Virtual Control Groups: Selection and Validation

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There is a constant strive in preclinical toxicology to reduce the dependence on animals for safety decision making. One possible step towards the reduction of animals is the replacement of control animals by virtual control groups (VCGs), a method where historical control data is re-used to analyze effects in newly performed studies. Within the IMI eTransafe project the aim is to establish VCGs for preclinical studies and to test their ability to reproduce results of toxicity studies.

The reproducibility of statistical test decisions from four-week rat toxicity studies (*i.e.*, legacy studies) after replacing the concurrent control groups (CCGs) with the VCGs was investigated. VCGs were created to simulate quantitative parameters, such as body weight, food and water consumption, hematology clinical chemistry and urine parameters. They were generated by sampling from a previously collected set of historical control data compromising 14 design-matching studies. Probability of test results was computed based on outcomes from 100 repetitions of VCG-samples replacing the CCG and repeating the study analysis. Afterwards, the obtained results were presented to a study director for interpretation and for decision whether the conclusion of the toxicity studies was changed or not.

Although VCGs have shown only a moderate ability to reproduce statistical test decisions, the general conclusions of all studies remained unchanged. It turned out that major study conclusions are derived mainly from observed effects in treatment-group animals considering parameters on mortality, in-life observations, and histopathological findings. Most significant differences between VCG and treatment groups in the quantitative parameters were then classified as irrelevant from a toxicological point of view.

Our results provide a first indication that carefully selected historical control data can be used to replace concurrent control without impairing the general study conclusion. The developed procedures and workflows lay the foundation for future validation of virtual controls for a use in regulatory toxicology. As next steps research on the usability of historical control data for creation of VCGs should aim on (i) virtual increase the number of control-group animals and hence increase power of statistical tests, (ii) create meaningful value ranges of control data to determine biological relevance, and (iii) consideration of effect sizes rather than *p*-value based test decisions.