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Statistical methods for the evaluation of bleeding frequencies in haemophilia trials

In haemophilia trials, an outcome of interest is the number of bleeds during a follow-up period, the time from study entry to the end of study or loss to follow-up, and the primary question of interest is whether treatment can reduce the annualized bleeding rate.

Bleeding frequencies are count data with right-skewed distributions and a high proportion of zeros, which create problems for regular linear modelling. Poisson regression is frequently used to model count data. The **simple Poisson model** does not account for the large variability (over-dispersion) observed across patients and the assumptions it requires are too restrictive (successive bleeds assumed to occur independently at a constant rate among all patients). A simple way to account for over-dispersion is to inflate the variance by a factor via a quasi-Poisson approach. No probability distribution is specified in the quasi-Poisson approach.

Mixed Poisson distributions have proved to be an alternative approach for modelling over-dispersed counts. In this distributional family, over-dispersion is modelled by a random effect for the mean, allowing each patient to differ from the others in the number of bleeds. When the mean in the Poisson model is assumed to follow a Gamma distribution (Poisson-Gamma mixture), the resulting distribution for the counts is the **Negative Binomial (NB) distribution.** Considering a larger family of mixture models includes the **Poisson-Inverse Gaussian (P-IG) mixture** in which the mean of the Poisson model is random, following the Inverse Gaussian distribution.

We have investigated distributions of bleeding frequencies based on data of one of our haemophilia trials. Maximum-Likelihood estimates were derived for the parameters of the NB and P-IG distribution and observed empirical distributions were compared versus estimated distributions via graphical inspection. We found that the NB distribution provides a reasonable good description of the observed data in the two groups. In particular, NB was superior to P-IG in accounting for the high number of zeros.

Finally, we cover **sample size and power estimation**, conducted by simulation with negative binomially distributed randomly generated data and using the generalized linear model (GLM) and maximum likelihood based estimation.