**Pharmacokinetic data analysis**

Phenobarbital is a benzodiazepine that is used to prevent convulsions in newborns. Pediatricians wonder whether the pharmacokinetics of phenobarbital in newborns that are treated with therapeutic hypothermia (TH) are the same for normal (normo-thermic) newborns. They have concentration (mg/L) – time (h) data available from patients that were treated with TH (=1) and patients of similar age that are not treated with TH (=0). All patients received a dose of 40 mg in this study.

**Question 1)**

Read in the dataset “*Phenobarbital\_TH.csv*” and describe the design of the study.

**Question 2)**

How many unique individuals are included in the dataset for both treatment arms?

**Question 3)**

Are there any differences between the pharmacokinetic profiles of phenobarbital patients treated with TH and patients that are not treated with TH? Base your assessment on a plot of the concentration-time data that includes all patients, and uses different colors for patients with and without TH. Do this on a linear scale and semi-logarithmic scale

**Question 4)**

Can you detect any outlying data points? Based your assessment on individual panel plots and make sure that you can identify both ID number and treatment arm for each graph in this plot. Do this on a linear scale and semi-logarithmic scale.

**Question 5)**

Make a subset of the dataset that does not include the outlying data points and use that dataset for the following questions. Make sure that it is clear in your script what subset of the data you have used (or what data points you have taken out), because traceability is very important!

**Question 6)**

What are the average maximum concentration (Cmax), average trough concentration (Cmin), and average average concentration (Cav) for both treatment arms? Does it make sense to compare these values between both groups given the study design?

**Question 7)**

The concentration-time data reveals a linear profile on a semi-logarithmic scale. To be able to perform a linear regression add a new column to the dataset that contains the LN-values of the concentrations.

**Question 8)**

Fit a linear model to the ln-transformed concentration values of both treatment arms. The peak concentration is mainly determined by the distribution volume of phenobarbital in this population, while the slope of the profiles is mainly determined by the clearance. Do you anticipate differences in distribution volume and clearance between patients on TH treatment and patients that are not on TH treatment, given the outcome of the model fits?

**Question 9)**

Fit a linear model to the ln-transformed concentration values of all individual patients in both treatment arms and make a table that includes ID number, treatment arm and the concentration at time = 0 (time0).

**Question 10)**

The concentration at time0 = dose / distribution volume. Assume that the distribution volume in the population is normally distributed and determine whether there is a statistically significant difference in the distribution volume of phenobarbital for patients with TH treatment and patients without TH treatment.