The Binomial Case

It can be shown that the influence statistic has a non-central chi-squared distribution with 2 d.f. with non-centrality parameter λ given by

$$\lambda = 0.5 * \left[\frac{\left(E\left(\hat{p}_1 - \hat{p}_{1(-i)}\right)\right)^2}{V_{11}} + \frac{\left(E\left(\hat{p}_2 - \hat{p}_{2(-i)}\right)\right)^2}{V_{22}} \right],$$

for $E\left(\hat{p}_1 - \hat{p}_{1(-i)}\right) = \frac{N_{1i}(p_{1i} - p_{1(-i)})}{N_{1(-i)} + N_{1i}}$, a similar expression for $E\left(\hat{p}_2 - \hat{p}_{2(-i)}\right)$,

$$V_{11} = Var\left(\hat{p}_1 - \hat{p}_{1(-i)}\right) = \frac{N_{1i}\, p_{1i}\left(1 - p_{1i}\right)}{\left(N_{1(-i)} + N_{1i}\right)^2} + \frac{N_{1i}^2\, p_{1(-i)}\left(1 - p_{1(-i)}\right)}{\left(N_{1(-i)} + N_{1i}\right)^2 N_{1(-i)}}$$

and a similar expressions for V_{22},

where, $\hat{p}_1$ is the proportion of responders in the first arm and $\hat{p}_{1(-i)}$ is the proportion of responders in the first arm after excluding the i^{th} possibly influential stratum. $N_{1(-i)}$ and N_{1i} are the number of subjects in the first arm for those outside stratum *i* and those in stratum *i* respectively. $\hat{p}_2$, $\hat{p}_{2(-i)}$, $N_{2(-i)}$ and N_{2i} are similarly defined for the second arm.

The scaled inflation in influence is then given by λ, the percent inflation in influence by 100*λ and the percent inflation in variance of the influence statistic is given by 200λ. These follow from the expected value of a central chi-square with n d.f. given as n and variance given as 2n. An aberrant large site/strata will lead to an influence statistic with a non-central distribution with expected value n+2λ and variance 2(n+4λ).

Return to Calculator at this link.

The Continuous Case

It can be shown that the influence statistic has a non-central chi-squared distribution with 2 d.f. with non-centrality parameter λ given by

$$\lambda = 0.5 * \left[\frac{\left(E\left(\overline{Y}_1 - \overline{Y}_{1(-i)}\right)\right)^2}{V_{11}} + \frac{\left(E\left(\overline{Y}_2 - \overline{Y}_{2(-i)}\right)\right)^2}{V_{22}} \right],$$

for $E\left(\overline{Y}_1 - \overline{Y}_{1(-i)}\right) = \frac{N_{1i}(\mu_{1i} - \mu_{1(-i)})}{N_{1(-i)} + N_{1i}}$, a similar expression for $E\left(\overline{Y}_2 - \overline{Y}_{2(-i)}\right)$,

$$V_{11} = Var\left(\overline{Y}_1 - \overline{Y}_{1(-i)}\right) = \frac{N_{1i}\sigma_{1i}^2}{\left(N_{1(-i)} + N_{1i}\right)^2} + \frac{N_{1i}^2\sigma_{1(-i)}^2}{\left(N_{1(-i)} + N_{1i}\right)^2 N_{1(-i)}}$$, and a similar expression for V_{22},

where, $\overline{Y}_1$ is the mean response in the first arm and $\overline{Y}_{1(-i)}$ is the mean response in the first arm after excluding the i^{th} possibly influential stratum. $N_{1(-i)}$ and N_{1i} are the number of subjects in the first arm for those outside stratum *i* and those in stratum *i* respectively. The mean and variance of the $N_{1(-i)}$ observations are denoted by $\mu_{1(-i)}$ and $\sigma_{1(-i)}^2$ and that for the N_{1i} observations are denoted by μ_{1i} and σ_{1i}^2. $\overline{Y}_2$, $\overline{Y}_{2(-i)}$, $N_{2(-i)}$ and N_{2i}, $\mu_{2(-i)}$, $\sigma_{2(-i)}^2$, μ_{2i} ,and σ_{2i}^2 are defined similarly for the second arm.

The scaled inflation in influence is then given by λ, the percent inflation in influence by 100*λ and the percent inflation in variance of the influence statistic is given by 200λ. These follow from the expected value of a central chi-square with n d.f. given as n and variance given as 2n. An aberrant large site/strata will lead to an influence statistic with a non-central distribution with expected value n+2λ and variance 2(n+4λ).

Return to Calculator [at this link.]()

The Survival Case

It can be shown that the influence statistic (the homogeneity of strata statistic- see Marubini E and Valsecchi MG. *Analyzing Survival Data from Clinical Trials and Observational Studies*) has a non-central chi-squared distribution with 1 d.f. with non-centrality parameter λ given by

$\lambda = 0.5*\left(V_{Li}(\xi_i - \bar{\xi})^2 + V_{L(-i)}(\xi_{-i} - \bar{\xi})^2\right)$ with $\bar{\xi} = V_{Li}\xi_i + V_{L(-i)}\xi_{-i} / (V_{Li} + V_{L(-i)})$.

The log hazard ratio in the *i*th and *i*-deleted strata are denoted by ξ_i and ξ_{-i}. The variances V_{Li} and $V_{L(-i)}$ can be obtained approximately as a the product r*(1-r) of the randomization fractions r and (1-r) multiplied by the expected number of events in the the *i*th and *i*-deleted strata (Schoenfeld, 1981, Bometrics). The variances V_{Li} is given as in the following (using expressions for the expected number of events from the Cytel EAST Manual.

$$V_{Li} = r(1-r)\left\{\frac{a_{1i}\lambda_{1i}}{\lambda_{1i}+\gamma}\left[A - \frac{e^{-(\lambda_{1i}+\gamma)l}}{\lambda_{1i}+\gamma}\left(e^{(\lambda_{1i}+\gamma)A} - 1\right)\right] + \frac{a_{2i}\lambda_{2i}}{\lambda_{2i}+\gamma}\left[A - \frac{e^{-(\lambda_{1i}+\gamma)l}}{\lambda_{2i}+\gamma}\left(e^{(\lambda_{2i}+\gamma)A} - 1\right)\right]\right\}$$

for variable follow up. For the first and second arm in the i^{th} site, a_{1i} and a_{2i} are the uniform accrual rates and λ_{1i} and λ_{2i} are the hazard rates. *A* is the accrual period and γ is the drop-out hazard rate and *l* is the calendar time (*A*+follow-up). For fixed follow-up the expression for V_{Li} can be obtained on taking the limit as *A* approaches zero as

$$V_{Li} = r(1-r)\left\{\frac{N_{1i}\lambda_{1i}}{\lambda_{1i}+\gamma}\left[1 - e^{-(\lambda_{1i}+\gamma)l}\right] + \frac{N_{2i}\lambda_{2i}}{\lambda_{2i}+\gamma}\left[1 - e^{-(\lambda_{1i}+\gamma)l}\right]\right\}$$

Similar expressions can be obtained for the $V_{L(-i)}$. The scaled inflation in influence is given by SQRT(2)*λ, the percent inflation in influence is 200λ and the percent inflation in variance is given by 400λ as the homogeneity of strata statistic is 1 d.f. chi-square.

Reference: Shankar Srinivasan and Arlene Swern. Measures of Expected Influence Provide Useful Constraints to Enrollment in Randomized Multi-Center Clinical Trials for Binomial, Continuous and Time-to-Event Endpoints, Journal of Statistical Science and Application, April 2015, Vol. 3, No. 3-4, 39-49.

Return to Calculator at this link.