



Existing good practice guidelines, focusing on operationalizing model validity, uncertainty analysis and their relationship

November 17th, 2021



Salah Ghabri, MSc, PhD, HDR
French National Authority for
Health (HAS)



HAUTE AUTORITÉ DE SANTÉ

- HTA model validation guidelines
- HTA uncertainty guidelines
- Uncertainty and validation of decision models :
 - Issues
 - HTA example: pilot HAS study
 - Literature example
- Conclusion and perspectives





“If you forsake a certainty for an uncertainty, you will lose both the certainty and the uncertainty”

Indian proverb

Model validation : HTA guidelines

- HTA guidelines make **common references** to economic model validation without relationship to uncertainty :

Guidelines	Key message
Canadian guidelines	- Describe alternative types of validation - The validation process should be documented, undertaken by 'someone impartial'
NICE England & Wales	- Rationale for the chosen validation types - Documentation whether presented results are different to the literature
PBAC Australia	- Present any approach to validate the results of an economic model - Compare model traces that correspond with observed or empirical data
KCE Belgium	- The results of the model should be intuitively correct - Explain the differences with other models for the same interventions - The outputs of the model should be consistent with real-life data
HAS France	- Mention aspects of internal and external validity - The model should produce results that are consistent and suitable for decision-making.

Uncertainty : HTA guidelines

- **HTA guidelines** describe often methods of uncertainty analysis without direct relationship to model validation



HTA Guidelines (NICE, HAS, ZIN...) and ISPOR Task Force (2011, 2020) :

- **Parameter uncertainty:** uncertainty in estimation of the parameter of interest :
 - Deterministic sensitivity analysis : univariate, multivariate
 - Probabilistic sensitivity analysis
 - Communication of uncertainty : scatter plot, Tornado, CEAC, CEAF, EVPI
- **Structural uncertainty** : choice and structure of the decision model



Review of economic appraisals to identify issues underling the link between uncertainty and model validation



Example : economic evaluation of cancer drugs

- 1. Use of external data for model validation**
- 2. Choice of type of decision model**

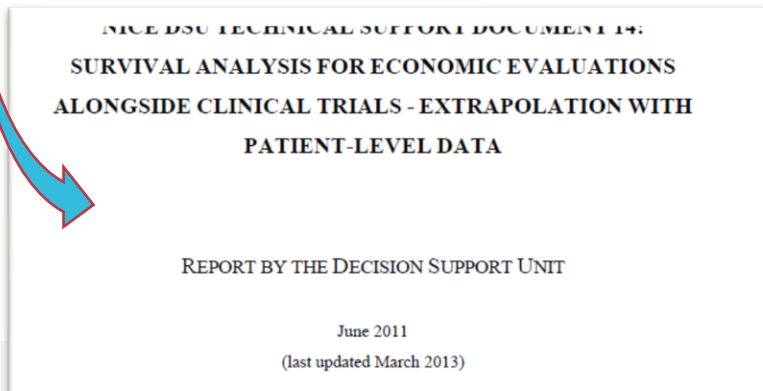
Uncertainty and validation of health decision models : issues (1)

Use of external data for model validation

Extrapolation of progression free survival (PFS) and overall survival (OS) and their calibration

- Short duration of clinical trials → long-term effect of a drug is rarely observed and uncertain
- Observed effects are extrapolated to provide a “best fit” for the long-term outputs
- Various options → **use of registries or long-term observational studies**

- When model calibration has been used to derive parameters, the “uncertainty around the calibrated values should be reported and reflected in deterministic or probabilistic sensitivity analyses or both” (Briggs et al, 2011)



Uncertainty and validation of health decision models : issues (2)

The choice of the decision model

- Structural uncertainty about the choice of the model (Strong et al. 2009, Ghabri & Cleemput, 2018, Rothery et al, 2020)
- Tricky issues :
 - What is the best decision model for the decision maker ?
 - How to validate the choice of the model ?
 - To analyze its uncertainty ?

Structural Uncertainty in Health Economic Decision Models

Mark Strong¹, Hazel Pilgrim¹, Jeremy Oakley², Jim Chilcott¹

December 2009

1. School of Health and Related Research, University of Sheffield, UK

2. Department of Probability and Statistics, University of Sheffield, UK

Address for correspondence: Dr Mark Strong, School of Health and Related Research, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA, UK. Email m.strong@sheffield.ac.uk

- **Current HTA agency guidelines and practices :**
 - Great attention is attributed to face validity/experts' opinion/ assumptions
 - No standard sensitivity analysis
 - Difficult exercise for testing different type of models
 - Constraints: deadlines, availability of data

Lack of examples in the economic appraisals

- **Literature:**
 - **Example:** partitioned survival vs Markov model ?
 - Simulations (Coyle, D, 2014)
 - OS and ICER compared between Markov and partitioned survival models
- **No consensus /No “one size fits all”**



Uncertainty and validation of health decision models : examples

Uncertainty and validation of health decision models : example (1)

External validation

- **HAS pilot study** : innovative anti-cancers drugs
- Published economic evaluations from January 2017- July 2021
- 45 appraisals
 - First-inscription : 17 (38%)
 - Reevaluation : 7 (15%)
 - Extension of indication : 21 (47%)

Predominant submissions

Use of external data

External aggregate data (literature)	28 (62,2%)
External individual data	6 (13,3%)
No external data	11 (24,5%)

Uncertainty and validation of health decision models : example (2)

Objective of the use of external data

Comparison of (%) survival outcomes simulated by the model to external data at # periods	17 (38%)
Validation of extrapolation with external data	10 (22%)
Calibration of survival outcomes with external data	3 (4,5 %)
Objective and methods not clearly stated	15 (40%)

Quality of external validation assessed by HAS

Adequate methods and analysis of external validation	10 (22%)
--	-----------------

Assessment of the impact of the limitation of external data validation on the model robustness

Minor	18 (40%)
Important	4 (8%)
Major (combined to other concerns)	3 (7%)
No identified impact	20 (44%)

Assessment of the use of external validation on the ICER

Deterministic sensitivity analysis (DSA)	5 (11%)
Probabilistic sensitivity analysis (PSA)	1 (2%)

Uncertainty and validation of health decision models : example (3)

The choice of the decision model

Partitioned survival models (PSM)

- Simple, predominant approach of modeling relating to oncology
- Time to event for mortality and progression are supposed independent
- Choice of PSM : 42 of 45 in the pilot HAS study

- **Source** : Coyle D.(SMDM, 2014)
- Simulated a complete clinical trial data set
- Estimated overall survival and ICER
- Comparison of the estimates from Markov model and partitioned survival models

“Partitioned survival over-estimated the incremental survival benefits and underestimated the ICER”

However, Markov model may also underestimate the ICER in case of use of heterogeneous data sources and inadequate adjustment of mortality of transition probabilities

Markov Models

- Separately estimate transition probabilities for different health states
- Possibility of taking into account time-dependent covariates

	Markov Model	Partitioned Survival	Complete Data
PFS (months)			
Standard care	3.33	3.33	3.42
New treatment	6.84	6.84	6.95
Increment	3.50	3.50	3.53
OS (months)			
Standard care	16.08	13.01	15.35
New treatment	19.22	17.95	18.53
Increment	3.15	4.94	3.19
Costs			
Standard care	\$6,200	\$5,100	\$6,000
New treatment	\$33,700	\$33,300	\$33,400
Increment	\$27,500	\$28,200	\$27,400
QALYs			
Standard care	0.96	0.8	0.94
New treatment	1.19	1.13	1.18
Increment	0.23	0.33	0.24
ICER	\$120,000	\$86,000	\$115,000

PFS = Progression free survival, OS = Overall survival, ICER = Incremental cost per QALY gained

Conclusion & discussion

- HTA guidelines often describe methods of uncertainty analysis without direct relationship to model validation
 - HTA Methods and analysis of external validation need to be improved :
 - Definition of clear objective of external validation
 - A statistical framework and good practices on calibration process
- This helps to explore uncertainty around the calibrated values in terms of DSA and PSA
- Consideration of external evidence should be used for model choice not only statistical fit
 - The validation of the choice of the decision model is a tricky problem related to structural uncertainty
 - Need of pragmatic and technical framework → identify what is feasible and what is necessary