Adjusting for multiple test when endpoints are correlated

Nowadays, researcher make assumptions based on their experience. However, these claims are not always true and can be tested against data which further support or contradict the researcher. Hypothesis testing procedure helps a researcher to draw a conclusion with evidence based on data. If the hypotheses are more than one in a sample, a multiple test scheme is expected.

The issue of multiple test is that as the number of hypotheses increases the probability of false rejection in m performed test increases. This probability is called family wise error rate (FWER).

$$FWER = 1 - (1 - \alpha)^m, \tag{1}$$

where α is our pre-specified significance level. In this project $\alpha = 0.05$. In a clinical trial, the FWER must be much controlled based on endpoints.In this study Endpoint is the outcome of a treatment. **Our Objective** was to investigate different methods of controlling he FWER art the pre-specified significance level when endpoints are correlated . The FWER control requirement is

$$FWER = P\{\text{Reject at least one true null hypothesis}\} \leq \alpha \tag{2}$$

Based on test statistic used within the study we compute the critical value due to the significant level to draw a conclusion according to the test statistics output. In our case the critical value will be (ρ, α) to satisfy Equation(2), where ρ is the correlation between endpoints.

In this project, using the MASS package and *mvrnorm* function in R, we simulated a bivariate normal distribution with mean $(0, 0)$ and covariance matrix $\begin{pmatrix} 1 & \rho \\ \rho & 1 \end{pmatrix}$. The data represents clinical trial endpoints. The correlation between endpoints is unknown but can be assumed to be known or estimated based on interim analysis (sample data) with different methods. Further more assumption is that $\text{corr}(E_1, E_2) \geq 0$. **The hypotheses are:**

$$\text{Endpoint 1; } H_o : \mu \geq 0, \; H_a : \mu < 0, \quad \text{Endpoint 2; } H_o : \mu' \geq 0, \; H_a : \mu' < 0 \tag{3}$$

with the global null hypothesis being that one or both hypotheses are true and alternative hypothesis is that none of the null hypothesis is true.

By performing Monte Carlo simulation with endpoints data, we find that the maximum FWER is 0.1, which is greater than our pre-specified significant level. This means that the FWER boundaries need to be adjusted at alpha level.

Methods that we used to adjust FWER when endpoints are correlated.

Adjusting for fixed assumed correlation: this method assumes correlation between endpoints which might lead to the worse result. **See page 14, Figure 3.2**

Plug-in estimated correlation: this method uses the estimated correlation from the outcome of endpoints in each group using different estimators (**Page 16, Table3.1**). This leads to the precise estimation with FWER inflation. **see page 25**.

Berger and Boos method: The method uses the lower bound of the nuisance parameter from estimated correlation by setting the confidence level within s^2(to use in the formula on page 20). Choosing a larger sample size and larger confidence level leads to the accurate control of the FWER around the significant level. **See page 28, figure 4.6**.

Conclusion: The research findings suggest that using Berger and Boos method leads to a better control of FWER by considering a larger sample size and larger confidence level in computing the lower bound of the nuisance parameter.