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The DIVE framework for using different types of information in estimating lifetime clinically plausible effectiveness in oncology

Panelist

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How can lifetime survival extrapolations be best supported?

Is a standardised structured framework needed in health technology assessment (HTA) submissions, and what implementation challenges might arise?

Background

Economic models capture all economic and humanistic consequences of novel therapies over the entire disease course.

This arguably means the following can be distinguished[1]:

- Median overall survival (OS) data are available at first pricing and reimbursement negotiations.
- Limited OS data are available at first pricing and reimbursement negotiations, and mature OS data are expected within the therapy lifecycle (before the therapy is off-patent or superseded).
- Incomplete or no OS data are available at first pricing and reimbursement decisions, or during the therapy lifecycle.

There are many agencies and researchers developing new methods related to survival extrapolations.

- National Institute for Health and Care Excellence (NICE)
- European Network for Health Technology Assessment (EUnetHTA)
- National Health Care Institute (Zorginstituut Nederland; ZIN)
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Institute for Clinical and Economic Review (ICER)

Today's presentation focuses on NICE guidance which has the most guidance documents in terms of technical support documents (TSD).

1. Lux MP, Ciani O, Dunlop WCN, Ferris A, Friedlander M. The Impasse on Overall Survival in Oncology Reimbursement Decision-Making: How Can We Resolve This? Cancer Manag Res. 2021 Nov 10;13:8457-8471

Background (cont.)

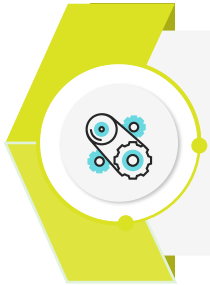
Technical support guidance related to modelling lifetime survival

- TSD 2: A general linear modelling framework for pair-wise and network meta-analysis of randomised controlled trials
- TSD 3: Heterogeneity: subgroups, meta-regression, bias and bias-adjustment
- TSD 4: Inconsistency in networks of evidence based on randomised controlled trials
- TSD 5: Evidence synthesis in the baseline natural history model
- TSD 13: Identifying and reviewing evidence to inform the conceptualisation and population of cost-effectiveness models
- TSD 14: Survival analysis for economic evaluations alongside clinical trials – extrapolation with patient-level data
- TSD 15: Cost-effectiveness modelling using patient-level simulation
- TSD 16: Adjusting survival time estimates in the presence of treatment switching
- TSD 17: The use of observational data to inform estimates of treatment effectiveness in technology appraisal: methods for comparative individual patient data
- TSD 18: Methods for population-adjusted indirect comparisons in submissions to NICE
- TSD 19: Partitioned survival analysis as a decision modelling tool
- TSD 20: Multivariate meta-analysis of summary data for combining treatment effects on correlated outcomes and evaluating surrogate endpoints
- TSD 21: Flexible methods for survival analysis

Overview

The lifetime relative clinical effectiveness of new oncology treatments vs. standard of care needs to be determined for HTAs. It is important that the estimated effectiveness for the new treatment and all relevant comparators are clinically plausible.

The DIVE concept framework shows the different ways to include all available information in the estimation process of lifetime clinical effectiveness to maximise clinical plausibility.



The framework can be used to assess whether all or the most relevant information has been used to inform clinical effectiveness.

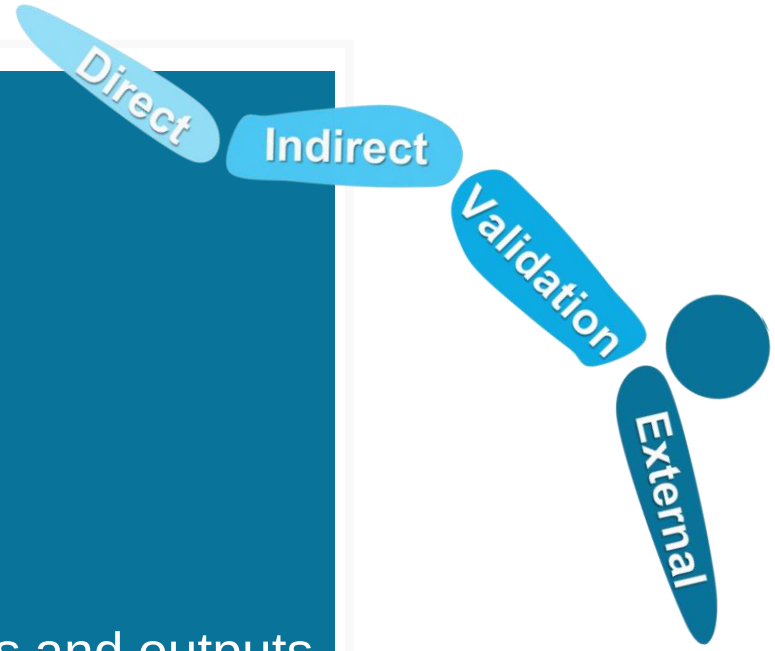
DIVE framework

Direct use of clinical trial information

Indirect use of external information

Use of external information to **V**alidate assumptions and outputs

Use of **E**xternal information to improve the estimation process



Availability of TSD guidance

No guidance

Guidance only applicable for trials with median OS data available at first pricing and reimbursement negotiations

Guidance also applicable for trials with limited OS data available at first pricing and reimbursement negotiations, and mature OS data are expected within the therapy lifecycle (before the therapy is off-patent or superseded)

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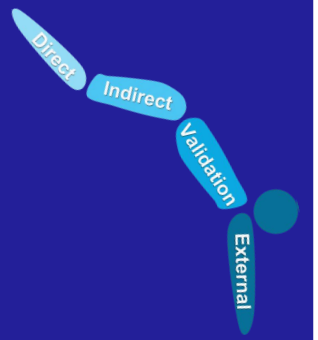
DIVE framework



Direct use of clinical trial information

Main considerations

Direct

Extrapolation of survival data

- Flexible models (TSD 21)
- Response-based landmark models (TSD 21)
- Model structures (TSD 19)
- Standard models (TSD 14)
- Relative survival (TSD 21)

Treatment switching

- Methods to adjust trial data for treatment switching (TSD 16)
- Multi-state/semi-Markov methods to overcome treatment switching (TSD 19)

Other considerations

- Is there confounding from switching to therapies that are not part of standard treatment pathways?
  - Skaltsa K, Ivanescu C, Naidoo S, Phung D, Holmstrom S, Latimer NR. Adjusting Overall Survival Estimates after Treatment Switching: a Case Study in Metastatic Castration-Resistant Prostate Cancer. Target Oncol. 2017 Feb;12(1):111-121.

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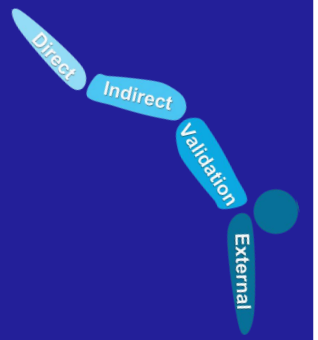
DIVE framework



Indirect use of external information

Indirect

Main considerations

Network meta-analyses (randomised clinical trials and/or single-arm trials)

- Treatment effect
  - Constant hazard ratio (TSD 2, TSD 3, and TSD 4)
  - Time-varying hazard ratio
- Anchored vs. unanchored analyses (TSD 17 and TSD 18)
- Population-adjusted indirect treatment comparisons (TSD 17 and TSD 18)

Other considerations

- Covariate selection and number of covariates; effect modifiers and prognostic factors?

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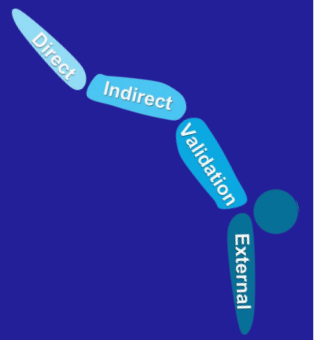
Use of external information to Validate assumptions and outputs

DIVE framework



Validate

Main considerations

Expert validation

- Collecting clinical expert opinion to test assumptions and validate outcomes (advisory board

External data validation

- Kaplan-Meier and surrogacy assumption testing and outcome comparison

Other considerations

- In what setting should expert validation input (e.g., advisory board vs. Delphi approach) be collected?
- What data are appropriate for external data validation (e.g., location, time window data collection)?

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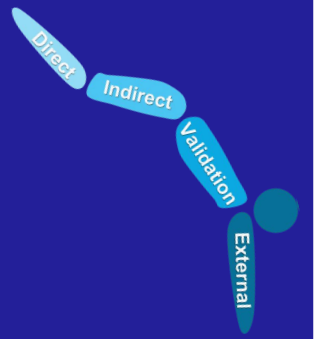
Use of External information to improve the estimation process

DIVE framework



Main considerations

External

Extrapolation using expert information

- Defining a priori distributions (TSD 21?)

Extrapolation using external data

- Defining a priori distributions (TSD 21?)
- Later-stage transition probabilities initial and recurrent events
  - Risk equations
  - Unadjusted probabilities
- Surrogacy (TSD 20)
- Modelling structure (TSD 15 and TSD 19)
  - Semi-Markov/multi-state modelling/ sequencing model/DES

Other considerations

- How should a priori distributions from expert opinion (e.g., SHELF method) be defined?
- What data are appropriate for external data extrapolations (e.g., location, time window data collection)?
- Is the early outcome in the risk equation a valid surrogate marker for all-cause mortality in the disease[1,2]?

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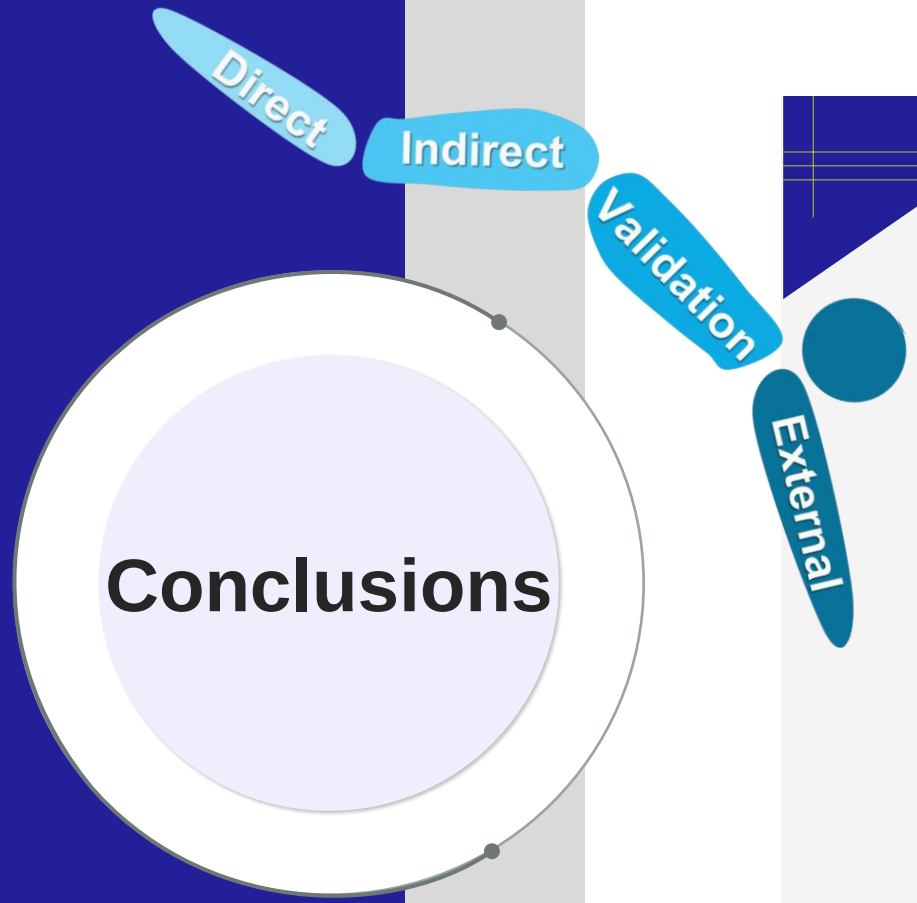
1.Daly MJ et al A Review of Economic Models Submitted to NICE's Technology Appraisal Programme, for treatments of T1DM & T2DM. Front Pharmacol. 2022 May 11;13:887298; 2.Baechle C et al Is HbA1c a valid surrogate for mortality in type 2 diabetes? Evidence from a meta-analysis of randomized trials. Acta Diabetol. 2022 Oct;59(10):1257-1263



DIVE is:

- Work in progress
- A step-wise tool that can increase transparency in the considerations made for lifetime survival extrapolations for economic models
- A central point of reference for related published guidance on this topic
- A living document

DIVE is <u>not</u>:

- A grading system

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Thank you