Developing Trial-Based Risk Prediction Models: At the Intersection of Clinical Opinion and Data-driven Insights

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Novo Nordisk

PSI, 17-Jun-2024

Can

we use it?

Should

we use it?

HEALTH TECHNOLOGY ASSESSMENT (HTA)

- Benefit-risk
- Quality

- Local comparators
- Local value perspective
- Health care budget
- Etc

Should

we use it?

HEALTH TECHNOLOGY ASSESSMENT

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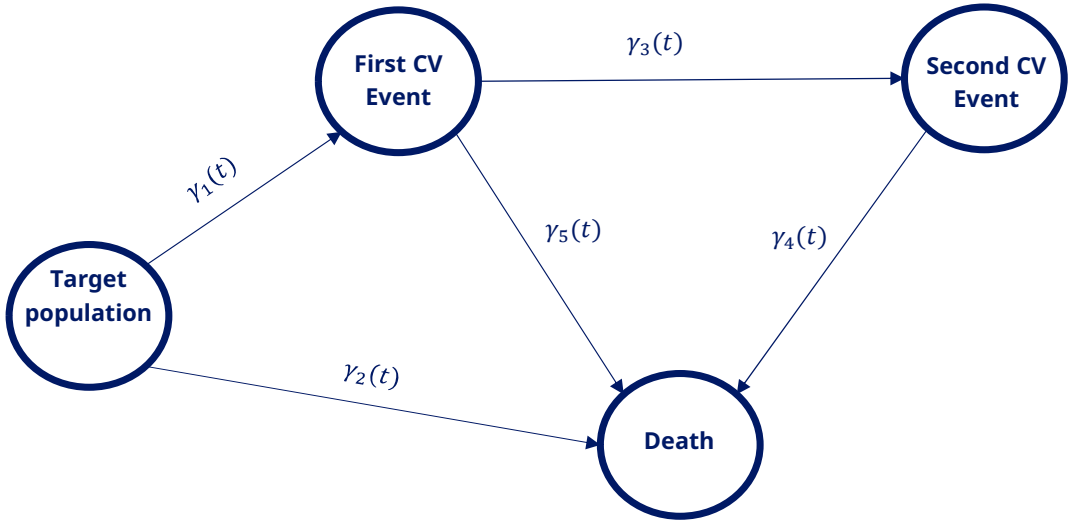
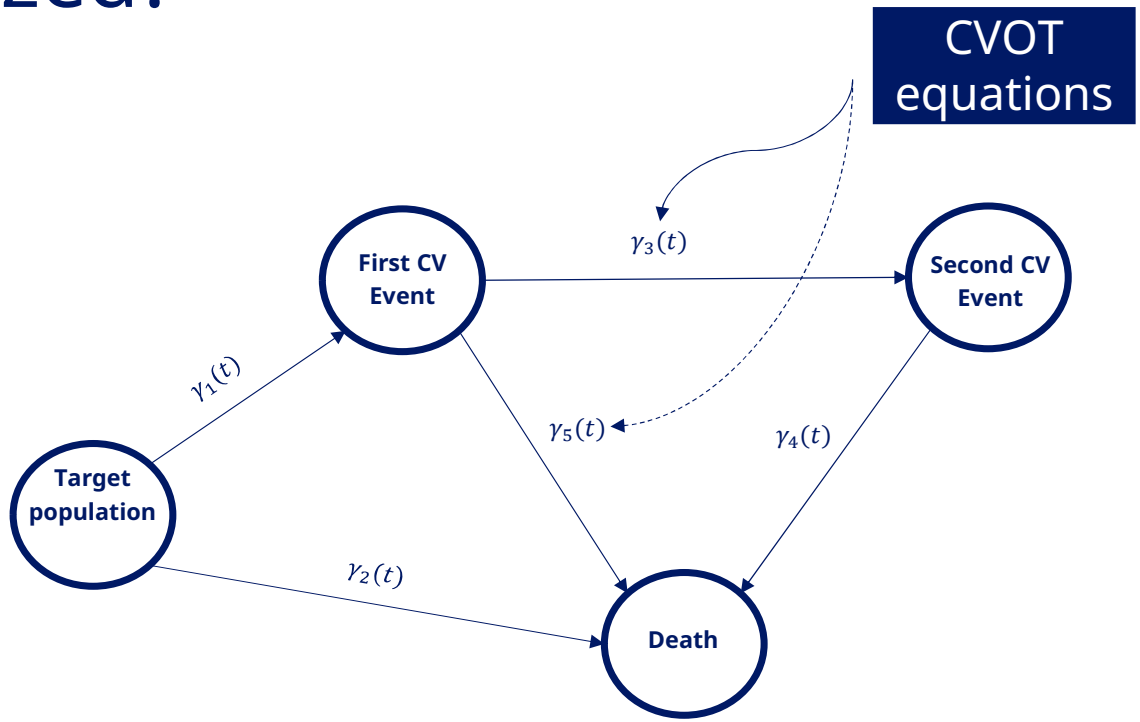
In some markets, cost-effectiveness models used to assess cost-benefit of new treatment vs standard of care, **over a lifetime**

High-level illustration of cost-effectivenes models in secondary CVD prevention



- **Decision Problem for HTA:**
  Compared to how we are currently treating the target population, how will adoption of this new treatment affect the distribution of costs and health benefits?
- **Analytical Approach:**
  - Simulate a cohort of subjects from target population
  - Start subjects on treatment of interest
  - Follow them from disease onset until death
  - Tally up costs to healthcare system and subject quality of life
  - Compare to starting subjects on current standard of care

How is cardiovascular outcome (CVOT) trial data utilized?



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(Simplified) Overview of Statistical Approach for Risk Equation Derivation

Risk Factor Long List

Objective:
Ensure all potential risk factors are considered

Risk Factor effect identified?

Objective:
Ensure feasibiltiy of inclusion of relevant risk factors, the most appropriate form, etc

Risk factor selection

Objective:
Use one of recommended statistical approaches for factor selection (e.g. LASSO)

Finalization

Objective:
Select final set of risk factors for model and validate

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AB0

Formalizing clinical input in HTA setting: NICE guidelines differentiate two approaches

"In the absence of empirical evidence from RCTs, non-randomised studies, or NICE health technology evaluations, registries, or when considered appropriate by the committee taking into account all other available evidence, expert elicitation can be used to provide evidence[...] ***Structured methods*** *are preferred because they attempt to minimise biases and provide some indication of the uncertainty..."*

"Clinical experts and patient experts can also provide opinions (both quantitative and qualitative). This is different to the methods applied for expert elicitation. This could be used to supplement, support, or refute any observed data from RCTs or non-randomised studies. Expert opinion may include any information relevant to the evaluation, including the technology, the comparators and the conditions for which the technology is used..."

NICE health technology evaluations: the manual.
Structured expert elicitation for healthcare decision making A practical guide.pdf (york.ac.uk)

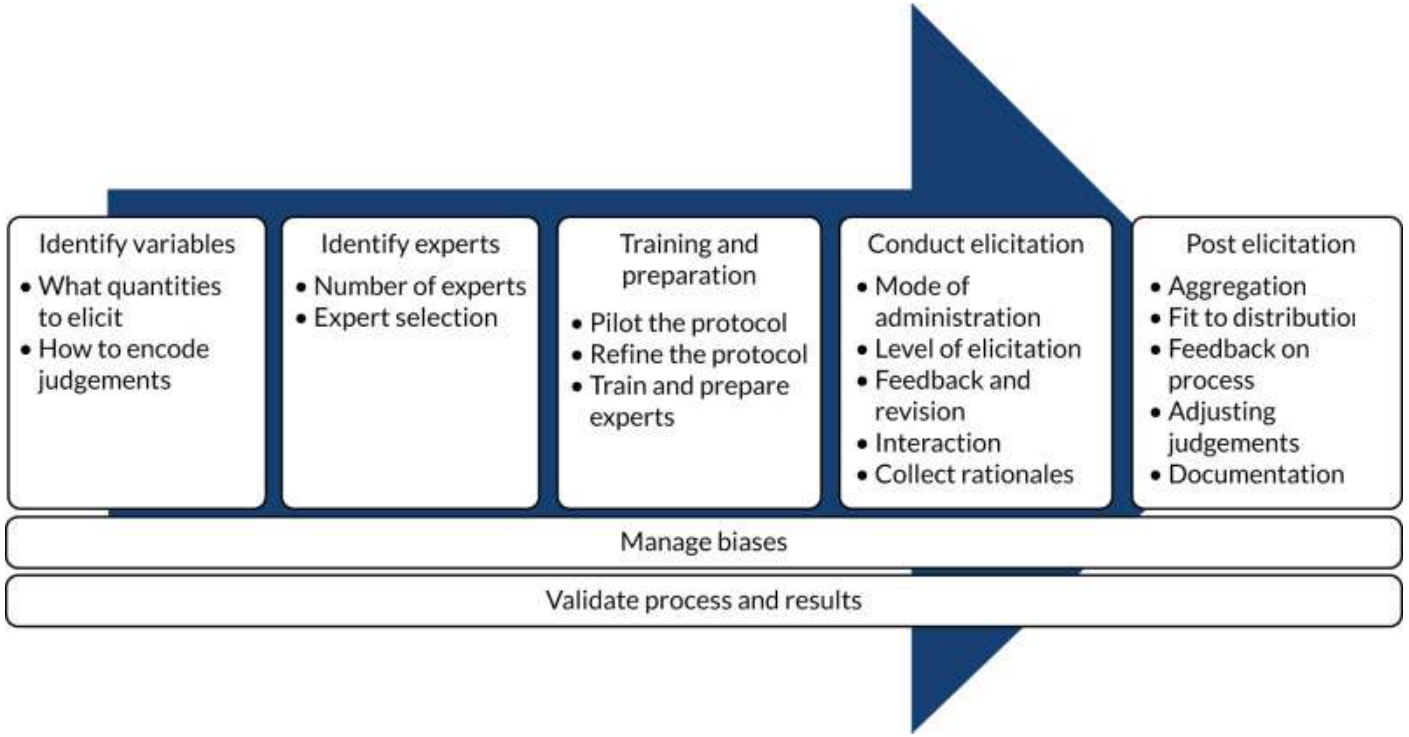
Slide 8

AB0 I think you need a bit more context here. Will a change of the title help? Can you find more cases, and then perhaps deep-dive into some?
AXBQ (Martin Bøg), 2024-05-22T07:28:50.401

MI0 0 Yes, I think cases will help and examples.
MQIV (Milana Ivkovic), 2024-05-22T07:56:01.241

MI0 1 Will try to find some of different types...
MQIV (Milana Ivkovic), 2024-05-22T07:56:16.226

What is the process of structured expert elicitation?



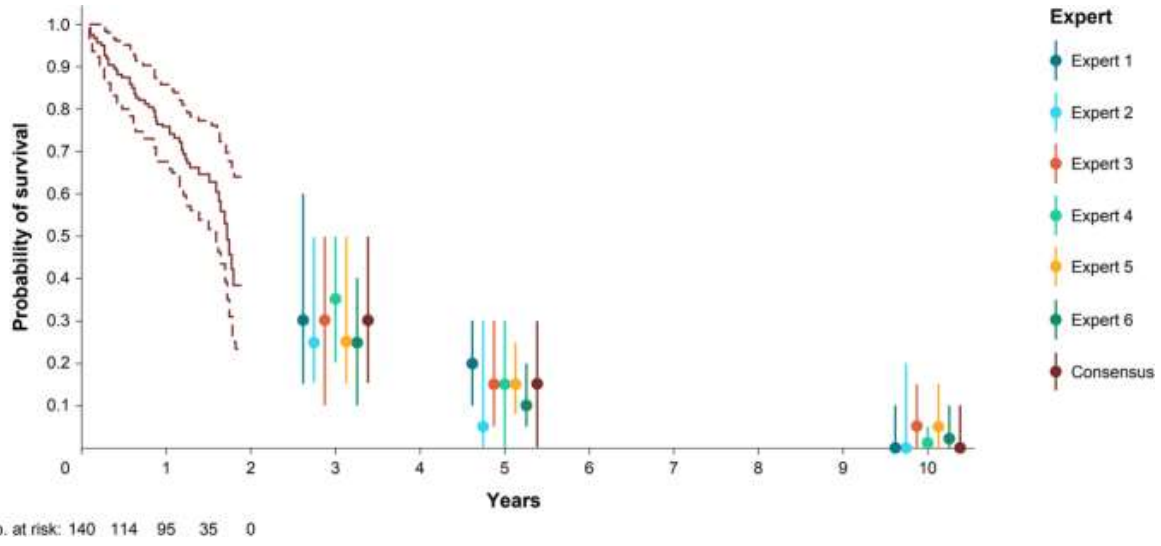
"At each step of the elicitation process, analysts are faced with a variety of methodological choices."

Bojke L, Soares M, Claxton K, et al. Developing a reference protocol for structured expert elicitation in health-care decision-making: a mixed-methods study. Southampton (UK): NIHR Journals Library; 2021 Jun.

Elicitation in HTA setting: case study of CAR T therapy for relapsed/refractory multiple myeloma

"…However, at the time of HTA evaluations, the long-term survival estimate was limited to less than 24 months of follow-up. This evidence is representative of the limited follow-up often available for many new interventions in oncology, where a novel mechanism of action makes it challenging to integrate external evidence regarding long-term survival. Therefore, this case study was used to illustrate how estimates from experts regarding long-term survival can be integrated into parametric models that would otherwise be limited to the IPD from a clinical trial."

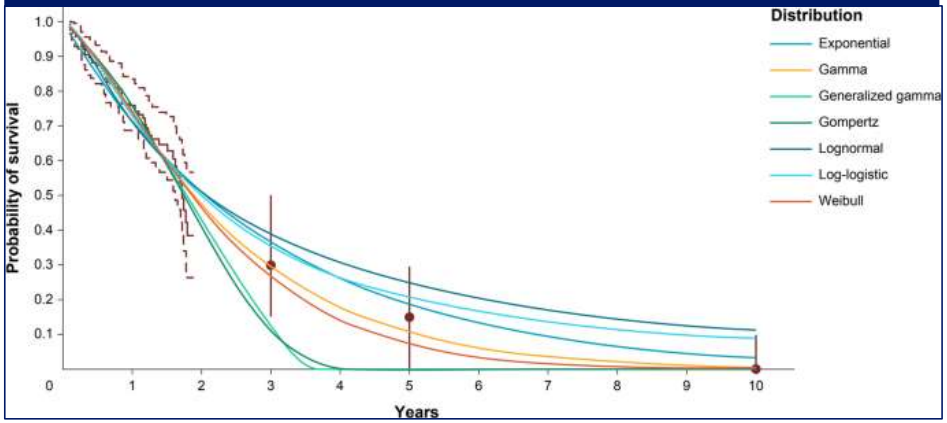
Experts' estimates of upper plausible limits and the most likely value for overall survival.



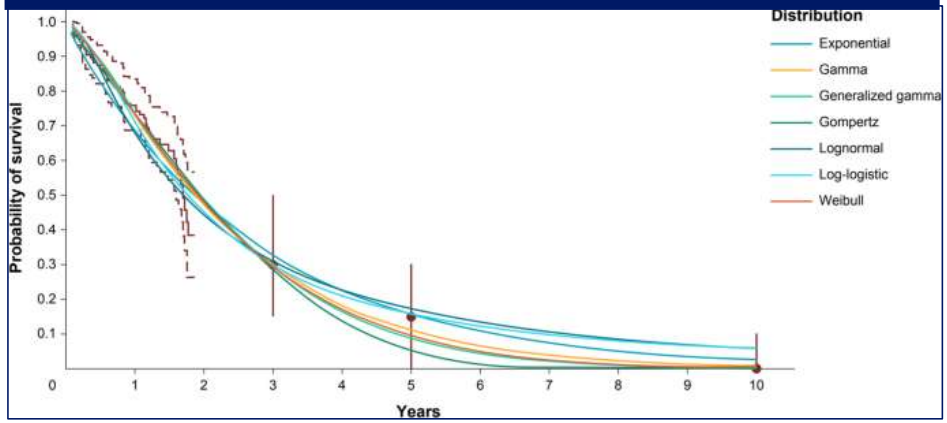
Ayers, D., Cope, S., Towle, K. *et al.* Structured expert elicitation to inform long-term survival extrapolations using alternative parametric distributions: a case study of CAR T therapy for relapsed/ refractory multiple myeloma. *BMC Med Res Methodol* **22**, 272 (2022).

Elicitation in HTA setting: case study of CAR T therapy for relapsed/refractory multiple myeloma

Long term survival estimates, based on observed data only



Long term survival estimates, based on observed data and clinical input



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Clinical input?

Elicitation in Risk Equation Derivation

Risk Factor Long List

Objective:
Ensure all potential risk factors are considered, and all considered are relevant

1. Is a systematic literature review sufficient to capture relevant risk factors?
2. Beyond ensuring completeness, what would be the benefit and feasibility of encoding clinical expectation into our derivation directly (e.g. as priors)?
3. Which approach of collecting input should we use?

Elicitation in Risk Equation Derivation

Finalization

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Select final set of risk factors for model and **validate**

Clinical validation of…?

- Magnitude and direction of estimated risk factors?
- Extrapolations beyond trial horizon?

Can we establish validity in another way?

Elicitation in Risk Equation Derivation

Finalization

Objective:
Select final set of risk factors for model and **validate**

1. How to integrate clinical opinion on validity of estimated magnitude, direction and presence of risk factors?
2. Should we verify plausibility of the extrapolated values or elicit expected quantities and integrate into analyses? Could we use real world data for either of the purposes instead?
3. Which approach of collecting clinical input should we use?

Conclusion

- In an HTA context, there are often questions which we cannot answer directly with clinical trial data (e.g. clinical outcomes over a lifetime in cost effectiveness modeling)
- There is a growing body of research into most appropriate ways to elicit clinical opinion to either validate assumptions or use elicited quantities directly in statistical analyses, and a shift in regulators' expectation in terms of the methodology used
- When approaching a problem, statisticians have a big role to play in the initial stages of framing the research question and assessing benefits and limitations of different ways to address it
- If moving forward with structured expert elicitation, there are additional methodological choices and complexities which require statistical expertise to address: choice of elicited quantities and uncertainty, methods of aggregation, etc.
- Clinical input can be a valuable resource, but requires cross-functional collaboration and thorough planning before implementation.

Thank you!