Survival extrapolation: How to draw the lines beyond the observed data, *if you must*

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Objective

The objective of this workshop is to present some methods for the inclusion of long-term data from sources other than the RCTs, that can be used to estimate parameters of times to events and other outcomes in health economic models.

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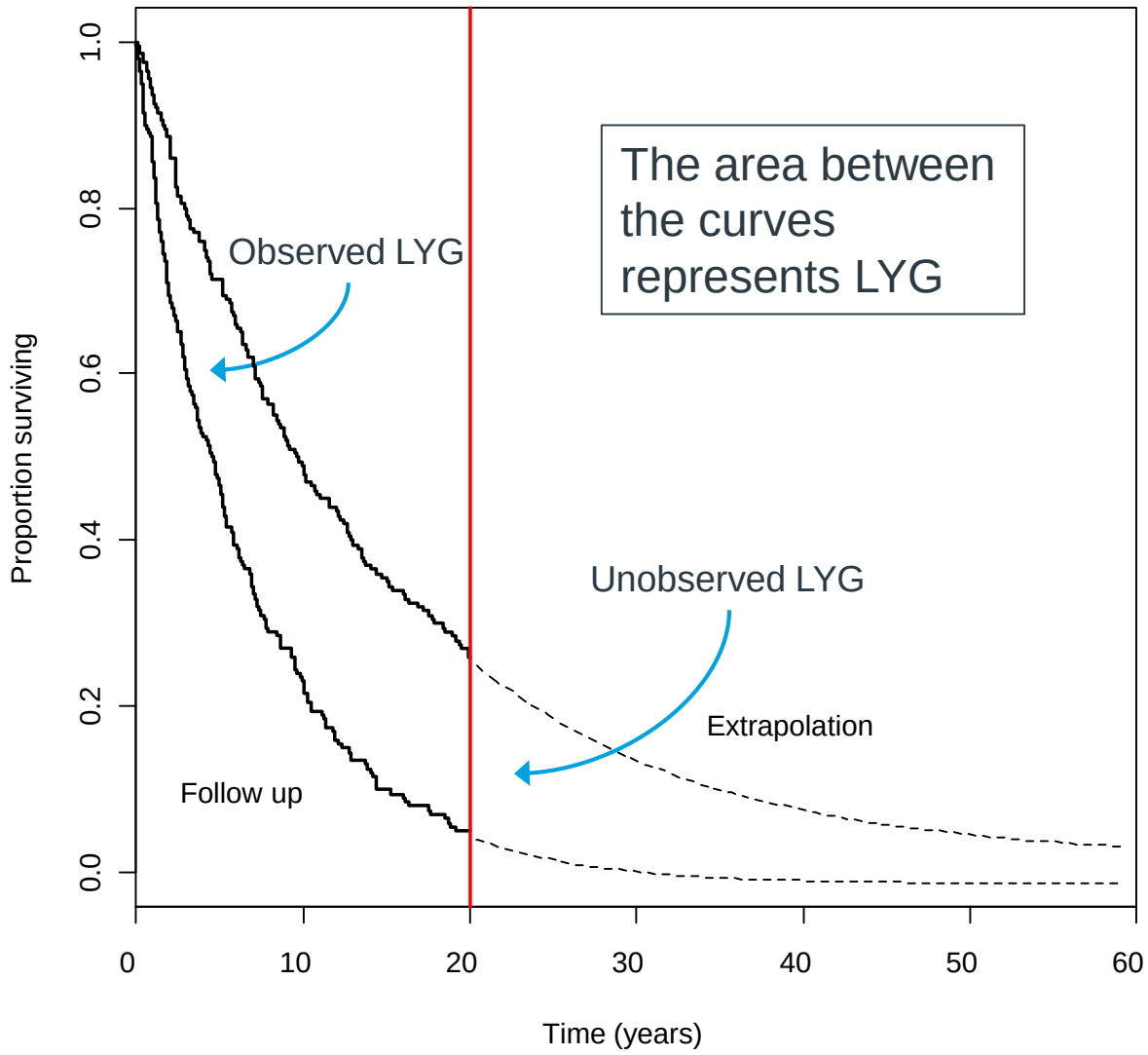
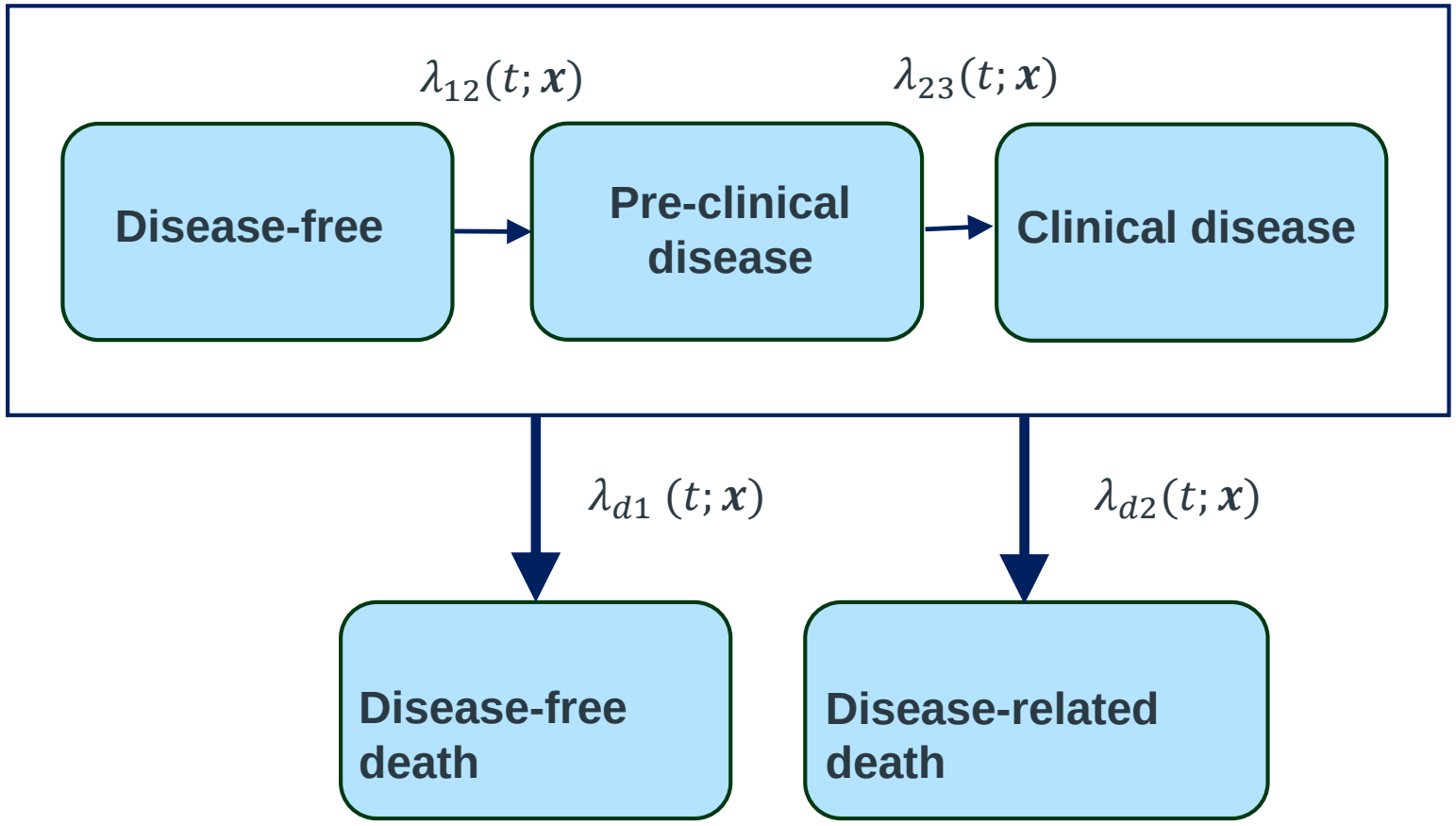
The problem: incomplete data

Mean LYG from incomplete data



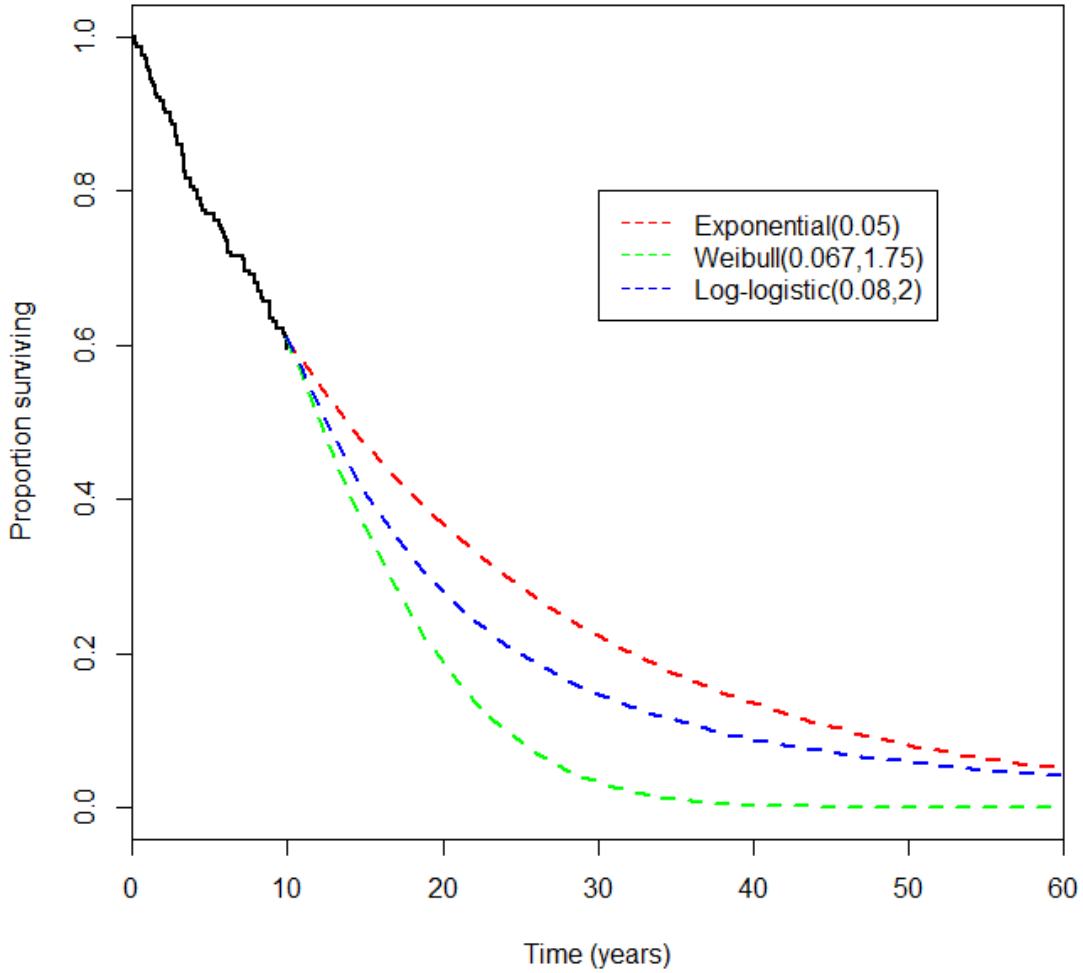
Who has had the need to extrapolate survival beyond the observed data?

Extrapolating state-transition models



- Estimate transition rates $\lambda(t;\boldsymbol{x})$ from short-term trial data
- Run model until all patients are in one of two death states

Use of parametric survival functions

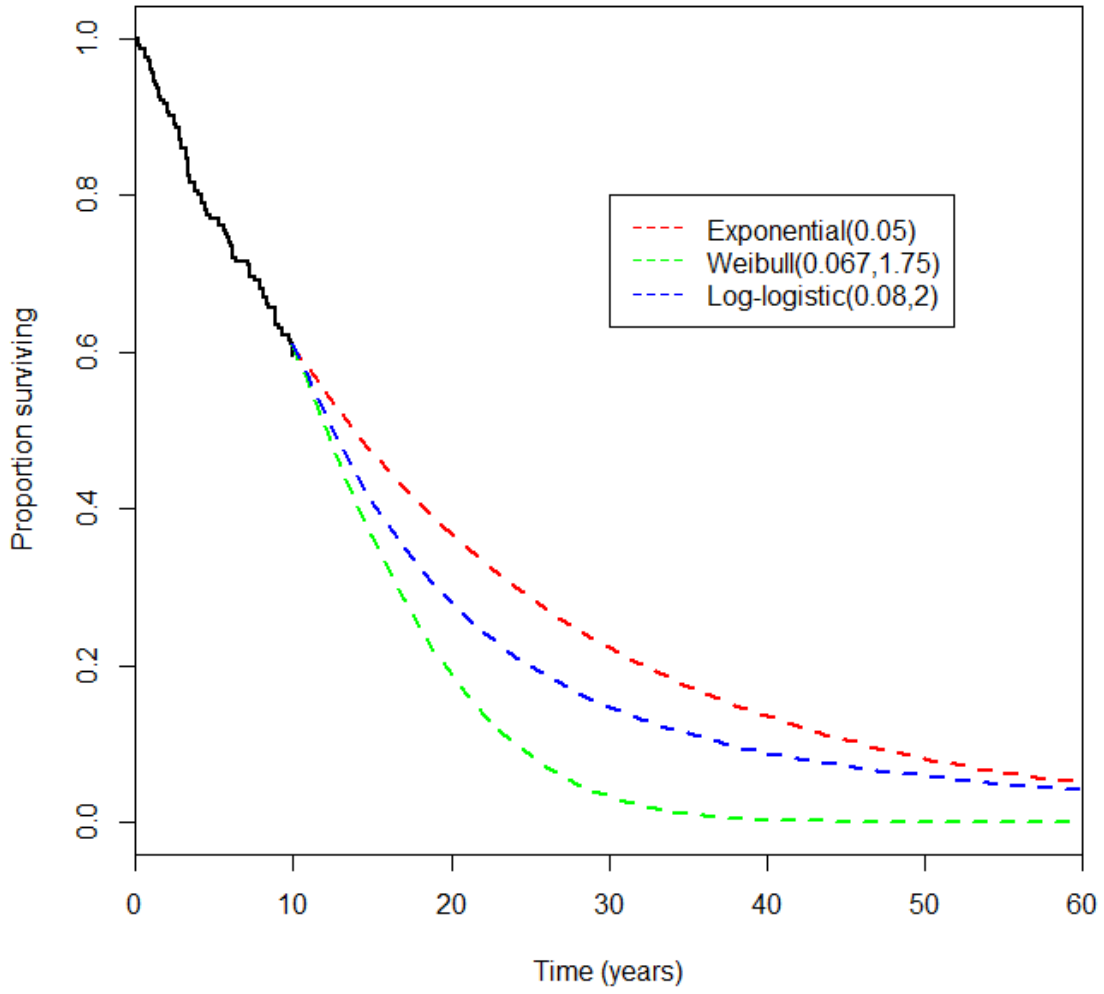


Traditional approach:

assume parametric survival

Short-term fit versus long-term plausibility

Use of parametric survival functions

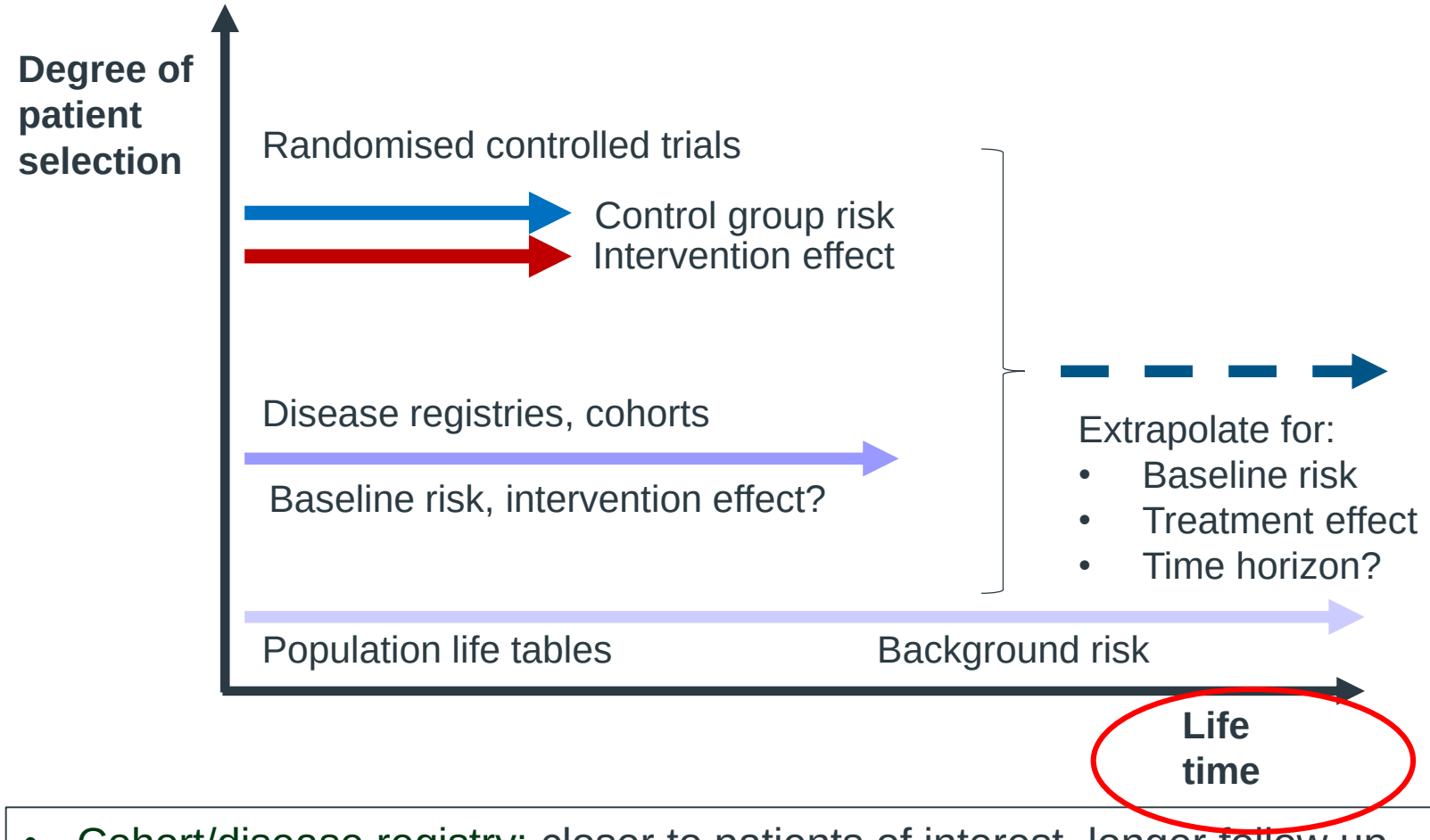


Parametric approach acceptable if,

- long-term follow up,
- well fitting parametric function throughout.

NB: All assumptions about future survival and treatment effects are ***untestable***

Types of external data



- Cohort/disease registry: closer to patients of interest, longer follow up, but not usually lifetime
- Population life tables: lifetime horizon, but requires more adjustment to represent patients of interest

RWE and its role in extrapolation

What is real world evidence?

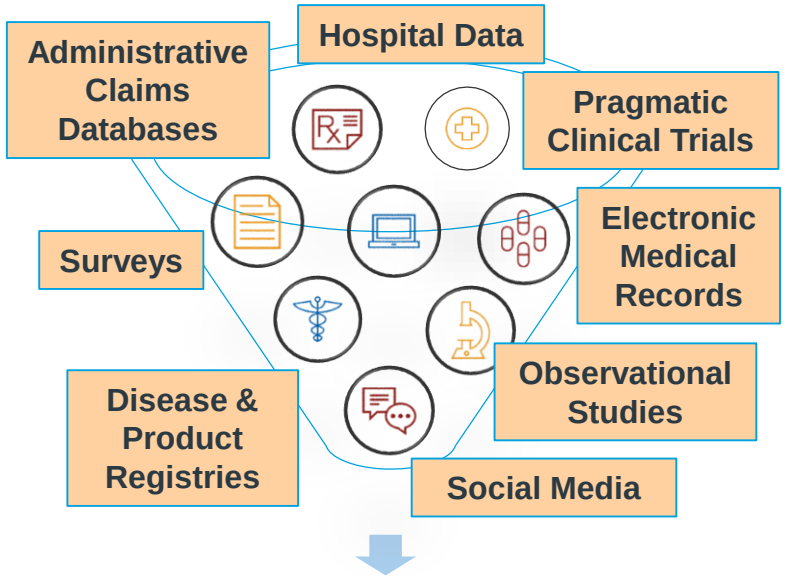
RWE is based **on data collected outside of clinical trials** that is used to support decision-making

RWE aims to understand the differences and needs of real patients to improve clinical care, safety, and access to medicines

Generating RWE from RWD

RWE can be generated by actively collecting new data (primary source) or by analyzing existing data (secondary source)

Real world data sources



Real World Evidence

Data collection can be either:

- Prospective →
- Retrospective ←
- Cross-sectional |

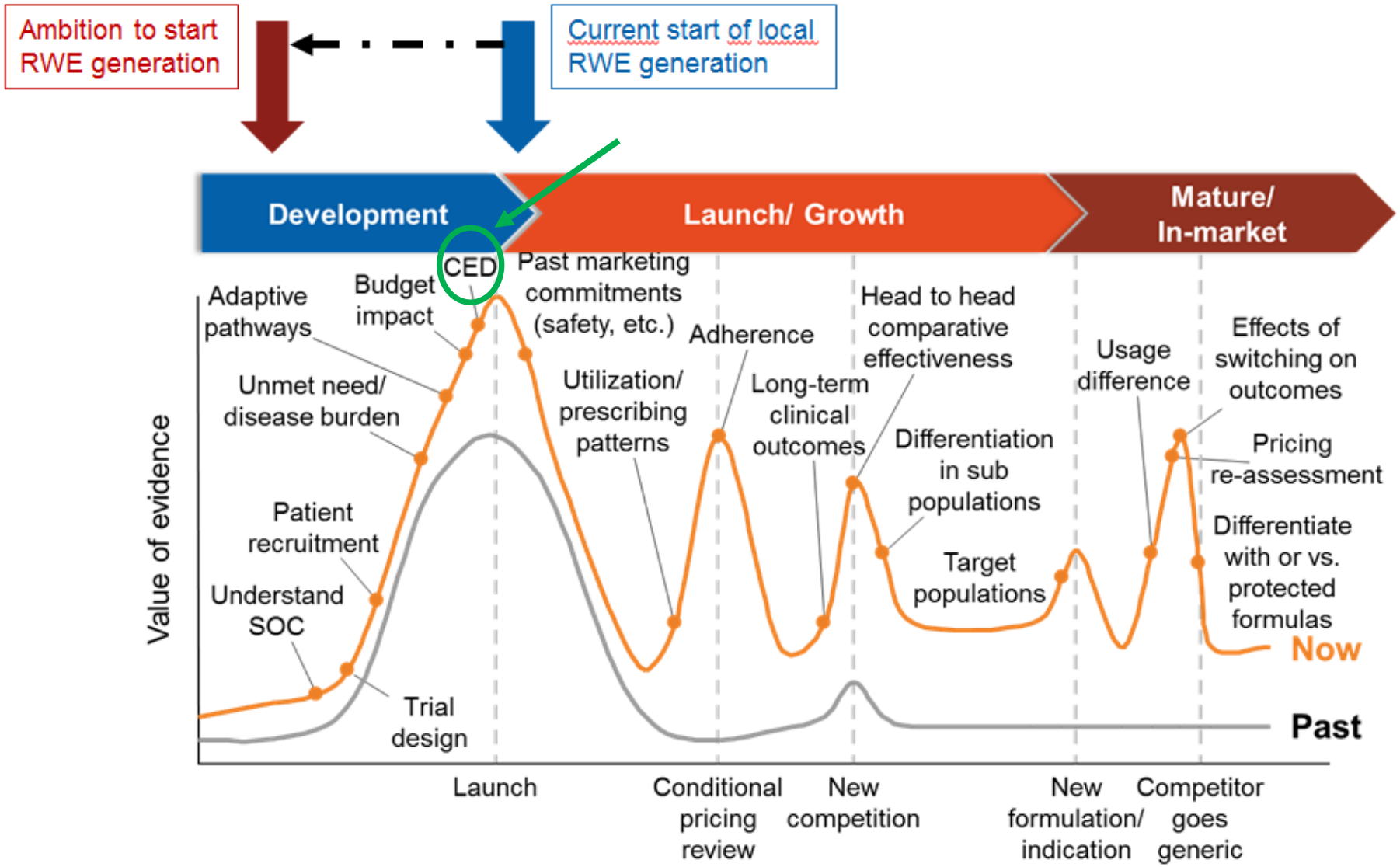
External data can be used in extrapolations beyond the time horizon of RCTs

Patient Registries

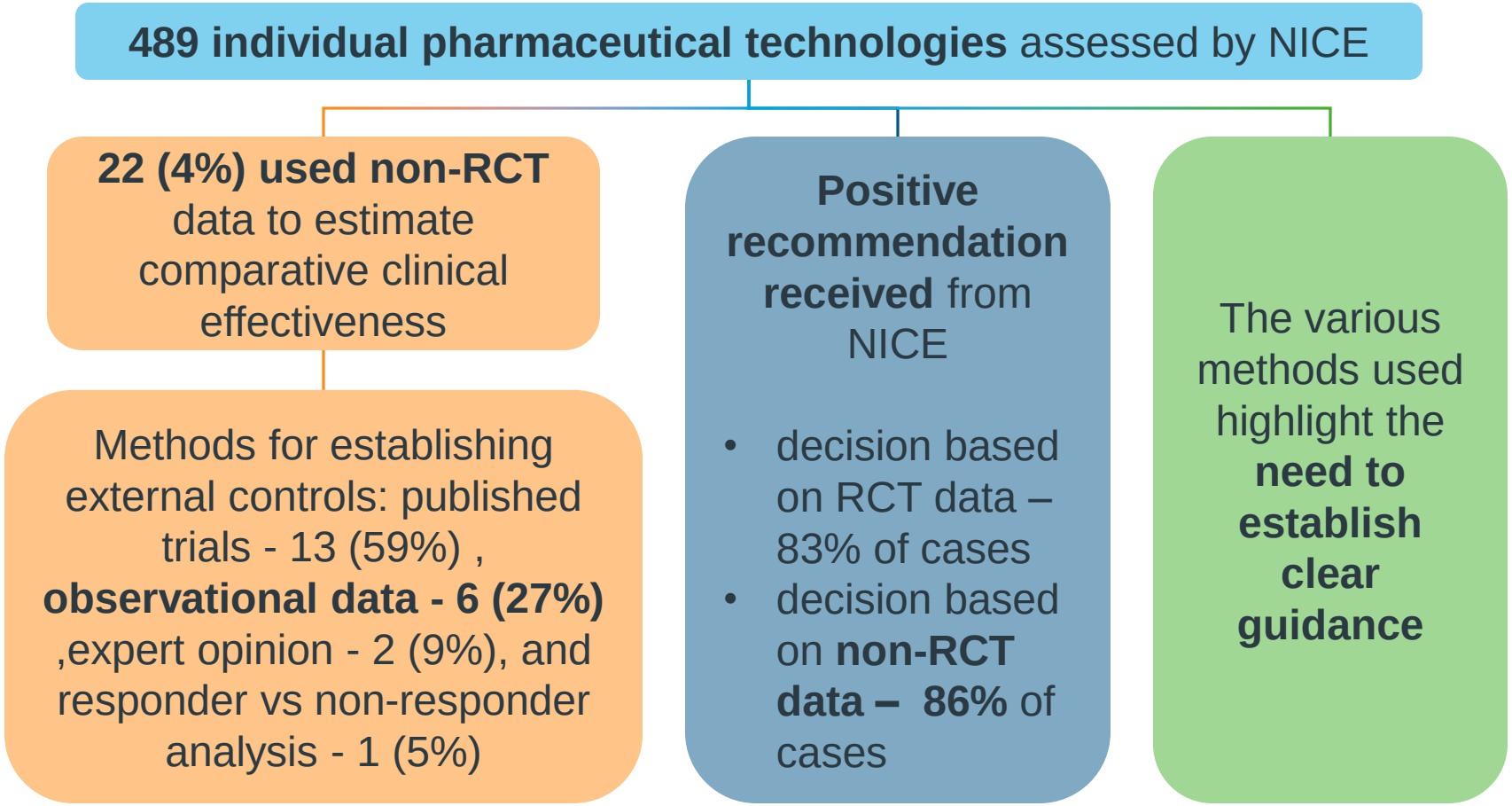
A **patient registry** is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves a predetermined scientific, clinical, or policy purpose(s).

Reference: Gliklich RE et al. Registries for Evaluating Patient Registries: A User's Guide: AHRQ publication No. 07-EHC001. Rockville, MD. April 2007

Increasing demand for RWE along the product lifecycle



Review of NICE appraisals of pharmaceuticals from 2000 to 2016



Reference: Anderson M.; Naci H.; Morrison D.; Osipenko L.; Mossialos E. A review of NICE appraisals of pharmaceuticals 2000-2016 found variation in establishing comparative clinical effectiveness. *J Clin Epidemiol* **2018**,

Regulatory & payer shift towards RWE

There has been **an increase in formal requests from European payers for more detailed real-life information** to:
- prove that a treatment works effectively, efficiently and is safe
- manage uncertainty when payers are making reimbursement decisions

Call for **FDA to publish draft guidance** on:
- RWE benefit to patients, regulators and industry
- RWE availability, quality and access challenges as well as mitigating strategies
- Methods for collection, analysis and communication of RWE
- Contexts for use of RWE in regulatory decision making

The new 21st Century Cures Act requires **FDA to explore the use of RWE to satisfy post-approval requirements and support indication expansion**.

Use of RWE in HTA submissions/ economic models is growing

Reference: Gill JL.; Albanell J.; Dank M.; Duncombe R.; Fink-Wagner A-H.; Hutton J.; Jahnz-Rozyk K.; Kössler I.; Podrazilova K.; Schramm W.; Spandonaro F.; Thomas M.; Vaz Carneiro A.; Wartenberg M.; Kanavos P.G; RWE in Europe Paper II: The use of Real World Evidence in the disease context. **2017**

Example: Use of life tables to capture survival beyond the end of the RCT

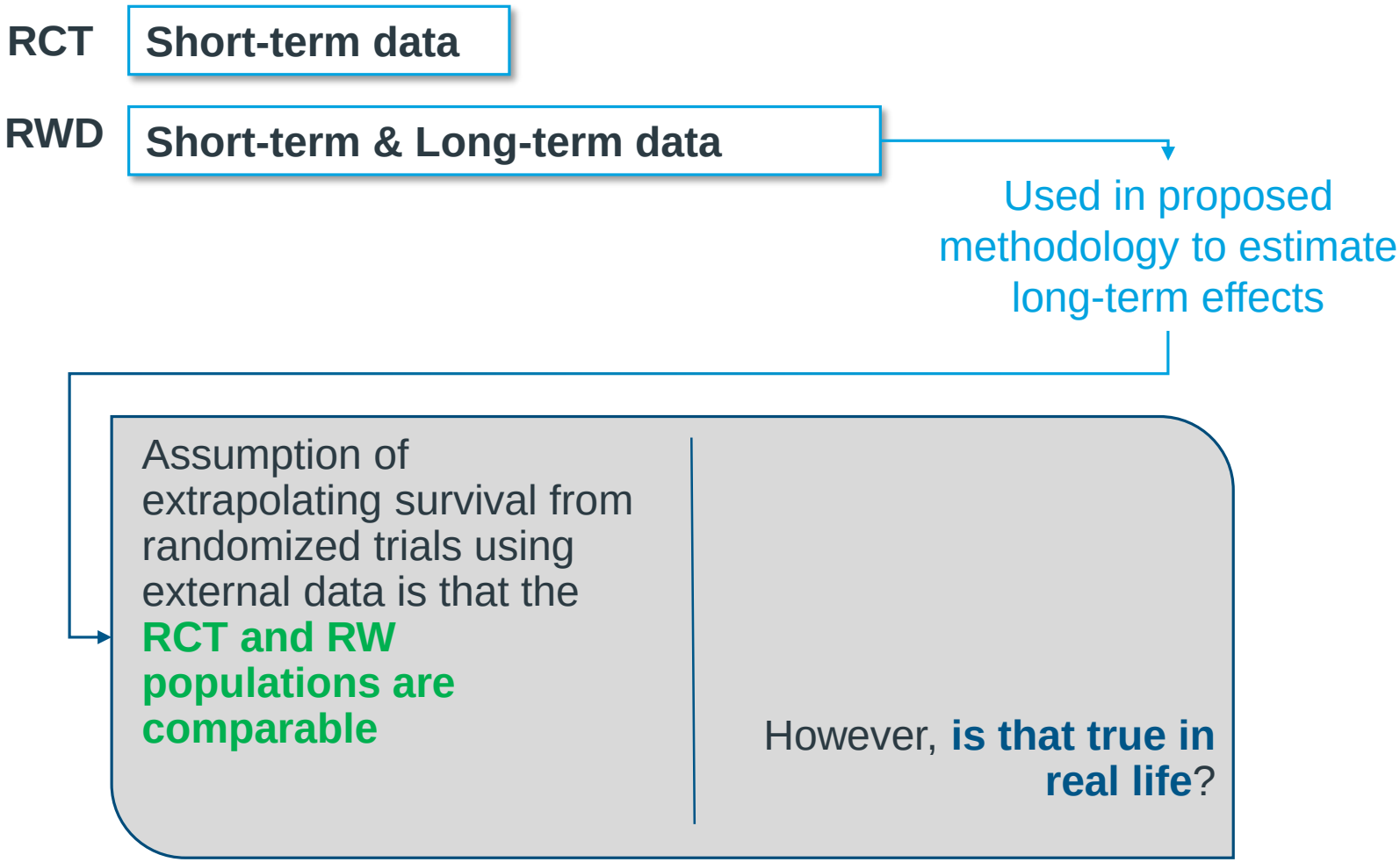
Economic experts recommended **use of life tables in order to capture survival beyond the end of RCT** in Acute Heart Failure

"NICE understands, from the response to clarification questions, that **UK life tables based on published literature will be used to capture survival beyond day 60**.

Experts note that these may not be easily available, although such data may be available from the National Heart Failure Audit (run by the Information Centre).

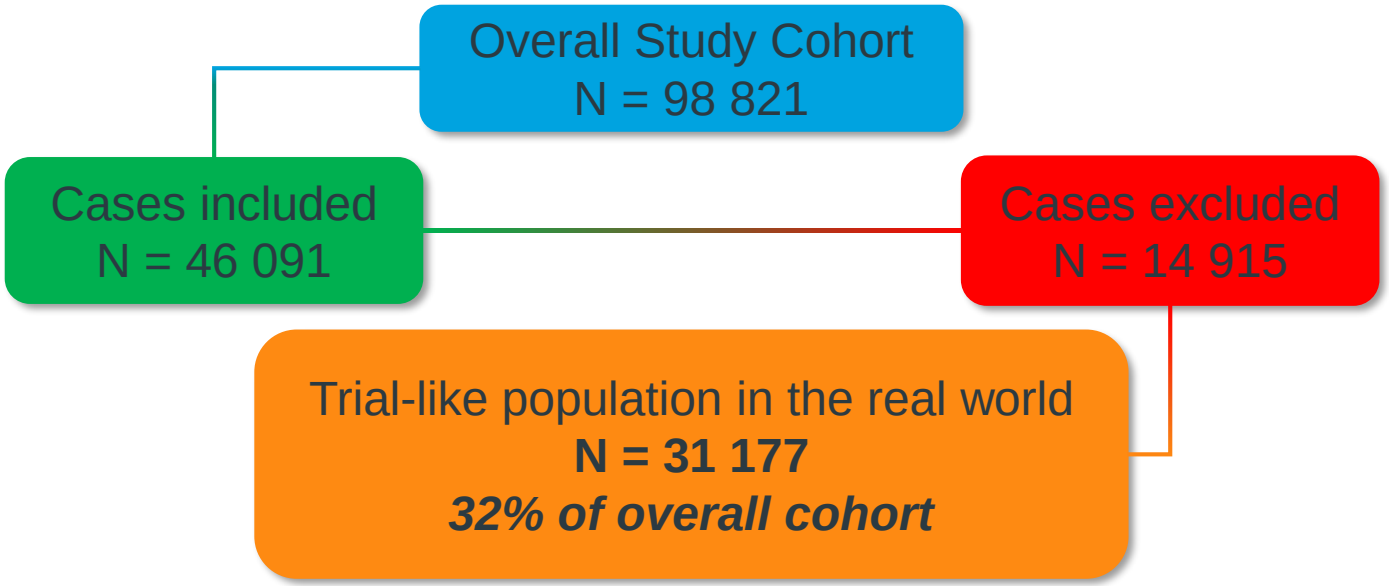
These tables must accurately reflect the patient population of interest (specifically, those patients who have survived the initial 60 days), as expert opinion is that survival past 60 days is very dependent on the baseline characteristics of the patients."

Assumptions of proposed methodology



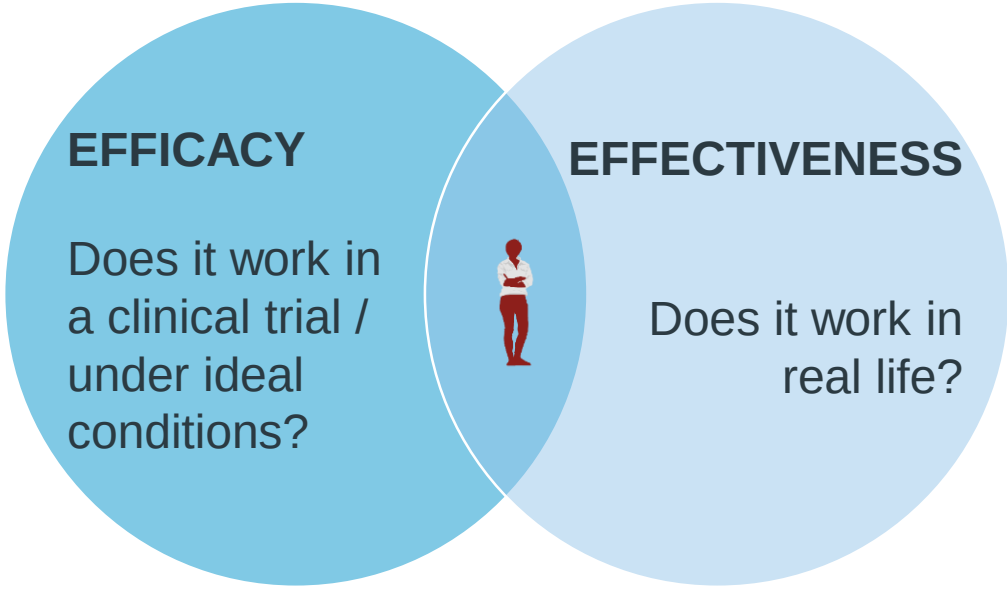
Example from Novartis study

In a Novartis non-interventional study an attempt was made to identify **a trial-like population in the real world** using criteria from the confirmatory program (pivotal trials)

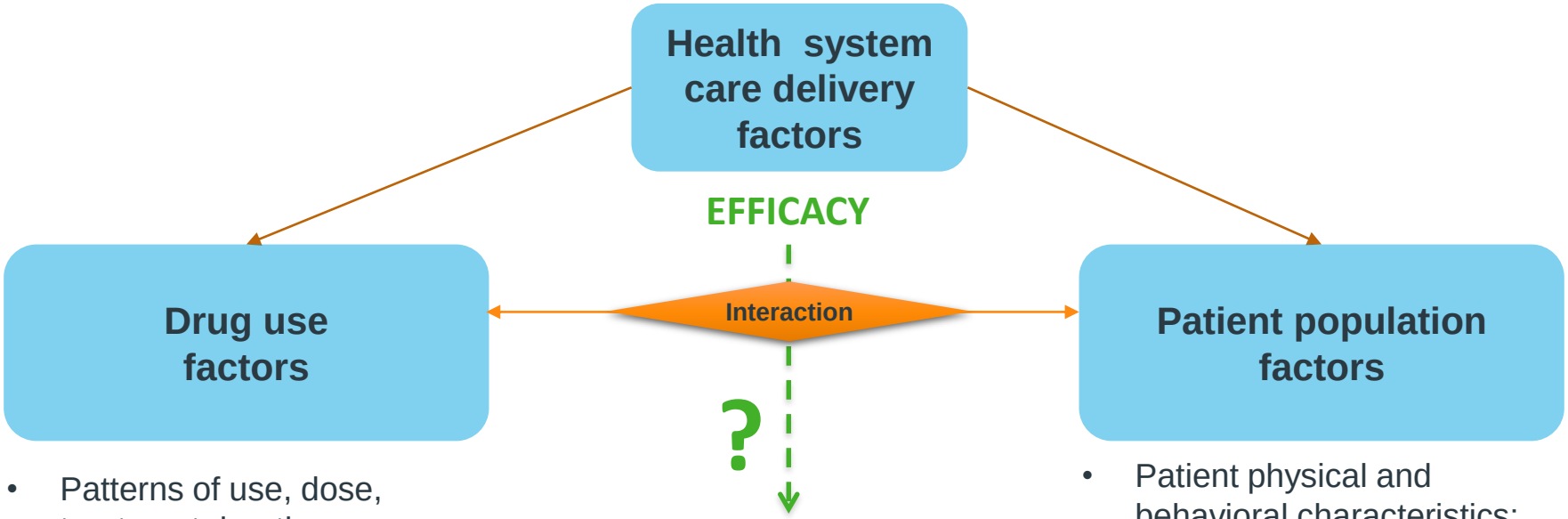


Major limitation: very few of the In-/Exclusion criteria of the RCT could be mapped, since information that is usually collected in RWD sources is very minimalistic

Difference between efficacy and effectiveness



Factors that Drive Effectiveness



- Patterns of use, dose, treatment duration
- Adherence of prescribers to label recommendations
- Adherence of patients to prescriptions
- Past history of exposure

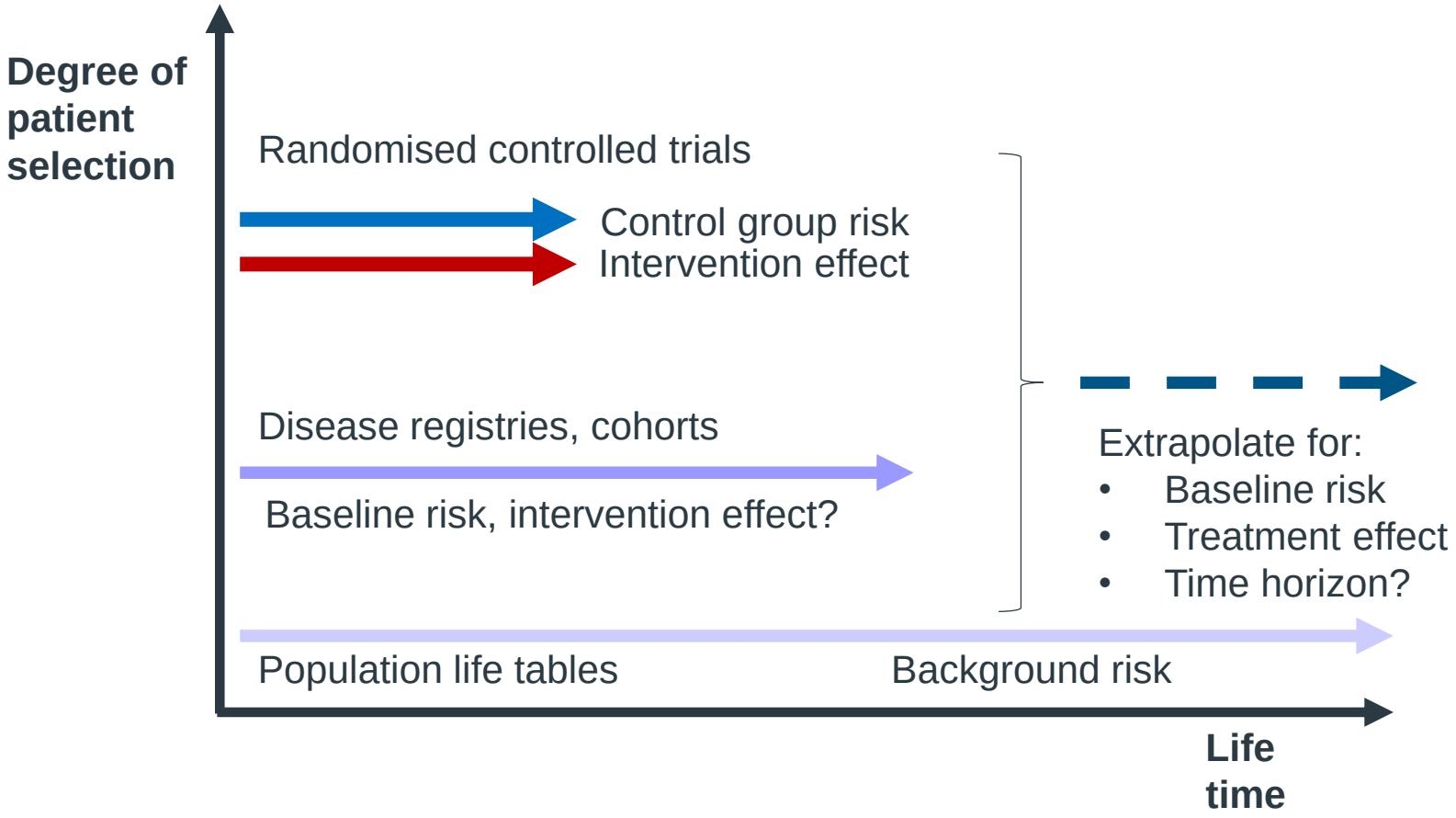
- Type of setting for care delivery (e.g, hospital, home)
- Type of prescriber : GP, specialist, nurse practitioner
- Socio-economic situation of health system, prescribers and patients

- Patient physical and behavioral characteristics: age, gender, weight, ethnicity, smoking/eating/exercise habits, etc.
- Co-morbidities
- Disease stage/severity
- Co-prescriptions
- Other baseline risk factors and genetics relevant to the disease/drug

Have you ever used external data to extrapolate survival beyond the observed data?

Combining evidence sources

Types of external data



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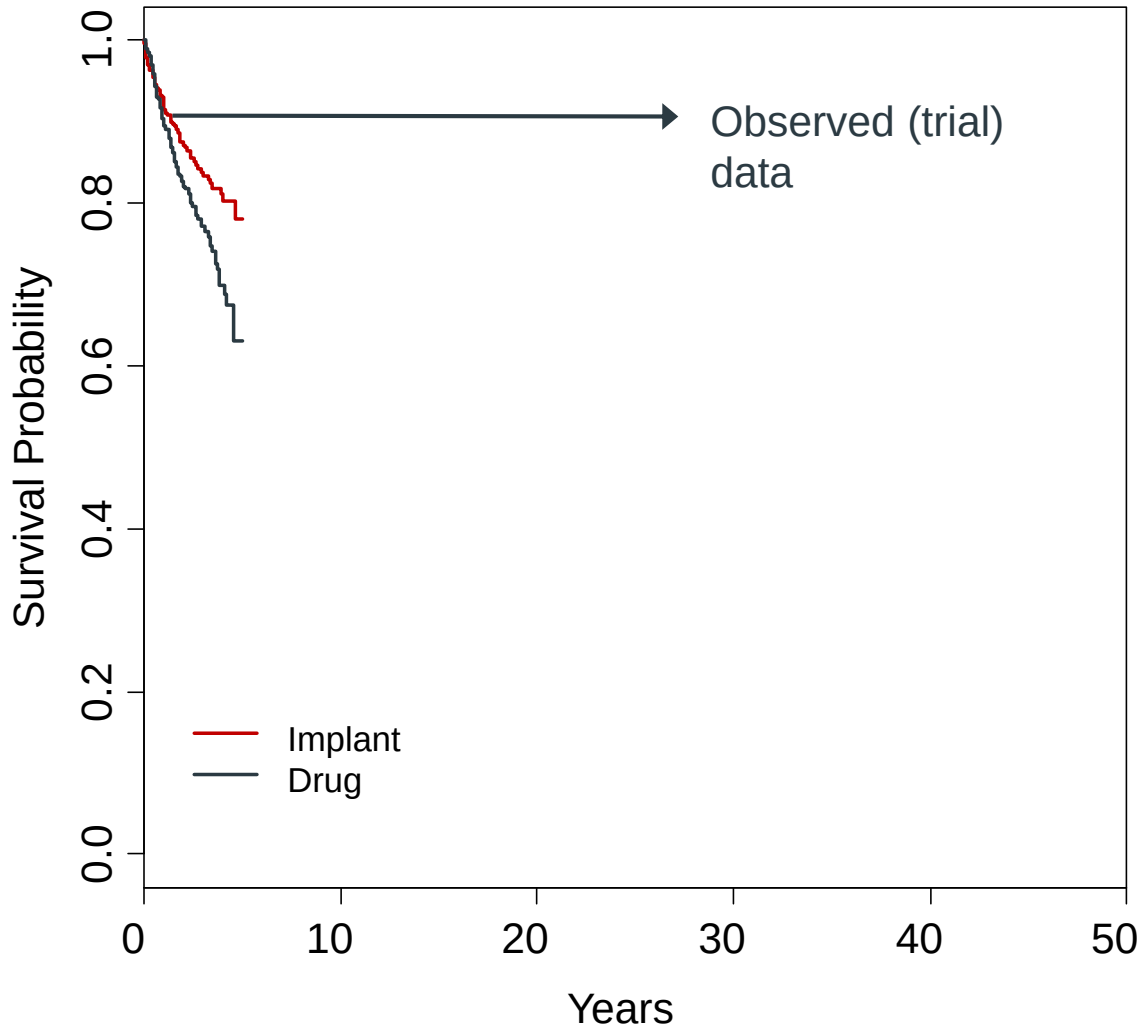
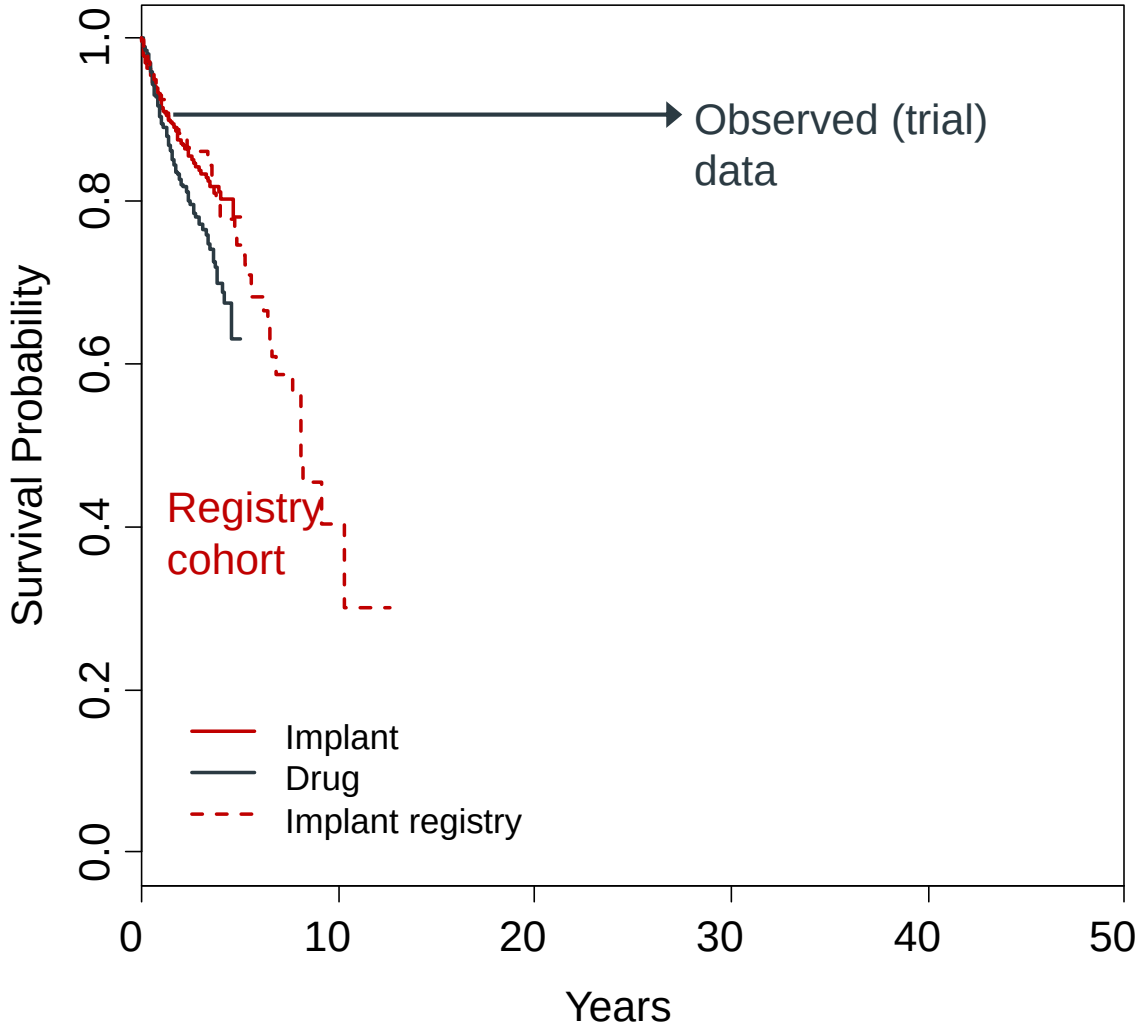
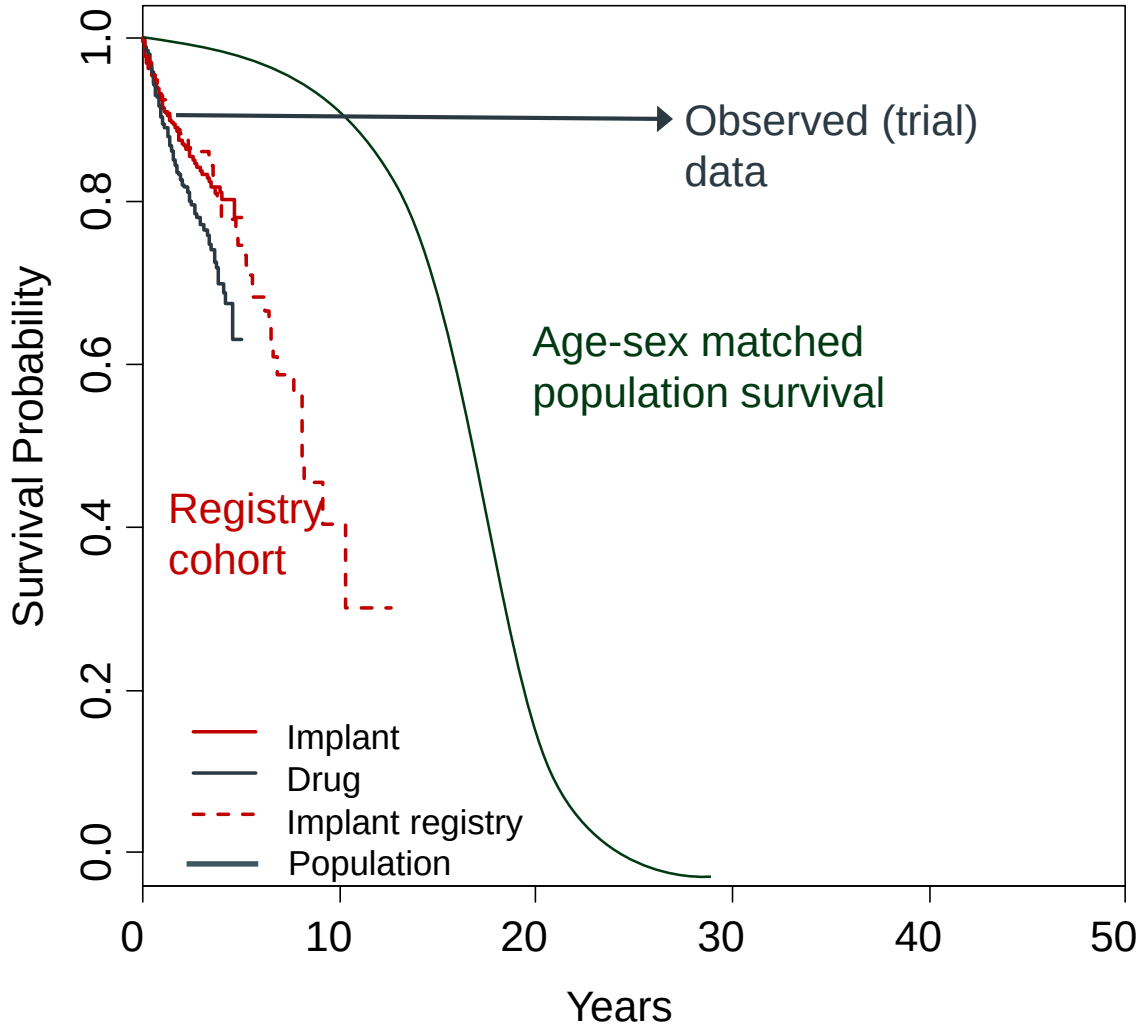
Mean LYG from incomplete data



Extrapolating from incomplete data



Extrapolating from incomplete data



Extrapolating from incomplete data

Suppose that we have short-term information on the survivor functions $S_{new}(t)$ and $S_{control}(t)$ (e.g. from an RCT).

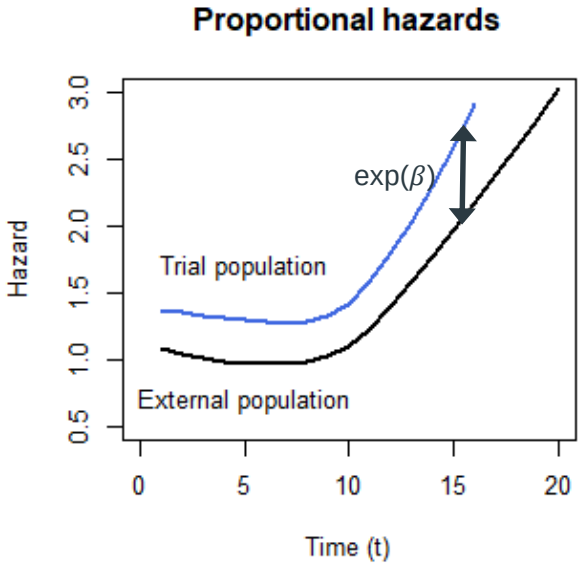
Further we have short and long-term information on $S_{external}(t)$

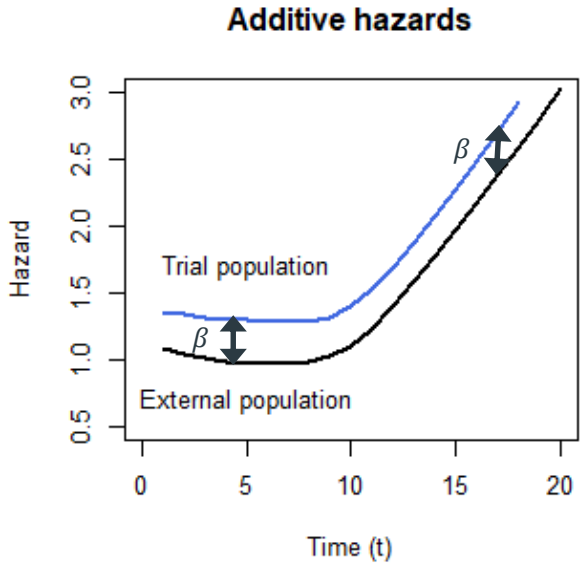
(e.g. from registries or population statistics).

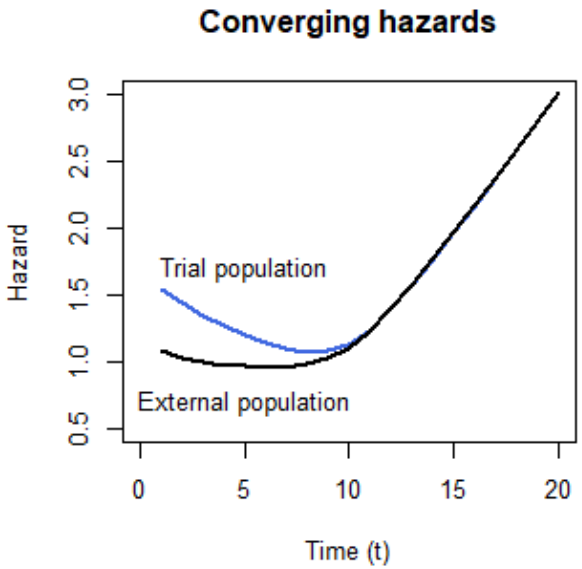
Then use external data to estimate long-term effects by making assumptions about:

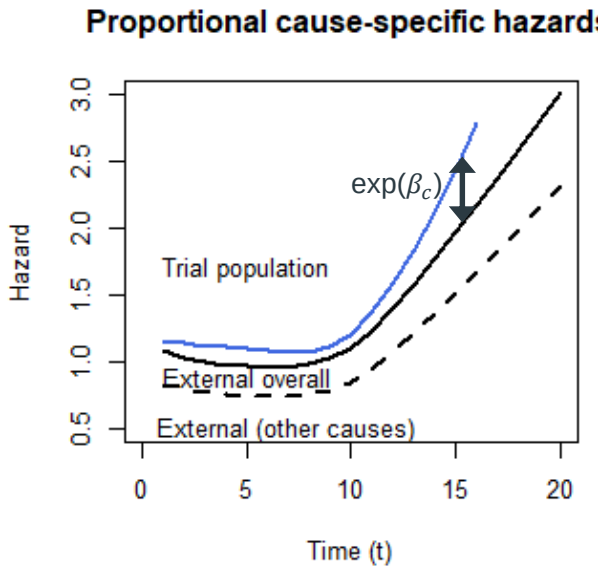
1. how survival differs between the RCT and external populations (β)
2. and how observed comparison of $S_{new}(t)$ and $S_{control}(t)$ will continue in the long term (θ)

Hazard options

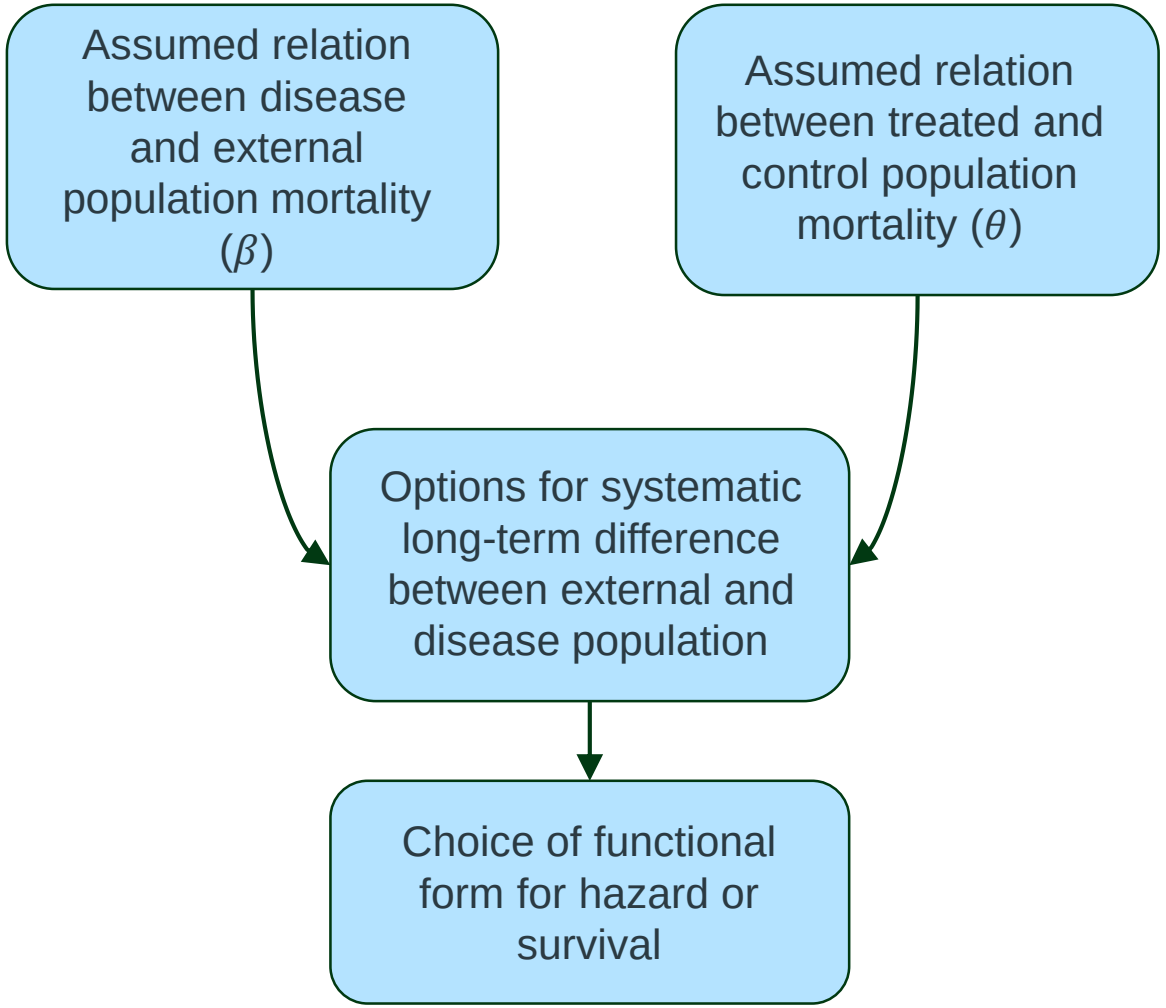








General framework reviewed



Minimum requirements

1. *Robust treatment effects:* a treatment effect size that is precise (large trial, meta-analysis), from a relevant population, with at least medium-term follow up

2. *External evidence:* long-term, complete and high quality (trial standard?) records from a relevant population (disease registry, population?)

3. *Synthesis parameters:* a minimum set of parameters that model the relationships between data sources (θ, β)

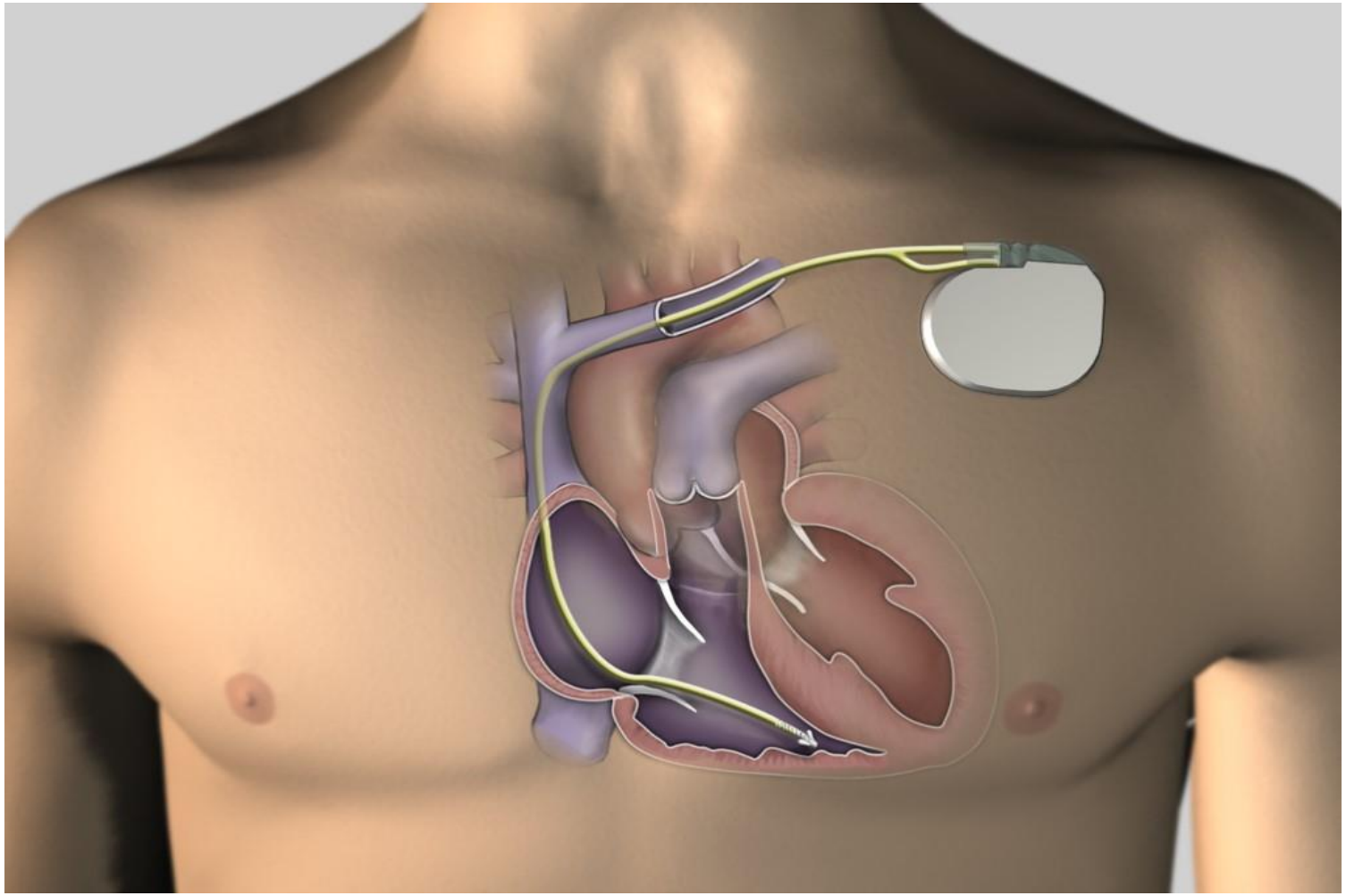
4. *Model assumptions:* well-fitting survival functions and 'plausible' (but non-verifiable) extrapolation

5. *Additionally:* if individual patient data are available, matching or standardisation to decision-problem target population

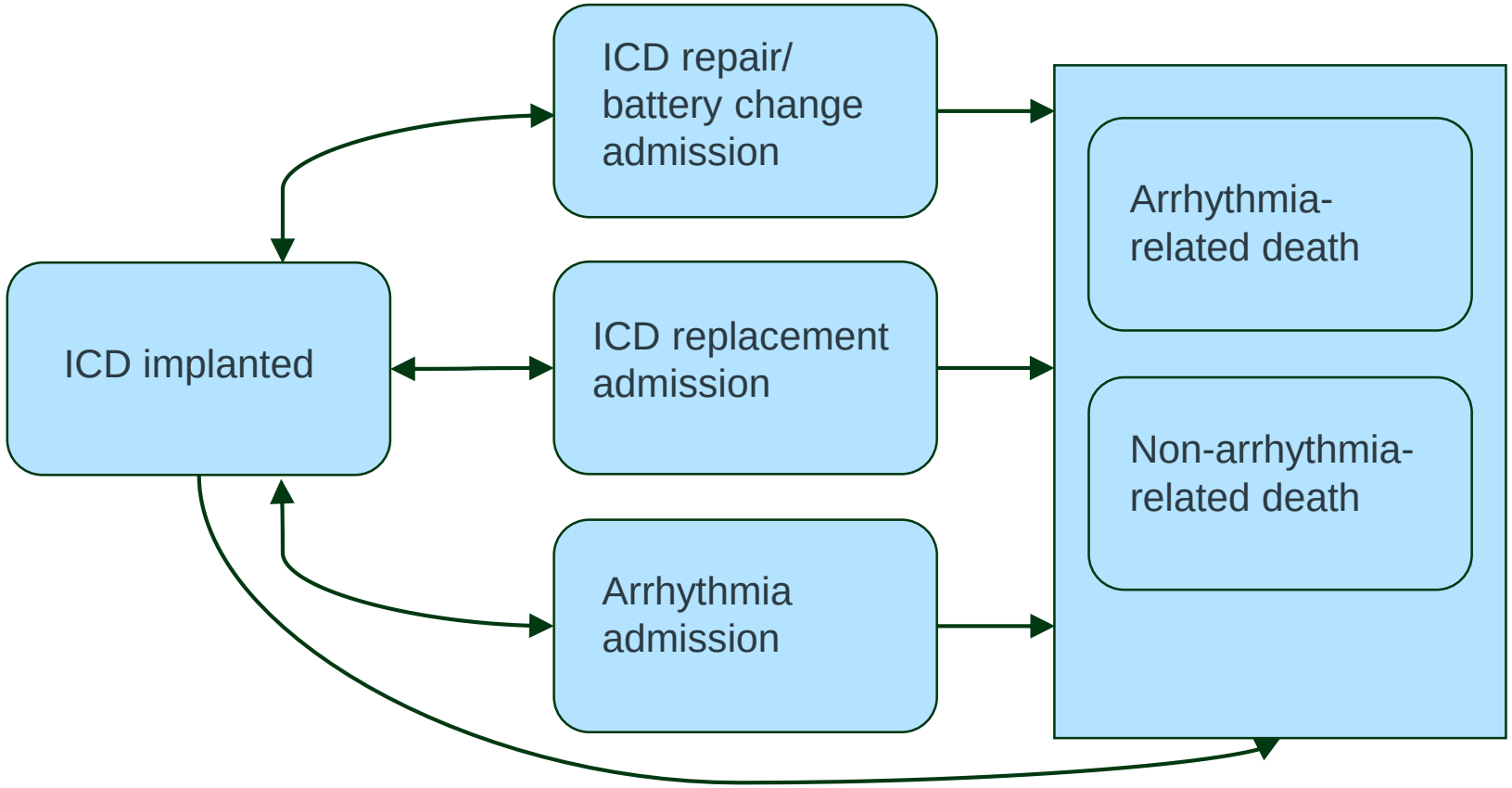
6. *Sensitivity analysis*

Application to Implantable Cardioverter Debrillators (secondary prevention)

ICDs for secondary prevention of SCD



ICDs for secondary prevention



ICD data sources

ICD implant compared to anti-arrhythmia drugs (AAD) for secondary prevention of sudden cardiac death

Data:

1. Meta-analysis of three (non-UK) RCTs (published HRs).

   Overall HR(ICD:AAD) = 0.72 (0.60, 0.87)

   Arrhythmia-related deaths HR = 0.50 (0.37, 0.67)

2. Individual patient data from cohort of 535 UK cardiac arrhythmia patients implanted with ICDs.

   Relatively short-term follow up: approximately 75% patients followed for less than 5 years, maximum 10 years

3. UK population mortality statistics

Aim:

- Estimate cost-effectiveness over the lifetime of ICD and AAD patients in the UK.

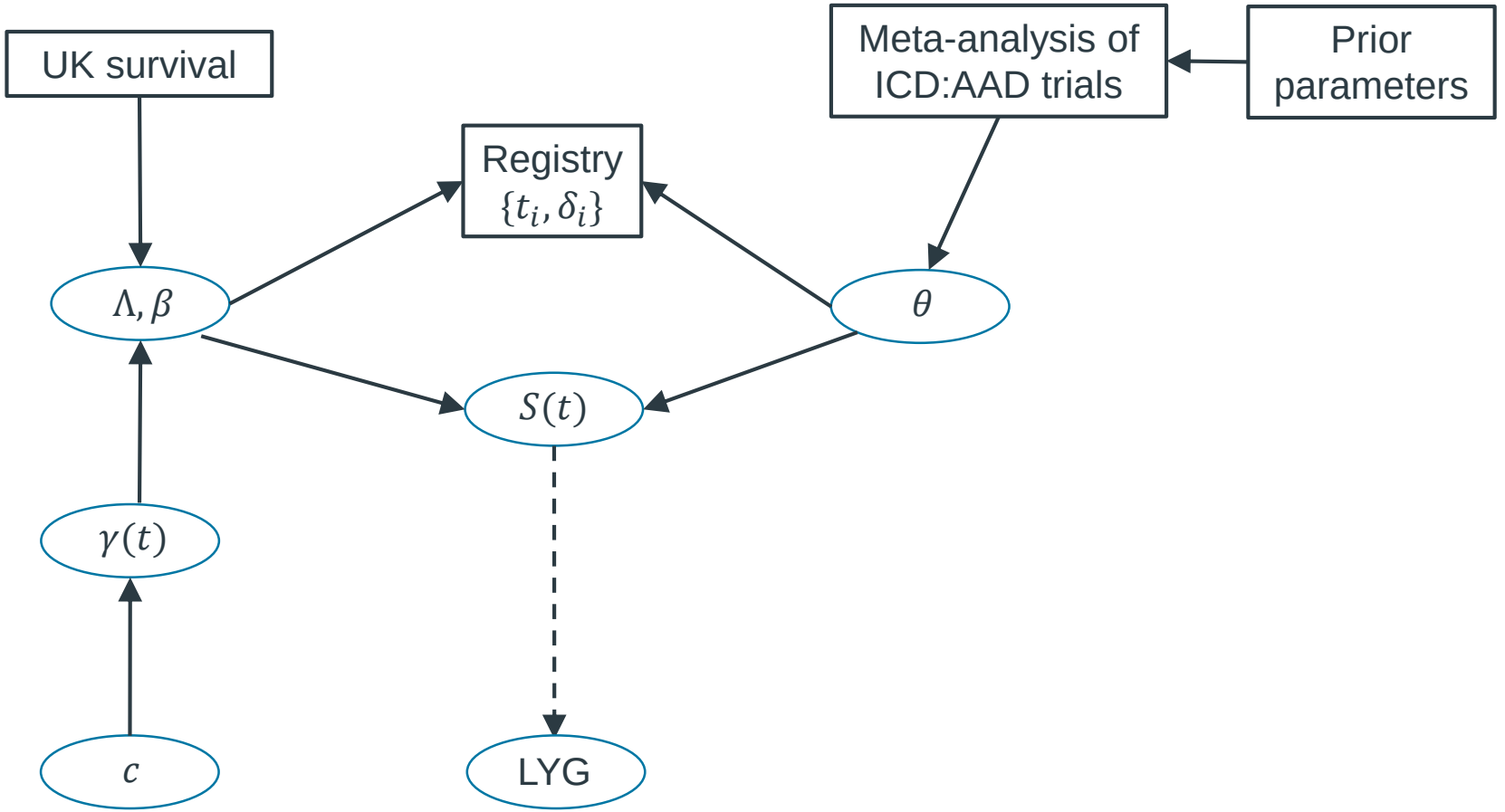
Application to ICD

Hazards for three groups:

$h_{UK}(t)$	Estimated from UK Government audit data
$h_{ICD}(t) = e^{\beta} h_{UK}(t)$	UK Government and registry data
$h_{AAD}(t) = e^{\beta+\theta} h_{UK}(t)$	UK Government, registry and meta-analysis results

The (UK population) baseline hazard can take non-parametric or parametric form (e.g. Weibull)

ICDs graphical model



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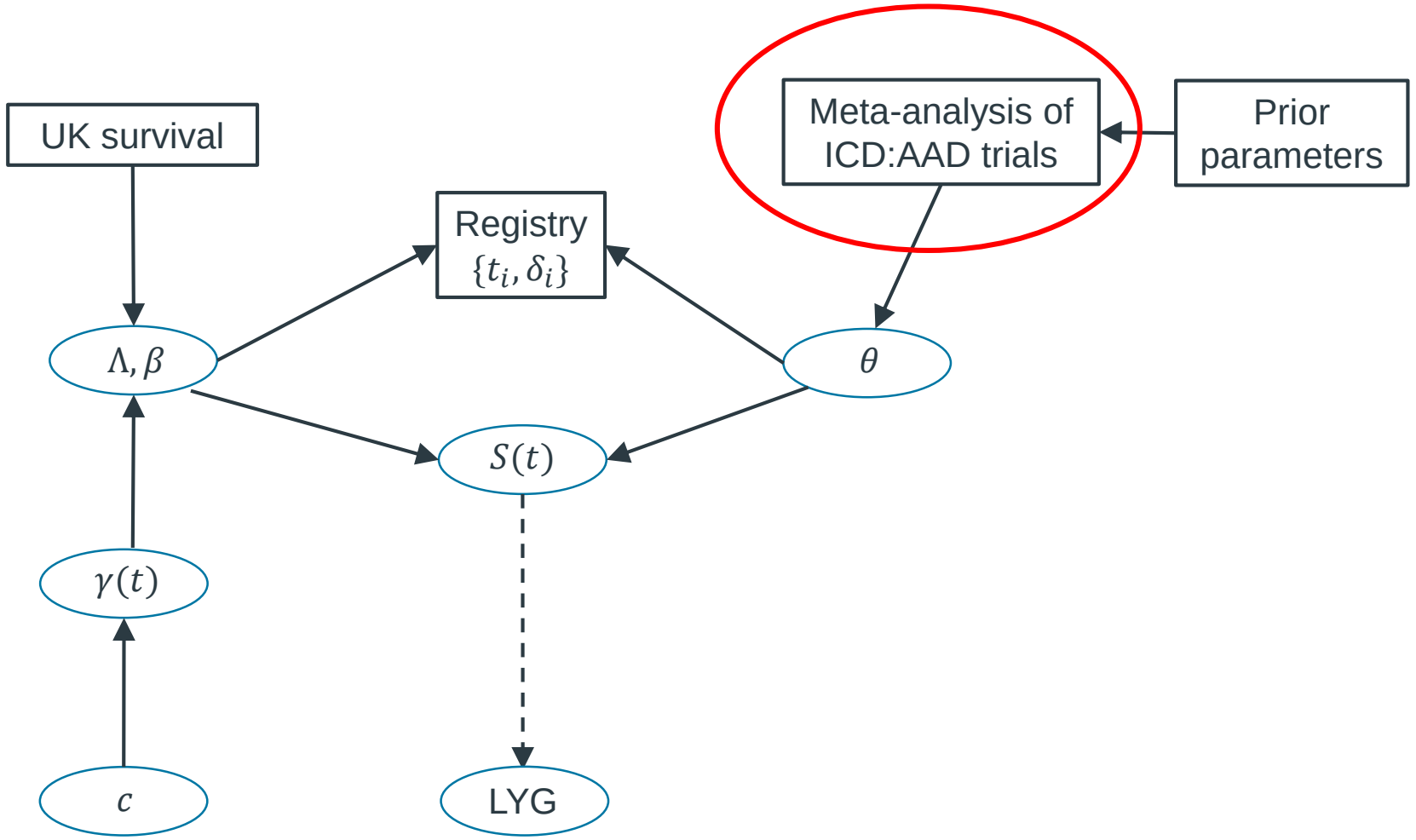

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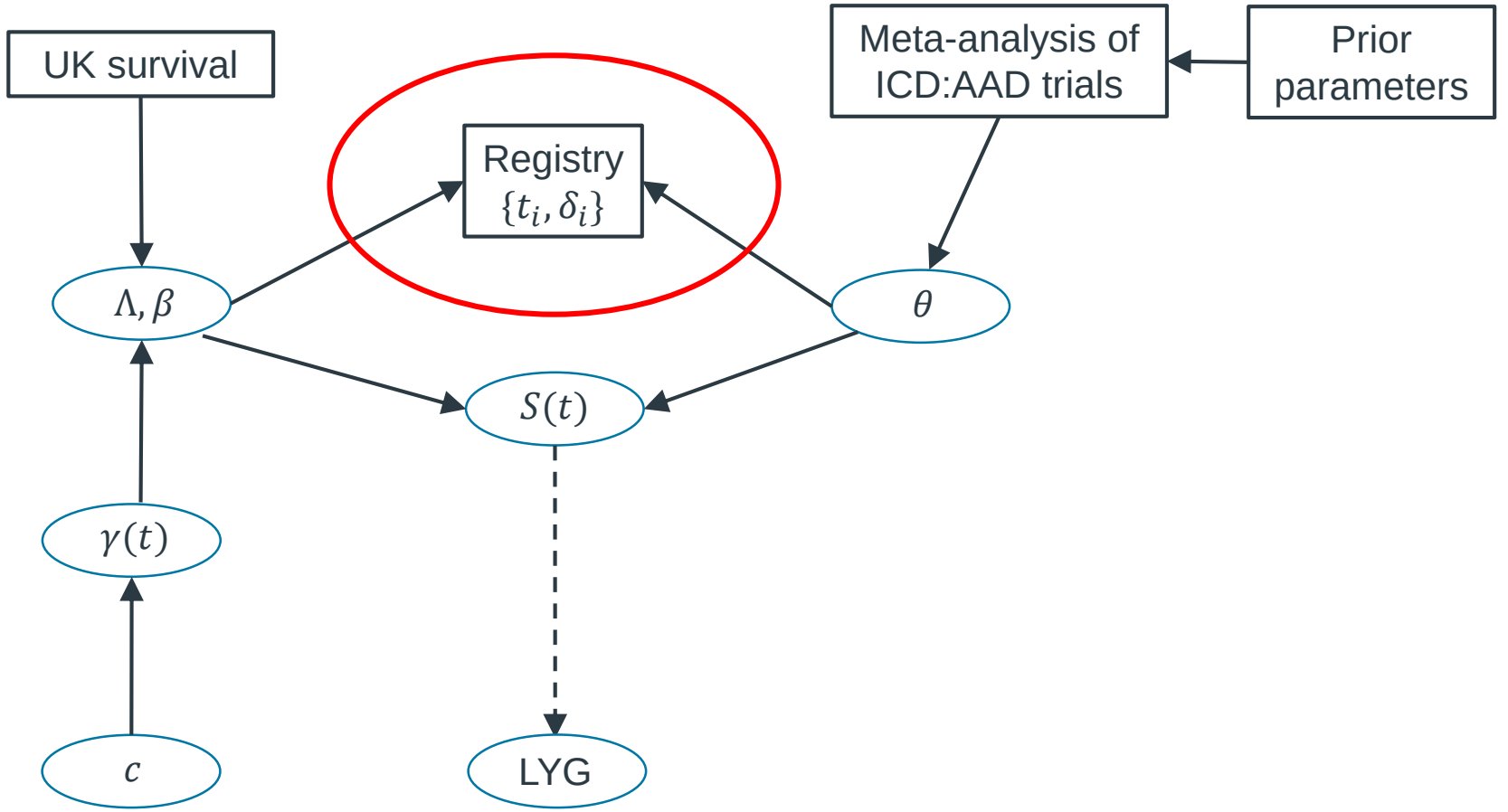

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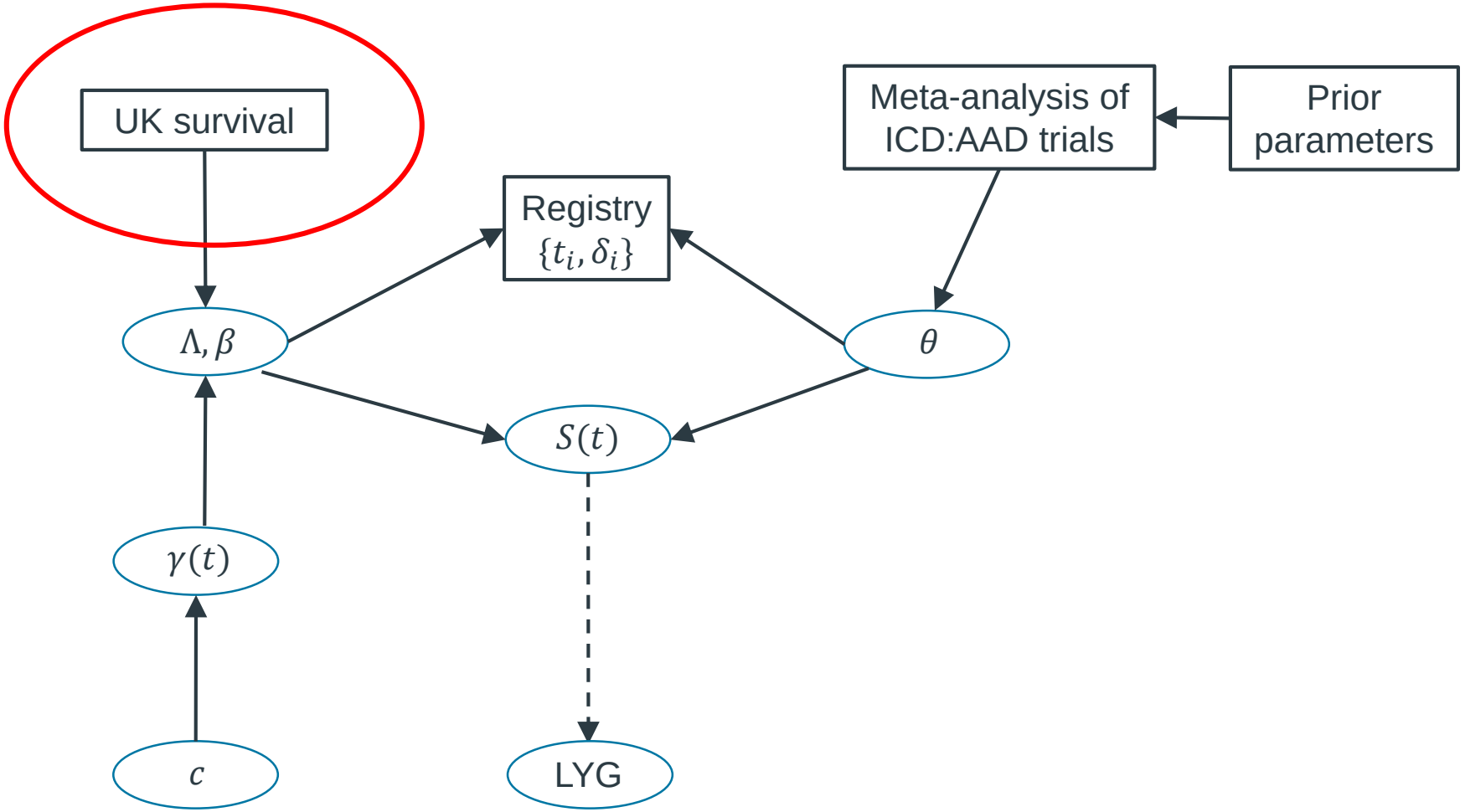

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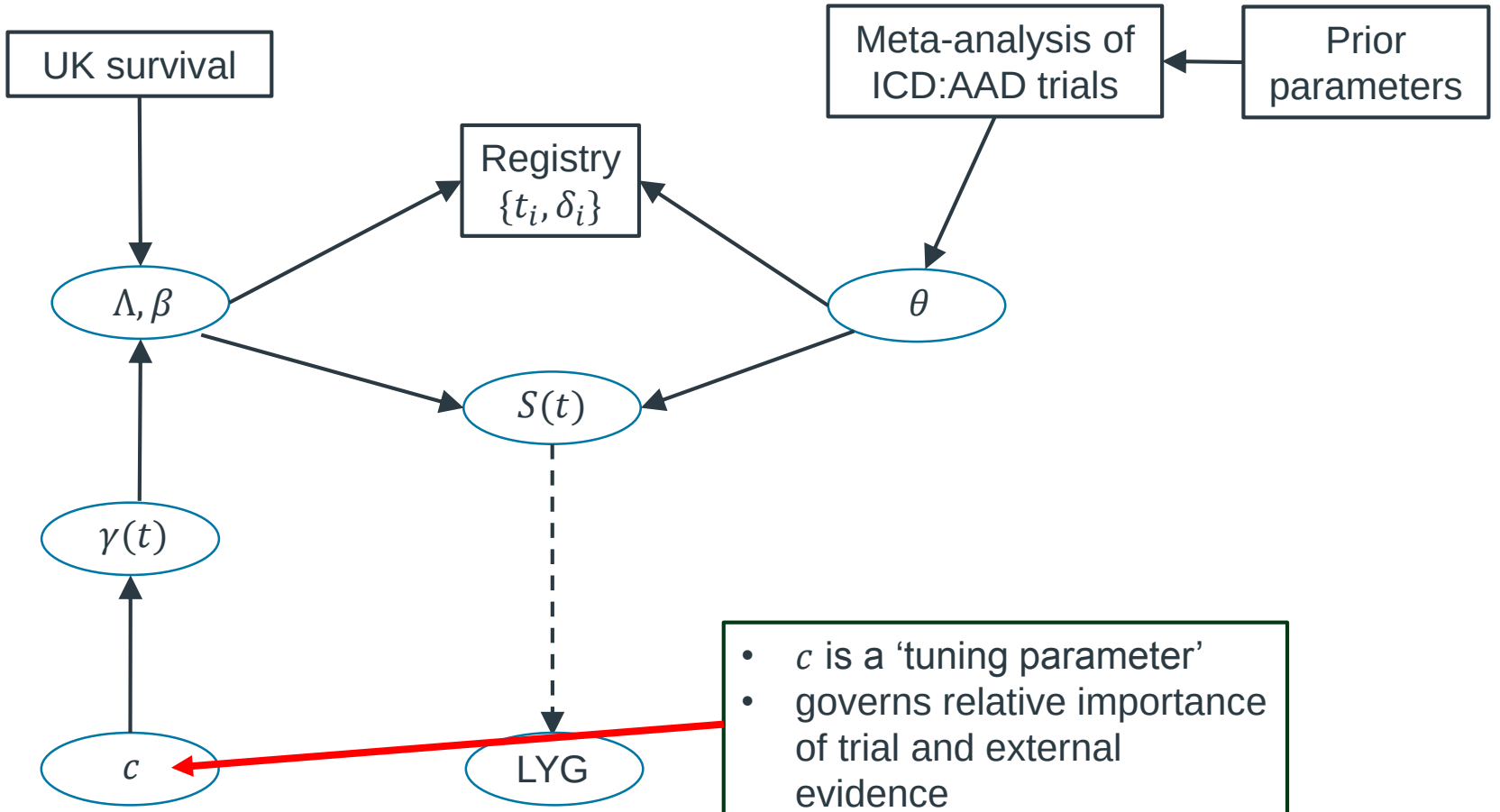
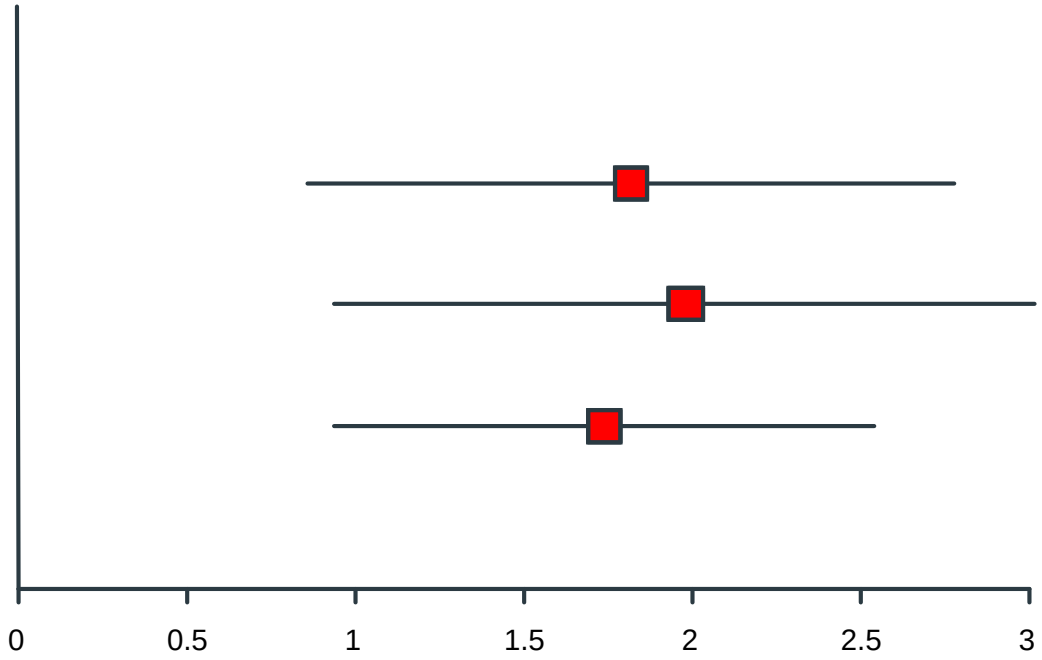


ICDs mean LYG by distribution

Model	LYG (SE)
Weibull	1.8 (0.5)
Cox	2.0 (0.5)
Additive (c=100)	1.7 (0.4)



Cause-specific hazards

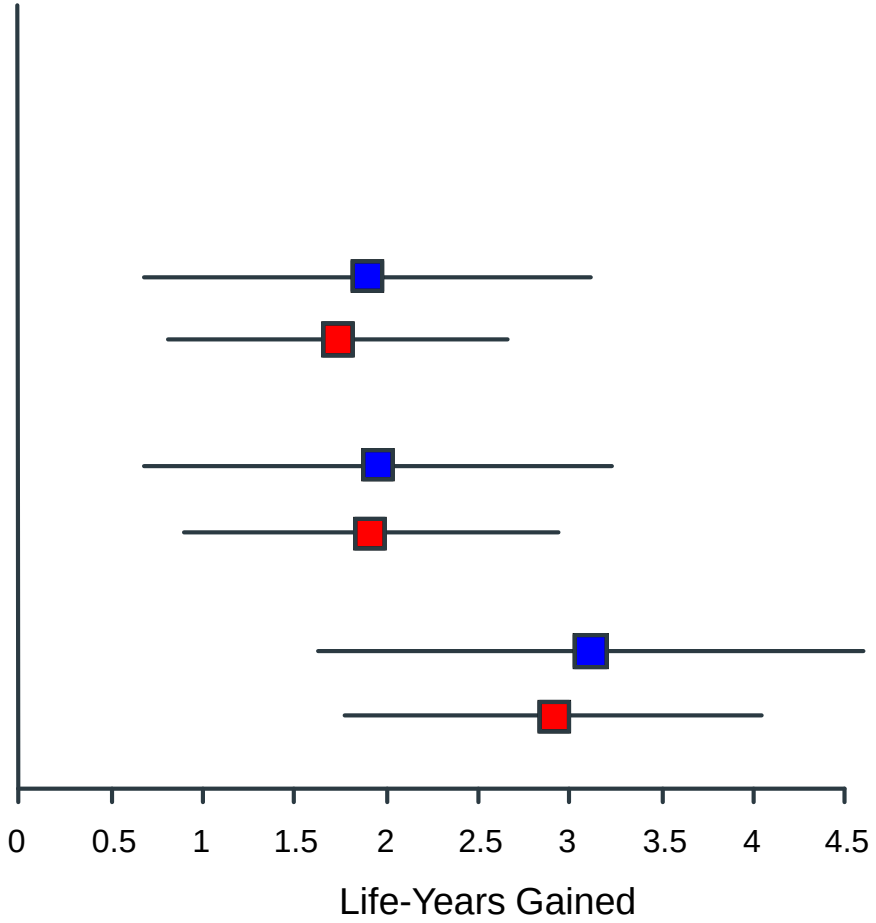
Does cause-specific hazard change as a proportion of total hazards?

Use cause-specific hazards for three groups:

$h_{UK.A}(t) + h_{UK.NA}(t)$	UK Government audit data
$h_{ICD}(t) = \boldsymbol{e^{\beta'} h_{UK.A}(t)} + h_{UK.NA}(t)$	UK Government and registry data
$h_{AAD}(t) = \boldsymbol{e^{\beta'+\theta'} h_{UK.A}(t)} + h_{UK.NA}(t)$	UK Government, registry and meta-analysis of cause-specific hazards

ICDs mean LYG by distribution

Model	Women LYG (SE)	Men LYG (SE)
Weibull	1.9 (0.6)	1.7 (0.5)
Cox-like	2.0 (0.7)	1.9 (0.5)
Poly-Weibull	3.1 (0.8)	2.9 (0.6)



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5. *Additionally:* if individual patient data are available, matching or standardisation to decision-problem target population

6. *Sensitivity analysis*

Which data sources are you thinking to use in order to leverage on RWD?

How organized the RWD sources are to be used for extrapolation purposes?

In absence of systematically captured longitudinal RWD, which are the actions you take?

Have you ever considered running pivotal trials as more pragmatic in order to generate clinical evidence that is closer to the real population?

Thank you!

- **Nikolaos Demiris**, Assistant Professor, Athens University of Economics and Business, Greece
- **Linda Sharples**, Professor in Statistics London, School of Hygiene & Tropical Medicine, UK
- **Alexandros Sagkriotis**, Director RWE, Novartis, Basel, Switzerland
- **Andreas Karabis**, Principal, Real World Insights, IQVIA, Amsterdam, the Netherlands

Back-up slides

FDA Real World Evidence meeting- Key highlights

FDA is open to RWE studies (data generated from sources that are outside of RCTs that are randomized or observational)

FDA is open to exploring RWE designs and methodologies to ensure key aspects are incorporated and encourages inclusion of RWE into clinical development programs

The Agency finds RWE to be valuable in order to close the gap on the external validity from RCTs

FDA encourages recruitment of patients from within the healthcare system to increase generalizability

The Agency does not see a major distinction between RCT and pragmatic/ randomized trials

Some of the key caveats that FDA believes **should be addressed in RWE:**

- Loss of power or diminished effect size in RWE trials and identifying ways to counteract this with enrichment factors (after randomization)
- Control for bias and unmeasured confounding
- Data Quality – sources, collection, analysis and validation
- Additional methods to establish causal inference in RWE
- Loss to follow up when patients switch insurance plans