A Predictive Probability Design Software for Phase II Cancer Clinical Trials Version 1.0.0

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1. Calculation Method

The calculation method used in this software is based on the publication:

Lee JJ, Liu DD. A predictive probability design for phase II cancer clinical trials. *Clinical Trials.* **5(2):**93-106. 2008

2. Calculation Implementation

Under the hypothesis testing framework, a phase IIA clinical trial is designed to test

H_0: $p \le p_0$

H_1: $p \ge p_1$

where p is the unknown response rate, p_0 represents a pre-specified response rate of the standard treatment and p_1 represents a target response rate of a new treatment. A study is designed such that

$Prob(Accept\ New\ Treatment \mid H_0) = \alpha$

and $Prob(Reject\ New\ Treatment \mid H_1) = \beta$

where α and β are type I and type II error rates, respectively. Given p_0, p_1, the maximum number of patients, number of stages, cohort size of each cohort at each stage, acceptance region and rejection region for each cohort, the type I and type II error rates, the probability of early termination (*PET*) of the trial and the expected sample size (*E(N)*) under H_0 can be calculated by applying the recursive formulas of Schultz et al. (1973).

In the Bayesian approach, we assume that the prior distribution of the response rate $\pi(p)$ follows a beta distribution, $beta(a_0, b_0)$. It represents the investigator's previous knowledge or belief of the efficacy of the new regimen. The quantity $a_0 / (a_0 + b_0)$ reflects the prior mean while size of $a_0 + b_0$ indicates how informative the prior is. The larger the value of $a_0 + b_0$, the more informative the prior and the stronger the belief it contains. We set a maximum accrual of patients to N_{max}. We assume the number of observed

responses in the current n ($n \leq N_{max}$) patients, X, follows a binomial distribution, $binomial(n, p)$, and the likelihood function for the observed data x is

$$L_x(p) \propto p^x \times (1-p)^{n-x}$$

Consequently, the posterior distribution of the response rate follows a beta distribution

$$P|x \sim beta(a_0 + x,\ b_0 + n - x)$$

Thus, the number of responses in the potential $m=N_{max}-n$ future patients, Y, follows a beta-binomial distribution, $beta\text{-}binomial(m, a_0 + x, b_0 + n - x)$.

When $Y=i$, we denote the posterior probability of P as $f(p|x, Y=i)$, where

$$P|x, Y=i \sim beta(a_0 + x + i,\ b_0 + N_{max} - x - i)$$

To calculate the predictive probability, we further define

$$B_i = Prob(P > p_0 \mid x)$$

which measures the probability that the response rate is larger than p_0 given x responses in n patients in the current data and i responses in m patients in the future. Comparing B_i to a threshold value θ_T yields an indicator I_i for considering that the treatment is efficacious at the end of the trial given the current data and the potential outcome of $Y=i$.

We define

$$\begin{aligned} Predictive\ Probability\ (PP) &= \sum_{i=0}^{m} \{Prob(Y=i \mid x) \times (Prob(P > p_0 \mid x, Y=i) > \theta_T)\} \\ &= \sum_{i=0}^{m} \{Prob(Y=i \mid x) \times I(B_i > \theta_T)\} \\ &= \sum_{i=0}^{m} \{Prob(Y=i \mid x) \times I_i\} \end{aligned}$$

where $Prob[Y=i \mid x]$ is the probability of observing i responses in future m patients given current data x. The weighted sum of indicator I_i over Y yields the predictive probability (PP) of concluding a positive result by the end of the trial based on the cumulative information in the current stage. A high PP means that the treatment is likely to be efficacious by the end of the study given the current data, whereas a low PP suggests that the treatment may not have sufficient activity. Therefore, PP can be used to determine whether the trial should be stopped early due to efficacy/futility or continued because the current data are not yet conclusive. The decision rules can be constructed as follows:

If $PP < \theta_L$, then stop the trial and reject the alternative hypothesis;

If $PP > \theta_U$, then stop the trial and reject the null hypothesis;

Otherwise continue to the next stage until reaching N_{max} patients.

Typically, we choose θ_L as a small positive number and θ_U as a large positive constant, both between 0 and 1 (inclusive). $PP < \theta_L$ indicates that it is unlikely the response rate will be larger than p_0 at the end of the trial given the current information. When this happens, we may as well stop the trial and reject the alternative hypothesis at that point. On the other hand, when $PP > \theta_U$, the current data suggest that if the same trend continues, we will have a high probability to conclude that the treatment is efficacious at the

end of the study. This result, then, provides evidence to stop the trial early due to efficacy. By choosing $\theta_L>0$ and $\theta_U<1.0$, the trial can terminate early due to either futility or efficacy. For phase IIA trials, we prefer to choose $\theta_L>0$ and $\theta_U=1.0$, to allow early stopping due to futility, but not due to efficacy.

3. Software

The software helps users search for ranges of θ_L and θ_T that yield the highest power at a maximum allowed type I error rate. After the software installation, user can launch the software by clicking the "Phase II PP" icon on the desktop or from Start/All programs/M.D. Anderson Cancer Center/Phase II PP. When the license window appears and user clicks the "Accept" button, the software main calculation window appears (Figure 1). User can click blue labels on input boxes to get the corresponding input explanation in the help box.

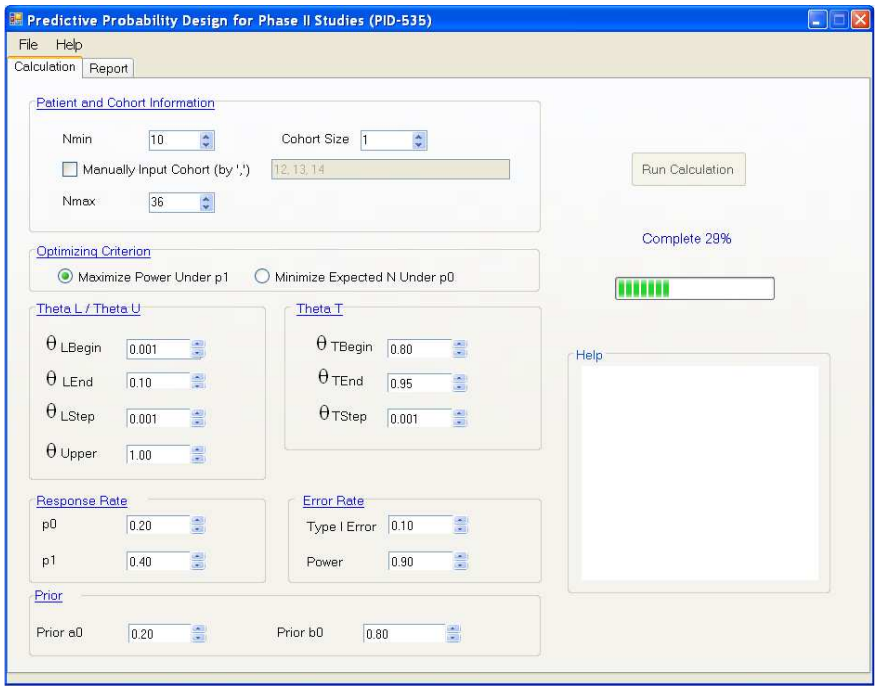

Figure 1 Software main calculation window

The input parameters on the main calculation window are

Parameters on the window	Explanation
Nmin	the number of patients in the first cohort being evaluated for response when *PP* interim decision starts to be implemented
Cohort Size	cohort size
Nmax	maximum sample size N_{max}

Manually input Cohort	users can also manually input the cohort to be evaluated by specifying the numbers are separated by ",". If user chose this option, the interim monitoring will be performed at these points. For instance, input "12,13,14" means that interim monitoring will be carried out after patient 12, 13 and 14.
Maximize Power Under p1	If there are many solutions satisfying the constraints, the program select the one with the maximum power value.
Minimize Expected N Under p0	If there are many solutions satisfying the constraints, the program select the one with the minimum expected sample size under the null hypothesis.
θ_L Begin	minimum value of the searching range for θ_L, threshold of early futility stopping.
θ_L End	maximum value of the searching range for θ_L
θ_L Step	grid size of the searching range for θ_L
θ_T Begin	minimum value of the searching range for θ_T
θ_T End	maximum value of the searching range for θ_T
θ_T Step	grid size of the searching range for θ_T
p0	response rate of the standard treatment p_0,
p1	target response rate of the new treatment p_1,
Prior a_0	the first parameter for prior distribution *beta(a_0, b_0)*
Prior b_0	the second parameter for prior distribution *beta(a_0, b_0)*
Type I error	nominal level of type I error rate
Power	nominal level of power
θ Upper	θ_U, threshold of early efficacy stopping.

When designing a trial, with p_0, p_1, *prior*, n, θ_U and the nominal level of type I error rate and power fixed, the searching algorithm finds ranges of θ_L and θ_T under an N_{max} that generates a boundary with the highest power under allowed type I error rate or the minimum expected sample size under the null hypothesis. We search over a range of total sample size N_{max}.

After the user inputs all parameters and clicks the run calculation button, the calculation process starts and the progress bar will illustrate the calculation progress. After the whole calculation is finished, the result table will appear (Figure 2). User can click the "Save Output File" button to save the results into a txt file.

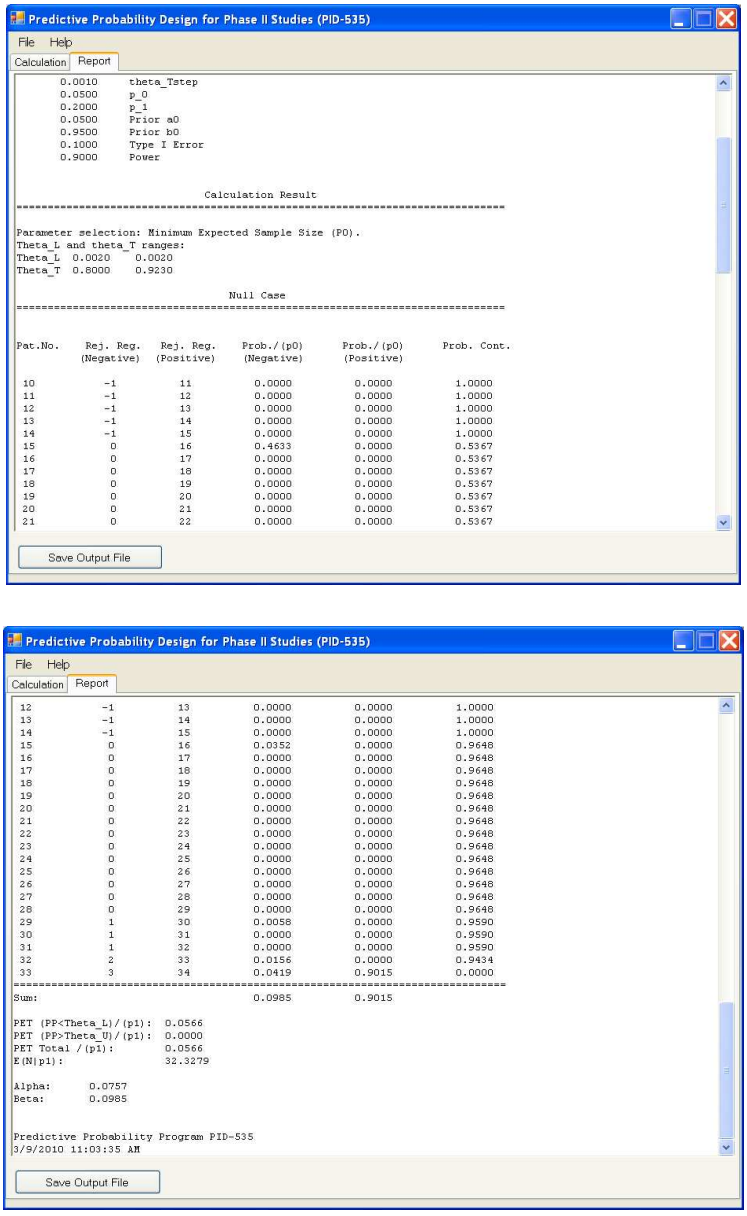

Figure 2 Calculation Result

The calculation results includes

Results	Explanation
theta_L and theta_T Range	suitable ranges of θ_L and θ_T under an N_{max} that satisfies the constrained Type I and Type II error rates
Rejection Reg.	There are two rejection regions. The first one is the maximum number of patients with positive response to terminate a trial. If the number of responses is less or equal to this boundary, stop the trial and reject the alternative hypothesis. The second one is the minimum number of patients with positive response to terminal a trial and claim to reject to null hypothesis.

Prob. / (p0) Negative	probability of making the negative decision under the null hypothesis
Prob. / (p0) Positive	probability of making the positive decision under the null hypothesis
Prob. Cont. / (p0)	probability of continuing the trial under the null hypothesis
Prob. / (p1) Negative	probability of making the negative decision under the alternative hypothesis
Prob. / (p1) Positive	probability of making the positive decision under the alternative hypothesis
Prob. Cont. / (p1)	probability of continuing the trial under the alternative hypothesis
PET (PP<Theta_L)	probability of early termination (PP<θ_L
PET (PP>Theta_U)	probability of early termination (PP>θ_U)
PET Total	total probability of early termination
E(N)	expected number of patients under the null hypothesis
Alpha	highest Type I error rate within the suitable ranges of θ_L and θ_T
Beta	lowest Type II error rate within the suitable ranges of θ_L and θ_T

Reference:

1. Lee JJ, Liu DD. A predictive probability design for phase II cancer clinical trials. Clinical Trials. **5(2):**93-106. 2008
2. Schultz JR, Nichol FR, Elfring GL, Weed SD: Multiple-stage procedures for drug screening. Biometrics **29**:293-300, 1973.

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