Example Statistical Analysis Plan for Supplemental Bayesian Analysis Demonstration Project: Parallel-Group Trial with a Continuous Outcome

Study Design

Study XY-01 is a double-blind parallel-group two-treatment randomized controlled trial of drug (group B) vs. placebo (group A) in acute hypertension in an emergency department setting. The primary analysis is intent-to-treat and the primary response variable is systolic blood pressure (SBP) measured at 2 hours post randomization.

Statistical Analysis

Note: In practice the test below would be replaced with analysis of covariance adjusted for baseline SBP. For simplicity in this example, baseline SBP is not included in the statistical model.

The Bayesian t test will be used to quantify the evidence for effectiveness of drug B in reducing SBP, specifically by computing the posterior probability that the B-A SBP difference is negative. As a secondary assessment, the posterior probability that the reduction exceeds 3mmHg will be computed. The analysis does not assume that the SBP variances are equal in the two treatment groups, and puts a prior on their ratio, favoring equality but allowing for inequality. The analysis does not assume that SBP is normally distributed, instead assuming the raw data come from a t distribution with ν degrees of freedom. This allows the data to be heavier-tailed than the normal distribution. When $\nu > 20$ the distribution is effectively normal. A gamma prior distribution is assumed for ν.

The prior distribution for the difference Δ in mean SBP was developed during a meeting between the sponsor and FDA statistical and medical reviewers. The chosen prior is such that a reduction and an increase are equally likely (the mean of the prior is zero) and such that it is very unlikely to achieve a reduction > 15mmHg or < -15mmHg. Specifically, the prior is chosen as normal with standard deviation (SD) σ chosen such that $\Pr(\Delta < -15) = \Pr(\Delta > 15) = 0.025$. This implies $\sigma = \frac{15}{\Phi^{-1}(0.975)} = \frac{15}{1.95996} = 7.653$.

Letting r denote the ratio of variances for the two treatment groups, assume a mean-zero normal prior for $\log(r)$ with standard deviation chosen so that $\Pr(r > 1.5) = \Pr\left(r < \frac{1}{1.5}\right) = 0.05$. The required SD is $\frac{\log(1.5)}{\Phi^{-1}(0.95)} = 0.2465$.

The prior for the degrees of freedom ν in the normal data distribution is gamma (2, 0.1), which is the default in the software setup below.

When the analysis is completed, secondary parameters will be summarized as well as the treatment effect parameter. This will assist in future study planning. Secondary assessments will include the posterior $\Pr\left(r > 1.5 \text{ or } r < \frac{1}{1.5}\right)$ and $\Pr(\nu > 20)$. The latter posterior probability is essentially the probability of normality of SBP.

A secondary analysis will be done to assess evidence for an age-dependent treatment effect. Age and age-squared and their interactions with treatment will be added to the model, with flat priors for the associated parameters. Evidence for heterogeneity of treatment effect due to varying age will be taken as a high posterior probability that the treatment effect evaluated at the lower quartile of age is greater than the treatment effect evaluated at the upper age quartile (this is not a subgroup analysis). This posterior probability is computed by the proportion of posterior draws for which the above difference is positive.

Software

The R brms package[1] brm function will be used for the analysis. Since both the mean and variance are allowed to change with treatment, a double model is specified. Prototypical code is below.

```
# flat (non-informative) prior for intercept
pr0 <- set_prior("", class="Intercept")
# normal(0, 7.653) prior for difference in mean SBP
pr1 <- set_prior("normal(0, 7.653)", class="b", coef="txB")
# normal(0, 0.2465) for log SD ratio
pr2 <- set_prior("normal(0, 0.2465)", class="b", coef="txB",
                 dpar="sigma")

brm(bf(sbp   ~ tx,
       sigma ~ tx),
       family=student, prior=c(pr0, pr1, pr2))
```

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.

[1] Paul-Christian Bürkner (2017). brms: An R Package for Bayesian Multilevel Models Using Stan. Journal of Statistical Software, 80(1), 1-28. doi:10.18637/jss.v080.i01