To present an example of Bayesian Network Meta-Analysis for time-to-event outcomes including both ‘traditional’ approaches based on relative effect Hazard-Ratio under proportional hazards (PH) assumption and more flexible parametric approaches that relax the PH assumption.

**Background**

- Time-to-event outcomes are important in oncology: overall survival and progression-free survival times are generally the primary endpoints in clinical trials of treatments for advanced cancer. Typically, the treatment effect is measured by the hazard ratio that relies on the assumption of proportional hazards (PH) between two treatment arms. Recent publications of clinical trials related to new immunological drugs showed a slight delay in treatment effect at the early stage of follow-up (e.g. KN-045), compared to standard of care such as chemotherapy. This suggests further investigation of the PH assumption.
- Non-proportional hazards (NPH) assessment is common for individual patient data (IPD). NPH assessment is less common in traditional pairwise meta-analyses (MA) and network meta-analyses (NMA) with time-to-event, where only published aggregated data are available. HTA agencies want to assess NPH in aggregated data from MA or NMA. The observed departure from PH assumption in individual trials may extend to the context of aggregated data.
- We conducted a case study of NMA to assess the impact of relaxing the PH assumption using published aggregated data of novel immunotherapies compared to standard of care. The fractional polynomial survival models proposed by Jansen (2011), Jansen and Cope (2012) which are alternative flexible approaches to handle appropriately non-PH survival models were used. HRs were illustrated graphically similarly to Amzal et al, 2017.

**Methods**

**Model:**
1. Approach based on relative effect Hazard-Ratio (HR):
   - No baseline effect, normal distribution for log(HR)
   - Likelihood:  \( L = L_1 \times L_2 \times \cdots \times L_n \)
   - For each study \( i \) and arm \( a \), where \( b \) is the reference arm.
   - \( L_i = \frac{1}{\sqrt{2\pi \sigma^2}} e^{-\frac{(y_i - \mu)^2}{2\sigma^2}} \)

2. Relax the Proportional Hazard Assumption

**Results**

**DATA:**
- **Population:** Patients treated for Advanced Melanoma
- **Intervention:** 9 identified treatments of interest
- **Comparisons of interest:** Pembrolizumab Q2W and Q3W, IP+GP100, IP alone and GP100 alone
- **Outcomes:** Overall Survival
- **Studies:** 6 studies, including Keynote 006 and Hodi et al.
- **Sources:** published aggregated data.
- Final 4 pairwise studies considered for illustration purpose

**NPH**

![Image of NPH model](image1.png)

**Hazard-ratio under PH assumption**

![Image of PH model](image2.png)

**Conclusions**

The results suggest that both unidimensional parameter as the HR under PH and more sophisticated time-dependent HR derived from parameter estimates are complementary for a correct interpretation, each one overcoming the limitation of the other. On one hand, constant HR can always be interpreted as an average treatment effect over time, in the other hand time dependant HR informed on the pattern of treatment effect.