Case study comparing anchored vs unanchored approaches to deriving time-varying hazard ratios under violation of the proportional hazards assumption

Hera Sandhu[1], Georgios Nikolaidis[1], Anastasios Tassoulas[2], Jennifer Gaultney[1]
[1]IQVIA, London, UK, [2]IQVIA, Athens, Greece; Contact: Hera Sandhu (hera.sandhu@iqvia.com)

Background

- Indirect treatment comparisons (ITC) of survival outcomes are typically derived in connected networks, with or without population-adjustment, just as any other continuous outcome, provided that the assumption of proportional hazards (PH) holds
- When PH does not hold, the hazard ratio (HR) cannot be considered constant through time, and a time-varying relative effect should be used

Objectives

- The focus of this research was the derivation of time-varying indirect HRs in the context of an anchored and unanchored ITC, in a case study in late-stage oncology where PH did not hold for any of the constituting direct comparisons

Time-varying HR overview

- The technique explored in this analysis is summarised below:
  - **HRs from fitted survival models** – time-varying HRs are generated from the hazard profiles of fitted parametric survival models (described in greater detail in Methods)
- However, there exist multiple other methods to derive a time-varying HR. Common techniques used in cost-effectiveness analysis are described below (and the relative advantages and disadvantages are described in Table 1):
  - **Fractional polynomial network meta analysis (FPNMA)** – the hazard over time for a connected network of pairwise comparisons are modelled using a multi-dimensional treatment effect (1)
  - **Multiple constant HRs** – the time horizon is divided into a sequence of intervals and a constant HR generated for each period

Table 1: HRs from fitted survival models approach advantages and disadvantages

Advantages
The increased speed/reduced complexity, and use in an unanchored ITC vs. FPNMA
There is no subjective break point needed to divide the time horizon into intervals, as is the case with the multiple constant HR approach
Disadvantages
Treatment differences are reflective of the parametric form rather than the treatment effect i.e. hazard ratios are directly derived from hazard profiles of the fitted survival curves and not vice versa
There is the assumption that the treatment effect or covariates are additive on the log hazard scale. This is a stronger assumption when compared to the interaction of the treatment effect in FPNMA

FPNMA: Fractional polynomial network meta analysis; HR: Hazard ratio; ITC: Indirect treatment comparison

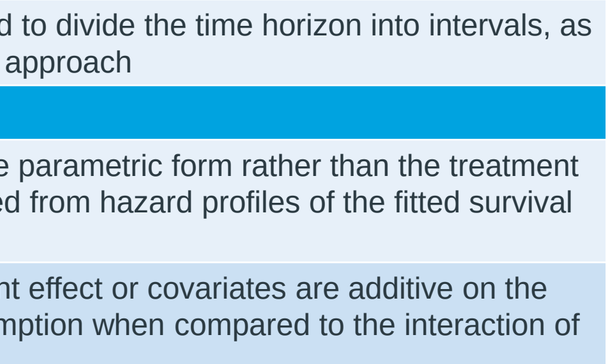
- It should be noted that all of these approaches, when analysing an anchored ITC, have a risk of bias when effect modifiers are not similarly distributed across the compared trials. The HRs from fitted survival models and multiple constant HRs approaches are also affected by any imbalance in prognostic factors when analysing an unanchored ITC

Methods

1. PH testing

- Population-adjusted Kaplan-Meier (KM) curves for overall survival and progression-free survival (PFS) were obtained from trial A (active-treatment-A, *A* vs placebo, p^A) and trial B (active-treatment-B, *B* vs placebo, p^B) and digitized using the Guyot algorithm (2)

Figure 1: PFS KM curves of trial data



KM: Kaplan-Meier; PFS: Progression-free survival

- The PH assumption was tested within each trial and shown to be violated in PFS using the Grambsch and Therneau's test and visual inspection of log-log hazard and Schoenfeld residual plots

2. Survival model fitting where PH does not hold

- Standard independent parametric models were fit to all trials' PFS arms and the time-varying hazard profiles of each parametric model were obtained, where $h_{jk}(t)$ is defined as the hazard of trial arm *j* with model *k* at time *t* (3)

3. Generating anchored and unanchored time-varying HRs

- The model *k* was constant for each trial arm *j* so the treatment effect or covariates are two-dimensional on both the shape and scale model parameters, and reducing obfuscation by differing model parameterisation
- The HR of *A* vs *B* with model *k* at time *t*, $HR_{ABk}(t)$ is presented as follows in the unanchored (Eq. 1) and anchored (Eq. 2) ITC:

$$\ln(HR_{ABk}(t)) = \ln(h_{Ak}(t)) - \ln(h_{Bk}(t)) \quad \text{(Eq. 1)}$$

$$\ln(HR_{ABk}(t)) = \ln(h_{Ak}(t)) - \ln\left(h_{p^A{}_k}(t)\right) - \left(\ln\left(h_{Bk}(t)\right) - \ln(h_{p^B{}_k}(t))\right) \quad \text{(Eq. 2)}$$

- The statistical fit within the anchored and unanchored ITC, for each model *k* is evaluated using the sum of the Akaike information criterion (AIC) or Bayesian information criterion (BIC) across all trials' arms *j*

Results

Figure 2: Time-varying HR, anchored & unanchored ITC comparisons by model

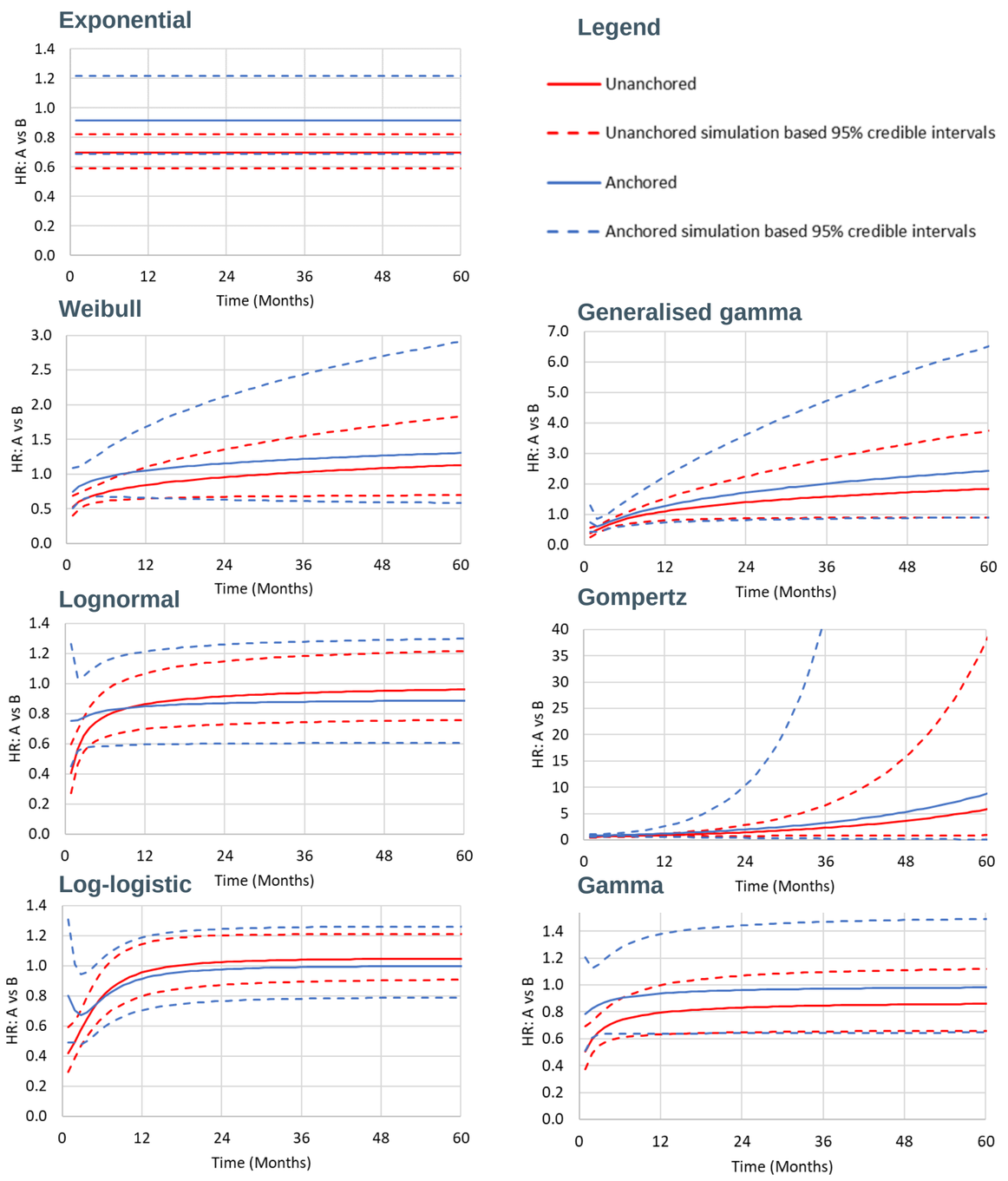


Table 2: Statistical fits for anchored and unanchored ITC models

Model	Anchored		Unanchored	
	AIC (rank)	BIC (rank)	AIC (rank)	BIC (rank)
Exponential	4415 (6)	4429 (6)	3057 (7)	3064 (6)
Weibull	4359 (5)	4387 (5)	3024 (5)	3039 (5)
Lognormal	4162 (3)	4190 (2)	2947 (2)	2962 (1)
Log-logistic	4158 (2)	4187 (1)	2968 (3)	2984 (3)
Gompertz	4415 (7)	4443 (7)	3054 (6)	3069 (7)
Gen. gamma	4154 (1)	4196 (3)	2946 (1)	2969 (2)
Gamma	4304 (4)	4332 (4)	3005 (4)	3020 (4)

AIC: Akaike information criterion; BIC: Bayesian information criterion; Gen. gamma: Generalised gamma

Conclusion

- **For an anchored ITC, the approach may be beneficial since it theoretically can compensate for prognostic factors, but the approach yielded additional uncertainty due to a larger number of arms included in the hazard extrapolations and HRs**
- **The approach did not suit either ITC for models with hazards tending to zero (small hazards generating skyrocketing HRs)**
- **Consequently, the methodology should not be used in isolation but supplemented with statistical testing, evaluating the similarity of HR outcomes across models, considering extreme values and clinical plausibility**
- **Future research is warranted, exploring the comparison of other time-varying HR methodology**

Source: 1) Jansen 2011, Network meta-analysis of survival data with fractional polynomials; 2) Guyot 2012, Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves; 3) Jackson 2016, flexsurv: A Platform for Parametric Survival Modelling in R

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