Flexible survival analysis approaches

Flexible survival methods:

We consider a range of advanced survival techniques not covered by previous TSDs, but that have started to appear in use:

- **Flexible parametric survival methods** (splines, fractional polynomials).
- **Cure models.**
- Other **mixture modelling** approaches.
- **Piecewise models.**
- **Landmark approaches.**
- **Incorporation of external reference rates** (as a competing risks approach).

Be explicit:

- What is the shape of the hazard function in the short- and long-term? **Plot it**.
- What are the **assumptions** of the approach? Are they reasonable?
- Have you considered the **effect of ageing**/competing mortality?
- Plot the marginal hazard function based on reference or registry population rates. Do the extrapolated hazards look **reasonable** in contrast?
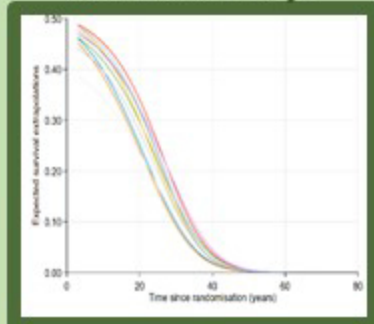- Justify why the method being used is **appropriate** to capture the likely survival for the cohort.

External data for ageing?
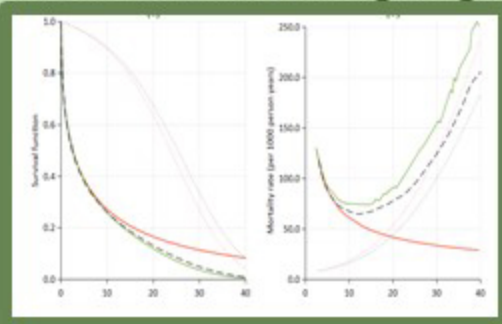
Plotting assumptions.
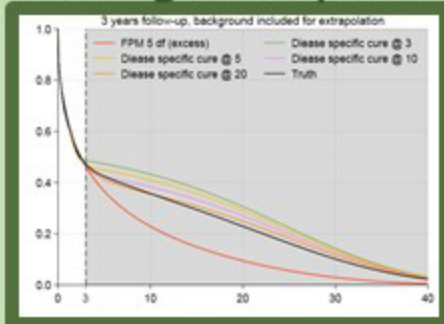
Uncertainty?

Short-term fit vs long-term assumptions:

- Allow sufficient flexibility of shape for hazard functions.
- May be a balance between the best method for extrapolation vs the best fit in the short-term.
- Evaluate and consider internal fit within the range of the data.
- Crucial also to consider what each approach assumes beyond the range of follow-up.
- Discuss the potential to couple complex modelling within the range of trial data with external information/data to make more plausible extrapolations.

  We simulate scenarios to stress our key points.

General Recommendations:

I. Fitted and extrapolated hazard and survival functions should always be presented.

II. A plot of the expected (general population) survival and hazard functions should be given as context for extrapolations.

III. Incorporation of background mortality should be strongly considered to avoid very poor extrapolations.

IV. Consider other external information (e.g. registry data) to help model long-term survival. More research needed.

V. Careful thought needed on how to extrapolate the effect of the intervention (long-term treatment effects).

All models make important assumptions and have limitations. Complex models do not solve all extrapolation problems, but may be useful