaviour of the drug parameter was investigated by calculating precision and bias, the former was high while the latter resulted in a consistant under prediction of an average of 15%.

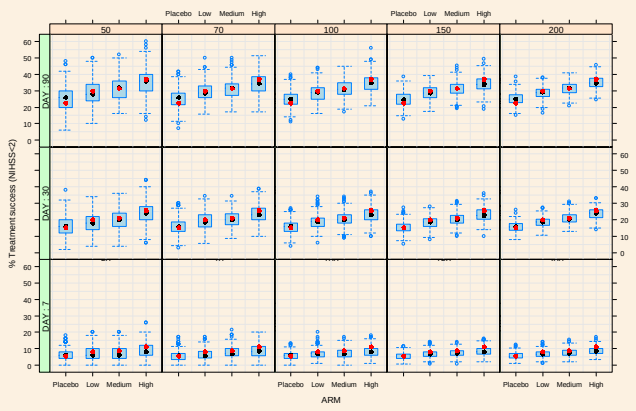

Figure 3. Percent fully recovered patients (NIHSS<2), stratified by day and number of patients per arm. The boxes represent the % fully recovered patients in each simulated study and the red dots represent the expected percentage.

The endpoint of the stroke study was measured as percentage fully recovered patients (NIHSS<2) at day 90; figure 3 display the expected and estimated percentage for each study arm, including the interim results at day 7 and 30.

References

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