Session Title: 121 - Frontiers in Survival Analysis for Health Technology Assessment

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Incorporating external opinion in survival extrapolations to inform long-term survival projections for HTA

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Abstract

Incorporating External Opinion in Survival Extrapolations to Inform Long-Term Survival Projections for Health Technology Assessment

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OBJECTIVES: Accurate long-term survival estimation is critical for health technology assessments (HTA), yet many trials lack sufficient follow-up, necessitating extrapolation to inform decision making. This study assessed the incorporation of expert opinion on survival extrapolations, using data from CheckMate-214 investigating nivolumab plus ipilimumab (NIVO+IPI) for advanced renal cell carcinoma as a case study.
METHODS: A three-state partitioned survival model was developed using digitized trial data to evaluate overall survival (OS) and progression-free survival (PFS). Standard parametric survival models were initially fit to these data and assumed hypothetical expert opinions were then incorporated by penalizing the likelihood function. Cost-effectiveness was assessed from the UK National Health Service perspective over a lifetime time horizon. Both deterministic and probabilistic sensitivity analyses were used to assess the robustness of the results.
RESULTS: Incorporating hypothetical expert opinion at one time point which indicated a clear survival benefit for the intervention arm reduced uncertainty in OS predictions and lowered the incremental cost-effectiveness ratio (ICER) for NIVO+IPI from £41,893 / quality-adjusted life year (QALY) to £27,685 / QALY. Patients receiving NIVO+IPI experienced increased incremental QALYs due to prolonged survival. The ICER fell below the £30,000 willingness-to-pay threshold, suggesting cost-effectiveness under these hypothetical survival assumptions. Deterministic and probabilistic sensitivity analyses were in accordance with the base-case results.
CONCLUSIONS: In the absence of long-term trial data, expert opinion can enhance long-term accuracy and reduce uncertainty in survival extrapolations. In this case study, expert-elicited insights sufficiently improved the ICER to fall below the commonly accepted threshold. However, only one method for incorporating expert opinion was examined, warranting further exploration of alternative methods to validate and expand these findings. Linking these efforts to structured expert elicitation, could enhance the reliability of findings compared to informal methods. Further research should refine these methods and assess their broader impacts on HTA decision making.

What is the problem with the current approach to survival analysis?

Survival analysis forms the foundation of robust cost-effectiveness modelling, especially in oncology where it directly influences treatment decisions and patient outcomes.

> Survival analysis has **large implications** for healthcare decision making.

> The selection of extrapolated curves is **highly influential**, and often a driver of cost-effectiveness.

> At submission stage immature survival data leading to **uncertainty in long term projections** may **delay access** to innovative treatments for patients.

> Currently there is **no clear consensus** on the **method to incorporate expert opinion into long term survival projections,** other than validating curve selections based on expert knowledge.

How can expert opinion be incorporated into survival extrapolations?

> We conducted a targeted literature review to identify and understand available methods.

> **Cooney & White** have presented a **general and easily implementable approach** to incorporate various types of expert opinions into parametric survival models using frequentist and Bayesian approaches.[1]

Frequentist

- Expert opinion is **included as a penalty** to the likelihood function.
- **Constrains parameter estimates** towards values consistent with survival probabilities as specific timepoints
- The models are fit using standard optimization method such as:
  - Maximum likelihood estimation.

Bayesian

- Expert belief is treated as a **prior on the survival function.**
- It uses a Bayesian approach to combine expert beliefs with trial data through **Markov Chain Monte Carlo** sampling.
  - $S(t) \sim N(\mu_{expert}, \sigma^2{}_{expert})$
- Blends trial data and expert beliefs in one coherent framework.

Original Research Article

MDM Medical Decision Making

Direct Incorporation of Expert Opinion into Parametric Survival Models to Inform Survival Extrapolation

SAGE

Philip Cooney and Arthur White

Background. In decision modeling with time-to-event data, there are a variety of parametric models that can be used to extrapolate the survival function. Each model implies a different hazard function, and in situations in which there is moderate censoring, this can result in quite different survival projections. External information such as expert opinion on long-term survival can more accurately characterize the uncertainty in these extrapolations. **Objective.** We present a general and easily implementable approach to incorporate various types of expert opinions into parametric survival models, focusing on opinions about survival at various landmark time points. **Methods.** Expert opinion is incorporated into parametric survival models using Bayesian and frequentist approaches. In the Bayesian method, expert opinion is included through a loss function and in the frequentist approach by penalizing the likelihood function, although in both cases the core approach is the same. The issue of aggregating multiple expert opinions is also considered. **Results.** We apply this method to data from a leukemia trial and use previously elicited expert opinion on survival probabilities for that particular trial population at years 4 and 5 to inform our analysis. We take a robust approach to modeling expert opinion by using pooled distributions and fit a broad class of parametric models to the data. We also assess statistical goodness of fit of the models to both the observed data and expert opinion. **Conclusions.** Expert opinions can be implemented in a straightforward manner using this novel approach; however, more work is required on the correct elicitation of these quantities.

Highlights

- Presentation of a novel and open-source method to incorporate expert opinion into decision modeling.
- Extends upon earlier work in that expert opinion can be incorporated into a wide range of parametric models.
- Provides methodological guidance for directly including expert opinion in decision modeling, which is a research focus area in NICE TSD 21.[1]

Keywords

survival models, extrapolation, expert opinion

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> As a pilot use-case of the overall method, the frequentist approach was taken forward in the analysis.

1. Cooney P, White A. Direct Incorporation of Expert Opinion into Parametric Survival Models to Inform Survival Extrapolation. *Medical Decision Making*. 2023;43(3):325-336. doi:10.1177/0272989X221150212

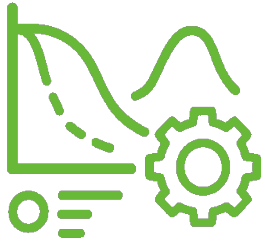
Summary of the process

Expert opinion elicitation

- ***Survival estimates are elicited*** *from experts at one or more time points (e.g. 60 months).*
- *Experts provide a most likely value, upper/lower plausible limits, or standard deviation.*
- *A suitable probability distribution (e.g. Beta, Normal, t) is fitted to represent each expert's belief.*

Coding

- ***Elicited beliefs*** *are encoded using the expertsurv R-package.*
- *These beliefs are integrated into survival models as penalties or prior beliefs (depending on approach).*
- *Pool multiple expert beliefs using linear or log pool*



Survival Analysis

- ***Trial data and expert opinion are combined*** *to improve long-term survival extrapolation.*
- *Models are selected based on goodness-of-fit and clinical plausibility.*

Cost effectiveness analysis

- ***Final model outputs*** *are used to support:*
  - *Cost-effectiveness model*
  - *Scenario analysis and sensitivity testing*
- ***Enhances transparency*** *of survival assumptions used in economic models.*

Common challenges and how incorporating expert opinion may address these challenges

Key challenges	How incorporating expert opinion may help
1. Limited Real-World Data *New product or short trial follow-up*	Provides **systematic expert estimates** when robust data on long-term survival are unavailable.
2. Small Patient Populations *High censoring or low enrolment*	**Supplements minimal trial data** with **expert insights**, improving reliability of survival extrapolation.
3. Uncertain Durability of Effect *Novel mechanisms with unclear longevity*	**Allows clinicians to leverage knowledge of similar therapies** to predict how treatment efficacy evolves over time (treatment waning assumptions).
4. Evolving Standard of Care *Changes in guidelines or competing therapies*	**Incorporates up-to-date expert perspectives** so survival estimates reflect current real-world clinical practice.
5. Payer & Regulatory Uncertainty *Demand for long-term data*	Demonstrates a **transparent, defensible approach to generating long-term survival estimates** despite data constraints.

Case Study

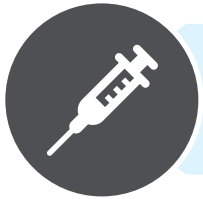
CheckMate 219*

Using hypothetical expert opinion

** This project was conducted by Adelphi Values PROVE™ without any connection to Bristol Myers Squibb. The views and opinions expressed in this case study do not represent those of Bristol Myers Squibb, and the trial was chosen to allow for a hypothetical case study. Results are therefore not indicative of treatment effect.*

Case Study Context: CheckMate 219

Advanced cancer setting
Simpler model structure (partitioned survival model); survival extrapolations heavily influence cost-effectiveness.



Immuno-oncology intervention
Long-term survival tails are expected; expert input helps model uncertainty beyond trial follow up.

Active comparator treatment
Similar mode of action allows for aligned curve selection across arms, reducing structural bias.

CheckMate 219 IPD data was reconstructed using Guyot algorithm.[2]

2. Guyot, P., Ades, A., Ouwens, M.J. et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol 12, 9 (2012). https://doi.org/10.1186/1471-2288-12-9

Hypothetical Expert Opinion

Hypothetical expert beliefs which indicated a clear survival benefit for the intervention arm were elicited from two experts at one timepoint (173 months) and only for overall survival (OS).

	Nivolumab + ipilimumab		Sunitinib	
Parameter	Expert 1	Expert 2	Expert 1	Expert 2
Time-point (months)	173	173	173	173
Distribution	Normal	Normal	Normal	Normal
Mean (% OS)	0.25	0.38	0.08	0.05
Standard Deviation	0.01	0.02	0.01	0.015
Weight	0.50	0.50	0.50	0.50

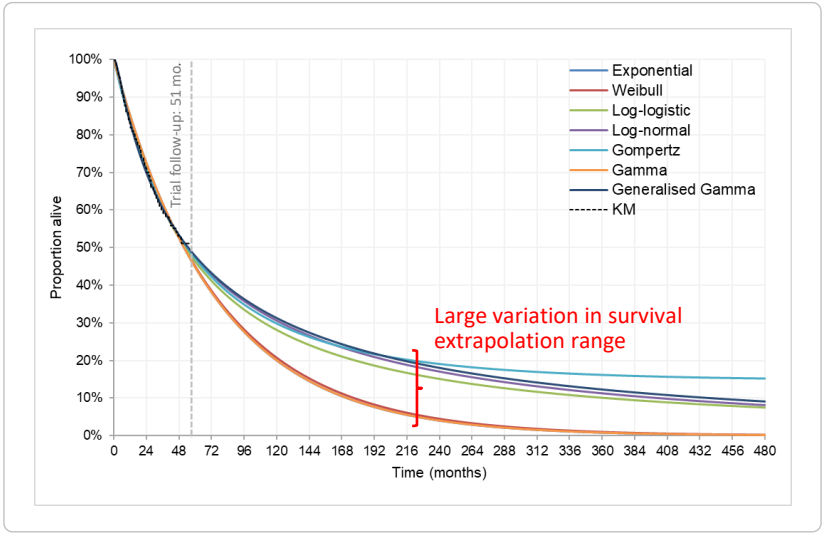
To pool multiple expert beliefs into a single distribution two pooling approaches were used:

- **Linear Pool**: Averaging each expert's survival probabilities (with weights), producing a single composite curve.
- **Logarithmic Pool**: Taking the product (geometric average) of each expert's survival probabilities.

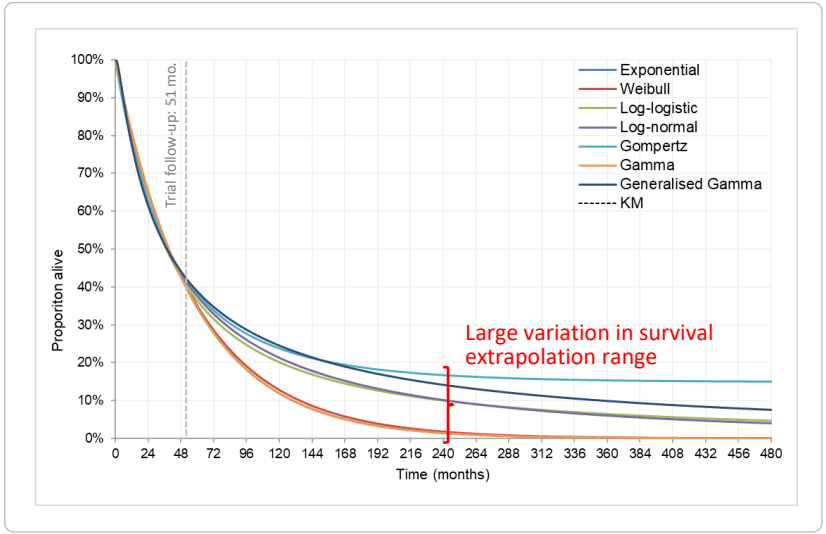
Abbreviations: OS – overall survival

Extrapolations without expert opinion

Nivolumab + ipilimumab



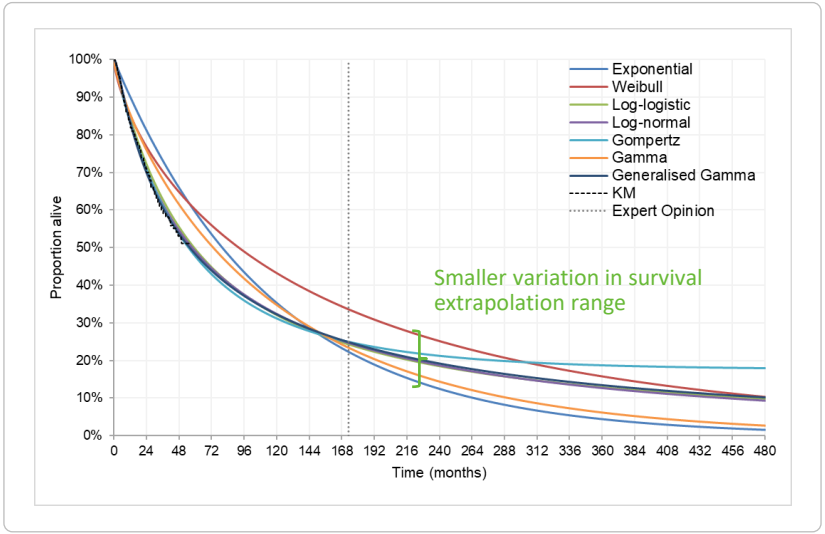
Sunitinib



Long-term survival extrapolations exhibit considerable variability and **may not reflect expert clinical expectations**.

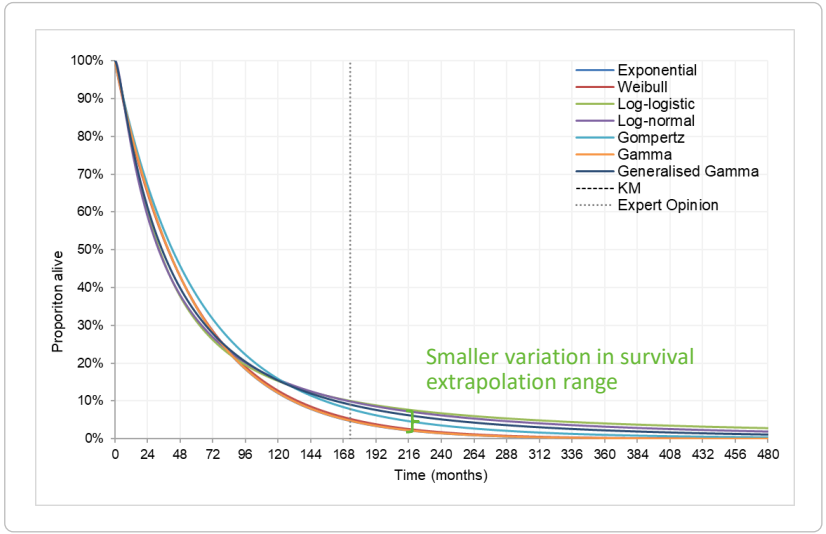
Extrapolations with expert opinion (linear pool)

Nivolumab + ipilimumab



Based on linear pooled expert opinion, overall survival at 173 months is expected to lie between 23% and 41%.

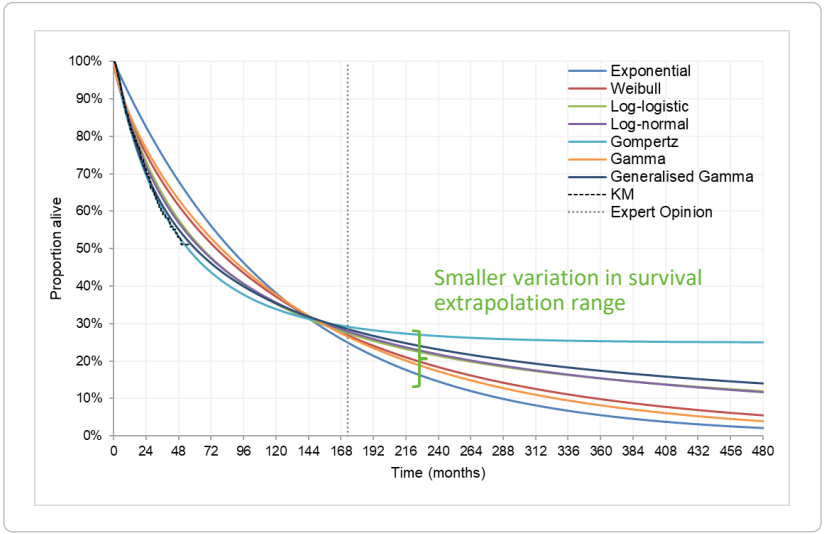
Sunitinib



Based on linear pooled expert opinion, overall survival at 173 months is expected to lie between 3% and 10%.

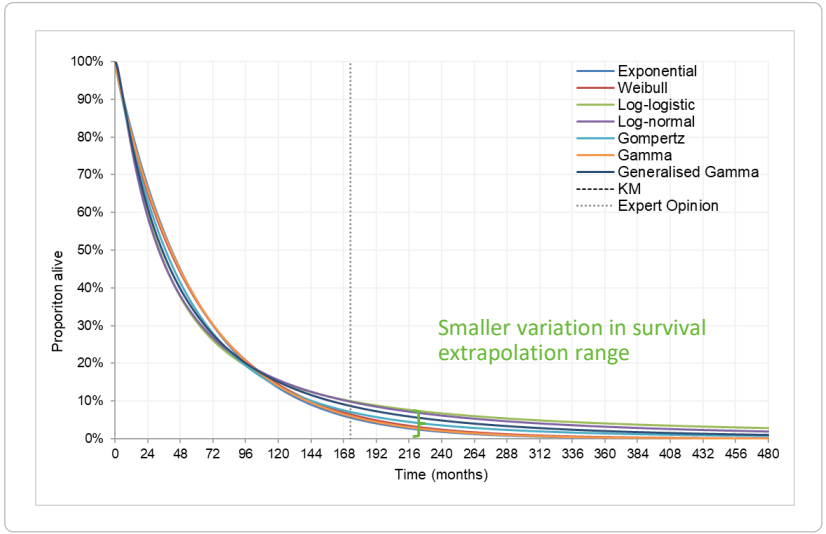
Extrapolations with expert opinion (log pool)

Nivolumab + ipilimumab



Based on log pooled expert opinion, overall survival at 173 months is expected to lie between 25% and 30%.

Sunitinib



Based on log pooled expert opinion, overall survival at 173 months is expected to lie between 4% and 10%.

Results from the hypothetical case study

- Base-case results show that incorporating external opinion in the curves is a key driver for an increase in the number of incremental QALYs as the long-term survival benefit is more pronounced.
- **Compared to a scenario where no expert opinion was incorporated** in the analysis:

Linear pooling of expert beliefs

- ↑ **0.78** Inc. QALYs
- ↑ **£4,276** Inc. Costs
- ↓ **£11,049** ΔICER

Log pooling of expert beliefs

- ↑ **1.15** Inc. QALYs
- ↑ **£6,428** Inc. Costs
- ↓ **£14,208** ΔICER

Abbreviations: Inc. – incremental; QALY – quality adjusted life years

Discussion

There is **no clear guidance** on how to incorporate or elicit* expert opinion specifically for survival extrapolations to support health technology assessment submissions.

Expert belief elicitation can be elicited using a **structured protocol**, like structured expert elicitation to ensure a standardized approach and minimize bias.

This method is useful for new products with limited long-term data. In these cases, expert clinical insight **helps anchor and improve survival extrapolations** beyond standard curve fits..

Further research into alternative methods and elicitation best practices may provide more robust and transparent estimates for decision-making.

** Note: On April 24, 2025, a technical support document (TSD) was published providing guidance on how expert knowledge and uncertainty about long-term survival outcomes should be obtained and reported in health technology assessments. (Oakley J. E., Ren S., Forsyth J. E., Gosling J. P., Wilson K., Latimer N., Rutherford M. J., Uttley L., Fotheringham J., NICE DSU Technical Support Document 26: Expert elicitation for long-term survival outcomes. 2025.)*

Key takeaways

1. When using these hypothetical expert inputs, the survival extrapolations decreased the ICER, bringing it below the UK willingness-to-pay threshold.
2. Although not applied in this case-study, structured elicitation methods can provide transparency and reproducibility when incorporating expert insights.
3. This analysis uses the frequentist method, however future research could compare Bayesian approaches to balance accuracy gains with added modelling and elicitation complexity.

Abbreviations: HTA – health technology assessment; ICER – incremental cost-effectiveness ratio; OS – overall survival; UK – United Kingdom

Thank you for listening

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