Bayesian Adaptive Designs for Dose-Ranging Studies in Rheumatoid Arthritis (RA)

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Introduction

An anti-inflammatory drug was in phase II development for Rheumatoid Arthritis (RA). Early small scale clinical studies, pre-clinical knowledge and the understanding of pharmacology and the mechanism of the compound strongly suggested that this drug could show clinical benefits for patients with RA. The purpose of this dose-ranging study was to find the minimum efficacious dose (MED) that is appropriate for investigation in the large scale phase III pivotal clinical studies in these patient populations

The clinical endpoint for the phase II study was based on the American College of Rheumatology definition of response using a composite clinical improvement of 20% (ACR20)). The response by current standard anti-inflammatory drugs on the market was used to set up the response (MinEff) that investigational drugs must show as a minimum.

A Bayesian adaptive design was proposed for this study in order to effectively and efficiently find the dose(s) which met the minimum effect. Compared to the traditional approach, the advantage of this method was that it allowed coverage of a wide range of doses without substantially increasing the number of treatment groups or subjects.

Objectives: The purpose of this work was to describe how the Bayesian adaptive method could be applied in practice, to show the validity of the method using clinical trial simulations, and to test the programs set up for practical use of this framework.

Methods

The Bayesian adaptive method is described briefly, and Figure 1 gives the graphical presentation of the framework. [Nc – Max. no of cohorts, K- no. of doses]

Endpoint: ACR20 response defined as yes or no.

Model: For illustration purpose, a simple logistic regression model of ACR20 response by log dose was used. Let **p**=probability of ACR20 response, and **x** = log(Dose+1), Dose=0 for placebo, the model is:

$$\text{logit}(p) = a + b*x + e$$

where ***a*** and ***b*** are the intercept and slope and ***e*** is the residual error

Let [La,Ua], [Lp,Up] represent the 95% credible interval of the posterior probability of ACR20 response for active and placebo, Ma and Mp were the posterior median of probability of ACR20 response for active and placebo. MinEff (=0.6, 60% ACR20 response obtained from literature) was the pre-defined criteria for a successful trial

At each step of the procedure, this model was fitted to the data obtained from the accrued data with given priors and posterior probability calculated using WinBUGS [1]. Following allocation and stopping rules were applied. The entire framework was programmed in R [2], WinBUGS was called and results returned back to R using R2WinBUGS [3]

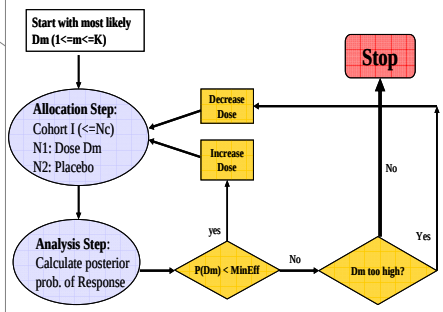
Adaptive Procedure

Allocation Rules:
Probability of ACR20 response from the current dose
- did not reach MinEff (Ma<MinEff), **increase** dose
- was too high (La>MinEff), **decrease** dose

Stopping Rules
- [La,Ua] included MinEff and Ma >= MinEff
- The lowest or highest dose in the selected dose range reached during the allocation steps

Safety data could be integrated into these rules.

Figure 1: General Framework of the Bayesian Adaptive Design



Decisions:

- MED achieved if stopped with first stopping rule (positive trial)
- Stopped with second stopping rule:
  - If Lowest dose reached and it showed response better than placebo (positive trial)
  - If Highest dose reached no acceptable response (negative trial)

Simulations

Scenarios: Three types of dose-response relationship were used for the simulations (Figure 2), assuming that probability of ACR20 response of the placebo was 20%. The three scenarios are:
- Case 1: ***a*** = -log(4) ; ***b*** =1
- Case 2: ***a*** = -log(4) ; ***b*** =0.45
- Case 3: ***a*** = -log(4) ; ***b*** = 0

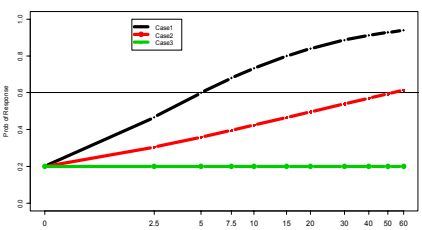
The dose ranges from 2.5-60mg (K=10)

Sample Size:
Sample size per cohort: 20 active and 20 placebo for first 3 cohorts, subjects in placebo arm reduced by half thereafter. Maximum no. of cohorts is set Nc=20

Priors:
Non-informative priors for both **a** and **b** were used in the simulations. Informative priors if available could be applied as well to make inference in practical situations

Total of 50 simulations for each scenario were run to show how the Bayesian adaptive up-and-down procedure works

Figure 2: Simulation Scenarios



Results

For these clinical trial simulations, the dose range was chosen to be between 2.5 and 60mg. The starting dose for the simulations was set at 15mg

Figure 3 shows the probability of ACR20 response from each cohort in a particular trial. The distribution of subjects allocated to each dose (upper panel) and the distribution of doses selected over the 50 simulations (lower panel) are shown in Figure 4

Figure 3: Probability of Response by Cohort of the Three Scenarios

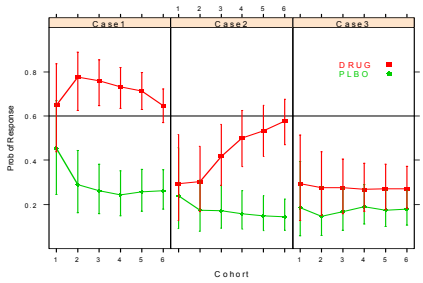
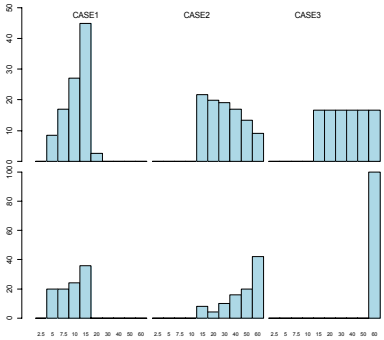


Figure 4: Distribution of Subjects Allocated by dose group (upper panel) and Doses Determined (lower panel)



For Case 1, 100% simulations found MED, while with Case 3, no simulation gave false positive results. For Case 2, only 2% of the simulation showed negative results, indicating a possible minimal chance of false negative result.

Summary and Discussions

- A Bayesian adaptive design framework for the purpose of finding MED which met the pre-defined MinEff *over a wide range of doses* was described
- The up-and-down rules allowed flexible selection for the starting dose, e.g. the most likely efficacious dose based on prior knowledge. These rules could be modified to allow faster/slower progress of the trial based on some pre-define criteria, such as, the probability of response observed
- Trials would be stopped early when target dose was reached, or escalated quickly if there was no sign of finding the target dose. Most subjects would be allocated to the most likely doses, while unlikely doses (either too low or too high) would be avoided. Also, simulations showed a minimal false negative or false positive results
- The procedure could be modified by setting up an acceptable precision on probability of response or minimal number of subjects included if stopping for efficacy with successful or positive outcomes
- More complicated model integrating both efficacy and safety data can be utilised and implemented in this framework. The method could also be modified if aiming for dose/exposure response relationships

References

[1] Spiegelhalter D et.al. WinBUGS User Manual, 2003, http://www.mrc-bsu.cam.ac.uk/bugs
[2] The R project for statistical computing, http://www.r-project.org
[3] Sturtz S et.al. R2WinBUGS: A package for running WinBUGS from R. Journal of statistical software, 2005, 12(3) 1-16.