Multi-Stage Design for Demonstration

Interim Analysis for Futility Using Bayesian Predictive Probability

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Summary of Interim Analysis for Futility

Futility evaluation is implemented in 4 interim analyses with 10, 10, 10, 10 patients in stage 1, 2, 3, 4, respectively, and 10 patients in the last stage, for a total of 50 patients. With an unfavorable rate set at 30% (null hypothesis) and posterior probability of 0.95 as the threshold, a total of at least 21 of the 50 patients must have response to be able to claim treatment efficacy. Given a 20% cutoff of the predictive probability (i.e. chance to stop the trial in the interim analyses) the stopping rule (Table 1) will be: the trial will be stopped if there are 2, 6, 10, and 15 or less patients with response in the 1st to 4th interim analysis, respectively.

Performance of the design (Figure 2 and Table 3) shows that if the true rate of response is 30%, the chance to reach at least a total of 21 patients with response at end of the study is 4% (Type I error), however the probability to stop the trial early is 91%. If true rate of response is indeed 50%, then the chance to reach at least 21 patients with response at end of the study is 83% (power), and the corresponding probability to stop the treatment early is 14%.

Details

A Bayesian approach for futility analysis is used to calculate posterior probability and predictive probability for the rate of response with a non-informative beta prior, beta(1,1), using the analytical form. We consider a 30% rate or lower of response as ineffective for the treatment. Thus, we expect the treatment arm is promising if the posterior probability of the rate (response) greater than 30% is higher than 0.95 (i.e., prob(rate of response>30% |data)>0.95)).

With a total 50 patients in treatment arm, the number of patients with response needs to be 21 or more in order to meet the criteria. Therefore, we use the number of 21 patients to guide the predictive probability. Specifically, given the number of patients with response, s, in the first 10 patients, we calculate predictive probability of $21-s$ or more patients with response in the future remaining 40 patients, i.e., $\sum_{i=21-s}^{40}\binom{40}{i}\frac{beta(1+s+i,1+(10-s)+(40-i))}{beta(1+s,1+(10-s))}$. Calculation of predictive probability is based on beta binominal distribution for the number of patients with response in the future remaining 40 patients given a beta distribution for the rate of response, $beta(1+s, 1+10-s)$. For example, if there are 2 patients with response in the first 10 patients, the predictive probability of 19 or more patients with response in the future remaining 40 patients would be $\sum_{i=19}^{40}\binom{40}{i}\frac{beta(1+2+i,1+(10-2)+(40-i))}{beta(1+2,1+(10-2))}=0.077$.

The predictive probability is also calculated for each of the remaining interim analyses to evaluate the chance of 21-s or more patients with response in the future remaining patients given s patients with response in the current stage of interim analysis. Figure 1 and Table 2 lists predictive probability for all scenarios of number of patients with response in each interim analysis and the associated largest number of patients with response needed in the future remaining patients to have at least a total of 21 patients with response.

We consider that a 20% cutoff of the predictive probability will give unlikely chance to have 21 patients or more with response at the end of study. Thus with this cutoff, the stopping rule (Table 1) will be: the trial

will be stopped if there are 2, 6, 10, and 15 or less patients with response in the 1st to 4th interim analysis, respectively. Performance of this stopping rule (Figure 2 and Table 3) shows that if the true rate of response is 30%, the chance to reach at least a total of 21 patients with response at end of the study is 4% (Type I error), however the probability of early termination (PET) is 91%. When the true rate of response is 50%, then the chance to reach at least 21 patients with response at end of the study is 83% (power), and the corresponding probability to stop the treatment early is 14%. Figure 3 shows the probability of stopping at each interim analysis.

Sensitivity analysis (Table 4-7 and Figure 4-7) evaluates four parameters for their impact on performance (PET, type I error, and power): cutoff for the predictive probability, threshold for posterior probability of response rate, sample size, and beta prior distribtuion of the response rate. Evaluation is conducted for each parameter when the values of other parameters are fixed. When the cutoff of the predictive probability for the stopping rule is 0.05-0.3, the range is 0.83-0.94 for PET, 0.03-0.04 for type I error, and 0.72-0.88 for power (Table 4 and Figure 4). When the threshold for posterior probability is 0.8-0.99, the range is 0.72-0.96 for PET, 0.01-0.16 for type I error, and 0.63-0.92 for power (Table 5 and Figure 5). When the sample size of each stage is in the magnitude from decrease by -5 to increase by 5, the range is 0.86-0.92 for PET, 0.03-0.06 for type I error, and 0.55-0.91 for power (Table 6 and Figure 6). When the beta prior varies from non-informative prior to the one with a response rate at the null or alternative hypothesis and a series of standard deviation (SD), the range is 0.87-1 for PET, 0-0.06 for type I error, and 0.13-0.86 for power (Table 7 and Figure 7).

Table 1: Stopping Boundary for Futility

Stage of interim analysis	1	2	3	4	Final
Sample size up to the current stage	10	20	30	40	50
Sample size at each stage	10	10	10	10	10
Stopping boundary	2	6	10	15	20

Table 2: Bayesian Predictive Probability for Stopping Rule

number of patients with response in the 1st interim analysis	minimum number of patients with response needed in the future remaining patients	predictive probability
0	21	0.001
1	20	0.014
2	19	0.077
3	18	0.241
4	17	0.497
5	16	0.750
6	15	0.913
7	14	0.980
8	13	0.997
9	12	1.000
10	11	1.000

number of patients with response in the 2nd interim analysis	minimum number of patients with response needed in the future remaining patients	predictive probability
0	21	0.000
1	20	0.000
2	19	0.000
3	18	0.001
4	17	0.007
5	16	0.033
6	15	0.107
7	14	0.255
8	13	0.467
9	12	0.690
10	11	0.858
11	10	0.950
12	9	0.987
13	8	0.998
14	7	1.000
15	6	1.000
16	5	1.000
17	4	1.000
18	3	1.000
19	2	1.000
20	1	1.000

number of patients with response in the 3rd interim analysis	minimum number of patients with response needed in the future remaining patients	predictive probability
1	20	0.000
2	19	0.000
3	18	0.000
4	17	0.000
5	16	0.000
6	15	0.000
7	14	0.001
8	13	0.006
9	12	0.029
10	11	0.094
11	10	0.230
12	9	0.437
13	8	0.664
14	7	0.844
15	6	0.946
16	5	0.986
17	4	0.998
18	3	1.000
19	2	1.000
20	1	1.000

number of patients with response in the 4th interim analysis	minimum number of patients with response needed in the future remaining patients	predictive probability
11	10	0.000
12	9	0.001
13	8	0.008
14	7	0.045
15	6	0.161
16	5	0.388
17	4	0.666
18	3	0.878
19	2	0.974
20	1	0.998

Table 3: Performance (Probability of Early Termination, Type I error, and Power)

true rate	overall probability of early stopping the trial	probability to have at least 21 patients with response
0.05	1.000	0.000
0.10	1.000	0.000
0.15	1.000	0.000
0.20	0.998	0.000
0.25	0.980	0.005
0.30	0.908	0.037
0.35	0.748	0.148
0.40	0.519	0.366
0.45	0.296	0.627
0.50	0.138	0.829
0.55	0.055	0.937
0.60	0.019	0.980

Table 4: Sensitivity Analysis: Predictive Probability

Cutoff of predictive probability	PET	typeI	power
0.05	0.83	0.04	0.88
0.10	0.86	0.04	0.85
0.15	0.87	0.04	0.84
0.20	0.91	0.04	0.83
0.25	0.93	0.03	0.74
0.30	0.94	0.03	0.72

Table 5: Sensitivity Analysis: Posterior Probability

threshold of posterior probability	PET	typeI	power
0.80	0.72	0.16	0.92
0.81	0.72	0.16	0.92
0.82	0.72	0.16	0.92
0.83	0.72	0.16	0.92
0.84	0.78	0.11	0.91
0.85	0.78	0.11	0.91
0.86	0.78	0.11	0.91
0.87	0.78	0.11	0.91
0.88	0.78	0.11	0.91
0.89	0.78	0.11	0.91
0.90	0.87	0.06	0.86
0.91	0.87	0.06	0.86
0.92	0.87	0.06	0.86
0.93	0.87	0.06	0.86
0.94	0.87	0.06	0.86
0.95	0.91	0.04	0.83
0.96	0.91	0.04	0.83
0.97	0.96	0.02	0.68
0.98	0.96	0.02	0.68
0.99	0.96	0.01	0.63

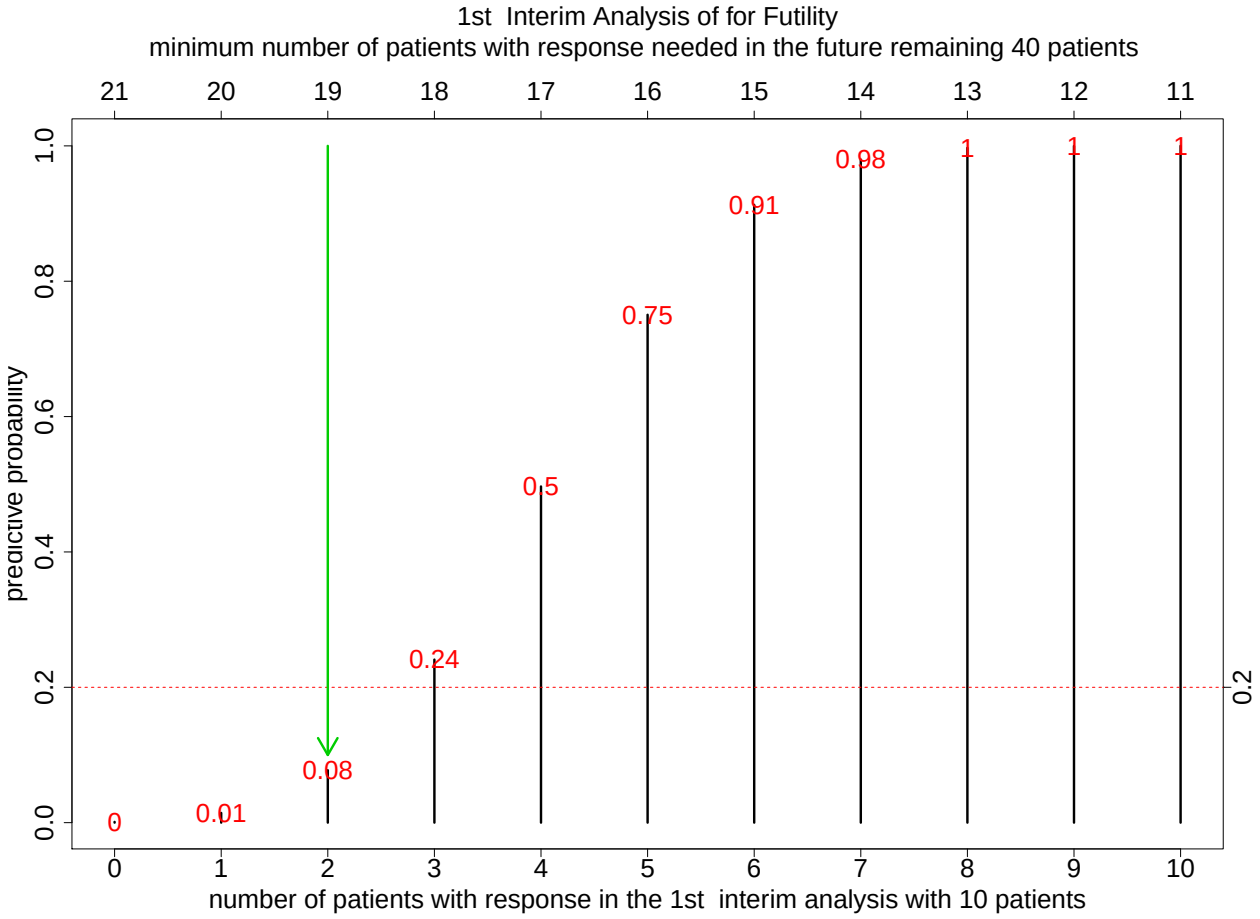
Table 6: Sensitivity Analysis: Sample Size

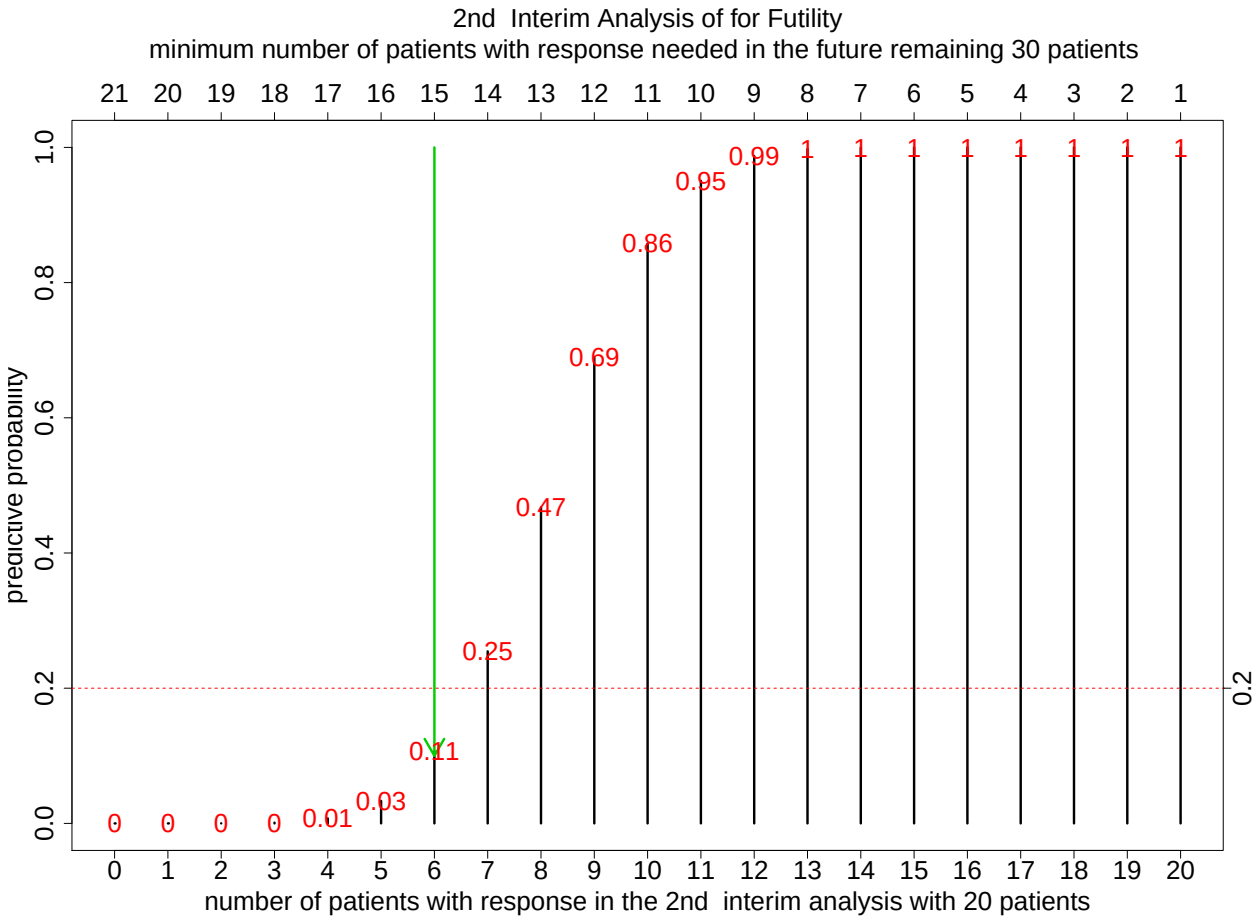
n1	n2	n3	n4	n5	PET	typeI	power
5	5	5	5	5	0.92	0.03	0.55
6	6	6	6	6	0.90	0.03	0.61
7	7	7	7	7	0.86	0.06	0.77
8	8	8	8	8	0.91	0.04	0.73
9	9	9	9	9	0.88	0.04	0.80
10	10	10	10	10	0.91	0.04	0.83
11	11	11	11	11	0.91	0.03	0.81
12	12	12	12	12	0.89	0.05	0.88
13	13	13	13	13	0.91	0.04	0.90
14	14	14	14	14	0.90	0.04	0.91
15	15	15	15	15	0.89	0.05	0.91

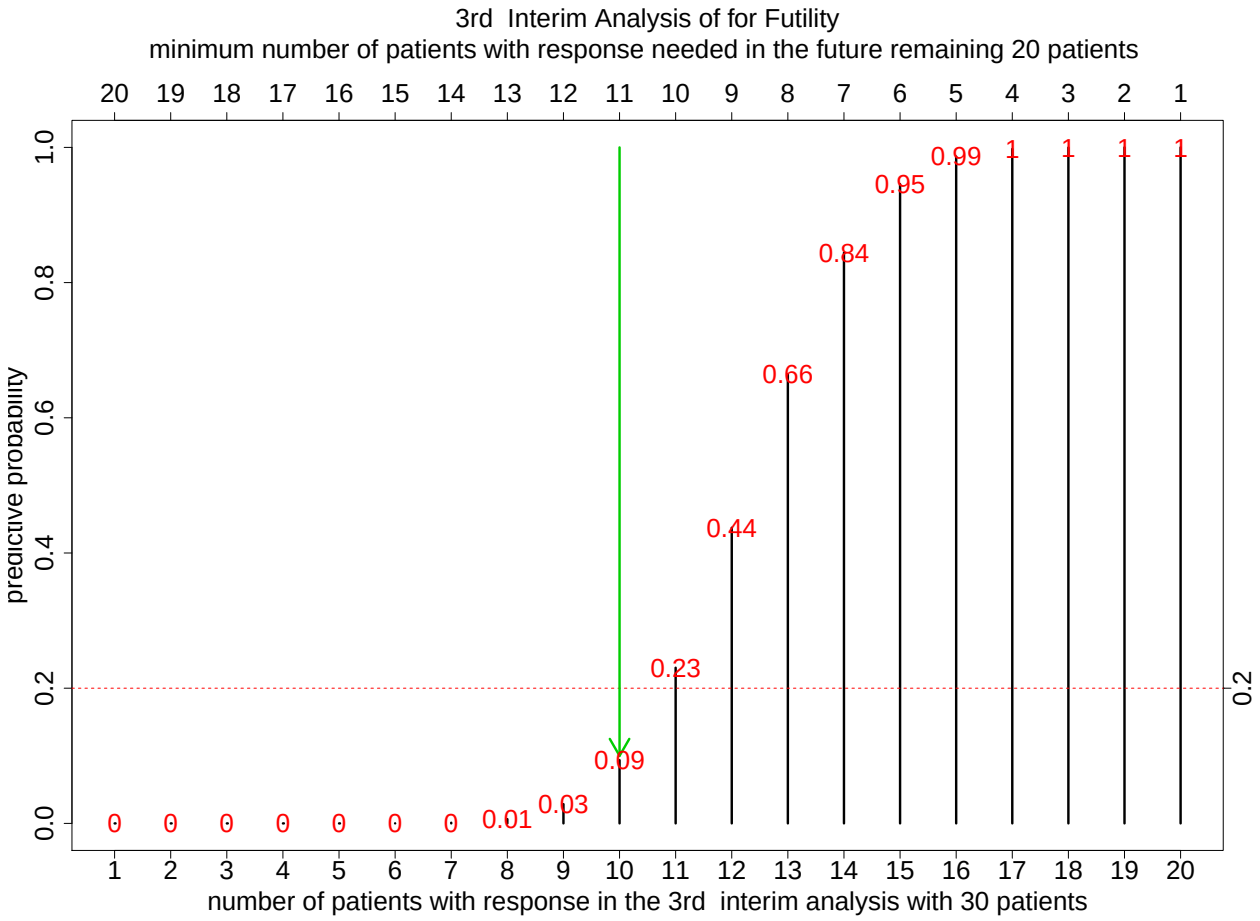
Table 7: Sensitivity Analysis: Beta Prior Distribution

	beta.a	beta.b	PET	typeI	power
0/0	0.00	0.00	0.92	0.03	0.75
0/1	0.00	1.00	0.94	0.03	0.72
1/0	1.00	0.00	0.87	0.06	0.86
1/1	1.00	1.00	0.91	0.04	0.83
0.3 (SD=0.05)	24.90	58.10	1.00	0.00	0.13
0.3 (SD=0.1)	6.00	14.00	0.98	0.01	0.52
0.3 (SD=0.2)	1.27	2.97	0.94	0.03	0.72
0.3 (SD=0.3)	0.40	0.93	0.92	0.03	0.75
0.5 (SD=0.2)	2.62	2.62	0.87	0.06	0.86
0.5 (SD=0.3)	0.89	0.89	0.91	0.04	0.83

Figure 1: Bayesian Predictive Probability for Stopping Rule




2nd Interim Analysis of for Futility
minimum number of patients with response needed in the future remaining 30 patients
21 20 19 18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1
predictive probability
0.0 0.2 0.4 0.6 0.8 1.0
0 0 0 0 0.01 0.03 0.11 0.25 0.47 0.69 0.86 0.95 0.99 1 1 1 1 1 1 1 1
0.2
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
number of patients with response in the 2nd interim analysis with 20 patients


3rd Interim Analysis of for Futility
minimum number of patients with response needed in the future remaining 20 patients
20 19 18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1
predictive probability
0.0 0.2 0.4 0.6 0.8 1.0
0 0 0 0 0 0 0 0.01 0.03 0.09 0.23 0.44 0.66 0.84 0.95 0.99 1 1 1 1
0.2
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
number of patients with response in the 3rd interim analysis with 30 patients

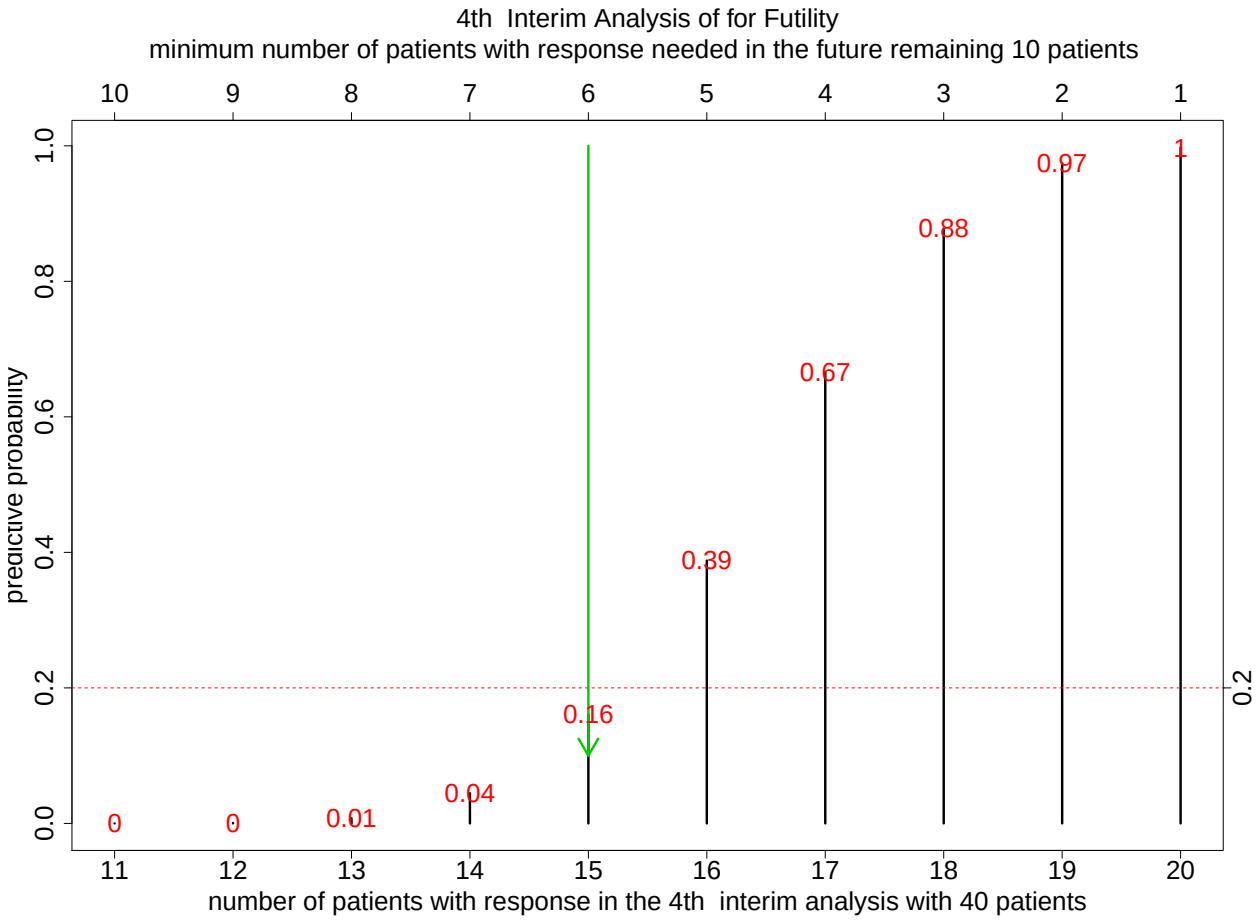

4th Interim Analysis of for Futility
minimum number of patients with response needed in the future remaining 10 patients
10 9 8 7 6 5 4 3 2 1
predictive probability
1.0 0.8 0.6 0.4 0.2 0.0
0.2
0 0 0.01 0.04 0.16 0.39 0.67 0.88 0.97 1
11 12 13 14 15 16 17 18 19 20
number of patients with response in the 4th interim analysis with 40 patients

Figure 2: Performance (Probability of Early Termination (PET), Type I error, and Power)

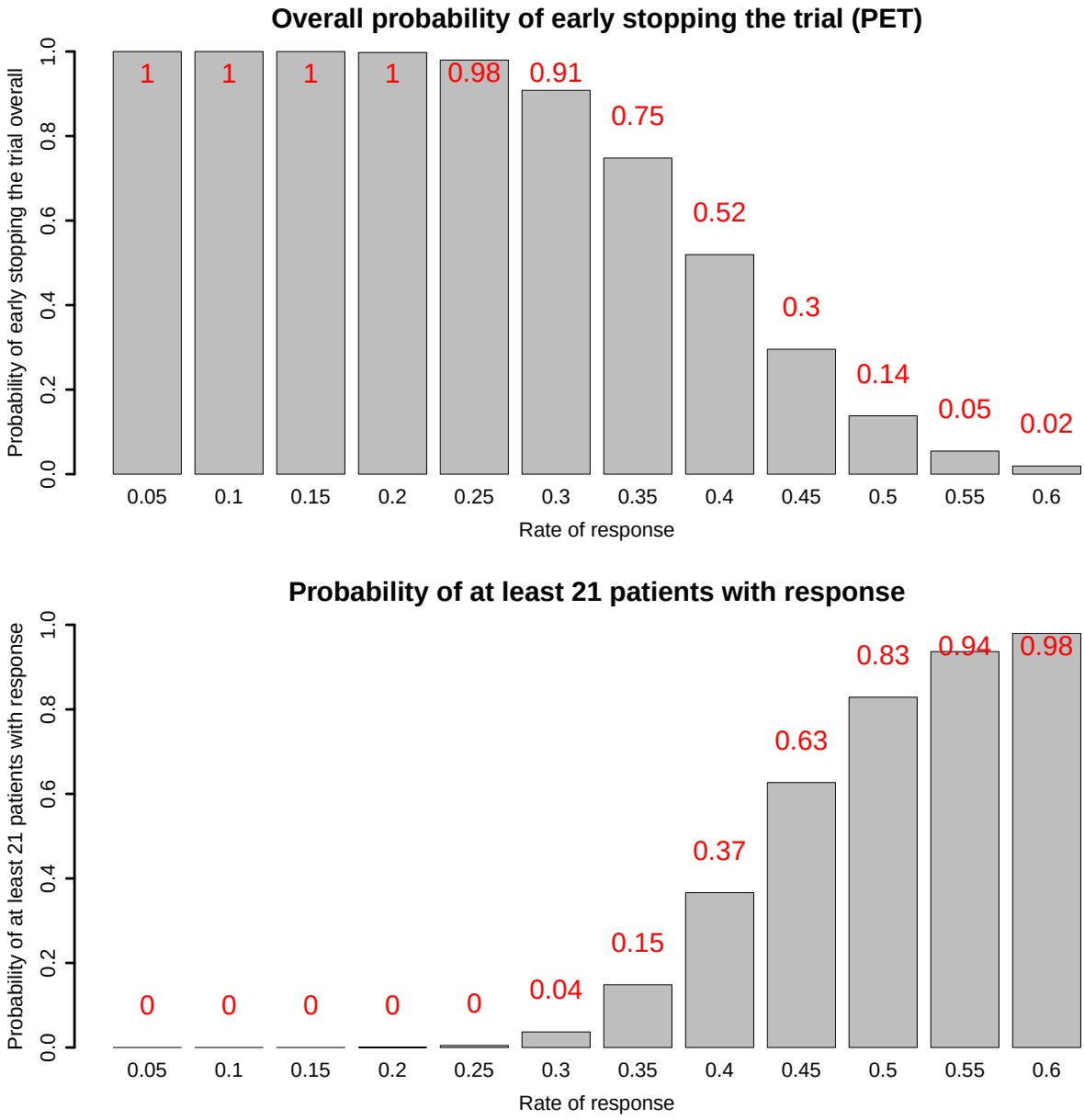
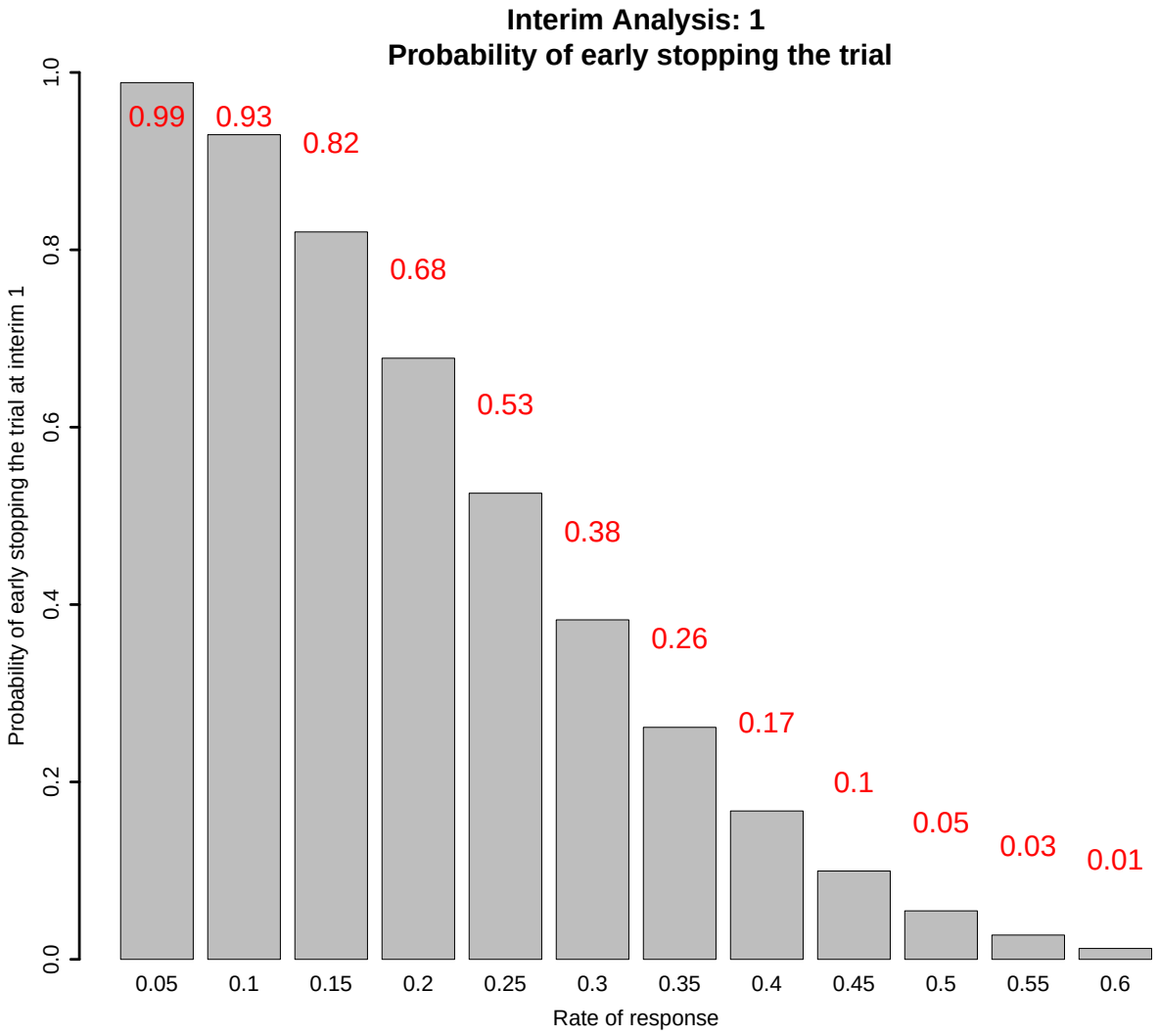
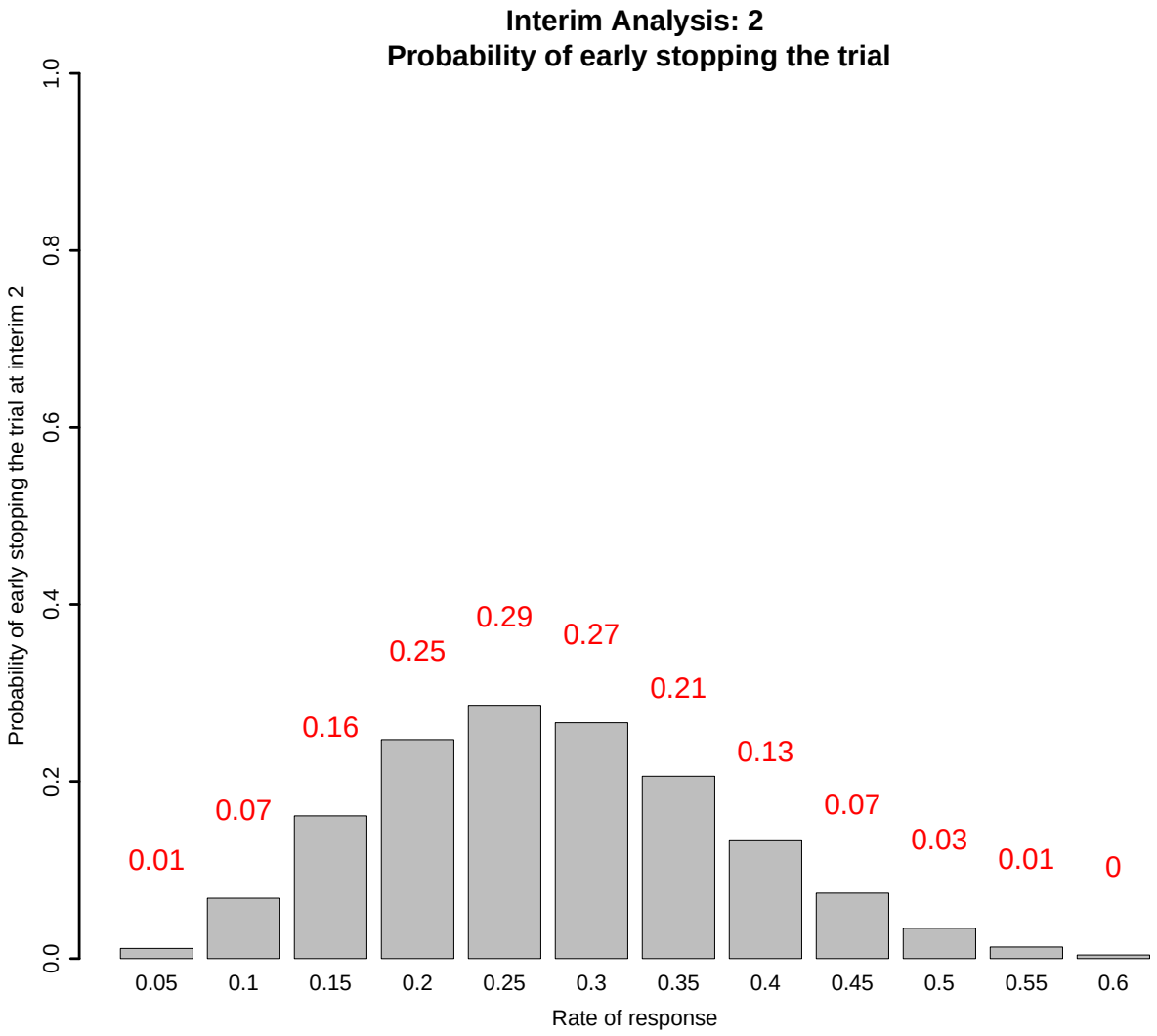
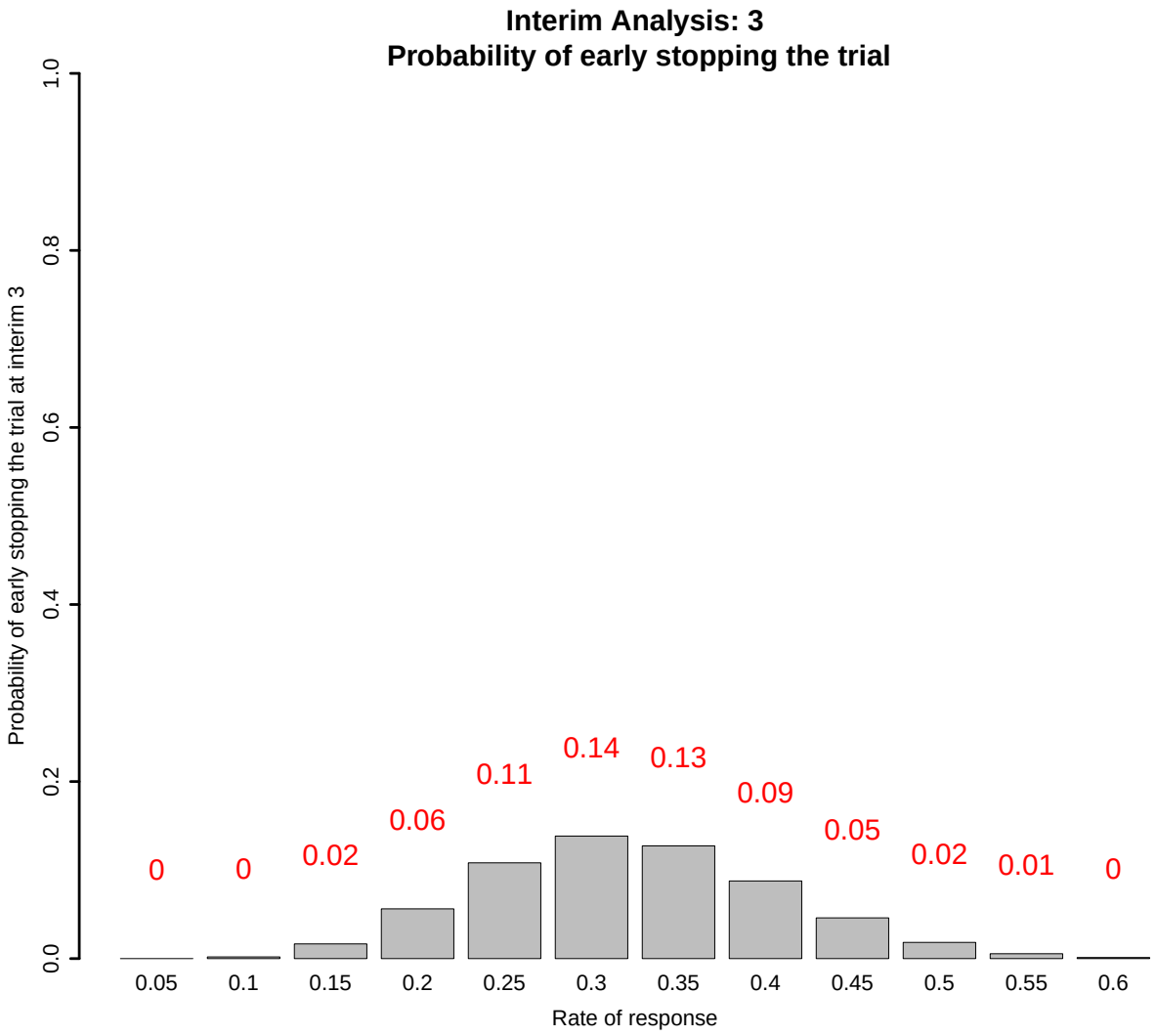


Figure 3: Probability of Early Stopping by Each Interim Analysis




Interim Analysis: 2
Probability of early stopping the trial
Probability of early stopping the trial at interim 2
0.0
0.2
0.4
0.6
0.8
1.0
0.01
0.07
0.16
0.25
0.29
0.27
0.21
0.13
0.07
0.03
0.01
0
0.05
0.1
0.15
0.2
0.25
0.3
0.35
0.4
0.45
0.5
0.55
0.6
Rate of response


Interim Analysis: 3
Probability of early stopping the trial
Probability of early stopping the trial at interim 3
0.0
0.2
0.4
0.6
0.8
1.0
0
0
0.02
0.06
0.11
0.14
0.13
0.09
0.05
0.02
0.01
0
0.05
0.1
0.15
0.2
0.25
0.3
0.35
0.4
0.45
0.5
0.55
0.6
Rate of response

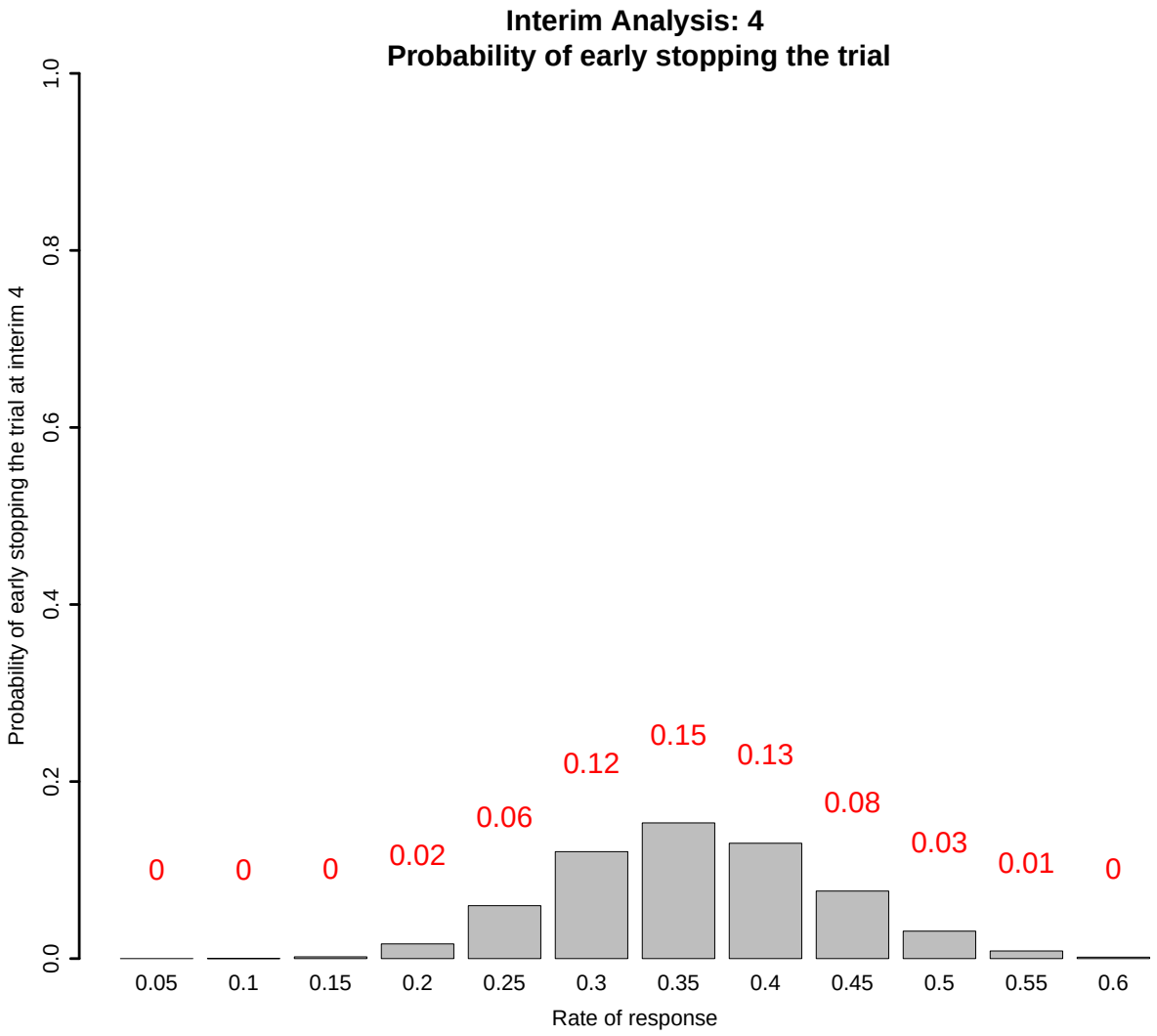

Interim Analysis: 4
Probability of early stopping the trial
Probability of early stopping the trial at interim 4
0.0
0.2
0.4
0.6
0.8
1.0
0
0
0
0.02
0.06
0.12
0.15
0.13
0.08
0.03
0.01
0
0.05
0.1
0.15
0.2
0.25
0.3
0.35
0.4
0.45
0.5
0.55
0.6
Rate of response

Figure 4: Sensitivity Analysis: Predictive Probability

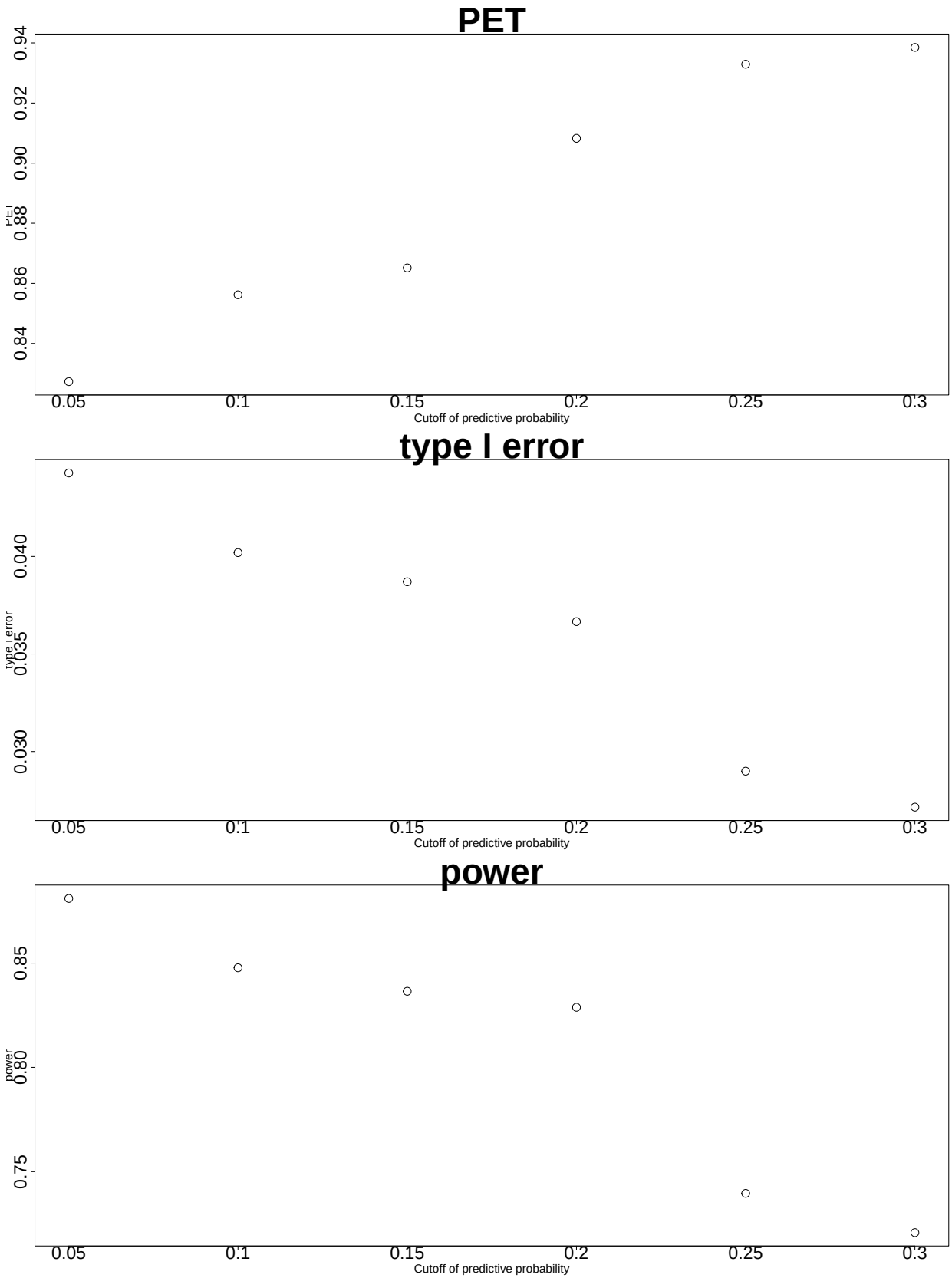


Figure 5: Sensitivity Analysis: Posterior Probability

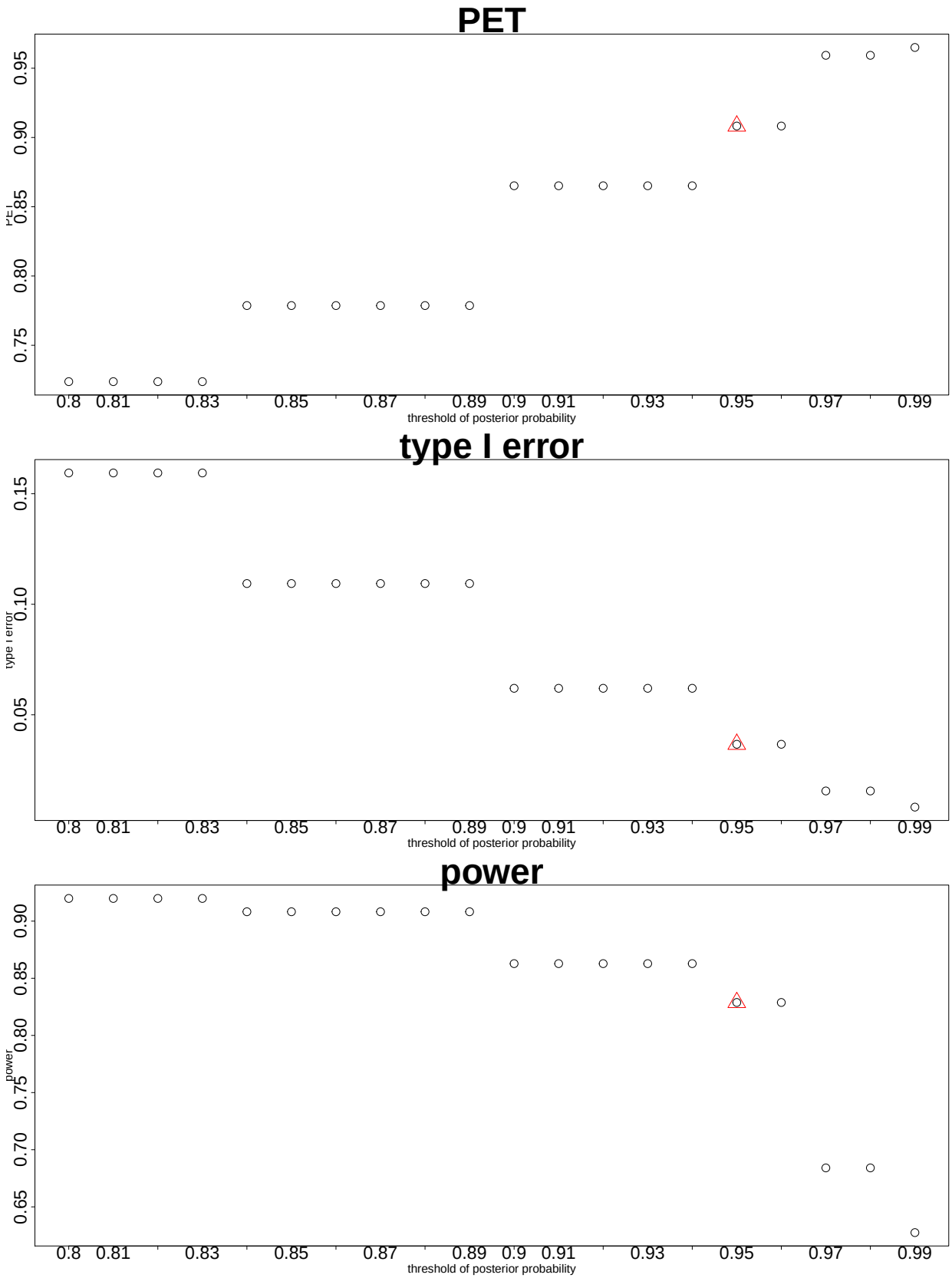


Figure 6: Sensitivity Analysis: Sample Size

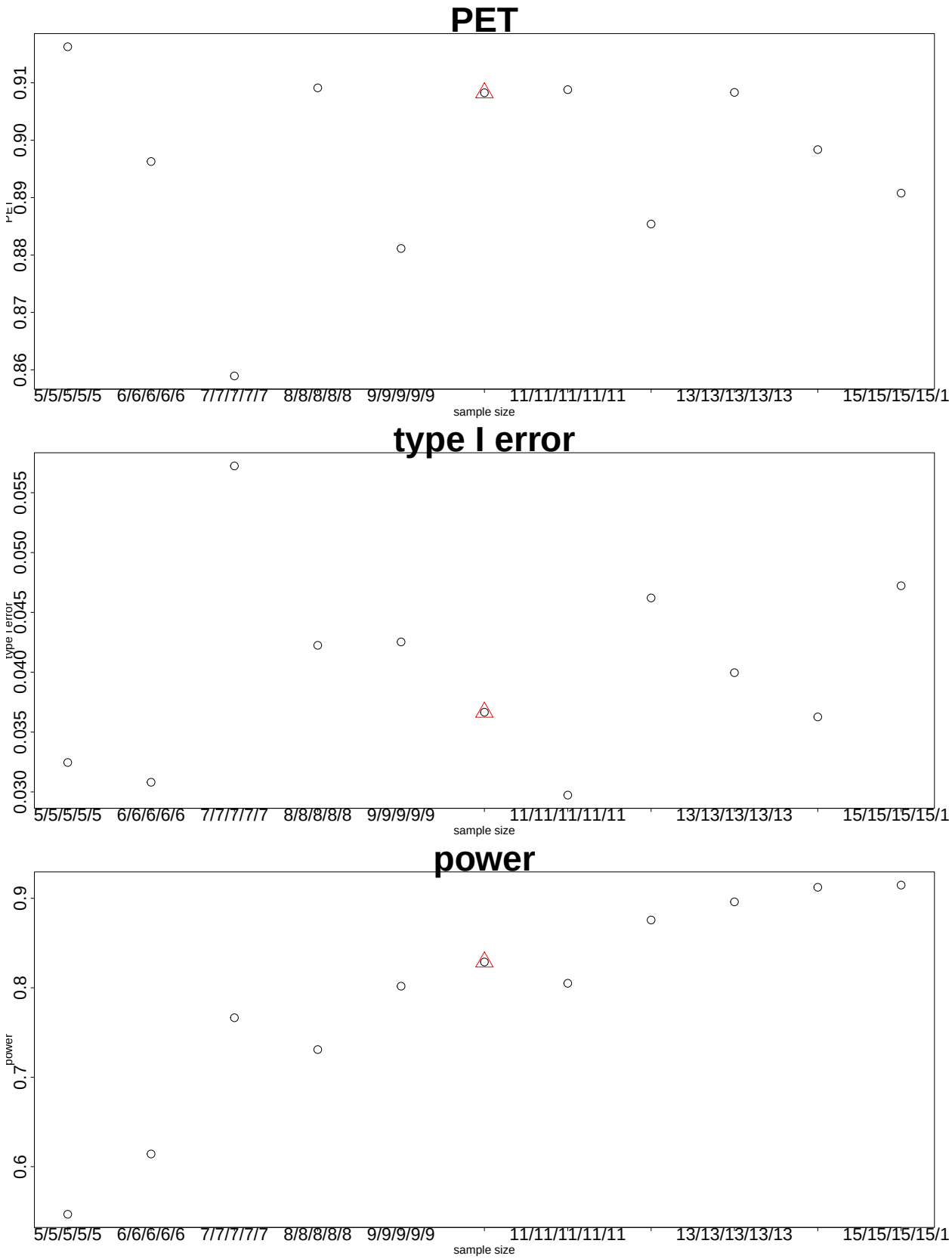
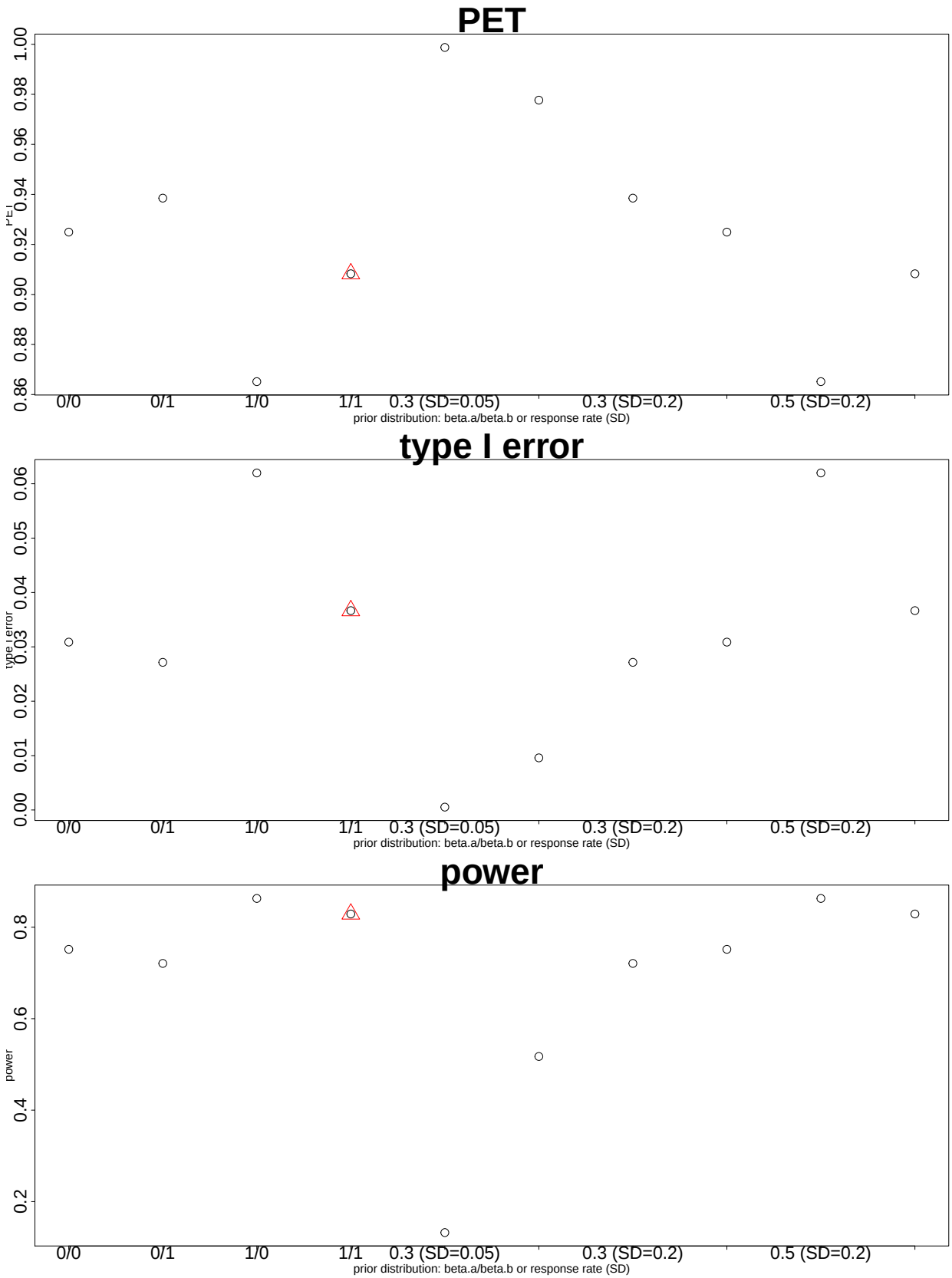


Figure 7: Sensitivity Analysis: Beta Prior Distribution



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