U.S. FOOD & DRUG ADMINISTRATION

Example Statistical Analysis Plan for Supplemental Bayesian Analysis: Unification of Evidence

Overview

When a clinical trial has multiple endpoints that are not easily combined into a single ordinal scale, it is standard practice to analyze the endpoints separately, providing separate evidence for treatment effect on each endpoint. Then the results are informally combined to judge overall evidence for treatment benefit. The Bayesian approach has a potential advantage of allowing investigators and regulatory authorities to define the condition that would determine therapeutic success, then computing the Bayesian posterior probability that the condition is satisfied.

Study Design

Study XY-02 is a double-blind parallel-group two-treatment randomized controlled trial of drug (group B) vs. placebo (group A). The primary analysis is intent-to-treat and the outcomes are survival time (with follow-up up to three years), infection (within 90 days), and patient performance status (within 30 days; PS). The disease setting is a high mortality one, and infections and PS are frequently not assessable as a result. So death is counted in both outcomes by making it the highest level of the ordinal outcome. The infection outcome thus has 3 levels (alive and infection-free for 90 days, alive and infection within 90 days, death), and PS has 6 levels. One could say that these outcomes are infection penalized for death and PS penalized for death.

A Bayesian approach provides a unique opportunity to state the condition that would change clinical practice, then to compute the probability the condition is satisfied. The condition can represent a compound assertion. For drug B, success is taken to be that the drug is superior on mortality, or non-inferior on mortality and superior on either infections or PS. The condition for success is then $A \cup \left(B \cap (C \cup D)\right)$ using the definitions below, and letting HR be a hazard ratio and OR be an odds ratio:

- $\cup$ = union (or)
- $\cap$ = intersection (and)
- A = any reduction in mortality (HR < 1.0)
- B = a reduction or only a small increase in mortality (HR < 1.1)
- C = a reduction in infection (OR < 1)
- D = an improvement in PS (OR < 1)

Statistical Analysis

A flexible Bayesian proportional hazards model will be used to analyze the drug effect on survival time. The other two endpoints will be analyzed with proportional odds models. The prior distributions for log (HR) and log (OR) will be normal with mean zero and variance chosen

to reflect the unlikeliness of very large benefits or very large harms, i.e., probabilities of only 0.025 that HR or OR exceed 4 or that they are less than $\frac{1}{4}$.

Within-patient correlations among the 3 outcomes will be modeled using either a Gaussian copula or by having separate subject-level random effects for each outcome, with these random effects having a multivariate normal distribution with correlations between-outcomes

The Bayesian posterior probability of success on the combination of three endpoints will be computed from the fraction of posterior draws for which the success criterion was met for the three efficacy parameters. Note that Bayesian power and required sample size can be computed by simulation.

Bayesian posterior probabilities of benefit (and non-inferiority for mortality) will also be computed, and 0.95 highest posterior density uncertainty intervals computed for the HR and two ORs.

Software

The three connected outcome models and their dependencies will be coded in Stan. Example code will be added at a later date.

Bayesian Markov Chain Monte Carlo simulation will be run in four independent chains with 4000 iterations per chain. Diagnostics including trace plots and Rhat value will be used to check for convergence of posterior distributions.