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Survival Analysis – methods often used in HTA

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What is survival analysis and why do we need it?

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Survival analysis: Intro

- The analysis of time-to-event data from a specified time origin (e.g. randomisation) until the occurrence of a particular event or endpoint (e.g. disease progression, death, incidence of complication etc.)

- Main problem and distinguishing feature of survival data:

  ➔ Sometimes events are not experienced during the study or follow-up period.

  ➔ This results in incompletely observed outcomes, called censored observations

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Why survival analysis?

- Uses information from censored patients – standard methods (eg logistic regression) would not
- Estimates how long it takes to experience event
- More informative and sensitive than rates at arbitrary point of time
- **Most importantly for economic evaluation – we can use survival analysis to extrapolate survival data and estimate mean survival times**

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Overview of survival analysis methods commonly used in NICE TAs

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Background

- Survival estimates are important parameters in a large % of HTAs
  - Eg, ≈40% of NICE Appraisals are in cancer area. Several others will also include survival data
- **Problem:** Survival data is rarely complete due to limited follow-up
  - Need to extrapolate to estimate total survival effect
  - Key for estimating total QALY gain
  - Need to fit some type of model to extrapolate

➔**But several modelling options are available**

- Potential for inconsistencies in methodology used, evaluation results and subsequent recommendations

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Parametric survival models

- Parametric survival models use the assumption that the survival data follows an underlying probability distribution
- Hence survival can be predicted beyond the end of the trial
- Several parametric survival models exist, e.g.:
  - Exponential
  - Weibull
  - Gompertz
  - Log-logistic
  - Log normal
  - Generalised Gamma

➔ **The key is to pick the most appropriate model based upon the plausibility of the underlying probability distribution**

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What is the ‘state of the art’?

- Different survival models will be appropriate in different circumstances

➔ The use of different models in different HTAs is not necessarily a problem

➔ **However, often chosen methods are not systematically justified**

➔ This could lead to the most appropriate survival model **not** being chosen

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What is the 'state of the art'?

- Reviewed 45 NICE TAs in advanced cancer

Method for Estimating Mean	Number of TAs (%)
Restricted Means	17 (38%)
Parametric Models	32(71%)
Weibull	23 (51%) (72%)
Exponential	20 (44%) (63%)
Gompertz	6 (13%) (19%)
Log-logistic	9 (20%) (28%)
Log normal	6 (13%) (19%)
Gamma	2 (4%) (6%)
Piecewise modelling	1 (2%) (3%)
Other 'hybrid' methods	2 (4%)

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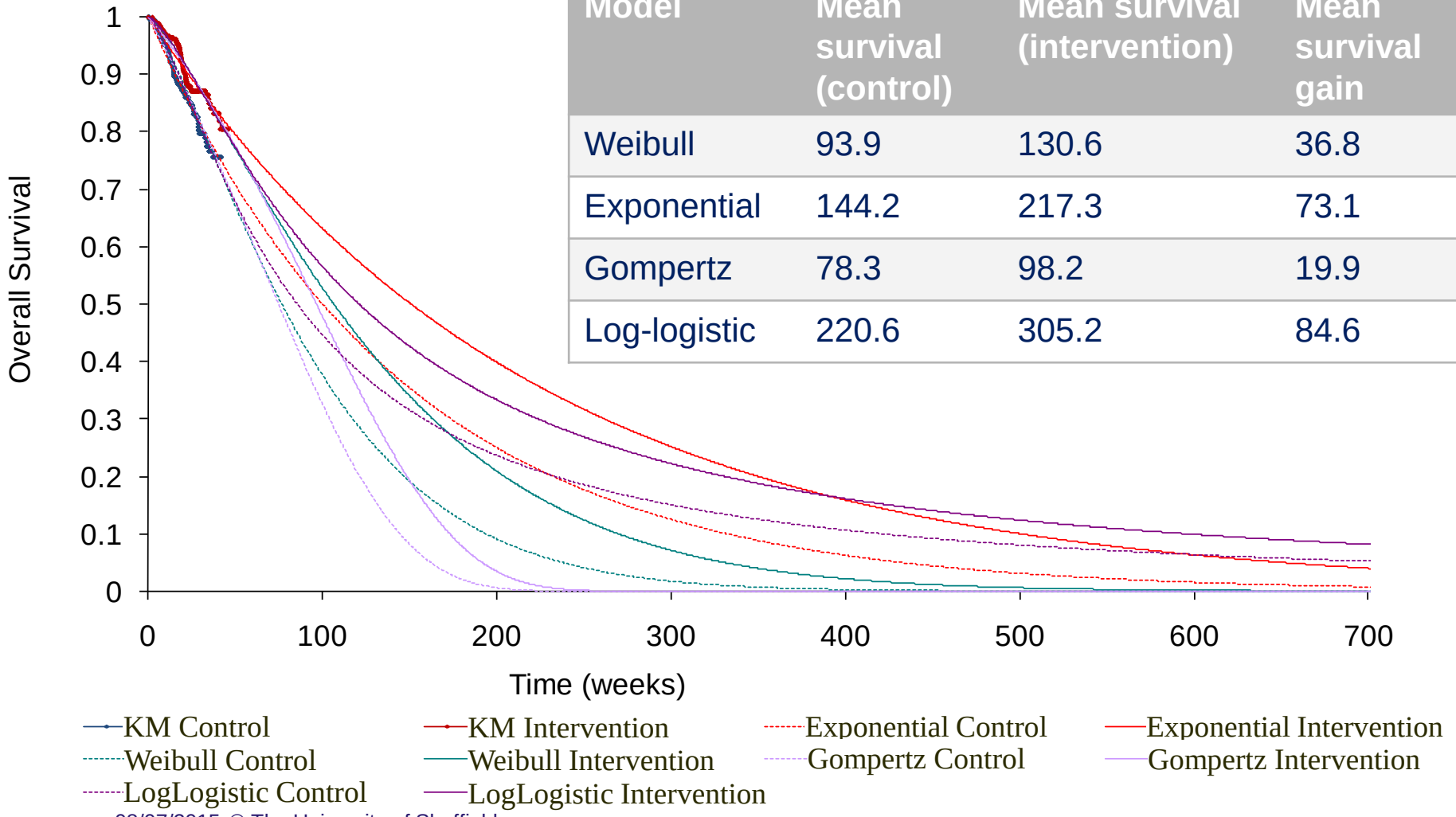
What is the 'state of the art'?

Method for Justifying Approach	Prevalence in TAs
Statistical tests	Relatively rare and not systematically done in combination with other methods of justification
AIC test	
BIC test	
Sum of squared deviations	
-2 log likelihood statistic	
Log cumulative hazard plot	
Other tests of the hazard function	
Visual inspection	Common, but often only 1 or a subset of possible models
External data	Rare
Clinical validity	Rare

Does it matter?

Model	Mean survival (control)	Mean survival (intervention)	Mean survival gain
Weibull	93.9	130.6	36.8
Exponential	144.2	217.3	73.1
Gompertz	78.3	98.2	19.9
Log-logistic	220.6	305.2	84.6



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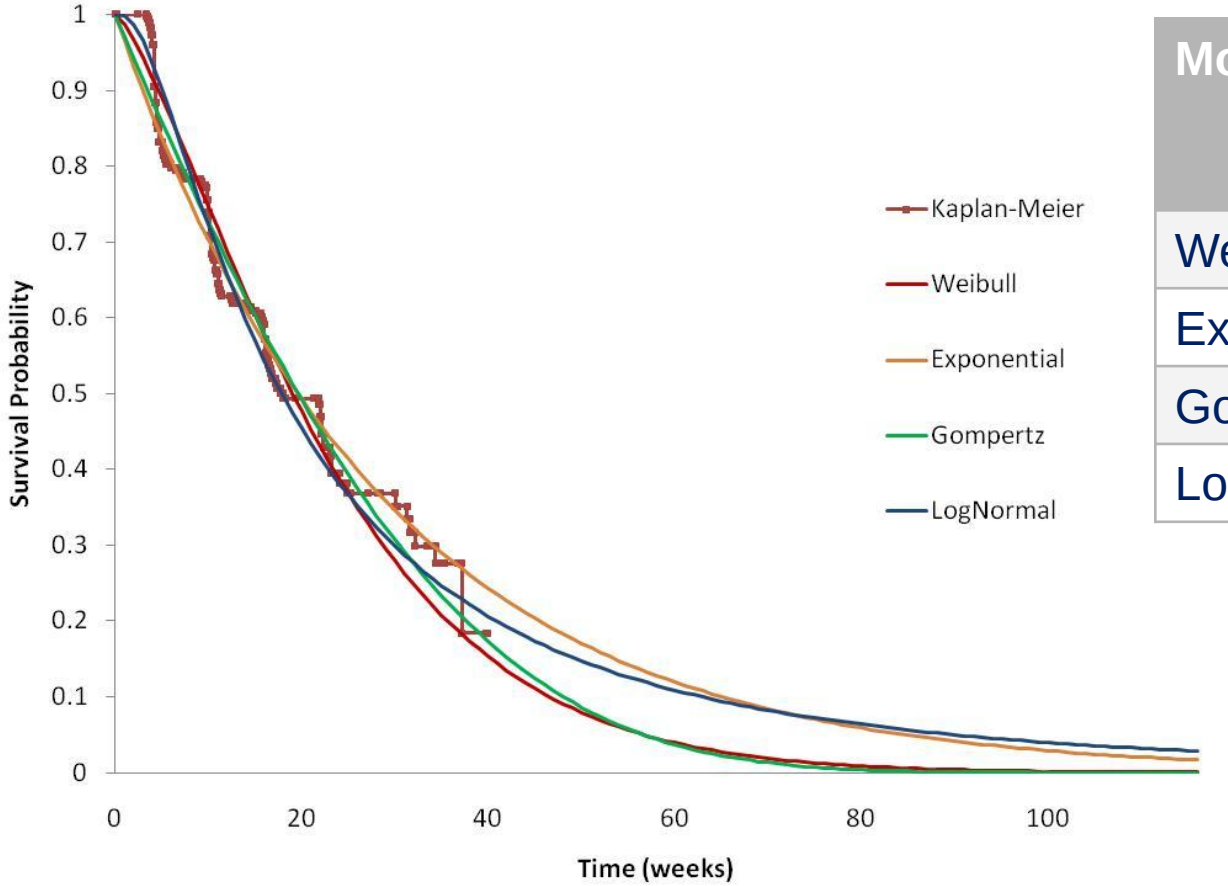
Does it matter?



Model	Mean Survival (weeks)
Weibull	22.9
Exponential	28.3
Gompertz	23.1
Log Normal	28.9

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‘State of the art’ summary

- A wide variety of models are used
- **Chosen models often not systematically justified**
- Standard models were usually used – very little use of more flexible models (Generalised F, Generalised Gamma, Piecewise models, spline-based models)
- Too often there was a reliance on justification by visual inspection of a small number of models
- External validity / clinical plausibility was rarely addressed

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A familiar story?

http://www.youtube.com/watch?v=MyaVq-UPD2A

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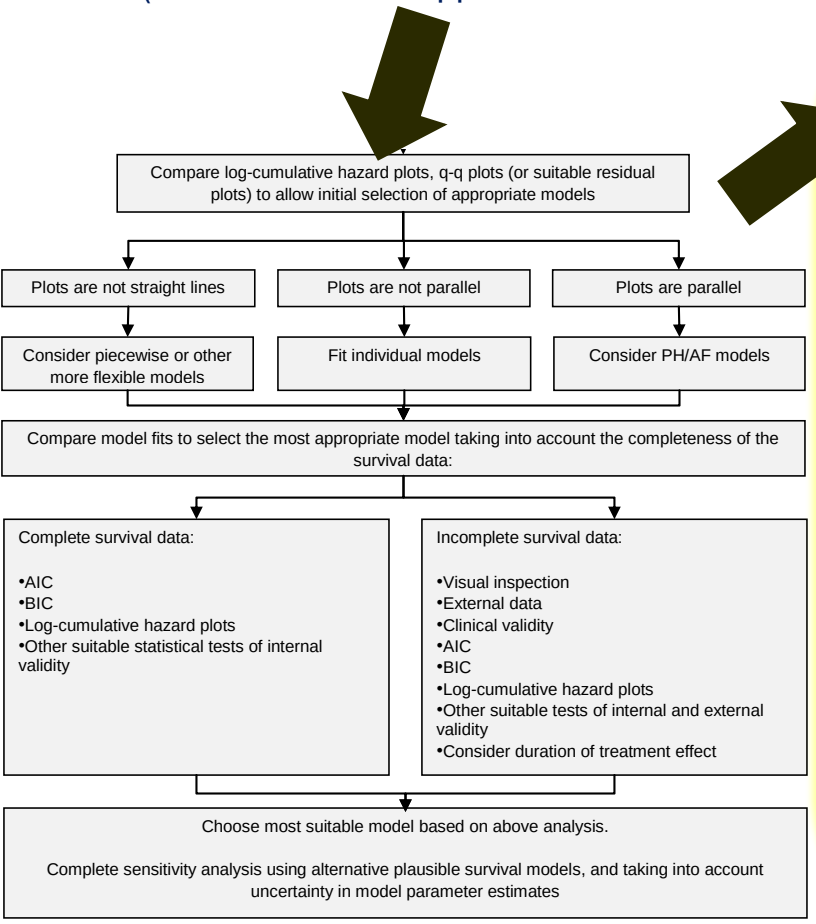
Recent developments

Choosing a model

- We need to take a systematic approach to survival modelling

➔NICE DSU have published a technical support document

(DSU Technical Support Document and Latimer MDM paper (2013))



- Construct plots to examine PH and AF assumptions
- Consider proportional treatment effect and fit appropriate models
- Assess internal validity of models (stats tests, monotonicity of hazards over time)
- Analyse external validity (external data, clinical plausibility)
- Present sensitivity analysis using alternative models
- **Don't just pick a Weibull!**

More complex methods

- Sometimes the standard parametric models won't be appropriate
  - Hazard plots will have kinks in them
  - Predicted survival times will not match up with external data
  - Models will not fit the data well
- In these circumstances other approaches are required:
  - Piecewise models
  - Royston and Parmar's flexible spline-based parametric models
  - Bayesian methods and explicit use of external information/data
- Note: extrapolation not based on fact (by definition) – opinions on how to extrapolate may differ. Impossible to ascertain "best" answer

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Conclusions

- We need to take a systematic approach to survival modelling
- Survival analyses often a key focus in HTA appraisals
- Some lack of consensus remains
  - Should we start with ‘standard’ models and go through the DSU TSD process
  - Or disregard these and move straight to other methods
- Further research is highly desirable
  - E.g. how to define and measure “valid” and “plausible”, how best to use external information/data

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Further reading

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- Royston, P. and Parmar, M.K.B. Flexible proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. *Statistics in Medicine 21:2175-2197; 2002*
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