HW3

Question 1

Already known that under logit model, we can have

$$logit\left(Prob(DLT \mid Dose = x)\right) = \frac{1}{\gamma - x_1}\{\gamma \cdot logit(\rho_0) - x_1 \cdot logit(\theta) + [logit(\theta) - logit(\rho_0)] \cdot x\}$$

To get the posterior distribution, R is employed. Please see Q1.R for details. Results are shown in the following table.

Prior Distribution	25 percentile after 2 patients	25 percentile after 12 patiens	
$\gamma \sim Unif(50, 400)$, $\rho_0 \sim Unif(0, 0.2)$	$\gamma = 160,\ \rho_0 = 0.0$	$\gamma = 250,\ \rho_0 = 0.0$	1
$\gamma \sim Unif(50, 650)$, $\rho_0 \sim Unif(0, 0.2)$	$\gamma = 230,\ \rho_0 = 0.0$	$\gamma = 290,\ \rho_0 = 0.0$	2
$\gamma \sim Unif(50, 400)$, $\rho_0 \sim Unif(0, 0.25)$	$\gamma = 150,\ \rho_0 = 0.1$	$\gamma = 240,\ \rho_0 = 0.0$	3
$\gamma \sim Unif(50, 650)$, $\rho_0 \sim Unif(0, 0.25)$	$\gamma = 240,\ \rho_0 = 0.0$	$\gamma = 280,\ \rho_0 = 0.1$	4

Thus we can answer that:

- **The next dose levels for different prior distribution differs.**
  - If the prior for the ρ_0 is fixed, the prior distribution for γ will hugely influence the posterior distribution no matter how many patients have been already enrolled. As we can see from above that posterior γ in group 2 is greater than those in group 1 .
  - However, when the prior for γ is fiexed, the posterior distribution for γ will not change with the prior for ρ_0. This may due to the two reasons:
    - The response from patients indicates that the ρ_0 should be small (from the data we can see that first 8 patients does not show AEs).
    - The prior distribution of ρ_0 does not change much (from 0.20 to 0.25) thus has a minor influence on γ.
- **The next dose levels given different patients information differs.**
  - As we can see from above form, the next dose level after 12 patients is always larger than the next dose level after 2 patients. This results from the ourcomes from patients since out of 12 patients only 9th patient and 12th patient reflects AEs, which gives more evidence that next dose can be set larger.

Question 2

2.1 Simon's optimal design

Given $p_1 = 0.6$, and $\alpha = \beta = 0.1$,by using https://linus.nci.nih.gov/brb/samplesize/otsd.html we have

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

thus

$$N_1 = 18, \quad a_1 = 7, \quad N = 46, \quad a_2 = 22$$

Therefore, if 7 or fewer successes in first 18 patients are observed then we should early stop here for futility.

If 22 or fewer successes in total 46 patients are observed then we should stop the trial.

2.2 Bayesian PP

Formulate this question as a hypothesis testing problem:

$$H_0 : p \leq 0.4, \quad v.s. \quad H_1 : p > 0.6$$

where $p_0 = 0.4, p_1 = 0.6$.

1. Prior Distribution for response rate p :

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

2. Posterior distribution of the response rate p given X_{10}

$$p \mid X_{10} \sim Beta(0.3 + X_{10},\ 0.7 + 10 - X_{10})$$

3. Future Distribution for Y

$$Y \mid X_{10} \sim Beta - Binomial(31,\ 0.3 + X_{10},\ 10.7 - X_{10})$$

Since $\alpha = \beta = 0.1$, set $Q_L = 0.1, Q_T = 0.9, Q_U = 0.9$. Thus, the predictive probability(pp) should be calculaed as:

$$PP = \sum_{i=1}^{31} P(Y = i \mid X_{10} = x) \times \mathcal{I}(Pr(p > 0.4 \mid Y = i, X_{10} = x) > 0.9)$$

Since we don't know the value for X_{10}, so R is employed to loop over all possible values. Please see Q2.R for details.

X_{10}	0	1	2	3	4	5	6	7	8	9	10
PP	1e-5	0.0007	0.0094	0.0575	0.2018	0.4567	0.7308	0.9112	0.9824	0.9982	0.9999

Thus , we have to

- Stop for futility if $X_{10} \leq 3$ and stop for efficacy if $X_{10} \geq 7$
- Continue the next state if $4 \leq X_{10} \leq 6$

So to monitor the trial continously, we have the following **rejection region (stop for futility)**:

- 3 / 10, 3 / 11, 4 / 12, 4 / 13, 5 / 14, 5 / 15, 6 / 16, 6 / 17, 7 / 18, 7 / 19, 8 / 20
- 8 / 21, 9 / 22, 9 / 23, 10 / 24, 10 / 25, 11 / 26, 11 / 27, 12 / 28, 12 / 29, 13 / 30,
- 13 / 31, 14 / 32, 14 / 33, 15 / 34, 16 / 35, 16 / 36, 17 / 37, 17 / 38, 18 / 39, 19 / 40, 20 / 41

and the following **accept region (stop for efficacy)**:

- 7 / 10, 8 / 11, 9 / 12, 9 / 13, 10 / 14, 10 / 15, 11 / 16 , 11 / 17, 12 / 18, 12 / 19, 13 / 20,
- 13 / 21, 14 / 22, 14 / 23, 15 / 24, 15 / 25, 16 / 26, 16 / 27, 16 / 28, 17 / 29, 17 / 30,
- 18 / 31, 18 / 32, 19 / 33, 19 / 34, 19 / 35, 20 / 36, 20 / 37, 21 / 38, 21 / 39, 21 / 40, 21 / 41

2.3 Table

Predictive probability based designs

θ_L	θ_T	r/N_{max}	$PET(p_0)$	$\mathbb{E}[N \mid p_0]$	α	β
0.001	$[0.861, 0.918]$	20 / 41	0.8711	31.07	0.0961	0.0977
		NA / 42				
0.001	$[0.869, 0.922]$	21 / 43	0.8785	32.12	0.0908	0.0926
		NA / 44				
0.001	$[0.876, 0.926]$	22 / 45	0.8854	33.12	0.0859	0.0880
0.022	$[0.847, 0.906]$	22 / 46	0.8721	27.45	0.1000	0.0838

2.4 Comparison

Parameter setting : $p_0 = 0.4, p_1 = 0.6, \alpha = \beta = 0.1$

Your input

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

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

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

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Result

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Calculation Result

Parameter selection: Maximize Power.
Theta_L and theta_T ranges:
Theta_L 0.0010 0.0010
Theta_T 0.8610 0.9180

Null Case

Pat.No.	Rej. Reg. (Negative)	Rej. Reg. (Positive)	Prob./(p0) (Negative)	Prob./(p0) (Positive)	Prob. Cont./(p0)
10	1	11	0.0464	0.0000	0.9536
11	1	12	0.0000	0.0000	0.9536
12	1	13	0.0000	0.0000	0.9536
13	2	14	0.0261	0.0000	0.9275
14	2	15	0.0000	0.0000	0.9275
15	2	16	0.0000	0.0000	0.9275
16	3	17	0.0213	0.0000	0.9062
17	3	18	0.0000	0.0000	0.9062
18	4	19	0.0295	0.0000	0.8767
19	4	20	0.0000	0.0000	0.8767
20	5	21	0.0342	0.0000	0.8425
21	5	22	0.0000	0.0000	0.8425
22	6	23	0.0369	0.0000	0.8056
23	6	24	0.0000	0.0000	0.8056
24	7	25	0.0383	0.0000	0.7673
25	7	26	0.0000	0.0000	0.7673
26	8	27	0.0386	0.0000	0.7286
27	8	28	0.0000	0.0000	0.7286
28	9	29	0.0383	0.0000	0.6903
29	10	30	0.0625	0.0000	0.6278
30	10	31	0.0000	0.0000	0.6278
31	11	32	0.0456	0.0000	0.5822
32	12	33	0.0670	0.0000	0.5153
33	12	34	0.0000	0.0000	0.5153
34	13	35	0.0449	0.0000	0.4703
35	14	36	0.0628	0.0000	0.4075
36	15	37	0.0670	0.0000	0.3405
37	16	38	0.0640	0.0000	0.2765
38	17	39	0.0574	0.0000	0.2191
39	18	40	0.0493	0.0000	0.1698
40	19	41	0.0408	0.0000	0.1289
41	20	42	0.0329	0.0961	0.0000
Sum:			0.9039	0.0961	

PET (PP<Theta_L)/(p0): 0.8711
PET (PP>Theta_U)/(p0): 0.0000
PET Total /(p0): 0.8711
E(N|p0): 31.0686

Compared with Simon Optimal Design (SOD for short), predictive probabilty (PP) is harder to stop at the early stage of trials. However, PP can provides a more precise and continous instruction about when we should stop the trial and the confidence level of our choice whereas SOD only gives two discrete rejection point. This is because PP includes the uncertatinty of priors while SOD ingores it.