Description of Variance and Confidence Interval SI for the LLNA: DA Interlaboratory Validation Studies

Excerpt taken from: "A measure for interlaboratory variation used in two validation studies of LLNA-DA [Draft ver. 0.9]"

Takashi Omori[1] and Takashi Sozu[2]

[1]Department of Biostatistics, Kyoto University School of Public Health, Yoshida Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan

[2]The Center for Advanced Medical Engineering and Informatics, Osaka University, 2-2 Yamadaoka, Suita, Osaka 565-0781, Japan

E-mail omori@pbh.med.kyoto-u.ac.jp

As outlined in Appendix D of the draft ICCVAM Background Review Document (BRD) for the LLNA: DA, Daicel Chemical Industries, Ltd. conducted two multi-laboratory validation studies. In order to evaluate interlaboratory reproducibility, they developed a measure to assess the reproducibility by applying the meta-analysis method along with the random effect model to these two validation studies. This measure (described below) describes the between-laboratory variation that is obtained by eliminating the variation in each stimulation index (SI) from the total variation in the SI.

Calculation of Variance and Confidence interval of SI

Let Mean(i) be the mean DPM/mouse in the i-th group, and let SE(i) be the standard error (SE) in this value for the i-th group; i indexes the examined substance group (Y) and the solvent control group (X). Thus, it follows that $\mathrm{SI} = \mathrm{Mean}(Y)/\mathrm{Mean}(X)$.

When being used the delta method, the variance of SI is:

$$\mathrm{Var}(\mathrm{SI}) = (\mathrm{SI})^2 \times \mathrm{Var}(\ln \mathrm{SI}), \qquad (1)$$

where

$$\mathrm{Var}(\ln \mathrm{SI}) = \frac{\mathrm{SE}(Y)^2}{\mathrm{Mean}(Y)^2} + \frac{\mathrm{SE}(X)^2}{\mathrm{Mean}(X)^2}. \qquad (2)$$

One of most important uses of this variance would be in the construction of confidence intervals for SI; we used the 95% confidence interval as

$$\exp\left(\ln(\mathrm{SI}) \pm 1.96\sqrt{(\mathrm{Var}(\ln \mathrm{SI}))}\right), \qquad (3)$$

and $\mathrm{Var}(\ln \mathrm{SI})$ is obtained from equation (2)."

Assessment of Interlaboratory Reproducibility

Let SI_j and $Var(SI_j)$ be the SI and variance of SI from the j-th laboratory (j = 1,…,m), respectively. Suppose the estimate of the log-transformed SI of the j-th laboratory follows a normal distribution with a location parameter, say q_j, and a scaled parameter, i.e., $\mathrm{Var}(\ln(\mathrm{SI}_j))$. Thus, it is considered that $\ln(\mathrm{SI}_j) \sim \mathrm{N}(\theta_j, \mathrm{Var}(\ln(\mathrm{SI}_j)))$. Note that this assumption allows different laboratories to have different locations and scaled parameters of the log-transformed SI. Further, consider a model in which the location parameter of the log-transformed SI of the j-th laboratory, i.e., q_j, follows a normal distribution with the location parameter q and the scaled parameter t^2. Then, it is considered that $\theta_j \sim \mathrm{N}(\theta, \tau^2)$.

In this model, the scaled parameter t^2 represents the interlaboratory reproducibility of the log-transformed SIs. Therefore, t^2 would be one of measures for the interlaboratory reproducibility of SI.

There are several methods to estimate t^2 based on the calculated SI_js and $\mathrm{Var}(\ln(\mathrm{SI}_j))$s values, and the restricted maximum likelihood method is one of the most popular. When using the method, t^2 is the solution of the following equation:

$$\tau^2 = \frac{\sum_j w_j^2(\tau^2)\left(\frac{m}{m-1}\left(\ln(\mathrm{SI}_j) - \mathrm{WM}_{\mathrm{REML}}\right)^2 - \mathrm{Var}(\ln(\mathrm{SI}_j))\right)}{\sum_j w_j^2(\tau^2)},$$

where $w_j^2(\tau^2) = 1/(\mathrm{Var}(\ln(\mathrm{SI}_j)) + \tau^2)$ and $\mathrm{WM}_{\mathrm{REML}} = \sum_j w_j(\tau^2)\ln(\mathrm{SI}_j) / \sum_j w_j(\tau^2)$

(Normand, 1999).

However, since t^2 is present on both sides of the equation, a closed-form solution cannot be obtained. However, the equation is solved by iteration, for example, by using the SAS MIXED procedure (Wang and Bushman, 1999).

References

Normand SLT. 1999. Meta-analysis: formulating, evaluating, combining, and reporting. Statistics in Medicine 18: 321–359.

Wang MC and Bushman BJ. 1999. Integrating results: through meta-analytic review using SAS software, pp. 273–302, SAS Institute Inc., Cary, NC.