A Bayesian design and analysis for dose-response using informative prior information

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Introduction

• We want to describe the dose-response relationship of a new compound when information about the dose-response of an existing compound within the same drug class is available and can be well described using a simple model. The drugs are both full agonists at the same receptor. A lack of successful biomarkers meant that these two drugs had to be compared in a clinical outpatient setting.

• We want to describe the relative potency of the new compound against the existing one using an efficient design, saving resources where possible. If the dose-response describing the placebo and maximal effect of the existing treatment can be adequately captured in an informative prior then fewer subjects will need to be allocated to these treatments and the randomisation for a new trial can be biased towards the new treatment where there is more uncertainty.

• Through Bayesian methods we can quantitatively incorporate the prior knowledge about the dose-response of the existing compound into the design and analysis of the new dose-response study.

Model & Methods

• A simple Emax model has been used to describe both the dose-response of the existing compound and the form shown below will be used to fit data from the new study. For dose *i of* compound *j* the average response is:

$$\overline{Response}_{i,j} = E0 - \frac{(Emax * dose_{i,j})}{(ED50_j + dose_{i,j})} + e_{i,j}$$

$$e_{i,j} \sim N(0, \sigma_w^2)$$

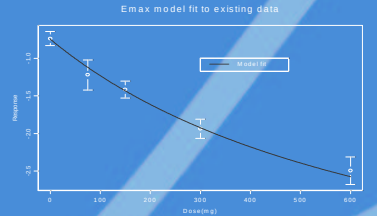
• E0 is the placebo effect. We assume the two compounds share the same maximal effect (Emax). The problem reduces to a simple case of using data from the new study to estimate the relative potency (ratio of ED50s).

• The dose-response relationship of the existing compound is represented by the prior distribution of the model parameters and the Bayesian analysis provides posterior estimates of the relative potency.

• The main assumption underlying this method is that data from the new study is exchangeable with that from the existing compound. In particular we assume that placebo patients will respond the same in the new study and that the maximal effect of treatment with this class of compound does not change over time. These assumptions can be mitigated by ensuring the inclusion / exclusion criteria are as similar as possible between the new study and previous studies.

• If the assumptions hold then the design of the new study can be weighted towards obtaining more information about the new compound, with only minimal information being obtained on placebo and the existing compound, mainly for safety purposes.

Figure 1 Derivation of the informative prior



$$\mu = \begin{bmatrix} E0 \\ \ln(ED50) \\ \ln(Emax) \\ B/line \end{bmatrix} = \begin{bmatrix} -0.741 \\ 6.63 \\ 1.744 \\ 0.630 \end{bmatrix} \qquad \Sigma/\rho = \begin{bmatrix} 0.09^2 & & & \\ -0.690 & 0.392^2 & & \\ 0.123 & 0.588 & 0.188^2 & \\ 0.032 & 0.037 & 0.034 & 0.158^2 \end{bmatrix}$$

Simulation methods

• The model has been implemented in WinBUGS. SAS has been used to simulate data and control the input and output of data from WinBUGS. Results have been summarised and plotted using S-Plus.

• A thorough program of simulations has been carried out to investigate the properties of the proof-of-concept design.

• Simulations have addressed issues such as total sample size, allocation ratio of patients to treatments and selection of doses. Sensitivity to different relative potencies and departures from assumptions has also been assessed.

• Type I and type II errors for the decisions made about the relative potency estimates have been assessed and calibrated by looking at the operating characteristics of the design for a variety of scenarios, ranging from no effect, to a clinically meaningful difference.

Results

• The model fit for the existing data (Fig.1) shows that the maximal effect is not particularly well characterised, resulting in high correlation between the Emax and ED50 parameters.

• Any informative prior needs to reflect this correlation.

Fig.2 shows results of 100 simulations for a design with 100 subjects, 10 on placebo, 10 on the existing compound and the other 80 subjects split equally between two doses of the new compound. The true relative potency for this simulation was four.

- The upper panel shows that we are able to accurately describe the relative potency with minimal bias.
- The lower panel shows the distribution of posterior probabilities of the relative potency being greater than a specified cutoff. These values confirm that the design has very low type II error in this case – P(Ratio>1) is high.

• Tables 1 and 2 present the results of simulations using criteria based on the relative potency estimate to classify the decisions made from each simulation. The table shows Type I and type II error rates and the ability of the design to make useful conclusions at the end of the study.

• Table 1 also shows the difference between equal allocation to all treatments and biased randomisation towards the new compound.

• Analysis of a standard parallel group study with 25 subjects per treatment group using an uninformative prior gives a power to detect a relative potency of 4 of only 50%.

• Incorporating prior information into this same design raises the power to 83%.

• Biasing randomisation towards the new compound increases this power to 95%.

• The accuracy and bias of results from the Bayesian analysis depend on the assumption that the new data is exchangeable with the existing data. Simulations have been carried out to check the robustness of conclusions to departures from this assumption.

Figure2 Results of 100 simulations where true relative potency = 4.

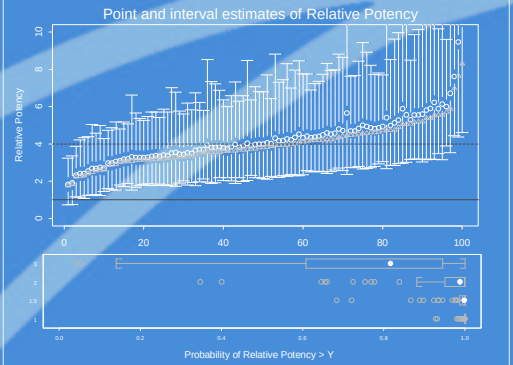


Table 1Proportion of simulations showing significant Relative Potency when true RP =4

Design	Prior	No significant difference in RP	Evidence of a significant difference in RP.
n=25/group PBO, existing compound; n=25/group Two doses of new compound. **(N=100)**	Uninformative	0.50	0.50
n=25/group PBO, existing compound; n=25/group Two doses of new compound. **(N=100)**	Informative	0.17	0.83
n=10/group PBO, existing compound; n=40/group Two doses of new compound. **(N=100)**	Informative	0.05	0.95

Table 2 Proportion of simulations showing significant Relative Potency when true RP =1

Design	Prior	No significant difference in RP	Evidence of a significant difference in RP.
n=25/group PBO, existing compound; n=25/group Two doses of new compound. **(N=100)**	Uninformative	0.99	0.01
n=25/group PBO, existing compound; n=25/group Two doses of new compound. **(N=100)**	Informative	>0.99	<0.01
n=10/group PBO, existing compound; n=40/group Two doses of new compound. **(N=100)**	Informative	>0.99	<0.01

Discussion and conclusions

• Use of an informative prior in this case substantially improves the efficiency of the design for a fixed resource. The results of simulations show that the posterior inferences give accurate and unbiased estimates of the true relative potency with good power and low Type I error.

• With this approach good quality drug candidates can be identified quickly while compounds with poor characteristics can be dropped with minimal investment.

• Probabilistic statements about the magnitude of the relative potency can help position the development of the new compound.

• The efficiency of the method is dependent on the underlying patient population being unchanged between the new study and the prior studies. This can be mitigated by ensuring that inclusion / exclusion criteria are as similar as possible. However simulations show that the design is robust to departures from our assumptions.

• Application of this approach has potential to increase efficiency of drug development strategy within therapeutic areas.