**DATE:** \*\*\*

**TO:**  \*\*\*, MD

Department of \*\*\*

**FROM:** \*\*\*

Department of Biostatistics

**SUBJECT:** Statistical design of trial “Phase II study of \*\*\* (name of the treatment) for \*\*\* (name of the disease)”.

STATISTICAL CONSIDERATIONS

This is an open label, phase II clinical trial to evaluate the efficacy and safety of \*\*\* (name of the treatment) given to patients with \*\*\* (name of the disease). The overall response, denoted as OR (to be assessed at \*\*\* (the point at which it is assessed)), and toxicity will be monitored simultaneously in cohorts of \* patients using the Bayesian approach of Thall, Simon, Estey (1995, 1996) as extended by Thall and Sung (1998). Toxicity is defined as \*\*\* (definition of toxicity, such as graded events). Historical data on similar patients show an overall response rate of \*\*% and toxicity rate of \*\*%. This information was given an Effective Sample Size of \*\*\* (should be large, such as 100 or more) patients. Independence was assumed between OR and toxicity. It is expected for the current trial that \*\*\* (name of the treatment) will improve the OR rate to \*\*% while the toxicity rate is maintained at \*\*%. A sample size of \*\* patients ensures that, if the trial is not terminated early, a posterior 90% credibility interval for overall response rate will have width of 0.\*\* at most, under the assumption of an \*\*% of overall response rate. The probabilities of OR and toxicity for the historical data are modeled by beta distributions (*Beta*(\*\*, \*\*) and *Beta*(\*\*, \*\*), respectively). The prior probabilities of OR and toxicity for the experimental regimen are also modeled by beta distributions (*Beta*(\*.\*, \*.\*) and *Beta*(\*.\*, \*.\*), respectively), which have the same *means* as the corresponding beta distributions for the historical data, and an Effective Sample Size of \* (should be small, such as 1). Denoting the historical probabilities of overall response rate and toxicity rate by {p(OR,H) , p(TOX,H)}, the following decision criteria will be applied:

1. Let E correspond to the experimental treatment, stop if

Prob{p(OR,H) + δOR > p(OR,E) | data} > 0.\*\*, where δOR =0.\*

1. Stop if Prob{p(TOX,H) + δTOX < p(TOX,E)| data}>0.\*\*, where δTOX =0.\*

Patients will be monitored according to the following stopping boundaries for overall response.

\*\*\* (insert the stopping boundary table for Response here)

At the same time, patients will be monitored according to the following stopping boundaries for toxicity.

\*\*\* (insert the stopping boundary table for Toxicity here)

The operating characteristics are summarized in the following table. The probabilities of stopping the trial early are exact calculations. \*\*\* (information from MultcLean Desktop about the average numbers of patients treated and the average numbers of responses and toxicities are also exact; the average trial durations if calculated are based on 10,000 simulations)

|  |  |  |
| --- | --- | --- |
| True Toxicity Rate | True OR Rate | Prob(stop the trial early) |
| 0.\*\* | 0.\*\* | 0.\*\* |
|  | 0.\*\* | 0.\*\* |
|  | 0.\*\* | 0.\*\* |
|  | 0.\*\* | 0.\*\* |
| 0.\*\* | 0.\*\* | 0.\*\* |
|  | 0.\*\* | 0.\*\* |
|  | 0.\*\* | 0.\*\* |
|  | 0.\*\* | 0.\*\* |
| 0.\*\* | 0.\*\* | 0.\*\* |
|  | 0.\*\* | 0.\*\* |
|  | 0.\*\* | 0.\*\* |
|  | 0.\*\* | 0.\*\* |
| 0.\*\* | 0.\*\* | 0.\*\* |
|  | 0.\*\* | 0.\*\* |
|  | 0.\*\* | 0.\*\* |
|  | 0.\*\* | 0.\*\* |
| 0.\*\* | 0.\*\* | 0.\*\* |
|  | 0.\*\* | 0.\*\* |
|  | 0.\*\* | 0.\*\* |
|  | 0.\*\* | 0.\*\* |

## Analysis Plan

# Summary statistics will be provided for continuous variables. Frequency tables will be used to summarize categorical variables. Logistic regression will be utilized to assess the effect of patient prognostic factors on the response rate and the toxicity rate. The distribution of time-to-event endpoints will be estimated using the method of Kaplan and Meier. Comparison of time-to-event endpoints by important subgroups will be made using the log-rank test. Cox proportional hazard regression will be employed for multivariate analysis on time-to-event outcomes.

# References

Thall, PF, Simon, R, Estey, EH: Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. *Statistics in Medicine* 14:357-379, 1995.

Thall, PF, Simon, R, Estey, EH: New statistical strategy for monitoring safety and efficacy in single-arm clinical trials. *J. Clinical Oncology* 14:296-303, 1996.

Thall, PF and Sung, H-G: Some extensions and applications of a Bayesian strategy for monitoring multiple outcomes in clinical trials. *Statistics in Medicine* 17:1563-1580, 1998.

# Appendix \*\*\* (Insert the scenario output file, pasted in with “keep source formatting” option)