# Web-Based Supplementary Materials for "Global Rank Tests for Multiple, Possibly Censored, Outcomes" by Ritesh Ramchandani, David Schoenfeld, and Dianne Finkelstein

## 1 Web Appedix A: Consistency of Variance Estimate in Equation (3)

We want to show that the variance estimate given in equation (3) is a consistent estimate of the asymptotic variance given in equation (2) under $H_0$. Consider the first term of the asymptotic variance, $\frac{1}{\lambda}E[\phi(\mathbf{r}_{ij})\phi(\mathbf{r}_{ij'})]$. Since we assume $\frac{N}{n} \to \frac{1}{\lambda}$, it suffices to show that $\hat{\xi}_1 \xrightarrow{p} \xi_1$, where $\hat{\xi}_1 = \frac{1}{nm^2}[\sum_i^n \sum_j^m \sum_{j' \neq j}^m \phi(\mathbf{r}_{ij})\phi(\mathbf{r}_{ij'})]$ and $\xi_1 = E[\phi(\mathbf{r}_{ij})\phi(\mathbf{r}_{ij'})]$. Observe that $U = \frac{2}{nm(m-1)} \sum_i^n \sum_j^m \sum_{j'<j}^m [\phi(\mathbf{r}_{ij})\phi(\mathbf{r}_{ij'})]$ is itself a U-statistic, and thus converges to the expected value of its kernel, which is $\xi_1$, under the condition that $\phi^4(\mathbf{r}_{ij}) < \infty$. We can rewrite $U$ as $\frac{1}{nm(m-1)} \sum_i^n \sum_j^m \sum_{j' \neq j}^m \phi(\mathbf{r}_{ij})\phi(\mathbf{r}_{ij'})$, which makes it easy to see that $\hat{\xi}_1$ is asymptotically equivalent to $U$, and thus converges to $\xi_1$. In a similar manner, we can show $\frac{N}{(nm)^2} \sum_i^n \sum_{i' \neq i}^n \sum_j^m \phi(\mathbf{r}_{ij})\phi(\mathbf{r}_{i'j}) \xrightarrow{p} \frac{1}{1-\lambda}E[\phi(\mathbf{r}_{ij})\phi(\mathbf{r}_{i'j})]$, which completes the proof.

## 2 Web Appendix B: Optimal Weights for Weighted Test Statistics

The proof follows the same argument given in Minas et al. [1] Let $\delta_w = \mathbf{w}'\boldsymbol{\theta}_\phi(\mathbf{w}'\boldsymbol{\Lambda}\mathbf{w})^{-1/2}$. As described in section 2.3, maximizing power corresponds to maximizing $\delta_w$ when $\boldsymbol{\theta}_\phi \geq 0$, or minimizing $\delta_w$ when $\boldsymbol{\theta}_\phi \leq 0$. Equivalently, we want to maximize $\delta_w^2$ with respect to $w$. The generalized Cauchy-Schwarz inequality states that for any positive-definite matrix $\Sigma$, $(\gamma' y)^2 \leq \gamma'\Sigma\gamma y'\Sigma^{-1}y$ [2, lemma 5.3.2]. It follows that if $\boldsymbol{\Lambda}$ is positive-definite, $\delta_w^2 \leq \dfrac{\mathbf{w}'\boldsymbol{\Lambda}\mathbf{w}\boldsymbol{\theta}_\phi'\boldsymbol{\Lambda}^{-1}\boldsymbol{\theta}_\phi}{\mathbf{w}'\boldsymbol{\Lambda}\mathbf{w}} = \boldsymbol{\theta}_\phi'\boldsymbol{\Lambda}^{-1}\boldsymbol{\theta}_\phi$. $\delta_w^2$ attains the maximum for $\mathbf{w} = \boldsymbol{\Lambda}^{-1}\boldsymbol{\theta}_\phi$.

## 3 Web Appendix C: ALS Simulation Model

We used a shared parameter model for generation of ALS and survival data in simulation scenario 2. Per Healy and Schoenfeld [3], the ALSFRS model is given by:

$$ALSFRS_{ij} = \beta_0 + \beta_1 \times time_{ij} + \beta_2 \times time_{ij} \times treat_i + b_{0,i} + b_{1,i} \times time_{ij} + \epsilon_{ij}$$

where the $\beta$ are fixed effects, the $b_i$ are patient specific random effects for subject $i$, and $e_{ij}$ are independent error terms that are normally distributed, i.e. $e_{ij} \sim N(0, 4.35)$. The $b_i$ follow a mean 0 bivariate normal distribution:

$$\begin{pmatrix} b_{0,i} \\ b_{1,i} \end{pmatrix} = N \begin{pmatrix} 0 & 28.38 & 0.79 \\ 0, & 0.79 & 0.71 \end{pmatrix}$$

The time to death outcome has a Weibull distribution with density $f(t) = \gamma\lambda t^{\gamma-1} exp(-\lambda t^{\gamma})$, where $\gamma = 2.28$, and $\lambda$ follows the model:

$$\lambda_i = exp[\epsilon_0 + \epsilon_1 \times (\beta_0 + b_{0,i}) + \epsilon_2 \times (\beta_1 + \beta_2 + b_{1,i}) + \epsilon_3 \times treat_i]$$

For these models, the following parameters were fixed:

- $\beta_0$ = 43.3; $\beta_1$ = -1.11
- $\epsilon_0$ = -7.55; $\epsilon_1$ = -.042; $\epsilon_2 = -1.39$

The parameters $\epsilon_3$ and $\beta_2$ are the treatment effect parameters for survival and ALSFRS, respectively. We varied these as follows:

| Effect Size | $\epsilon_3$ | $\beta_2$ |
|---|---|---|
| None | 0 | 0 |
| Mild | log(4/6) | 1/6 |
| Moderate | log(3/6) | 2/6 |
| Strong | log(2/6) | 3/6 |

## References


[1] Giorgos Minas, Fabio Rigat, Thomas E Nichols, John AD Aston, and Nigel Stallard. A hybrid procedure for detecting global treatment effects in multivariate clinical trials: theory and applications to fmri studies. *Statistics in medicine*, 31(3):253–268, 2012.

[2] Theodore Wilbur Anderson. *An introduction to multivariate statistical analysis*, volume 3. New York: Wiley-Interscience, 2003.

[3] Brian C Healy and David Schoenfeld. Comparison of analysis approaches for phase iii clinical trials in amyotrophic lateral sclerosis. *Muscle & nerve*, 46(4):506–511, 2012.