Supplementary Appendix 1. Asymptotic Relative Efficiency (ARE)

Calculation of ARE for multiple observations in parallel design

Let $Var\{b_2\}$ be the variance of the random slope, σ^2 be the variance of the residual errors, T be the followup time, N be the total sample size, the patients with i = 1, ..., $\frac{N}{2}$ are assigned to control and the remainder are assigned to treatment, and assume there are k observations at baseline and end of study.

The treatment effect is the difference in annualized rate of change between treatment and control and is estimated by $\hat{\theta} = \frac{N}{2}\sum_{i=\frac{N}{2}+1}^{N} \frac{\frac{Y_{i,k+1}+\cdots+Y_{i,2k}}{k} - \frac{Y_{i,1}+\cdots+Y_{i,k}}{k}}{T} - \frac{2}{N}\sum_{i=1}^{\frac{N}{2}} \frac{\frac{Y_{i,k+1}+\cdots+Y_{i,2k}}{k} - \frac{Y_{i,1}+\cdots+Y_{i,k}}{k}}{T}$. The null hypothesis is that the expected value of $\hat{\theta}$ is less than or equal to 0 and the one-sided alternative is that the expected value is greater than 0.

For a single subject, the variance of the annualized rate of change is

$$Var\left\{\frac{\frac{Y_{i,k+1}+\cdots+Y_{i,2k}}{k} - \frac{Y_{i,1}+\cdots+Y_{i,k}}{k}}{T}\right\}$$

$$= Var\left\{\frac{b_{2,i}T + \frac{\varepsilon_{i,k+1}+\cdots+\varepsilon_{i,2k}}{k} - \frac{\varepsilon_{i,1}+\cdots+\varepsilon_{i,k}}{k}}{T}\right\}$$

$$= Var\{b_{2,i}\} + \frac{2\sigma^2}{kT^2}$$

The variance of the estimated treatment effect is

$$Var\{\hat{\theta}\} = \left\{Var\{b_{2,i}\} + \frac{2\sigma^2}{kT^2}\right\}\frac{4}{N}$$

Thus, the ARE when k=2 relative to k=1 is $\frac{Var\{b_{2,i}\}+\frac{2\sigma^2}{T^2}}{Var\{b_{2,i}\}+\frac{\sigma^2}{T^2}}$

For the parameters used in the simulations, the ARE would be $\frac{6.6+\frac{2\times 5.8^2}{2^2}}{6.6+\frac{5.8^2}{2^2}} \approx 1.56$.

In other words, the design with only one measurement at baseline and at end of study would need about 56% more subjects than the design with two measurements at each time point to achieve the same power.

Calculation of ARE for crossover study with pooled test compared to parallel study

Assume one observation per time point and each period has duration T so that in the crossover study $t_{i,1}$=0, $t_{i,2}$=T, and $t_{i,3}$=2T. Also, assume the subjects are order so that the first $\frac{N}{2}$ subjects are in the placebo group in Period 1 while the remainder are in the experimental arm in Period 1. Furthermore, assume a constant rate of change in the placebo arm. The estimated treatment effect from the pooled data is

$$\hat{\theta}_p = N^{-1}\left\{\sum_{i=\frac{N}{2}+1}^{N}\left\{\frac{Y_{i,2}-Y_{i,1}}{T}\right\} - \sum_{i=1}^{\frac{N}{2}}\left\{\frac{Y_{i,2}-Y_{i,1}}{T}\right\} + \sum_{i=1}^{\frac{N}{2}}\left\{\frac{Y_{i,3}-Y_{i,2}}{T}\right\} - \sum_{i=\frac{N}{2}+1}^{N}\left\{\frac{Y_{i,3}-Y_{i,2}}{T}\right\}\right\}$$

$$= N^{-1}\left\{\sum_{i=\frac{N}{2}+1}^{N}\left\{\frac{2Y_{i,2}-Y_{i,1}-Y_{i,3}}{T}\right\} + \sum_{i=1}^{\frac{N}{2}}\left\{\frac{Y_{i,3}-2Y_{i,2}+Y_{i,1}}{T}\right\}\right\}$$

The expected value of $\hat{\theta}_p$ is β_2-$\frac{\beta_3}{2}$ where β_2 is the chronic effect on the slope and β_3 is the carryover effect. The variance of $\hat{\theta}_p$ is

$$(NT)^{-2}Var\left\{\left\{\sum_{i=\frac{N}{2}+1}^{N}\{2Y_{i,2}-Y_{i,1}-Y_{i,3}\}+\sum_{i=1}^{\frac{N}{2}}\{Y_{i,3}-2Y_{i,2}+Y_{i,1}\}\right\}\right\}$$

$$=(NT)^{-2}N\ Var\{2Y_{1,2}-Y_{1,1}-Y_{1,3}\}$$

$$=(NT)^{-2}N\ Var\left\{2\{b_{1,2}T+\varepsilon_{1,2}\}-\{\varepsilon_{1,1}\}-\{2b_{1,2}T+\varepsilon_{1,3}\}\right\}=\frac{6\sigma^2}{NT^2}$$

If there are k measurements at each time point, then the variance would be $\frac{6\sigma^2}{kNT^2}$. The ARE for the crossover design with pooled test statistic relative to the parallel design is

$$\frac{\left\{Var\{b_{2,i}\}+\frac{2\sigma^2}{kT^2}\right\}\frac{4}{N}\left(\beta_2-\frac{\beta_3}{2}\right)^2}{\beta_2{}^2}\frac{}{\frac{6\sigma^2}{kNT^2}}=\frac{2}{3}\left\{\frac{kT^2Var\{b_{2,i}\}}{\sigma^2}+2\right\}\left(1-\frac{\beta_3}{2\beta_2}\right)^2$$

Thus, if no carryover effect and with the parameters used in the simulation, the ARE is

$$\frac{2}{3}\left\{\frac{2\times 2^2\times 6.6}{5.8^2}+2\right\}\approx 2.38$$

If the carryover effect is ¼ of the treatment effect, then ARE is approximately 2.38 $\left(\frac{7}{8}\right)^2$≈1.82