Applications of the Wei-Lachin Multivariate One-Sided Test for Multiple Outcomes on Possibly Different Scales
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Supporting Information

A Expected Event Probabilities and Durations at Risk.

Let $\lambda_{ij}$ denote the hazard rate for the $j$th event in the $i$th group with sample size $N_{\xi_i}$, assuming that each subject is observed for some fraction of time for each event type, i.e. that $\xi_{ia} = \xi_{ib} = \xi_{iab} = \xi_i$. Herein we assume that all subjects are at risk for some time for all events in which case the same sample fractions apply within the $i$th group. Then let $\pi_{ij}$ denote the probability that a subject in the $i$th group reaches the $j$th event marginally, i.e. either alone or jointly. Lachin and Foulkes (1986) assume recruitment over an interval of $(0, R]$ according to a monotone increasing function $G(r) = \int_0^r g(u)du$. For uniform (linear) recruitment, $g(r) = 1/R$. For non-linear recruitment, Lachin and Foulkes use a truncated exponential distribution with density

$$g(r) = \frac{\gamma e^{-\gamma r}}{1 - e^{-\gamma R}},$$

for $0 < r \leq R$, and $\gamma \neq 0$, that yields a concave (delayed) recruitment pattern for $\gamma < 0$, or a convex (accelerated) pattern for $\gamma > 0$. The total study duration is $Q > R$ units of time so that the administrative censoring time for a subject is then $Q - r$. Lachin-Foulkes also assume exponential losses with hazard rate $\eta_{ij}$ assuming that the loss times for the two events are independent, with $h_{ij}(u) = \eta_{ij}e^{-\eta_{ij}u}$ and cumulative distribution function $H_{ij}(u) = 1 - e^{-\eta_{ij}u}$. Then the expected potential exposure time (not factoring events) is

$$E(U_{ij}) = \int_{r=0}^R g(r) \left( \int_{u=0}^{Q-r} u h_{ij}(u) du + (Q - r) [1 - H_{ij}(Q - r)] \right) dr$$

that is readily evaluated using numerical integration. Note that in this instance we allow for different risks of loss-to-follow-up for the different types of events within and between groups. Then the probability of the $ij$th event ($\pi_{ij}$) with linear or non-linear exponential recruitment is provided by equations (4.1) or (4.3), respectively, in Lachin-Foulkes. Note that these equations are of the form $\lambda^2 \{\pi\}^{-1}$, so that the term in braces is the quantity of interest. Then

$$E(D_{ij}) = N_{\xi_i} \pi_{ij}$$

The expected time at risk for the $ij$th event, i.e. time to event or right censoring, is provided by

$$\tau_{ij} = \int_{r=0}^R g(r) \left( \int_{x=0}^{Q-r} x f_{ij}(x) [1 - H_{ij}(x)] dx + \int_{u=0}^{Q-r} u h_{ij}(u) [1 - F_{ij}(u)] du + (Q - r) [1 - H_{ij}(Q - r)] [1 - F_{ij}(Q - r)] \right) dr$$

that is readily evaluated by numerical integration. Then

$$E(T_{ij}) = N_{\xi_i} \tau_{ij}$$

that is the expected denominator for the $ij$th hazard rate estimate.
B Covariance of Exponential Hazard Differences.

Consider the case of two exponentially-distributed event times, neither being a competing risk for the other, with group differences \( \delta_a = (\hat{\lambda}_Ca - \hat{\lambda}_Ca) \) and \( \delta_b = (\hat{\lambda}_Cb - \hat{\lambda}_Cb) \). To obtain the covariance \( \text{Cov}(\delta_a, \delta_b) \), it is readily shown that

\[
\text{Cov}(\delta_a, \delta_b) = \text{Cov} \left[ \frac{D_{Ea}}{T_{Ea}}, \frac{D_{Ca}}{T_{Ca}} \right] \frac{D_{Eb}}{T_{Eb}} - \frac{D_{Cb}}{T_{Cb}} \]  

(6)

where

\[
\begin{align*}
\text{Cov}[D_{ia}, D_{ib}] &= E[D_{ia}D_{ib}] - E[D_{ia}]E[D_{ib}] \\
&= E \left[ \left( \sum_k X_{iak} \right) \left( \sum_k X_{ibk} \right) \right] - E \left[ \sum_k X_{iak} \right] E \left[ \sum_k X_{ibk} \right] \\
&= \sum_k \text{Cov}[X_{iak}, X_{ibk}] = \sum_k (E[X_{iak}X_{ibk}] - E[X_{iak}]E[X_{ibk}]) \\
&= \sum_k (\pi_{iabk} - \pi_{iak}\pi_{iak}) = E[D_{iab}] - E[D_{iab}] \\
\end{align*}
\]

where \( \pi_{iabk} \) is the probability of the kth subject experiencing both events and \( \pi_{ijk} \) is the probability of experiencing the jth event, both a function of the entry time of the kth patient and the other design parameters. Thus, \( D_{iab} \) is the number of subjects who experience both the A and B events and \( E[D_{iab}] \) is the expected number of subjects with both events under the assumption that the Bernoulli variables \( X_{iak} \) and \( X_{ibk} \) are conditionally independent.

Thus,

\[
\text{Cov}(\delta_a, \delta_b) = \frac{E[D_{Eab}] - E[D_{Eab}]}{E[T_{Ea}] E[T_{Eb}]} + \frac{E[D_{Cab}] - E[D_{Cab}]}{E[T_{Ca}] E[T_{Cb}]} \\
\]

(7)

(8)

that is consistently estimated from the observed numbers of events and total time at risk. The sample estimate \( D_{iab} \) is computed as

\[
D_{iab} = \sum_k \hat{E}[X_{iak}]E[X_{ibk}] = \sum_k \left[ 1 - \exp(-\hat{\lambda}_{ia}U_{iak}) \right] \left[ 1 - \exp(-\hat{\lambda}_{ib}U_{ibk}) \right].
\]

(9)

For the evaluation of sample size or power, these quantities are easily obtained from a simulation model.

Alternatively, from a model that provides hazard rates for the individual and joint events under the study design, the expected event counts can be obtained as

\[
\begin{align*}
E[D_{iab}] &= \pi_{iab}N_{xi} \\
E[D_{iab}] &= \pi_{iab}N_{xi} \\
\end{align*}
\]

(10)

where \( \pi_{iab} \) is obtained from the Lachin-Foulkes equations cited above using the hazard rate for experiencing both events \( \lambda_{iab} \). The probability of experiencing both events assuming independence can then be obtained from

\[
\pi_{iab} = \int_0^R g(r) \left( (1 - \exp(-\lambda_{ia}U_{iak}(r))) [1 - \exp(-\lambda_{ib}U_{ib}(r))] \right) \, dr
\]

(11)

where the expected exposure for a subject with recruitment at time \( r \) is obtained from (2) as

\[
U_{ij}(r) = \int_{u=0}^{Q-r} u \, h_{ij}(u) \, du + (Q - r) \left[ 1 - H_{ij}(Q - r) \right]
\]

(12)