Alternative Variance (Estimator) Representation of the Relative Treatment Effect Estimator of Dobler and Möllenhoff (2024)

We wish to find an estimator for the variance of the relative treatment effect. One presentation of the asymptotic variance is given in the Supplement of Dobler and Möllenhoff (2024). To offer a perhaps more accessible approach for the construction of a variance estimator, we offer a step-by-step derivation in the present document. An implementation of both variance estimators confirmed that both presentations (the new one in this document and the other one from Dobler and Möllenhoff, 2024) indeed coincide.

To find the asymptotic variance of $\hat{\theta}_n$, we first rewrite, in the notation of our paper,

$$\begin{aligned}\hat{\theta}_n &= \hat{F}_{2,n}(\tau) + \tfrac{1}{2}\hat{F}_{3,n}(\tau) = \hat{F}_{2,n}(\tau-) + \tfrac{1}{2}\hat{F}_{3,n}(\tau-) + \tfrac{1}{2}\hat{S}_n(\tau-) + o_p(n^{-1/2}) \\ &= \tfrac{1}{2} + \tfrac{1}{2}\hat{F}_{2,n}(\tau-) - \tfrac{1}{2}\hat{F}_{1,n}(\tau-) + o_p(n^{-1/2}) \\ &= \tfrac{1}{2}\Big[1 + \int_0^{\tau-} \hat{S}_n(u-) d(\hat{A}_{2,n} - \hat{A}_{1,n})(u)\Big] + o_p(n^{-1/2})\end{aligned}$$

Thus, it suffices to analyze the variance of the statistic in brackets. We have

$$\begin{aligned}&\int_0^{\tau-} \hat{S}_n(u-) d(\hat{A}_{2,n} - \hat{A}_{1,n})(u) - \int_0^{\tau-} S(u-) d(A_2 - A_1)(u) \\ &= \int_0^{\tau-} (\hat{S}_n(u-) - S(u-)) d(A_2 - A_1)(u) + \int_0^{\tau-} S(u-) d(\hat{A}_{2,n} - A_2 - \hat{A}_{1,n} + A_1)(u) + o_p(n^{-1/2}) \\ &= -\int_0^{\tau-} S(u-) \int_0^{u-} \frac{d(\hat{A}_{\bullet,n} - A_\bullet)(w)}{1 - \Delta A_\bullet(w)} d(A_2 - A_1)(u) \\ &\quad + \int_0^{\tau-} S(u-) d(\hat{A}_{2,n} - A_2 - \hat{A}_{1,n} + A_1)(u) + o_p(n^{-1/2}) \\ &= -\int_0^{\tau-} \int_0^{u-} \frac{d(\hat{A}_{\bullet,n} - A_\bullet)(w)}{1 - \Delta A_\bullet(w)} d(F_2 - F_1)(u) \\ &\quad + \int_0^{\tau-} S(u-) d(\hat{A}_{2,n} - A_2 - \hat{A}_{1,n} + A_1)(u) + o_p(n^{-1/2}).\end{aligned}$$

Here, we used in the first equality that $\int_0^{\tau-} (\hat{S}_n(u-) - S(u-)) d(\hat{A}_{2,n} - A_2 - \hat{A}_{1,n} + A_1)(u) = o_p(n^{-1/2})$, and in the second equality the asymptotically linear presentation of the Kaplan-Meier estimator. By means of integration by parts, we rewrite the first integral. Hence, the previous display equals

$$\begin{aligned}&-(F_2 - F_1)(\tau-) \int_0^{\tau-} \frac{d(\hat{A}_{\bullet,n} - A_\bullet)(u)}{1 - \Delta A_\bullet(u)} + \int_0^{\tau-} \frac{(F_2 - F_1)(u)}{1 - \Delta A_\bullet(u)} d(\hat{A}_{\bullet,n} - A_\bullet)(u) - 0 \\ &\quad + \int_0^{\tau-} \frac{S(u)}{1 - \Delta A_\bullet(u)} d(\hat{A}_{2,n} - A_2 - \hat{A}_{1,n} + A_1)(u) + o_p(n^{-1/2}) \\ &= \int_0^{\tau-} \frac{(F_2(u) - F_2(\tau-) - F_1(u) + F_1(\tau-) - S(u)) d(\hat{A}_{1,n} - A_1)(u)}{1 - \Delta A_\bullet(u)} \\ &\quad + \int_0^{\tau-} \frac{(F_2(u) - F_2(\tau-) - F_1(u) + F_1(\tau-) + S(u)) d(\hat{A}_{2,n} - A_2)(u)}{1 - \Delta A_\bullet(u)} \\ &\quad + \int_0^{\tau-} \frac{(F_2(u) - F_2(\tau-) - F_1(u) + F_1(\tau-)) d(\hat{A}_{3,n} - A_3)(u)}{1 - \Delta A_\bullet(u)} + o_p(n^{-1/2})\end{aligned}$$

By the continuous mapping theorem, in combination with Slutzky's lemma and a central limit theorem for the multivariate Nelson-Aalen estimator on a function space (Dobler, 2017), it follows that the asymptotic variance of

$\sqrt{n}(\hat\theta_n - \theta)$ is given by

$$\begin{aligned}
\sigma^2_\theta =& \frac{1}{4}\int_0^{\tau-} \frac{(F_2 - F_2(\tau-) - F_1 + F_1(\tau-) - S)^2 d\sigma^2_1}{(1-\Delta A_\bullet)^2} \\
&+ \int_0^{\tau-} \frac{(F_2 - F_2(\tau-) - F_1 + F_1(\tau-) + S)^2 d\sigma^2_2}{(1-\Delta A_\bullet)^2} \\
&+ \int_0^{\tau-} \frac{(F_2 - F_2(\tau-) - F_1 + F_1(\tau-))^2 d\sigma^2_3}{(1-\Delta A_\bullet)^2} \\
&+ \frac{1}{2}\int_0^{\tau-} \frac{(F_2 - F_2(\tau-) - F_1 + F_1(\tau-) - S)(F_2 - F_2(\tau-) - F_1 + F_1(\tau-) + S) d\sigma_{12}}{(1-\Delta A_\bullet)^2} \\
&+ \frac{1}{2}\int_0^{\tau-} \frac{(F_2 - F_2(\tau-) - F_1 + F_1(\tau-) - S)(F_2 - F_2(\tau-) - F_1 + F_1(\tau-)) d\sigma_{13}}{(1-\Delta A_\bullet)^2} \\
&+ \frac{1}{2}\int_0^{\tau-} \frac{(F_2 - F_2(\tau-) - F_1 + F_1(\tau-) + S)(F_2 - F_2(\tau-) - F_1 + F_1(\tau-)) d\sigma_{23}}{(1-\Delta A_\bullet)^2}
\end{aligned}$$

Here, σ^2_j and $\sigma^2_{j\ell}$ are the asymptotic variances and covariances of $\sqrt{n}\hat A_{j,n}$ and $\sqrt{n}\hat A_{j,n}$ and $\sqrt{n}\hat A_{\ell,n}$, respectively, $j,\ell = 1,2,3$; cf. Dobler (2017). Note that we have omitted the integration variable u, and we will also do so henceforth to keep the formulas shorter. A consistent estimator of σ^2_θ is given by

$$\begin{aligned}
\hat\sigma^2_{\theta,n} =& \frac{1}{4}\int_0^{\tau-} \frac{(\hat F_{2,n} - \hat F_{2,n}(\tau-) - \hat F_{1,n} + \hat F_{1,n}(\tau-) - \hat S_n)^2 d\hat\sigma^2_{1,n}}{(1-\Delta \hat A_{\bullet,n})^2} \\
&+ \frac{1}{4}\int_0^{\tau-} \frac{(\hat F_{2,n} - \hat F_{2,n}(\tau-) - \hat F_{1,n} + \hat F_{1,n}(\tau-) + \hat S_n)^2 d\hat\sigma^2_{2,n}}{(1-\Delta \hat A_{\bullet,n})^2} \\
&+ \frac{1}{4}\int_0^{\tau-} \frac{(\hat F_{2,n} - \hat F_{2,n}(\tau-) - \hat F_{1,n} + \hat F_{1,n}(\tau-))^2 d\hat\sigma^2_{3,n}}{(1-\Delta \hat A_{\bullet,n})^2} \\
&+ \frac{1}{2}\int_0^{\tau-} \frac{(\hat F_{2,n} - \hat F_{2,n}(\tau-) - \hat F_{1,n} + \hat F_{1,n}(\tau-) - \hat S_n)(\hat F_{2,n} - \hat F_{2,n}(\tau-) - \hat F_{1,n} + \hat F_{1,n}(\tau-) + \hat S_n) d\hat\sigma_{12,n}}{(1-\Delta \hat A_{\bullet,n})^2} \\
&+ \frac{1}{2}\int_0^{\tau-} \frac{(\hat F_{2,n} - \hat F_{2,n}(\tau-) - \hat F_{1,n} + \hat F_{1,n}(\tau-) - \hat S_n)(\hat F_{2,n} - \hat F_{2,n}(\tau-) - \hat F_{1,n} + \hat F_{1,n}(\tau-)) d\hat\sigma_{13,n}}{(1-\Delta \hat A_{\bullet,n})^2} \\
&+ \frac{1}{2}\int_0^{\tau-} \frac{(\hat F_{2,n} - \hat F_{2,n}(\tau-) - \hat F_{1,n} + \hat F_{1,n}(\tau-) + \hat S_n)(\hat F_{2,n} - \hat F_{2,n}(\tau-) - \hat F_{1,n} + \hat F_{1,n}(\tau-)) d\hat\sigma_{23,n}}{(1-\Delta \hat A_{\bullet,n})^2}
\end{aligned}$$

Here, $\hat\sigma^2_{j,n}(u) = n\int_0^u \frac{1-\Delta\hat A_{1,n}}{(1-\Delta\hat A_{\bullet,n})^2 Y} d\hat A_{j,n}$ and $\hat\sigma^2_{j\ell,n} = n\int_0^u \frac{\Delta\hat A_{j,n}}{(1-\Delta\hat A_{\bullet,n})^2 Y} d\hat A_{\ell,n}$ are the Greenwood-type variance and covariance estimators of $\sqrt{n}\hat A_{j,n}$ and $\sqrt{n}\hat A_{j,n}$ and $\sqrt{n}\hat A_{\ell,n}$, respectively, $j,\ell = 1,2,3$; cf. Dobler (2017). All in all, the variance estimator reduces to

$$\begin{aligned}
\hat\sigma^2_{\theta,n} =& \frac{n}{4}\sum_{D_0^{\tau-}} \Big[\frac{(\hat F_{2,n} - \hat F_{2,n}(\tau-) - \hat F_{1,n} + \hat F_{1,n}(\tau-) - \hat S_n)^2 (1-\Delta\hat A_{1,n})\Delta\hat A_{1,n}}{(1-\Delta \hat A_{\bullet,n})^2 Y} \\
&\qquad + \frac{(\hat F_{2,n} - \hat F_{2,n}(\tau-) - \hat F_{1,n} + \hat F_{1,n}(\tau-) + \hat S_n)^2 (1-\Delta\hat A_{2,n})\Delta\hat A_{2,n}}{(1-\Delta \hat A_{\bullet,n})^2 Y} \\
&\qquad + \frac{(\hat F_{2,n} - \hat F_{2,n}(\tau-) - \hat F_{1,n} + \hat F_{1,n}(\tau-))^2 (1-\Delta\hat A_{3,n})\Delta\hat A_{3,n}}{(1-\Delta \hat A_{\bullet,n})^2 Y} \Big] \\
&- \frac{n}{2}\sum_{D_0^{\tau-}} \Big[\frac{(\hat F_{2,n} - \hat F_{2,n}(\tau-) - \hat F_{1,n} + \hat F_{1,n}(\tau-) - \hat S_n)(\hat F_{2,n} - \hat F_{2,n}(\tau-) - \hat F_{1,n} + \hat F_{1,n}(\tau-) + \hat S_n)\Delta\hat A_{1,n}\Delta\hat A_{2,n}}{(1-\Delta \hat A_{\bullet,n})^2 Y} \\
&\qquad + \frac{(\hat F_{2,n} - \hat F_{2,n}(\tau-) - \hat F_{1,n} + \hat F_{1,n}(\tau-) - \hat S_n)(\hat F_{2,n} - \hat F_{2,n}(\tau-) - \hat F_{1,n} + \hat F_{1,n}(\tau-))\Delta\hat A_{1,n}\Delta\hat A_{3,n}}{(1-\Delta \hat A_{\bullet,n})^2 Y} \\
&\qquad + \frac{(\hat F_{2,n} - \hat F_{2,n}(\tau-) - \hat F_{1,n} + \hat F_{1,n}(\tau-) + \hat S_n)(\hat F_{2,n} - \hat F_{2,n}(\tau-) - \hat F_{1,n} + \hat F_{1,n}(\tau-)) d\Delta\hat A_{2,n}\Delta\hat A_{3,n}}{(1-\Delta \hat A_{\bullet,n})^2 Y}.
\end{aligned}$$

Here, $\sum_{D_0^{\tau-}}$ denotes the sum over all event times in $(0,\tau)$. An alternative representation for the variance estimator in terms of counting process notation is:

$$
\begin{aligned}
\hat{\sigma}^2_{\theta,n} = \frac{n}{4} \sum_{D_0^{\tau-}} \Big[& \frac{(\hat{F}_{2,n} - \hat{F}_{2,n}(\tau-) - \hat{F}_{1,n} + \hat{F}_{1,n}(\tau-) - \hat{S}_n)^2 (Y - \Delta N_1)\Delta N_1}{(Y - \Delta N_\bullet)^2 Y} \\
& + \frac{(\hat{F}_{2,n} - \hat{F}_{2,n}(\tau-) - \hat{F}_{1,n} + \hat{F}_{1,n}(\tau-) + \hat{S}_n)^2 (Y - \Delta N_2)\Delta N_2}{(Y - \Delta N_\bullet)^2 Y} \\
& + \frac{(\hat{F}_{2,n} - \hat{F}_{2,n}(\tau-) - \hat{F}_{1,n} + \hat{F}_{1,n}(\tau-))^2 (Y - \Delta N_3)\Delta N_3}{(Y - \Delta N_\bullet)^2 Y} \Big] \\
-\frac{n}{2} \sum_{D_0^{\tau-}} \Big[& \frac{(\hat{F}_{2,n} - \hat{F}_{2,n}(\tau-) - \hat{F}_{1,n} + \hat{F}_{1,n}(\tau-) - \hat{S}_n)(\hat{F}_{2,n} - \hat{F}_{2,n}(\tau-) - \hat{F}_{1,n} + \hat{F}_{1,n}(\tau-) + \hat{S}_n)\Delta N_1 \Delta N_2}{(Y - \Delta N_\bullet)^2 Y} \\
& + \frac{(\hat{F}_{2,n} - \hat{F}_{2,n}(\tau-) - \hat{F}_{1,n} + \hat{F}_{1,n}(\tau-) - \hat{S}_n)(\hat{F}_{2,n} - \hat{F}_{2,n}(\tau-) - \hat{F}_{1,n} + \hat{F}_{1,n}(\tau-))\Delta N_1 \Delta N_3}{(Y - \Delta N_\bullet)^2 Y} \\
& + \frac{(\hat{F}_{2,n} - \hat{F}_{2,n}(\tau-) - \hat{F}_{1,n} + \hat{F}_{1,n}(\tau-) + \hat{S}_n)(\hat{F}_{2,n} - \hat{F}_{2,n}(\tau-) - \hat{F}_{1,n} + \hat{F}_{1,n}(\tau-)) d\Delta N_2 \Delta N_3}{(Y - \Delta N_\bullet)^2 Y} \Big].
\end{aligned}
$$

This expression can be simplified once more by using the binomial rule:

$$
\begin{aligned}
\hat{\sigma}^2_{\theta,n} = & -\frac{n}{4} \sum_{D_0^{\tau-}} ((Y - \Delta N_\bullet)^2 Y)^{-1} [(\hat{F}_{2,n} - \hat{F}_{2,n}(\tau-) - \hat{F}_{1,n} + \hat{F}_{1,n}(\tau-) - \hat{S}_n)\Delta N_1 \\
& \qquad + (\hat{F}_{2,n} - \hat{F}_{2,n}(\tau-) - \hat{F}_{1,n} + \hat{F}_{1,n}(\tau-) + \hat{S}_n)\Delta N_2 \\
& \qquad + (\hat{F}_{2,n} - \hat{F}_{2,n}(\tau-) - \hat{F}_{1,n} + \hat{F}_{1,n}(\tau-))\Delta N_3]^2 \\
& + \frac{n}{4} \sum_{D_0^{\tau-}} \frac{(\hat{F}_{2,n} - \hat{F}_{2,n}(\tau-) - \hat{F}_{1,n} + \hat{F}_{1,n}(\tau-) - \hat{S}_n)^2 \Delta N_1}{(Y - \Delta N_\bullet)^2} \\
& + \frac{n}{4} \sum_{D_0^{\tau-}} \frac{(\hat{F}_{2,n} - \hat{F}_{2,n}(\tau-) - \hat{F}_{1,n} + \hat{F}_{1,n}(\tau-) + \hat{S}_n)^2 \Delta N_2}{(Y - \Delta N_\bullet)^2} \\
& + \frac{n}{4} \sum_{D_0^{\tau-}} \frac{(\hat{F}_{2,n} - \hat{F}_{2,n}(\tau-) - \hat{F}_{1,n} + \hat{F}_{1,n}(\tau-))^2 \Delta N_3}{(Y - \Delta N_\bullet)^2} \\
= & -\frac{n}{4} \sum_{D_0^{\tau-}} \frac{[(\hat{F}_{2,n} - \hat{F}_{2,n}(\tau-) - \hat{F}_{1,n} + \hat{F}_{1,n}(\tau-))\Delta N_\bullet + \hat{S}_n(\Delta N_2 - \Delta N_1)]^2}{(Y - \Delta N_\bullet)^2 Y} \\
& + \frac{n}{4} \sum_{D_0^{\tau-}} \frac{(\hat{F}_{2,n} - \hat{F}_{2,n}(\tau-) - \hat{F}_{1,n} + \hat{F}_{1,n}(\tau-))^2 \Delta N_\bullet}{(Y - \Delta N_\bullet)^2} \\
& + \frac{n}{2} \sum_{D_0^{\tau-}} \frac{\hat{S}_n(\hat{F}_{2,n} - \hat{F}_{2,n}(\tau-) - \hat{F}_{1,n} + \hat{F}_{1,n}(\tau-))(\Delta N_2 - \Delta N_1)}{(Y - \Delta N_\bullet)^2} \\
& + \frac{n}{4} \sum_{D_0^{\tau-}} \frac{\hat{S}_n^2(\Delta N_1 + \Delta N_2)}{(Y - \Delta N_\bullet)^2}
\end{aligned}
$$

References

Dennis Dobler. A discontinuity adjustment for subdistribution function confidence bands applied to right-censored competing risks data. *Electronic Journal of Statistics*, 11(2):3673–3702, 2017.

Dennis Dobler and Kathrin Möllenhoff. Supplementary material for: “A nonparametric relative treatment effect for direct comparisons of censored paired survival outcomes”. *Statistics in Medicine*, In press; pages:1–22, 2024.