

Partitioned survival analysis for decision modelling in health care: a critical review

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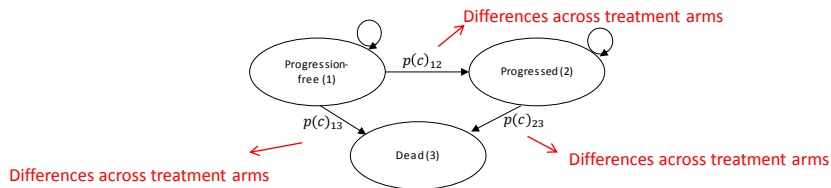
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Decision modelling

- State transition models (STMs) used extensively for modelling chronic diseases including cancer
- Describe biological/clinical processes and way interventions effect these processes
- Key role of decision models in NICE TAs
 - Synthesis of all relevant evidence
 - Comparison of all relevant interventions
 - Extrapolation of observed information over time
 - Characterise heterogeneity and uncertainty

Conceptual differences between PartSA and state transition models (STMs)

- PartSA: endpoints are modelled as independent
OS determined only by time to death data
- STMs: clinical events explicitly and structurally related



OS reflects % in progressed state, and differences in mortality between progression-free and progressed patients

i.e. OS depends on all three transitions

Is there really any difference?

- PartSA and STM: Within-trial relationships between endpoints should be reflected in the data
- **Extrapolation of OS in PartSA**
 - reflect within-trial trends in mortality rates, and
 - reflect the within-trial difference in hazard of death
- **Extrapolation of OS in STM**
 - reflect within trial estimates of each transition probability (conditioned by model structure), and
 - combined effect of treatment effects on individual transition probabilities
- Data requirements

State transition models, STMs

- Allow both the natural history of the disease and treatments effects on this to be reflected when extrapolating beyond the trial data
- Allows assumptions underpinning these extrapolations to be made explicit and therefore subject to scrutiny and sensitivity analyses

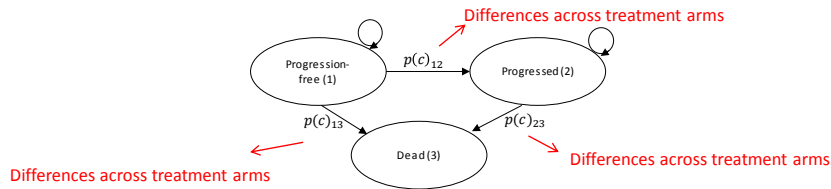
Non-PartSA approaches used in NICE appraisals

- 8/30 non-PartSA models (27%)
- One used a response-stratified PartSA (haematological cancer)
- Seven STMs
 - Vehicle to introduce assumptions (e.g PPS independent of treatment)
 - Did not always use OS data that was available, or predict OS well

Did not use established survival analytic methods for competing and sequential events

Poor use of available data

Challenges in implementing STMs



- (i) Estimation: when IPD available/recoverable
- (ii) Estimation: Data availability
- (iii) Implementation

Challenges in implementing STMs:

(i) in estimating transition probabilities when IPD available/recoverable

- Competing risks and multi-state modelling [tutorial in Williams MDM 2016]
- However:
 - Limited guidance on model selection and assessment
 - Challenges in modelling PPS (a 'non-entry' state): due to selection effects and dependent censoring
e.g. covariates/time dependency
- Naïve PPS analysis insufficient
- More difficult to achieve reasonable fit to OS

Challenges in implementing STMs:

(ii) Data availability

- Require data on individual transitions in aggregate or IPD form
- Unlikely to be available for external data
- Currently, no approach available
- Multi-parameter evidence synthesis / calibration may be feasible
- Trialists should be encouraged to report individual endpoint outcomes and share IPD

Challenges in implementing STMs:

(iii) Implementing time-dependent transition probabilities

- Need for more advanced methods
 - Tunnel states
 - Semi-Markov approaches
 - Patient-level simulation
 - “Payoff” approaches
 - do not produce OS graphs

Summary

- PartSA's defining feature is that state membership is determined by independently modelled non-mutually exclusive survival curves
- No concerns where data is fully observed
- For extrapolation, however, PartSA use prior trends in mortality, while STMs explicitly link mortality with intermediate prognostic events
- STMs allow assessing plausibility of extrapolations and meaningful sensitivity analyses (but are difficult to specify)

TSD recommendations (summary)

- Emphasis on importance of model conceptualisation and stakeholder recognition of limitations of PartSA
- Survival curves corresponding to individual clinical events requested alongside PartSA models
- Further research and guidance to support routine use of multi-state survival analysis
- State transition modeling recommended for use alongside the PartSA approach (currently...)
 - assist in verifying the plausibility of PartSA's extrapolations
 - address further uncertainties in the extrapolation period
 - even if only for pivotal trial

TSD recommendations: Selecting, documenting and justifying the modelling approach

Recommendation 1: The model conceptualisation process should be routinely reported and the rationale for the chosen modelling approach explicitly justified on the basis of theoretical and practical considerations.

- Approach aligned with disease process and intervention effects
- Appropriateness as vehicle for extrapolation
- Evidential constraints

Recommendation 2: Consistent and appropriate terminology should be applied in future appraisals when describing the PartSA approach (e.g. use of the term “Partitioned survival analysis”).

Recommendation 3: A summary of the main structural assumptions should be routinely reported and justified as required by the NICE guide to the methods of technology appraisal.

TSD recommendations: Representing uncertainties associated with extrapolation

Recommendation 4: All stakeholders should recognise the specific limitations of PartSA for the purposes of extrapolation.

- Limitations of prediction and limitations for exploring key uncertainties

Recommendation 5: Modelling choices that influence outcomes in the extrapolation period should reflect all relevant evidence.

- External data, within-trial data (recommendation 6), expert opinion

Recommendation 6: Within-trial survival curves corresponding to individual clinical events should be supplied alongside PartSA models.

Recommendation 7: When extrapolation is required, PartSA models should easily facilitate the investigation of alternative assumptions in accordance with current NICE methods guidance.

TSD recommendations: Use of alternative modelling approaches

Recommendation 8: Transition probabilities within state transition models should be estimated using appropriate statistical methods and reflect all relevant evidence.

- Competing risks and multi-state modelling, consideration of selection effects and dependent censoring, careful validation.
- Care when incorporating external evidence given lack of established methods.
- ERGs/AGs access to IPD may be necessary.

Recommendation 9: Further research and guidance is required to support appropriate specification of state transition models using multi-state survival analysis.

Recommendation 10: Further research is required to support incorporation of data external to the pivotal trial, and in particular data used to inform indirect comparisons, in to state transition models.

TSD recommendations: Use of alternative modelling approaches

Recommendation 11: State transition modelling should be used alongside the PartSA approach to assist in verifying the plausibility of PartSA's extrapolations and to address uncertainties in the extrapolation period, even if this is only plausible for the pivotal trial.

Recommendation 12: Presentation of results from all PartSA and state transition models should include tabulations showing the states in which life year and QALY differences between interventions accrue and a justification of why these differences should be considered plausible.

Recommendation 13: Further research is required to identify the extent of possible biases associated with PartSA and state transition models, and how this varies according to the context in which the approaches are used

Thank you

Woods B, Sideris E, Palmer S, Latimer N, Soares M. NICE DSU Technical Support Document 19. Partitioned Survival Analysis for Decision Modelling in Health Care: A Critical Review. 2017 [Available from <http://www.nicedsu.org.uk>]

Selection effects



- Post-progression mortality will be overestimated in both arms
- PPS $HR > 1.0$ will be estimated for treatment

Dependent censoring

