Statistical Analysis of Cardiovascular Data

The analysis of data from cardiovascular (CV) studies present unique characteristics that require appropriate statistical methodology. Failure to customize the statistical analysis to match the study design may lead to costly misinterpretations and subsequent delays in submission.

Study Design: In addition to the common parallel group design that is employed in most other nonclinical animal studies, the unique characteristics of CV responses allow for the employment of Latin square, escalating dose, and hybrid study designs. Efficiencies in these designs require fewer animals to achieve the same statistical power as a parallel group design, but only if the statistical model used for analysis is customized to accurately reflect the specific study design. (1)

Data Bins: Because CV data are collected over an extended period (24 hours or more), data are often "binned" into smaller time intervals for analysis. Bins should be defined in the protocol taking into consideration drug characteristics, delivery mechanism, environmental conditions, and the statistical analysis. Individual bins should be large enough that the variability is relatively stable (a 1-minute bin presents substantial, unstable variability within and between animals), yet not so large that a test article effect is diluted by surrounding unremarkable data. (2) "Super intervals", in which data are subjectively binned into time intervals of 6 hours or more, may be useful as a preliminary screening tool but is not an effective statistical analysis of true test article effect.

Repeated Measures: Statistically analyzing each bin (time interval) separately treats the data as if they are independent observations, which they are not. CV data require statistical methodology that accounts for the correlation of repeated measurements on the same animal. A repeated measures (RM) model distinguishes within-animal variation (responses from the same animal) from between-animal variation (responses from different animals). (3, 4) RM methodology also allows for a direct evaluation of the progression of test article effect, if any, over time through the model's interaction term for treatment and time after dose. (5) Finally, RM methodology, along with other techniques such as dose-response trend testing, reduces the number of statistical tests and resulting p-values thus reducing the chance of false positives (statistically significant findings that are not biologically relevant.)

Baseline Adjustment: Most CV study designs include baseline data collected prior to dose administration. The benefit of baseline data is that it can be used in the statistical model as a "covariate". Including a baseline covariate in the analysis adjusts for naturally inherent differences between animals in their naïve state that cannot be controlled by the study design. Adjusting the statistical analysis with a covariate term is often more powerful than simply analyzing change from baseline. (6) Even if the analysis is conducted on change from baseline values, it is recommended that the baseline covariate is included in the model to aid in precision of estimates. (7)

BioSTAT Perspective: BioSTAT has provided statistical analysis of CV studies for more than 20 years. This document provides a very brief description of some of the unique characteristics of the statistical analysis CV data. More detailed BioSTAT internal documents on the analysis and interpretation of repeated measures analysis of covariance are available upon request.

References:

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4) Vidmar T, Freshwater L, Collins R, *A Comprehensive Guide to Toxicology in Preclinical Drug Development, First Edition. Chapter "*Biostatistics for Toxicologists". Edited by Ali S Faqi, Elsevier Inc., November 2012.

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6) Bonate, P. 2000 . *Analysis of Pretest-Posttest Designs*. New York: Chapman and Hall/CRC.

7) *Guideline on adjustment for baseline covariates in clinical trials,* Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency, February 2015.