Bayesian Methods for Clinical Trials

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Practical 2: Fixed-sample designs & JAGS

You are asked to design a Phase II singe-agent PoC clinical trial of a new anti-cancer agent. The team would like to evaluate a particular dose of the new agent in terms of the objective response rate (ORR) at Week 12 after the start of the treatment. The uninteresting response rate that would not suggest a promising activity is $p_0 = 0.30$ and an interesting treatment effect that would trigger the further development of the compound is $p_1 = 0.50$.

Let Y be the number of objective responses. $H_0 : p \leq p_0$ is tested against $H_1 : p > p_0$. The treatment is deemed efficacious if $Y \geq u$ for a suitable u. Then n and u are chosen such that:

$$\mathbb{P}(Y \geq u; p_0) \leq \alpha \quad \text{and} \quad \mathbb{P}(Y \geq u; p_1) \geq 1 - \beta.$$

(a) Given that the trial consists of $n = 40$ patients and that $u = 16$, write out the expressions for the type I error and power for the above trial in terms of the binomial distribution. Then write a function in R that takes in the values of n, u, p_0 and p_1 and returns the type I error and power. *(Hint: you will need the pbinom() function)*

(b) We will now compute the sample size n (and an associate critical value, u) that achieves a statistical power of 80% of finding this treatment efficacious at the one-sided 5% significance level.

(i) Use a for loop and your function from (a) to do an exhaustive search over a number of plausible values of n and u and find the values that satisfy the power and error constraints. What is the smallest sample size required?
Hint: to define the combinations of u and n to search over you can use the following code

```
combo <- data.frame(nb=rep(1:maxN,1:maxN),ub=sequence(1:maxN))
```

where maxN *is a maximum sample size to be defined.*

(ii) Give a brief explanation of why these values are not exactly 5% and 80% as targeted?

(c) We will now consider a Bayesian design wherein efficacy decisions are made based on posterior probabilities, comparing the posterior response rate to the null and target response rates.

The treatment is deemed efficacious if $\mathbb{P}(p > p_0|Y = u) \geq \eta$, where $\eta = 0.95$ is chosen to be close to 1. Any values of Y greater than u will also be deemed efficacious.

The treatment is abandoned if $\mathbb{P}(p < p_1|Y = u - 1) \geq \zeta$, where $\zeta = 0.8$ is chosen to be close to 1. Any values of Y less than u will also be abandoned.

Thus, as before, the treatment is deemed efficacious if $Y \geq u$.

(i) Write a function in R that computes the two probabilities: $\mathbb{P}(p > p_0|Y = u)$ and $\mathbb{P}(p < p_1|Y = u - 1)$ given the prior $p \sim \text{Beta}(a, b)$.

(ii) Using a for loop and your function from (c)(i), do an exhaustive search over a number of plausible values of n and u and find the values that satisfy the two probability constraints, implementing the following priors:

$$p \sim \text{Beta}(1, 1); \quad p \sim \text{Beta}(10, 10); \quad p \sim \text{Beta}(15, 15); \quad p \sim \text{Beta}(5, 15).$$

What is the smallest sample size required under each prior?

(iii) Describe how the prior affects sample size determination. Is it the more informative the better?

(d) Simulate a dataset using the code below.

```
set.seed(100)
MyDat1 <- rbinom(n = 49, size = 1, prob = 0.50)
```

(i) Write a JAGS model for this data with a vague prior $p \sim \text{Uniform}(0, 1)$. Run the model and plot the prior and posterior distributions.

(ii) Given that we establish treatment benefit if $\Pr(p > 0.3 \mid \boldsymbol{x}) \geq 95\%$, otherwise claim the treatment as not efficacious. What conclusion would you draw following your analysis of `MyDat1`?
Hint: You can include the probability computation in the jags model using step(x) which computes the probability that $x > 0$. You can then extract this probability from the jags output.

(iii) Sticking with the Uniform prior, write a function in R (using JAGS) that computes the two probabilities: $\mathbb{P}(p > p_0|Y = u)$ and $\mathbb{P}(p < p_1|Y = u - 1)$.
(Hint: You can either run two jags models: one to compute the first probability and one to compute the second or do this in a single model. For a single model you will need to specify the two values of Y (i.e. u and $u - 1$) and their distributions, with separate p parameters and priors in order to avoid a hierarchy structure.)

(iv) Using a for loop and your function from (d)(iii), do an exhaustive search over a number of plausible values of n and u and find the values that satisfy the two probability constraints $\mathbb{P}(p > p_0|Y = u) \geq \eta$, where $\eta = 0.95$ and $\mathbb{P}(p < p_1|Y = u - 1) \geq \zeta$, where $\zeta = 0.8$. Implement the following two priors:

$$p \text{ Uniform}(0, 1); \quad p \sim \text{Uniform}(0.25, 0.75).$$