

Correlated Data in Clinical Trials

Note: My [BS857 Notebook](#) on Correlated Data goes much further in depth than the below.

So far we have focused on independent outcomes in clinical trials, but often times we work with correlated or non-independent outcomes in clinical trials; Such as crossover trials, repeated measurement designs or cluster randomized designs.

In a crossover trial each subject is used as its own control. Subjects are randomized to A then B or B then A. There is a "Wash-out" period used to avoid "carry-over" effect. It is best used for interventions whose effects can be measured after short period of administration. **Carryover** is the persistence of a treatment effect applied in one period in a subsequent period of treatment.

The advantages of this design is there is no between-subject variability in statistical comparison; only within-subject variability. Since there is less variability we can use a smaller sample size.

The disadvantages are that there are very strict assumptions about carry-over effects. It is inappropriate for certain acute diseases, and doubles the duration of the study.

A simple analysis of a continuous outcome can be performed with a paired t-test. But to test if there is a carry-over effect we need to perform the treatment by period interaction.

In SAS, the PROC MIXED statement is used to account for correlated outcomes. The REPEATED statement tells SAS where the correlation occurs and how to handle it; Within the repeated statement *time* tells SAS what variable represents the repeated measurements, *subject=id* tells SAS what the clustering variable is, and *type=un* indicates a unstructured covariance matrix.

A **covariance matrix** is a collection of outcomes and variances at each time point and covariances and between outcomes at different points. Unstructured means that there are no restrictions placed on these values (all are estimated separately). There may be reasons to make simplifying assumptions.

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