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Modelling for clinical trial driven economic analyses: development and validation issues

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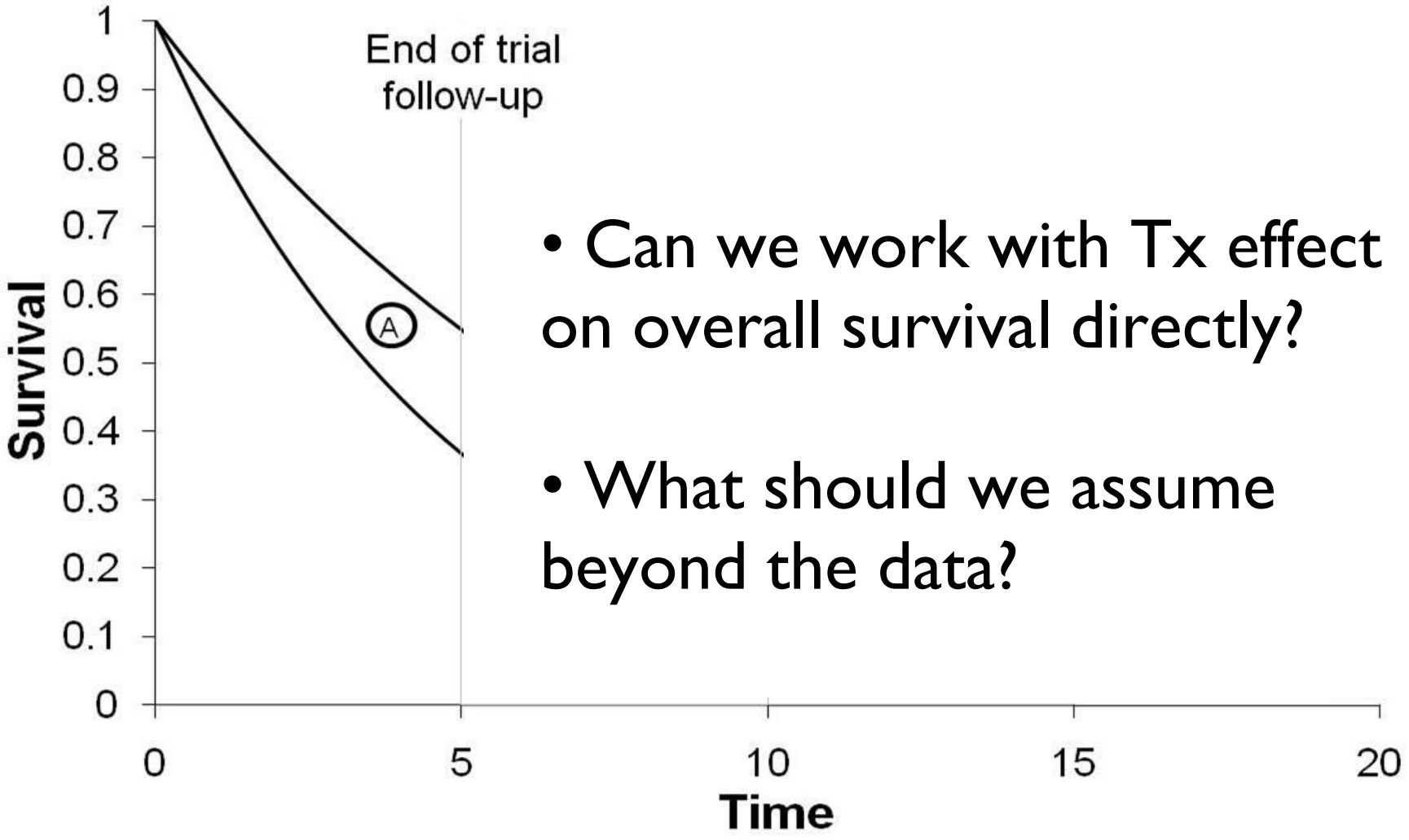
Aims of cost-effectiveness analysis

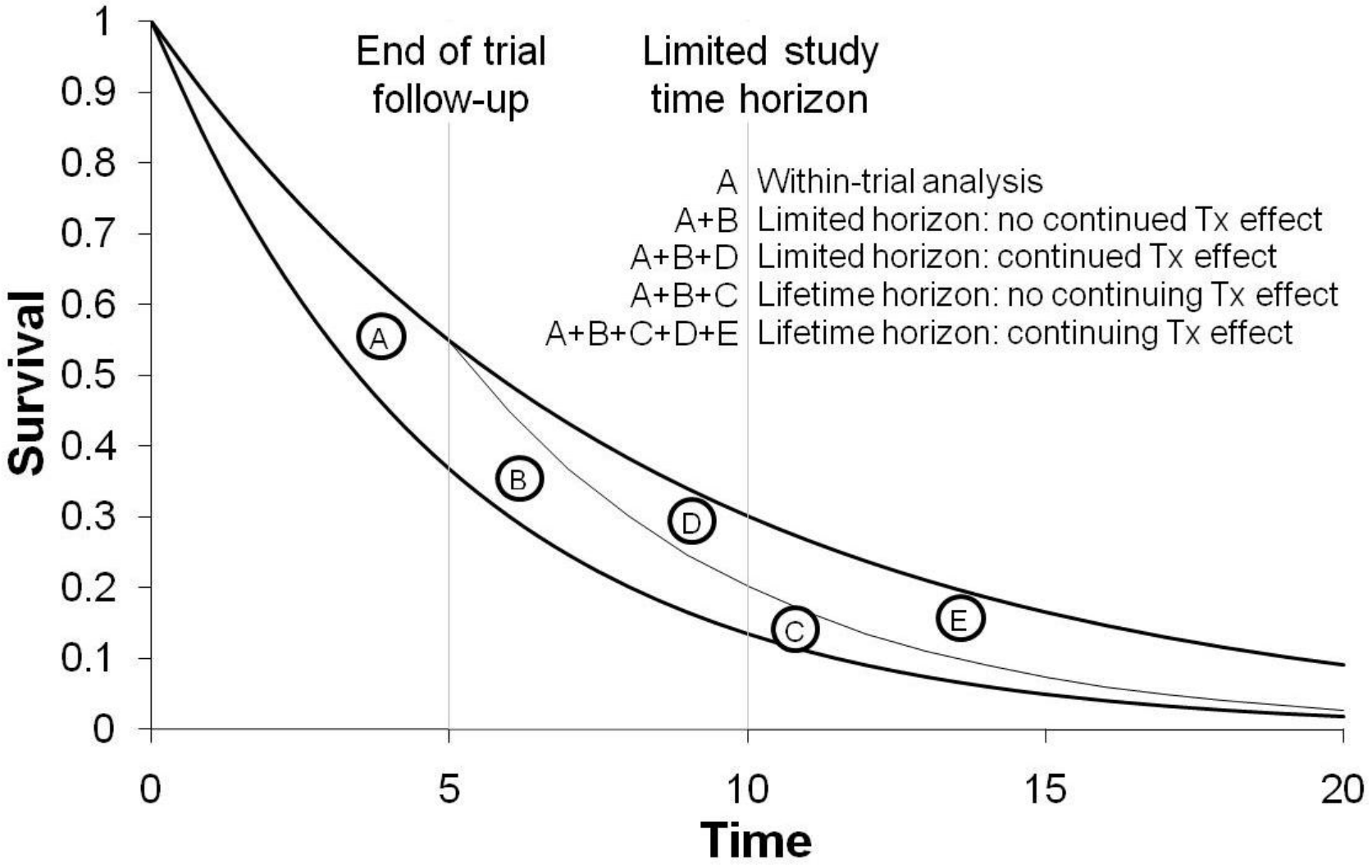
- To evaluate the FULL absolute impacts of interventions on health outcomes (QALYs ultimately of interest) and healthcare costs
    - Duration over which the differential effects between the strategies fully realized (eg. over lifetime)
- To address possible heterogeneity of these effects in different population groups/ individuals

Issue: Trials are of limited duration (and limited power on overall survival)

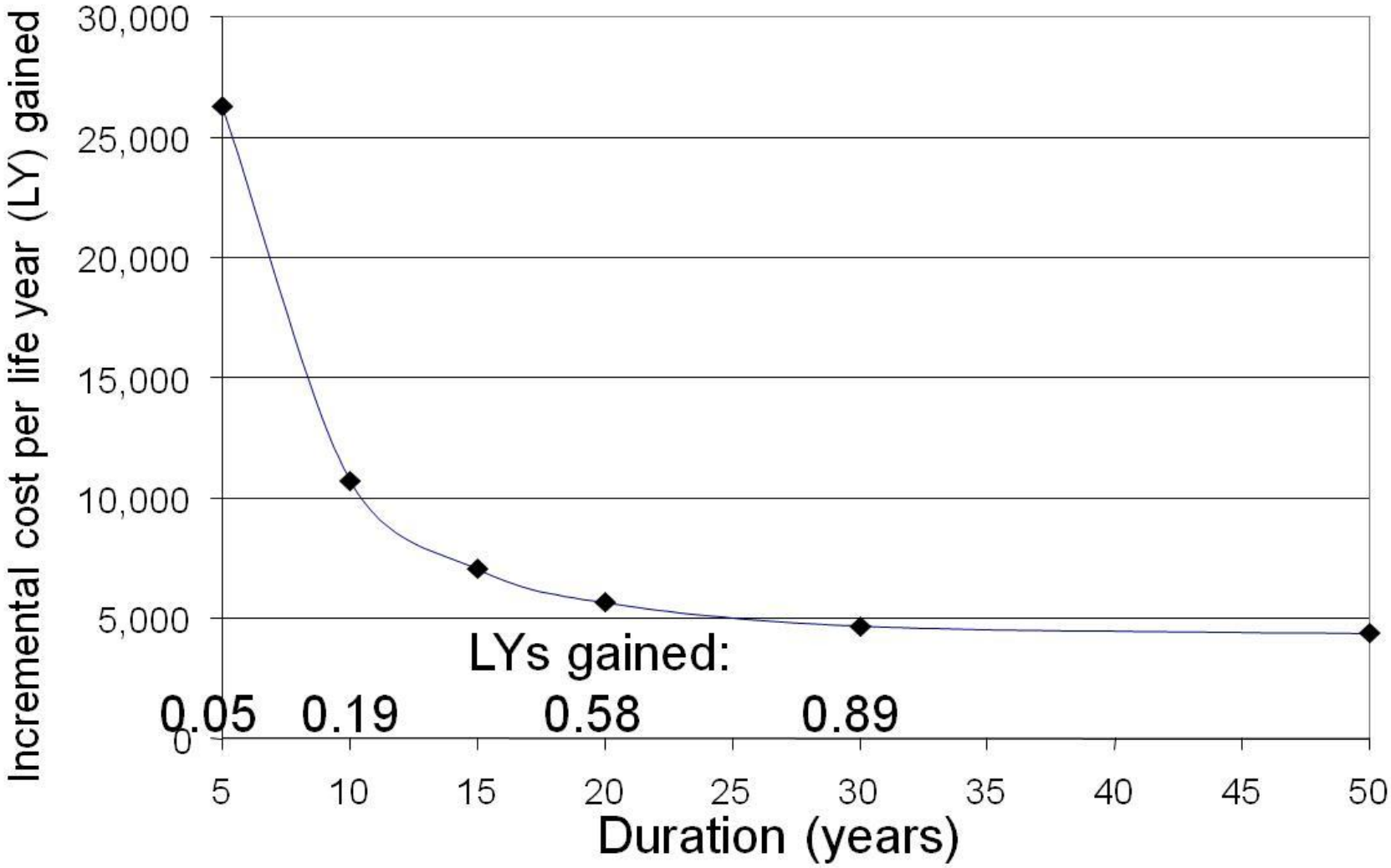


- Can we work with Tx effect on overall survival directly?
- What should we assume beyond the data?

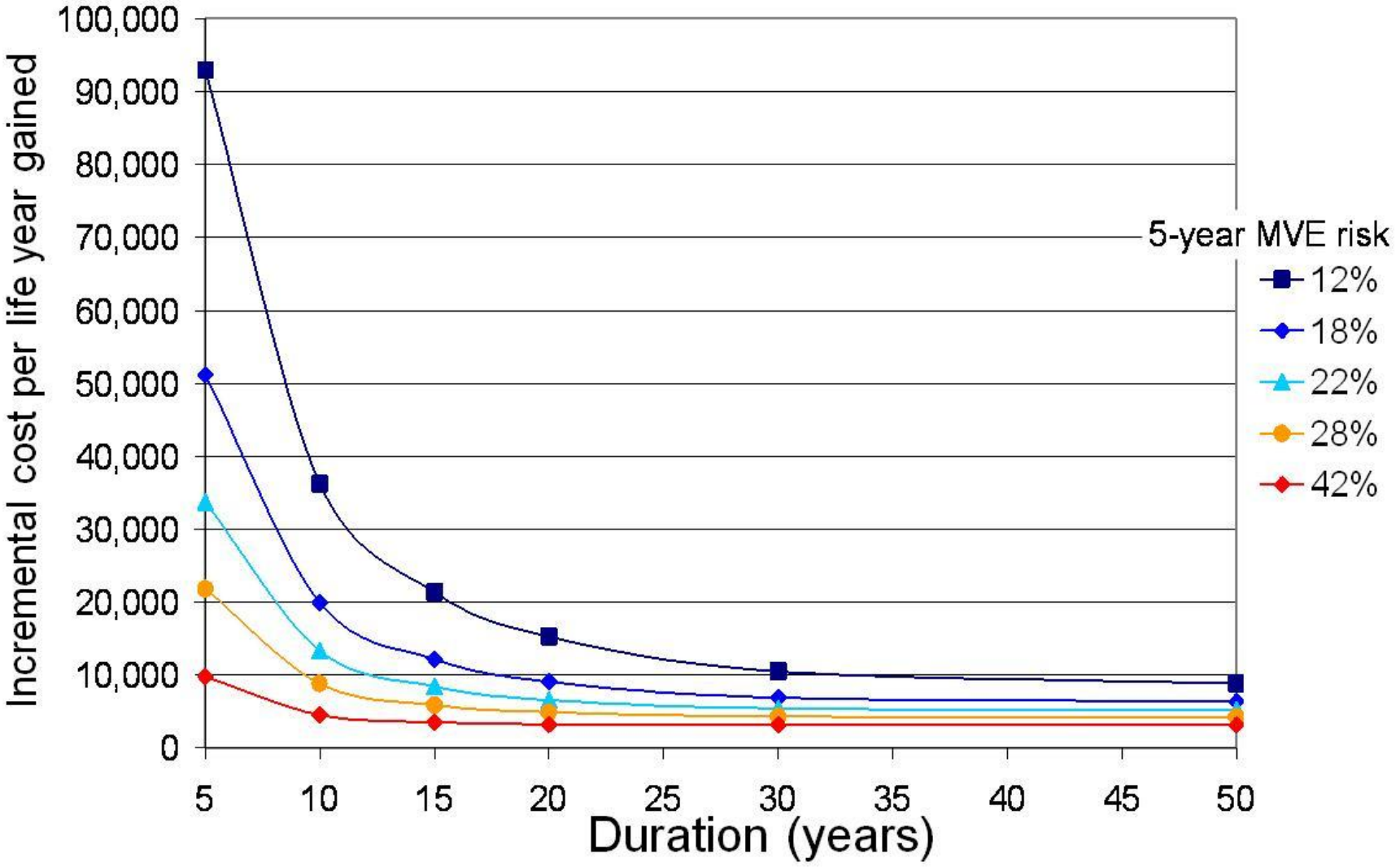
Need for extrapolation



Implications: Cost-effectiveness of 40mg simvastatin daily (40 mg simvastatin at £1 daily)



Implications for different populations (40 mg simvastatin at £1 daily)



Approaches to extrapolation for trial based economic analysis

1. Decision analytic models
- Markov models
- Decision trees

etc.

+ model states drive health **outcomes and costs**
* Transitions and model state-related effects and costs could be based on trial data or external sources
+ adjustment for risk factors etc. facilitated by trial data
+ Tx effects easy to implement
-assumptions are made (e.g. structure of model, parametric survival models)

2. Directly modelling survival
- Life tables
- Actuarial estimates

etc.

-only extrapolation of survival is facilitated (extrapolation of quality of life and healthcare costs not facilitated)
-adjustment for risk factors limited
-Tx effects might be difficult to propagate beyond trial
*based on external data (usually)
-assumptions are made

No method can make up for the lack of data: thoughtful model development and validation essential!

Decision analytic models: Event driven economic analyses?

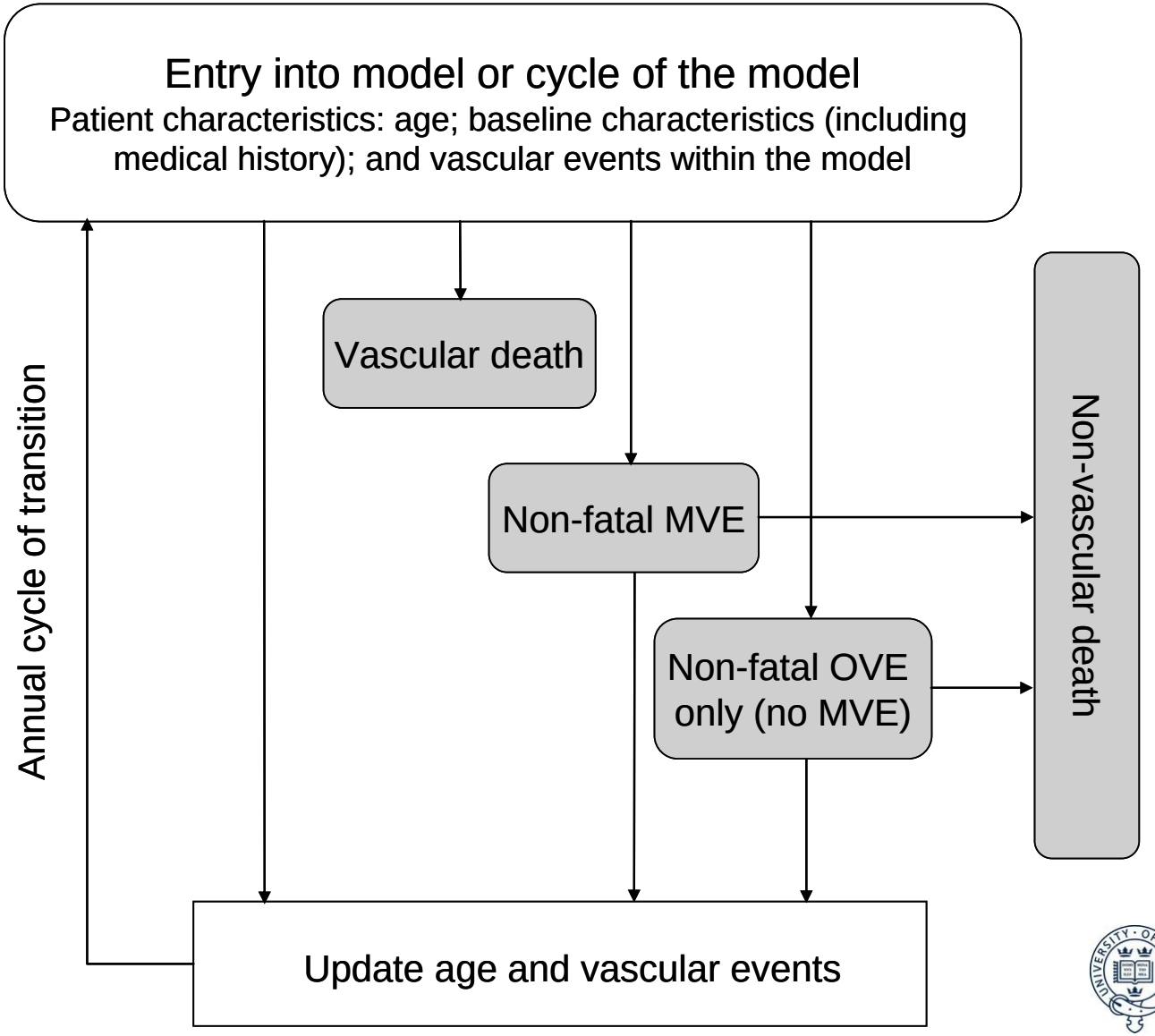
- **Decision model**: Disease pathways modelled through (important) clinical events
- **Treatment effects**: impact of intervention on occurrence of these clinical events (main endpoints in trials) incorporated
- **Impact on QALYs** and **healthcare costs** primarily driven by the occurrence (or not) of these events
- Adds structure to the analysis (assumptions are made!) and *precision* to estimates

Example: Cost-effectiveness of 40mg simvastatin daily (Heart Protection Study)

Markov model

MVE, major vascular event (i.e. heart attack stroke or any revascularisation procedure)

OVE, other vascular event (angina, transient ischemic attack, etc.)



Example: Elements of decision model

- 3 parametric risk equations in the backbone of the model

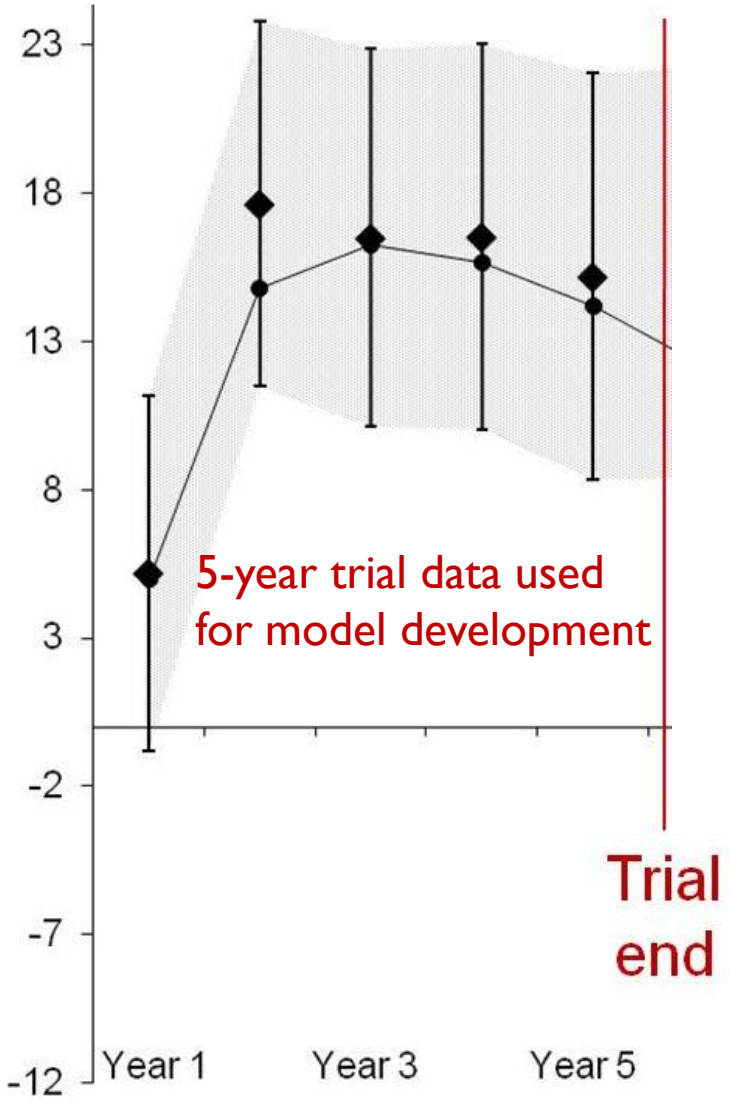
  (1) Vascular death (Weibull)

  (2) Major vascular event or vascular death (Exponential)

  (3) Any vascular event (Exponential)

- ➢ Model selection criteria
- ➢ Time dependent variables (age, in-trial events (MVE, OVE, VD and histories of nonfatal events), compliance with statin) reduces reliance on parametric assumptions
- Nonvascular death: life table with VD eliminated
- Annual vascular hospitalisation cost equation
- ➢ in-trial events (MVE, OVE, VD and histories of nonfatal events

Validation (1): Difference in annual MVEVD rates between placebo and simvastatin groups (per 1000)

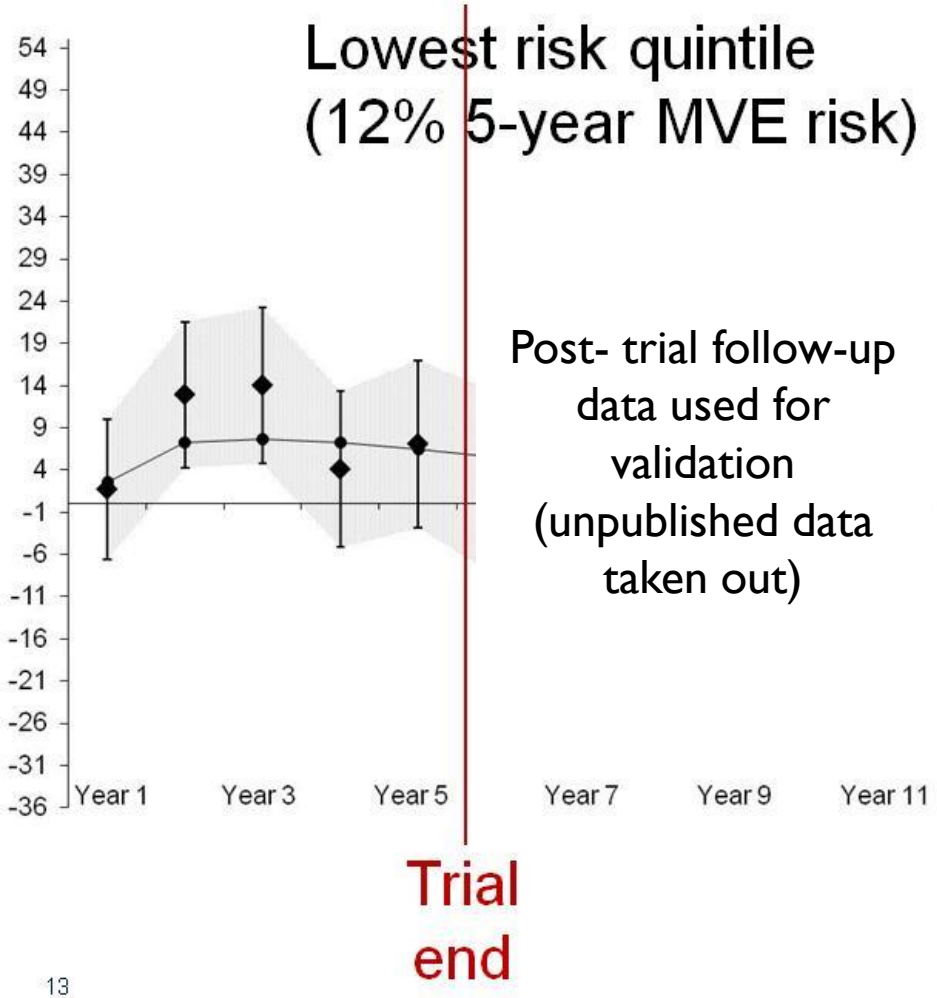


Observed (95% CI)

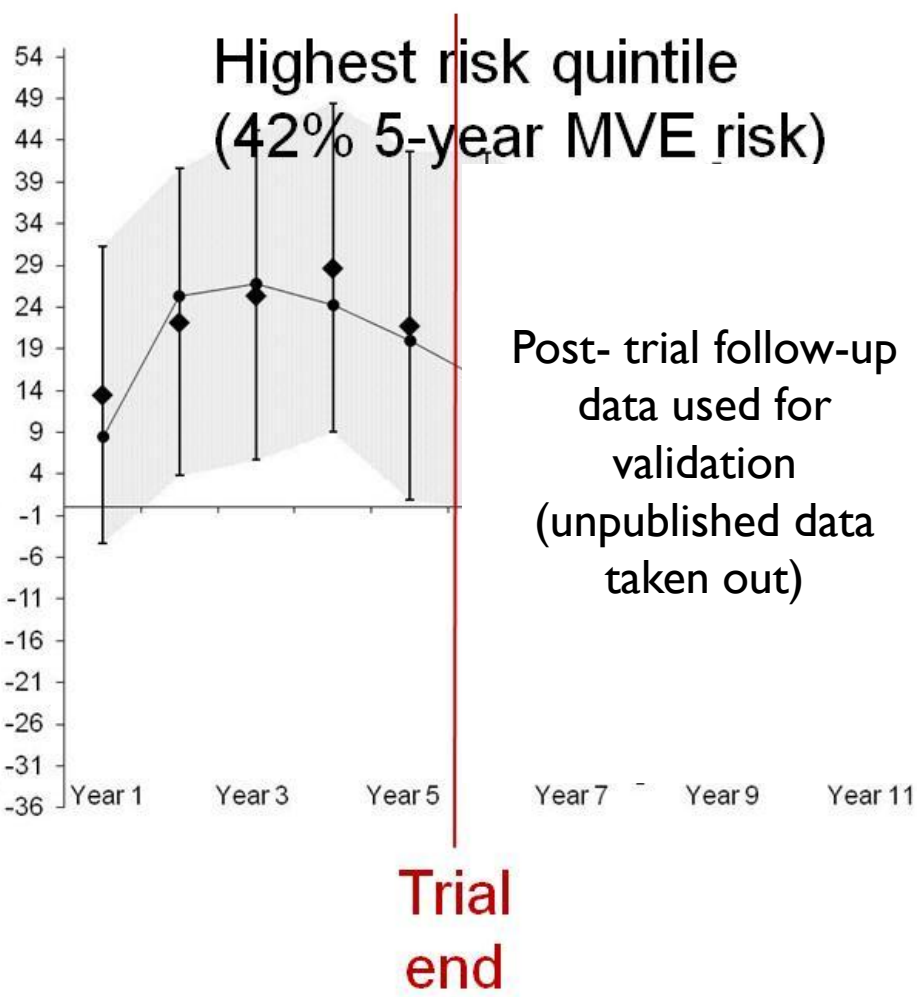
Predicted

Post- trial follow-up data used for validation (unpublished data taken out)

Validation (2): Difference in annual MVEVD rates between placebo and simvastatin groups (per 1000)



Post- trial follow-up data used for validation (unpublished data taken out)

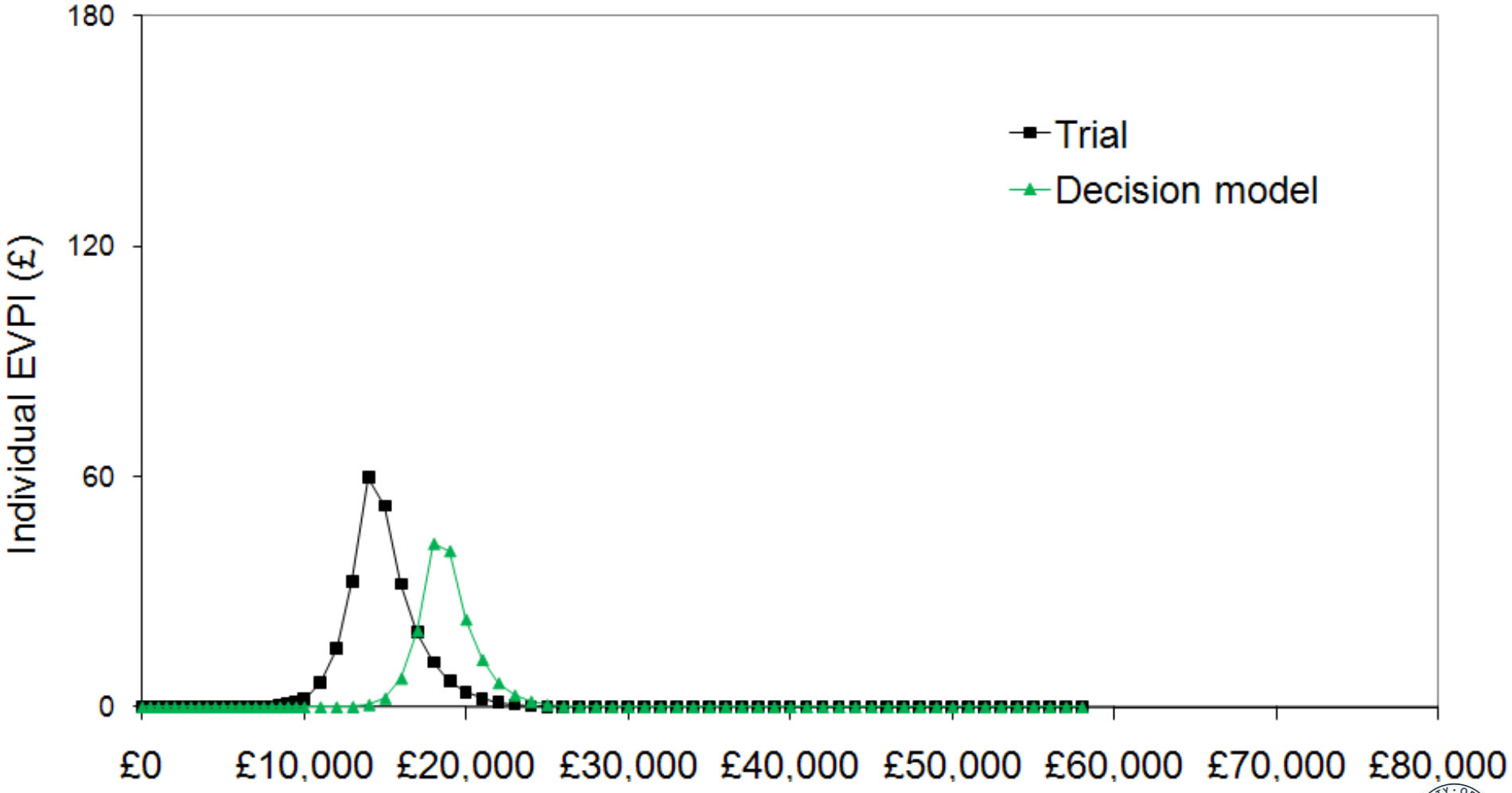


Post- trial follow-up data used for validation (unpublished data taken out)

Cost-effectiveness modelling and value of information

- Models do influence the uncertainty and the value of information estimates
  - Therefore, Value of information (VOI) is *always* conditional on model or the analytical framework as well as data used
- Comparing cost-effectiveness results fully based on trial data with corresponding analysis fully based on a model evaluated based on the same trial data illustrates this well
  - Effects are even more pronounced within separate participant subgroups

Example: Impact of modelling on VOI



Research questions

- Data synthesis (e.g. trial and external data, many trials)?
- Heterogeneity in cost-effectiveness?
- Parametric methods for extrapolation?
  - Implications for cost-effectiveness?
- What is the appropriate approach to provide timely and informative good quality evaluation?
  - Data to support validation work not usually available
- Relevance of trial population for economic analysis
  - E.g. Statin trials: cost-effectiveness results hold for people at similar levels of risk and age in typical general population…