Health technology assessment (HTA) bodies require lifetime estimates of mean costs and outcomes for treatment and control groups. The IPD can then be used for pairwise meta-analysis and network meta-analysis (NMA) are commonly used to estimate relative treatment effects for time-to-event endpoints, which should be based on systematic reviews of the clinical literature.

These analyses often use published hazard ratios (HR) as the measure of relative treatment effect. However, we believe TRs are not commonly utilised in evidence synthesis due to uncertainty in interpretation, which may have discouraged their use. In addition, TRs are rarely reported in clinical trial publications. Therefore, evidence synthesis conducted for cost-effectiveness analysis should no longer rely on point estimates of treatment effects or on the assumption that the PH assumption holds. This assumption can be tested by plotting the cumulative hazard against time (either log-log or Gompertz) for treatment vs. control. The PH assumption is satisfied if the resulting line is parallel.

Time ratios (TR), which are estimated from accelerated failure time (AFT) models, are recognised as an alternative measure of relative treatment effect when the PH assumption is violated, provided the associated AFT assumption holds. ATRs can be calculated directly from published survival curves. The direction of the treatment effect is equivalent for HRs and AFs.

HRs act on the baseline hazard scale (Box 1):
- HR = 1, the event hazard is smaller on treatment vs. control
- HR > 1, the event hazard is larger on treatment vs. control
- HR < 1, the event hazard is smaller on treatment vs. control

An example of how to interpret a HR is provided in Box 1.

TRs act on the log-hazard scale (Box 1):
- TR > 1, TR < 1, the time-to-event is shorter on treatment vs. control
- TR = 1, TR = 1, the event hazard is equal on treatment vs. control
- TR = 1, the time-to-event is equal on treatment vs. control

A TR of 1 represents the relative treatment effect.

These should be based on systematic reviews of the clinical literature. HRs are commonly reported in clinical trial publications, which makes them less accessible than TRs for evidence synthesis. Survival data is commonly presented graphically as a KM curve which can be re-constructed. Reconstructed IPD or summary survival data can be used to estimate TRs using AFT parametric survival models.

Conclusions

- TRs are alternatives to HRs as relative treatment effect that can be considered in cases where the PH assumption does not hold, provided the associated AFT assumption holds.

- Application of HRs when the PH assumption is violated can lead to biased estimates of relative treatment effect.

References

- Parkes, D. Health technology assessment (HTA) bodies require lifetime estimates of mean costs and outcomes for all relevant technologies.