

Opportunities and challenges applying structured frameworks in future lifetime extrapolation of survival analyses

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- I have no real or apparent relevant financial relationships to disclose.
- I am employed by AstraZeneca BioPharmaceutical Medical Sweden and may have AZ shares and have nothing else to disclose.
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Aim of presentation:

- In this presentation I will give feedback to my previous presenters around the proposals for a framework for **lifetime extrapolation of survival analyses**
- In this session, we will discuss
 - Merits a framework should have in general
 - Challenges faced during survival extrapolation analyses for Dapagliflozin CKD for a low-mortality risk indication as presented in ISPOR workshop 2021
 - Personal opinion about proposals presented by other presenters

Framework first reflections

- Does it solve an important challenge?
- Is it unique
- Does the decision maker(s) agree to the framework/Can it be broadly accepted
- Is it user-friendly/Is it short
- Is it expected to still be valid in 2040
- Is it findable (Will people search for it anyhow?)
- Do case-studies support the easiness of use of the framework
- Are there more important things to do
- There should be room for bespoke work
- ...

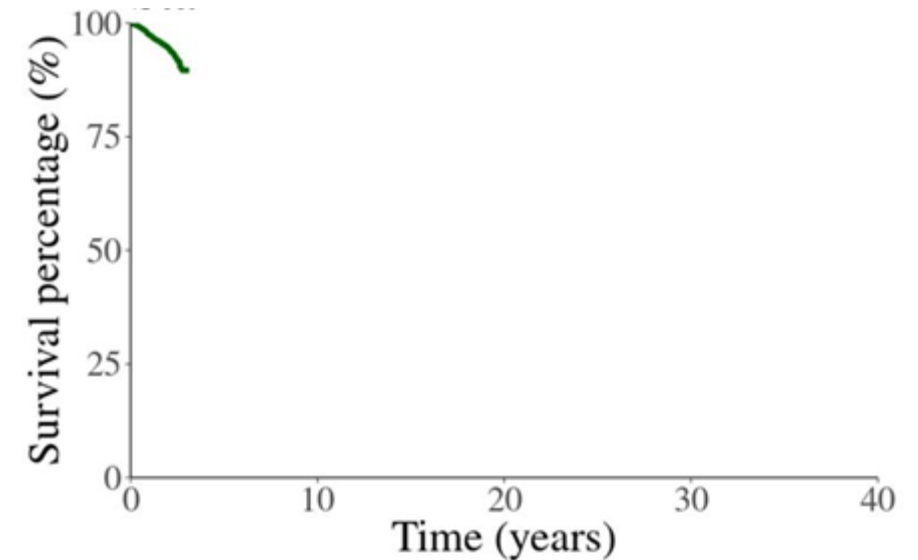
Frameworks



- Guidance in several different documents to guidance in one short framework causes
 - Consistency
 - less/not missing of important steps
 - Insight in where current guidance can be improved

Patient survival in the DAPA-CKD trial (ISPOR 2021)

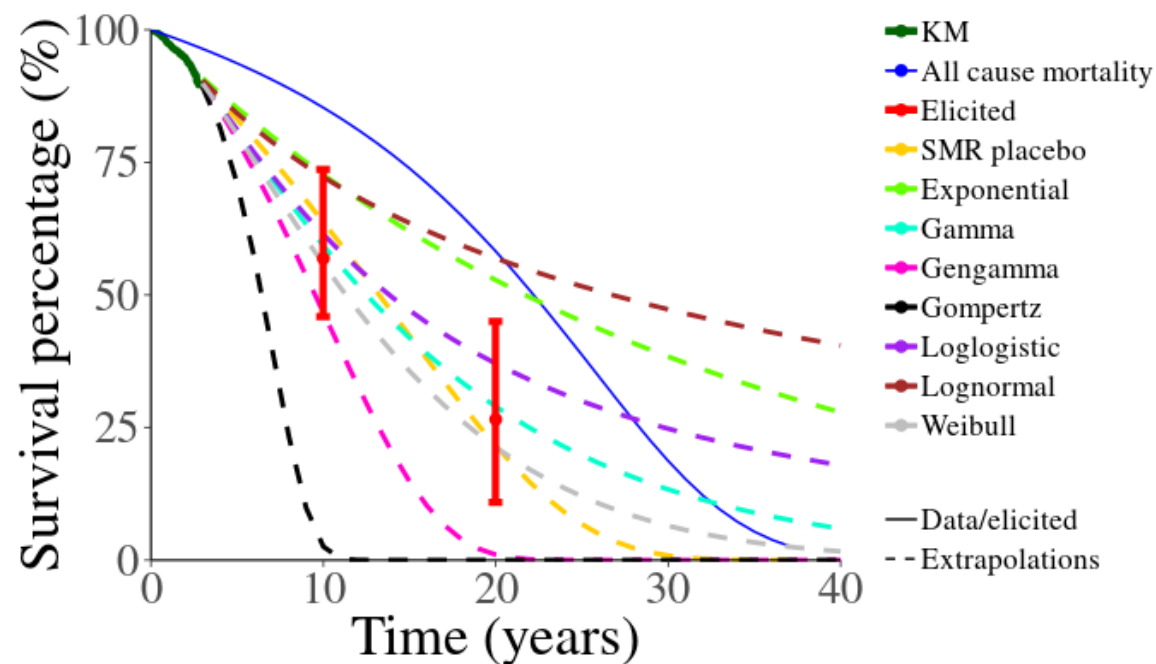
- In DAPA-CKD, more than 90% of patients were still alive at the end of the trial¹
- Clinical trials may provide immature survival data (from about 3.5 years follow-up)
- In DAPA-CKD, dapagliflozin showed beneficial effects on mortality
- Extrapolation and thus long-term evaluation of ICER, QALY and costs, is challenging for chronic diseases



Standard survival modelling approaches (ISPOR 2021)

Frequentist

KM curve only



What approach should we use?

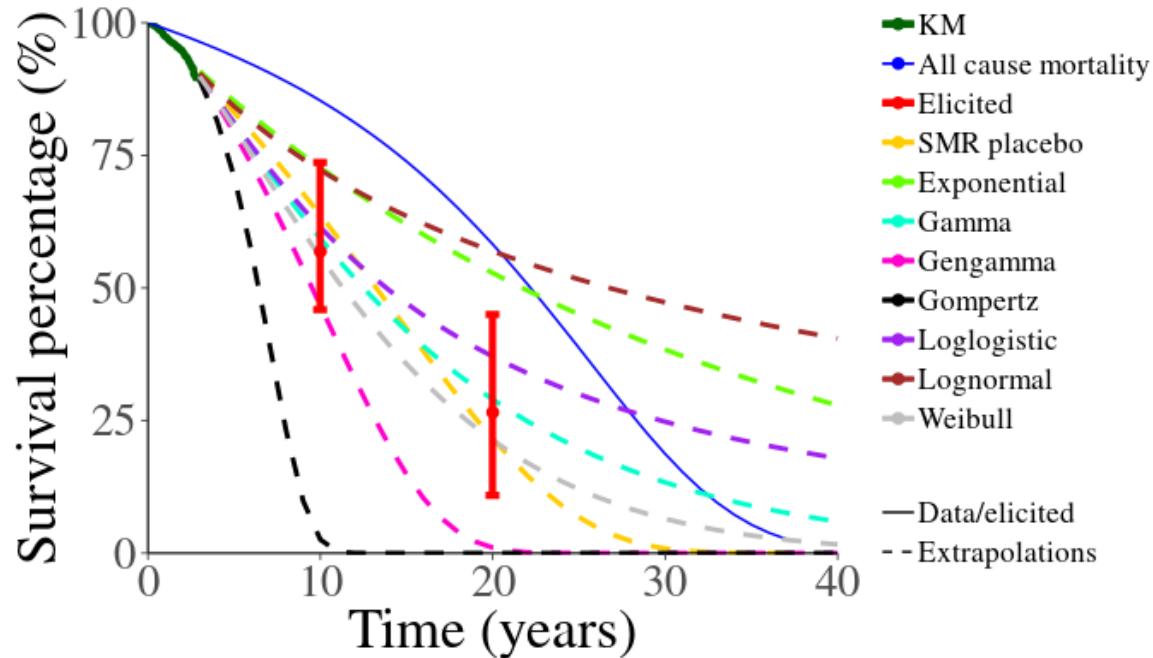
- Only use parametric distributions?
- Follow NICE DSU TSD21 and assume that the underlying distribution is more complex?

Note: to ensure survival at 20 years is lower than survival at 10 years, we asked for the survival at 20 years of those patients alive at 10 years

Relative survival helps, but which national database?

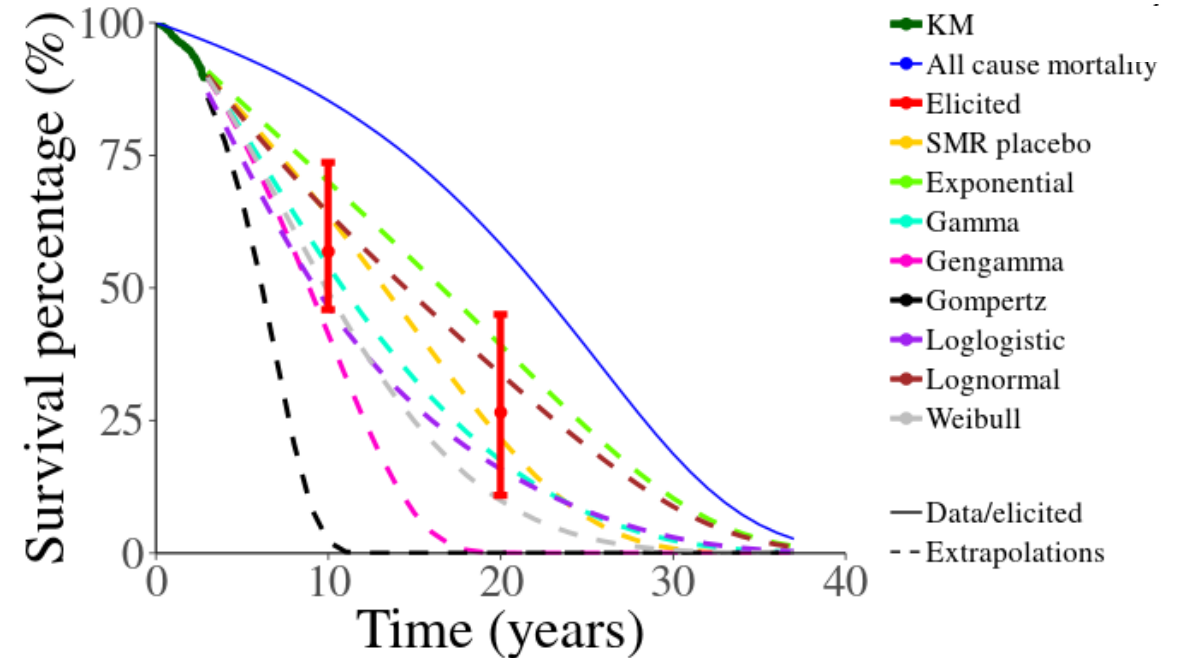
Frequentist

KM curve only

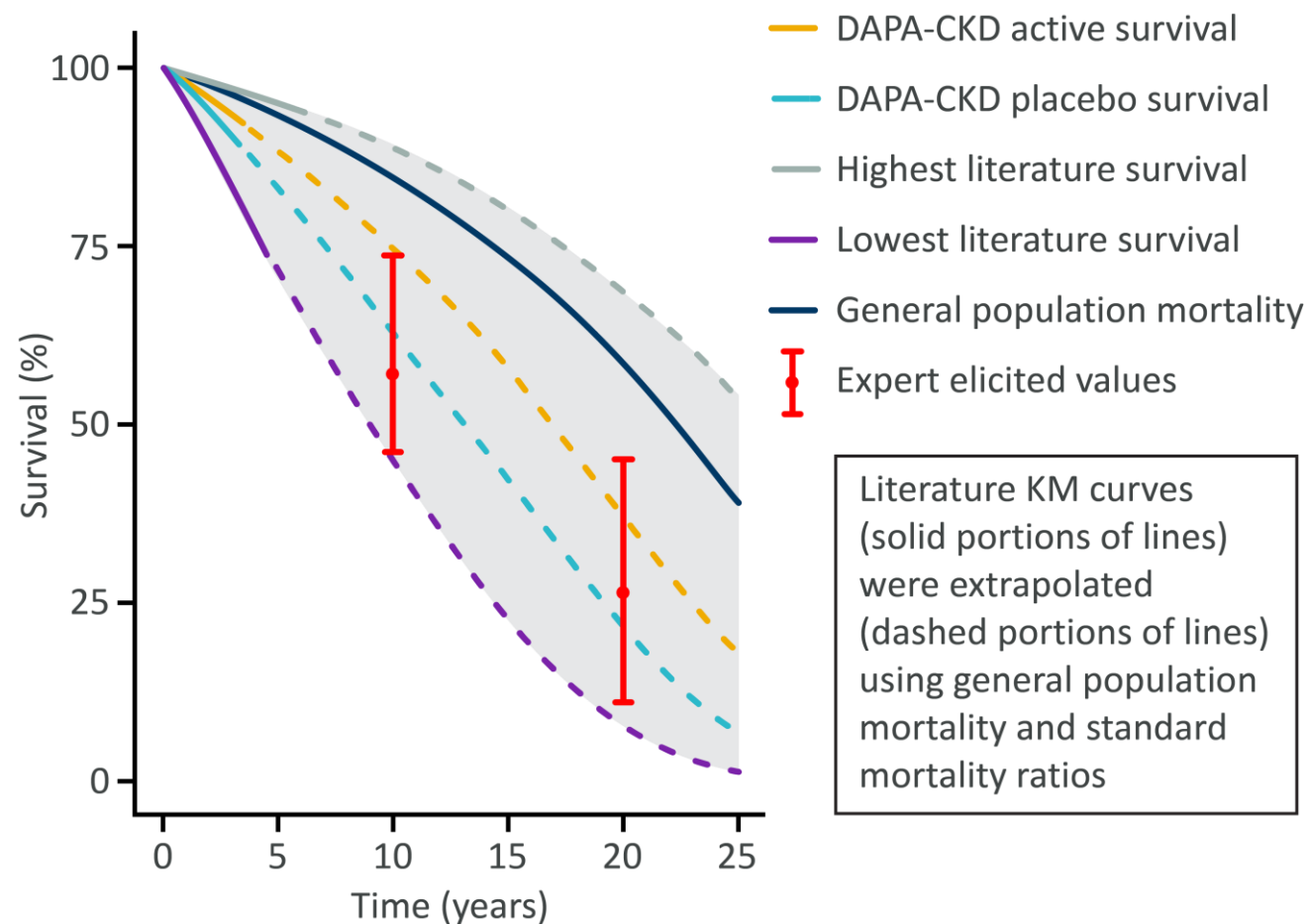


Frequentist accounting for general population mortality

KM curve, general population mortality

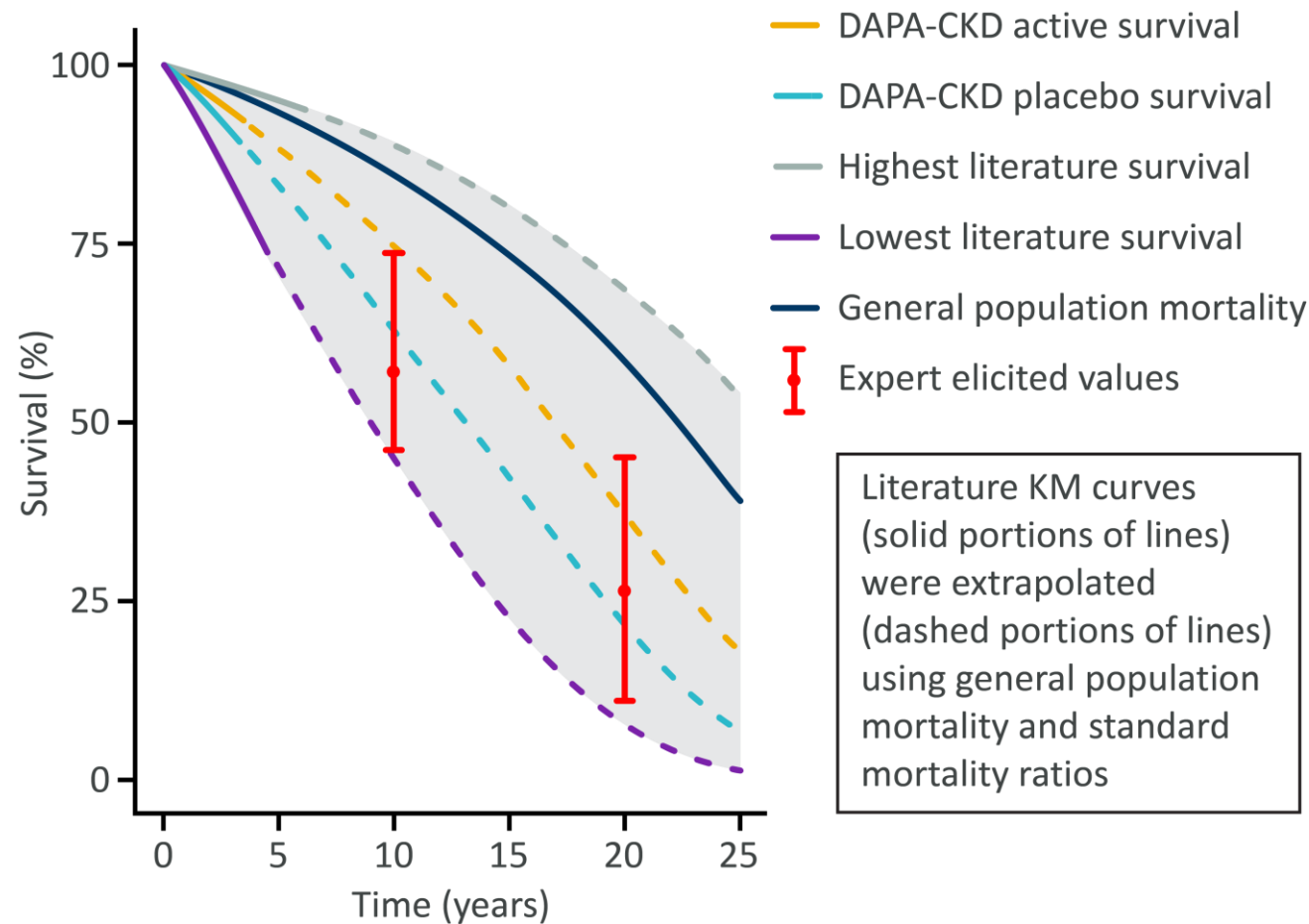


Use of external data (ISPOR 2021)



- Use of external data is indicated, but HTA guidance is very limited in how external data can be selected and used
- External data can differ largely across sources and may not even be aligned with RCT

Use of expert elicitation (ISPOR 2021)

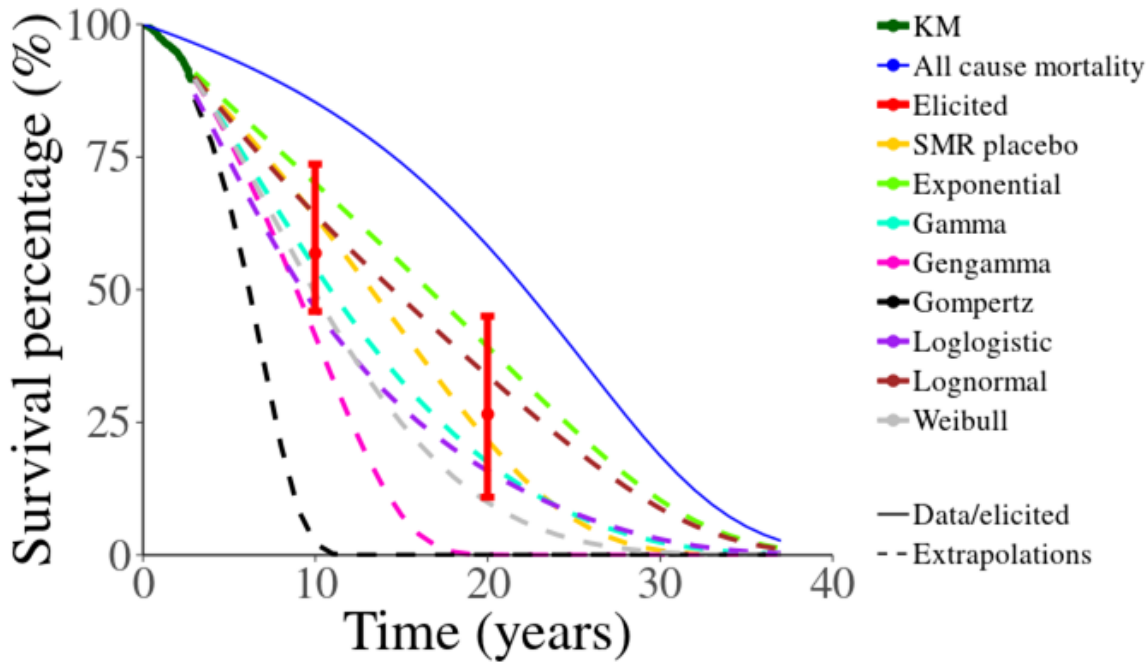


- We have elicited the expert elicitation at 10 and 20 years for the comparator arm
- Are we allowed to elicit relative treatment effects as well? (in other words, the active treatment)
- Are HTA agents convinced about this methodology?
- No expert elicitation TSD neither Bayesian analyses TSD exists ...

But expert elicitation gives greater consistency (ISPOR 2021)

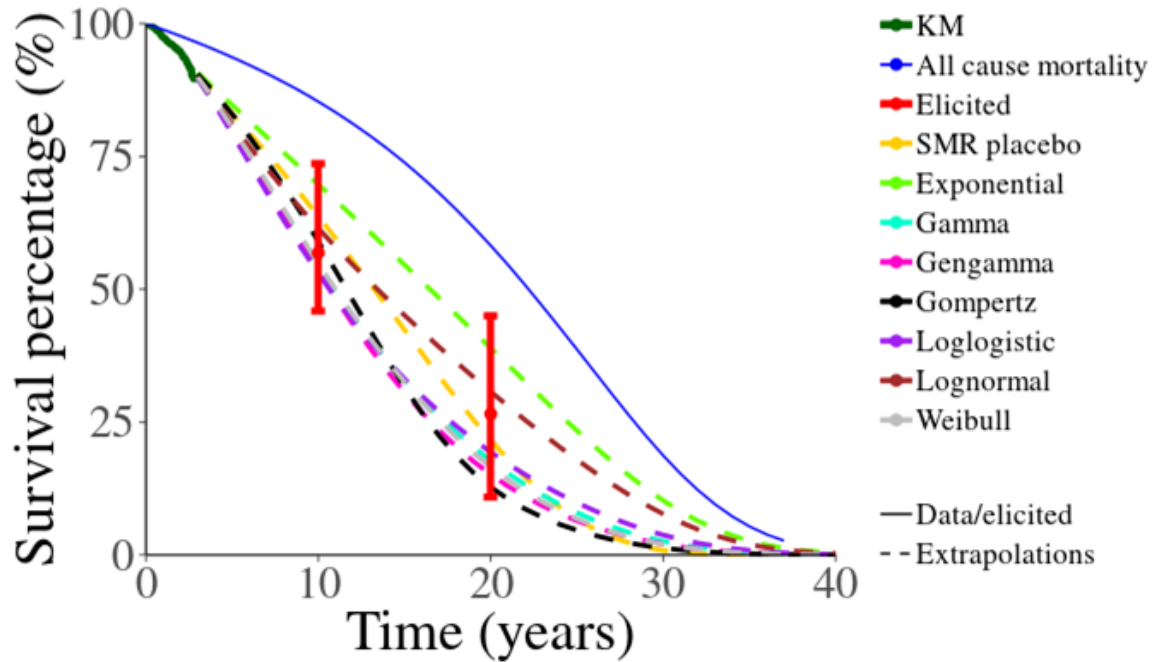
Frequentist accounting for general population mortality

KM curve, general population mortality



Bayesian approach

KM curve, expert elicited values, general population mortality



Note: to ensure survival at 20 years is lower than survival at 10 years, we asked for the survival at 20 years of those patients alive at 10 years

Some additional points for which guidance is limited

- When to choose for risk equations + how to select the appropriate risk equations
- When to choose for patient-level simulation models and when for cohort models given low mortality rate?
- When to choose multi-state models/Markov models/decision trees and when to choose for partitioned survival
- When to choose for elicitation
- Simplification: When to choose for standard mortality ratios and when for more complex modelling

Conclusion low mortality risk diseases

- We need more guidance
 - From HTA to know what is acceptable and what is not
 - From Academia to develop best practices
- A framework may let us stay in the high mortality risk arena, while there is a lot of work to do for chronic diseases

Conclusion slides frameworks

- Does it solve an important challenge? YES
- Is it unique YES
- Does the decision maker(s) agree to the framework/Can it be broadly accepted
 - There is no consistency across decision makers, but having such a framework, discussions may take place
 - Best would be when HTA would work together to deliver the framework which then could be responded to by pharma industry, academia, among others
- Is it user-friendly/Is it short The developers of the framework need to aim for this
- Is it expected to still be valid in 2040 Most developments in modelling are known by now for high mortality-risk diseases. Don't know for low mortality risk
- Is it findable Likely NICE DSU has an important role in this, among others
- Do case-studies support the easiness of use of the framework Would be great when beside the technical support documents, HTA agents could provide best practices case studies for different types of diseases