Assignment 1

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1 Problem 1

Summarizing the posterior 25th percentile of γ in a table according to the R code,

Prior Dist	After 2 patients	After 12 patients
γ is uniform on [50, 400] mg/m^2, ρ_0 is uniform on [0, 0.2]	158.6	248.6
γ is uniform on [50, 650] mg/m^2, ρ_0 is uniform on [0, 0.2]	223.6	288.1
γ is uniform on [50, 400] mg/m^2, ρ_0 is uniform on [0, 0.25]	161.7	243.4
γ is uniform on [50, 650] mg/m^2, ρ_0 is uniform on [0, 0.25]	231.7	280.4

Therefore the Next Dose is summarizing in the following table

Prior Dist	Next Dose After 2 patients	Next Dose After 12 patients
γ is uniform on [50, 400] mg/m^2, ρ_0 is uniform on [0, 0.2]	160	250
γ is uniform on [50, 650] mg/m^2, ρ_0 is uniform on [0, 0.2]	220	290
γ is uniform on [50, 400] mg/m^2, ρ_0 is uniform on [0, 0.25]	160	240
γ is uniform on [50, 650] mg/m^2, ρ_0 is uniform on [0, 0.25]	230	280

From the table, we can make a conclusion that the posterior 25th percentile of γ is sensitive to the choice of those prior distributions for γ but is not sensitive to the choice of those prior distributions for ρ_0 after 2 patients and after 12 patients.

The reason is obvious. ρ_0 represents the probability of initial drug toxicity, which has little relationship with MTD. However, it can be seen from $\pi(\gamma|data) = h(\gamma) * f(data|\gamma)$, we can get that the posterior probability distribution of MTD is extremely related to the prior probability distribution, so the above conclusion is correct.

2 Problem 2

2.1 a

Simon optimal design constructed to minimize the expected sample size under H0. Therefore, the stopping rules with the Simon's optimal design is that, in the first stage of the trial, a predefined number(N1) of patients is enrolled. If the number of observed responses is too low regarding a prespecified critical value(a_1), the trial is stopped and the treatment is considered inefficient. Otherwise, another fixed number of patients(N2) is enrolled in the trial. Again the number of observed responses is examined, and the treatment is considered inefficient if the total number of observed responses is too low compared with a prespecified critical value(a_2), otherwise the treatment is considered efficient if the total number of observed responses is high compared with a prespecified critical value(b_2).

According to the data, the result is

Your input

Alpha ----------> 0.10

Beta ----------> 0.10

Response Probability of Poor Drug (P0) ---> 0.40

Response Probability of Good Drug (P1) ---> 0.60

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Result

Optimal Two Stage Design	Optimum Design	MinMax Design
First Stage Sample Size (n1)	18	28
Upper Limit For 1st Stage Rejection of Drug (r1)	7	11
Maximum Sample Size (n)	46	41
Upper Limit for 2nd Stage Rejection of Drug (r)	22	20
Expected Sample Size If Response Probability = P0	30.22	33.84
Probability of Early Termination at P0	0.56	0.55

Therefore there are less than 7 responses out of the first stage sample size 18, stop the trail.

2.2 b

According to the question,

$$H0 : p = 0.4 \quad vs \quad H1 : p = 0.6$$

The prior distribution for the response is,

$$p \sim beta(0.3, 0.7)$$

$m = N_{max} - n$, $Q_T = 0.9$, $Q_L = 0.1$ and $Q_U = 0.95$, then

$$P(Y|X) \sim Beta - Binomial(m, a_0 + X, b_0 + n - X)$$

$$p|(X = x, Y = i) \sim Beta(a_0 + X + i, b_0 + N_{max} - X - i)$$

$$Bi = P(p > p_0|x, Y = i)$$

$$PP = \sum_{i=0}^{m} Pr(Y = i|X = 10) * I(Bi > Q_T)$$

if $PP > Q_L$. We can stop the trial due to futility.

if $PP < Q_U$. We can stop the trial due to efficacy.

Otherwise, based on the interim data, we should continue the study because the evidence is not yet sufficient to draw a definitive conclusion in either direction.

Therefore, according to the $Q2\_2.txt$, the corresponding rejection regions are:

1/10, 1/11, 1/12, 2/13, 2/14, 2/15, 3/16, 3/17, 4/18, 4/19, 5/20, 5/21, 6/22, 6/23, 7/24, 7/25, 8/26, 8/26, 9/28, 10/29, 11/31, 12/32, 12/33, 13/34, 14/35, 15/36, 16/37, 17/38, 18/39, 19/40, 20/41

That is, X/Y represents if less than or equal to X response when the total number is Y, we stop for futility.

2.3 c

For each N_{max} between 41 and 46, we can search the Q_L and Q_T space to generate designs that both have Type I and Type II errors under the pre-specified 0.1 level.

Q_L	Q_T	γ/N_{max}	$PET(p_0)$	$E(N\|p_0)$	α	β
0.0010	$[0.8610, 0.9180]$	10/41	0.8711	31.0686	0.0961	0.0977
		10/42 no solution				
0.0010	$[0.8690, 0.9220]$	10/43	0.8785	32.1237	0.0908	0.0926
		10/44 no solution				
0.0010	$[0.8760, 0.9260]$	10/45	0.8854	33.1210	0.0859	0.0880
0.0220	$[0.8470, 0.9060]$	10/46	0.8721	27.4460	0.1000	0.0838

2.4 d

When $N_{max} = 46$, Rejection regions for the Simon's optimal design is at two discrete points.we would stop for futility if there are 7 or less responses out of first 18 patients or ≤ 22 responses out of the total sample size 46.The probability of early termination at p_0 is 0.56

In fact, the Bayesian predictive probabilities design can also be regarded as two stages to some extent. In the first stage, we only cumulate the data of the subjects and do not monitor (monitoring after enrolling 10 subjects). The second stage is that every enroll a subject, we observe the response of this subject, and then calculate pp based on the data of this subject (and all previous subjects), make a decision to see if stop for futility or efficacy. Therefore, when the $N_{max} = 46$, the probability of early termination at p_0 is 0.8721.

From the above results, it can be concluded that PP design terminates earlier if the new drug is futility, so it is more efficient.