THE UNIVERSITY OF MELBOURNE

Faculty of Medicine, Dentistry and Health Sciences

Trial-Based vs Model-Based Cost-Effectiveness Analyses:

Methodologies and Decision-Making Criteria in Healthcare

MISCH *Hub*

Methods and Implementation Support for Clinical and Health Research

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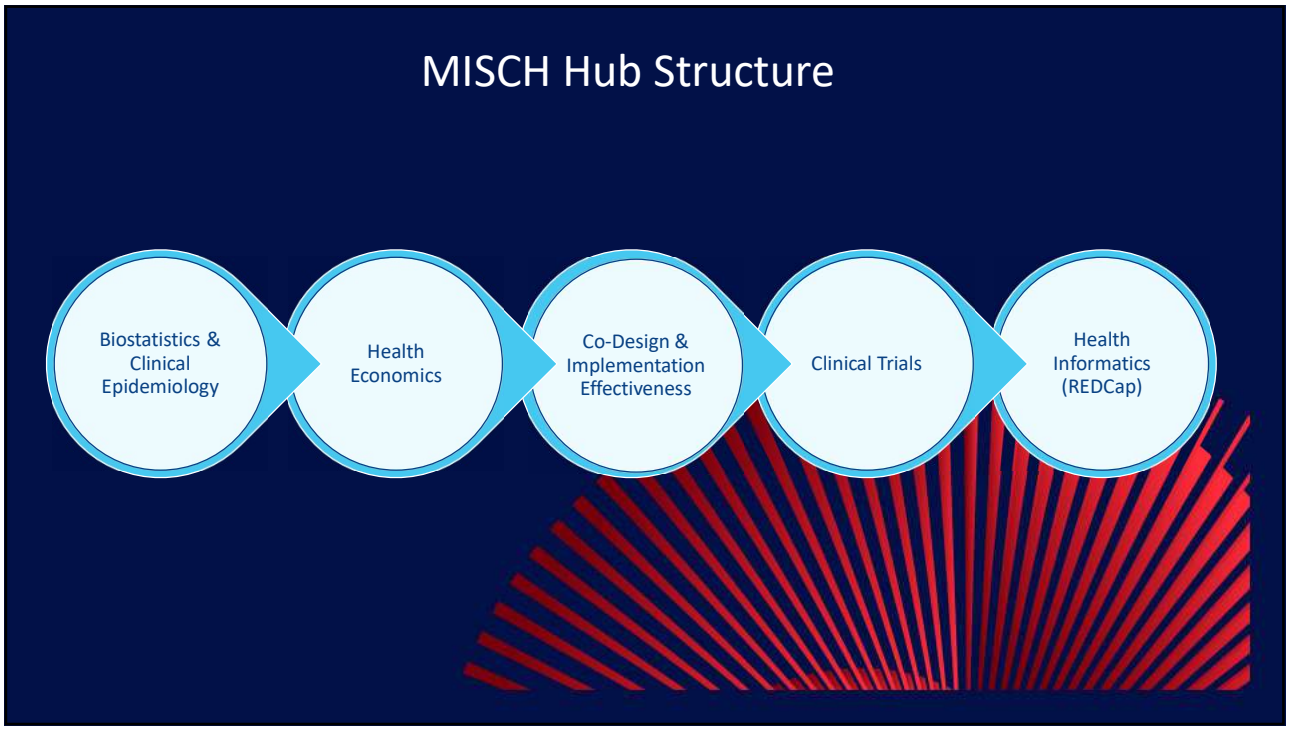
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Acknowledgement

I would like to acknowledge the Traditional Custodians of the land on which we meet today. I pay my respect to their Elders, past and present, and extend that respect to all Aboriginal and Torres Strait Islander people today. I acknowledge and respect that Aboriginal and Torres Strait Islander people have always used resources from the land and waters for nourishment, medicine and healing.

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MISCH Hub Structure
Biostatistics & Clinical Epidemiology
Health Economics
Co-Design & Implementation Effectiveness
Clinical Trials
Health Informatics (REDCap)

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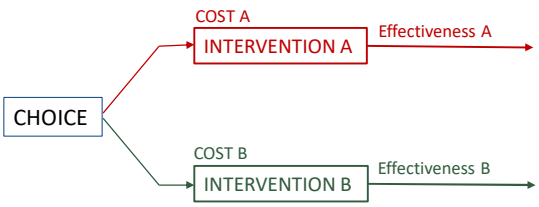
Contents

1. **Fundamentals of Cost-Effectiveness Analysis (CEAs)**
2. **Principals of Trial-Based CEAs**
3. **The Need for Modelling in CEAs**
4. **Concluding Remarks: Comparisons of the Approaches**

What is a cost-effectiveness analysis (CEA)?

Comparative analysis of alternative interventions in terms of both costs and effectiveness (e.g., changes in blood glucose level, incidence of cardiovascular events, quality-adjusted life years)

Basic tasks involves identification, measurements, valuation, and comparison of costs and effectiveness



Principle:
Difference in cost is compared with difference in effectiveness

Why CEAs?

- Health care resources are scarce
  - People
  - Time
  - Facilities
  - Equipment
- Cost-effectiveness seeks to inform decisions in health care on how the available resources should be used to maximise health gain
- Cost-effectiveness help to make the criteria for making decision explicit (e.g., avoid a situation where a decision is made based on "gut feeling"

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Cost-effectiveness in Health Technology Assessment (HTA)

- HTA is a process to inform policy makers about safety, efficacy, patient-reported outcomes, real-world effectiveness, cost and **cost-effectiveness** of a new intervention
- Early model of HTA was established in the United States (US) in the 1970s, followed by those in several European countries (e.g., Sweden, the Netherlands and UK)
- HTA organisations are independent, public bodies to provide scientific assessment of health interventions to health care decision makers
- In Australia, applications for medicines to be subsidized by the PBS are assessed by the Pharmaceutical Benefits Advisory Committee (PBAC) which gives advice to the Minister
- **Since 1993, it has been mandatory for sponsors to provide economic evaluation in HTA submissions to PBAC**

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Important metric for making decision

Alternative 1	Alternative 2
Cost 1 (C_1)	Cost 2 (C_2)
Effect 1 (E_1)	Effect 2 (E_2)

Incremental cost-effectiveness ratio (ICER)

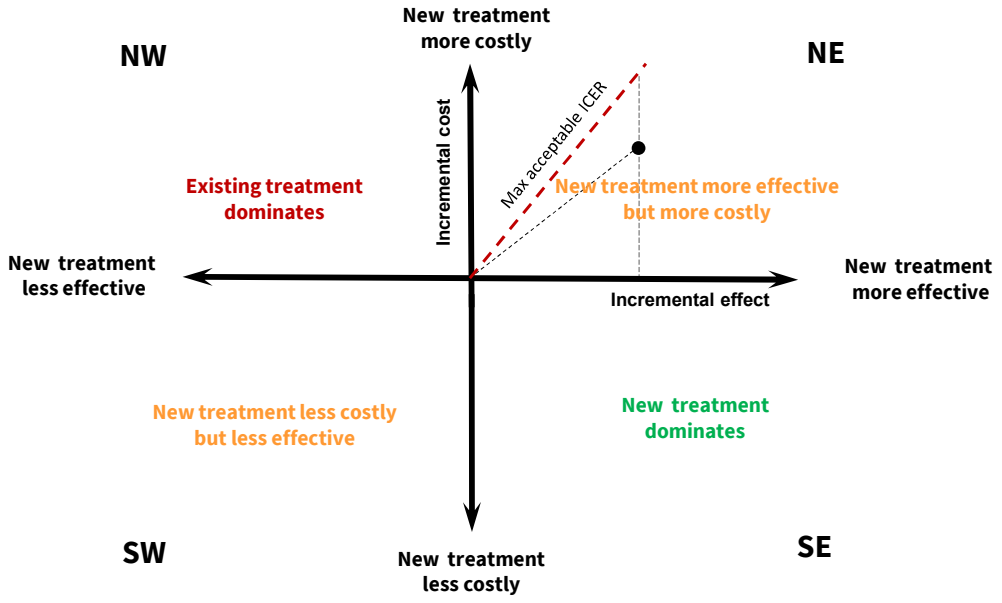
$$ICER = \frac{C_2 - C_1}{E_2 - E_1}$$

If quality-adjusted life years (QALYs) are used as the measure of effectiveness, the cost-effectiveness analysis is typically referred to as a cost-utility analysis. In this case, the ICER represents the incremental cost per QALY gained

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Cost-effectiveness plane



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Key factors influencing ICER

Costing perspectives *(e.g., healthcare payer, healthcare sector, societal)*
Frequency of measures *(e.g., every 3 months)*
Costing approaches *(e.g., micro- vs macro-costing)*
Methods for extrapolating costs *(e.g., linear regression, two-part models)*
Discount rate *(e.g., 5% annually)*
Methods for uncertainty assessment *(e.g., bootstrap, Monte-Carlo simulation)*

$$ICER = \frac{C_2 - C_1}{E_2 - E_1}$$

Instruments for outcome measures *(e.g., EQ-5D-5L, Time-Trade Off)*
Frequency of measures *(e.g., every 3 months)*
Methods for extrapolating outcomes *(e.g., Tobit models, survival models)*
Discount rate *(e.g., 5% annually)*
Methods for uncertainty assessment *(e.g., bootstrap, Monte-Carlo simulation)*

Cost-effectiveness threshold

- The maximum amount society is willing to pay for an extra unit of health gain
- Varies across countries:
  - Australia: AU$40K-AU$70K per life year gained[1] and AU$45K-AU$60K per QALY gained[2]
  - UK: NICE states £20-30K per QALY gained[3]
  - US: ≥ US$50K per QALY gained[4]

1. George B et al. Cost Effectiveness Analysis and the Consistency of Decision Making: Evidence from Pharmaceutical Reimbursement in Australia 1991-96. *PharmacoEconomics* 2001;19:1103-9.
2. Wang S et al. Comparing the ICERs in medicine reimbursement submissions to NICE and PBAC—does the presence of an explicit threshold affect the ICER proposed?. *Value in health* 2018;21:938-43.
3. Devlin. Does NICE have a cost-effectiveness threshold and what other factors influence its decisions? A binary choice analysis. *Health Economics* 2004;13:437-52.
4. Neumann PJ et al. Updating cost-effectiveness – the curious resilience of the $50,000-per-QALY threshold. *N Engl J Med* 2014;371:796-797.

Collecting resource utilisation and cost data in clinical trials

- Consideration of perspective of the study
- Payer (health service, patients)
- Societal (payer, productivity losses, informal care)
- Types of resource use relevant to the comparison
- Knowledge of the treatment pathways (e.g., resources needed to implement the treatment)
- Knowledge of disease progression (e.g., resources needed to deal with complications)
- Target user of the study

Resource use categories

Health sector	Community health and personal social service	Patient and family	Other government sector cost	Productivity gains/losses
Hospital stay	Community-based social care	Travel time and expenses	Housing employment	Changes in productivity
Outpatient hospital attendances	Nursing home	Out-of-pocket costs	Education	Transfer payments
Staff time	Residential care	Over-the-counter medications	Home affairs and justice	
Drugs	Local authority day care	Opportunity cost of leisure time	Social welfare	
Consumables	Foster care service	Childcare costs	Transport	
Theatre time		Domestic costs		
Equipment				
Community-based healthcare visits				
Emergency service				
Paramedic service				

Costing approach

- Micro-costing
  - Bottom-up costing
  - Ingredients method
    - number of tests, time with counsellor, frequency of visits
    - Type and number of medications

- More accurate
- More relevant to a specific context
- More costly to collect

- Macro-costing
  - Top-down costing
  - Ignores variation
    - Average per day
    - DRG cost weight

- Less accurate (hidden uncertainty)
- Less relevant to a specific context
- Less costly to collect

Example: Micro-costing via health records

- Medicare Benefits Schedule (MBS) records (GP visits, Specialist consultations, diagnostic tests, pathology, allied health)

	A	B	C	D	E	F	G	H	I	J	K
1	AIHW	Date service	Medicare	Item description	Provider charge	Schedule fee	Benefit paid	Patient OOP	Hospital	Item category	
2	1	6/03/2014	66551	Glycosylated Haemoglobin	22.45	16.9	12.7	9.75	H	P2 Chemical	
3	1	19/03/2014	23	LEVEL 'B' Consultation	35.6	35.6	35.6	0		A1 General Practitioner	
4	2	21/03/2014	72816	Histo complexity level 3, 1 s	73.95	86.95	73.95	0		P5 Tissue Pathology	
5	2	21/03/2014	73926	Initiation of a patient episo	7.05	8.25	7.05	0		P10 Patient Episode Initiation	
6	3	21/06/2014	105	Subsequent Specialist Atter	80	42.2	35.9	44.1		A3 Specialist	
7											

- Pharmaceutical Benefits Scheme (PBS) records (pharmaceuticals use)

	A	B	C	D	E	F	G	H	I
1	AIHW	Supply	PBS item	Item description	Patient category	Patient OOP	Net benefit	Form category	ATC code
2	1	20-Apr-14	09302N	GLICLAZIDE 60MG TABLET MC	Concessional - Ordinary	0	9.05	REPEAT	A 10 B B 09
3	2	30-Aug-14	09007C	PERINDOPRIL 5MG TABLET AR	General Safety net	6.1	9.89	ORIGINAL	C 09 A A 04
4	3	16-May-14	08214H	ATORVASTATIN 20MG TABLET	General Ordinary	37.7	44.61	REPEAT	C 10 A A 05
5	4	16-Mar-14	08189B	ACARBOSE 100MG TABLET-	Concessional - Ordinary	0	39.83	REPEAT	A 10 B F 01
6	4	28-May-14	08607B	METFORMIN 1G TABLET HCL-	Concessional - Ordinary	0	9.87	REPEAT	A 10 B A 02
7									

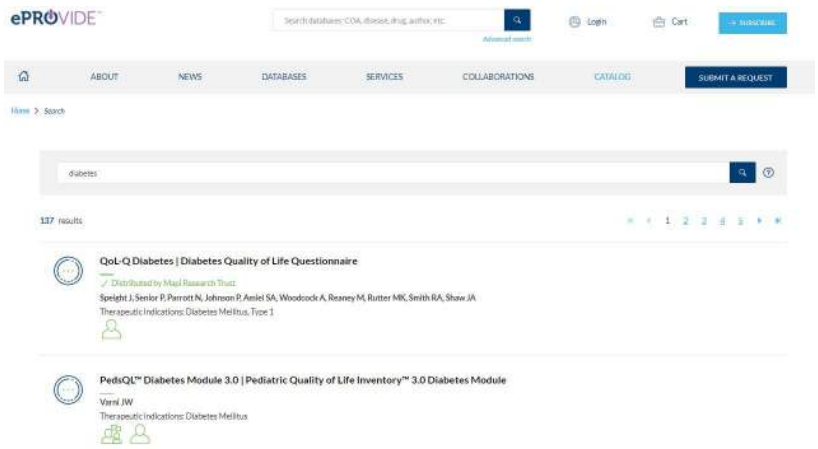
Health outcomes in CEAs

- Clinical outcomes
  - appropriate only when there is only one major objective of the intervention
  - specific to the health condition concerned *(not allow comparisons of treatments for different diseases)*
  - difficult to make decision if the clinical outcome is the final endpoint
- Patient-reported quality of life (QoL) measures
  - Disease specific QoL measures (*issues with comparisons of treatments for different diseases*)
  - Generic QoL measures:
    - consider a broad range of dimensions of quality of life (*physical function, mental well-being, social function and pain*)
    - most widely used is the Short Form 36 (SF-36)
    - comparisons of treatments for different diseases requires a summary score
- Generic measures of health gain
  - Quality-adjusted life year (QALY): capture gains from reduced morbidity (quality gains) and mortality gains (quantity gains)
  - Disability-adjusted life year (DALY): conceptually similar to QALYs but different in several ways (life expectancy constant; disability weights set by a health care worker panel for only 9 health states; including age weights).

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Selection of instruments for health outcomes

- The ePROVIDE™ platform developed by Mapi Research Trust provides the PROQOLID database containing more than 2300 Clinical Outcomes Assessments (https://eprovide.mapi-trust.org)



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Which instrument to use?

Example: Some aspects used for judging the merits of a preference-based instrument for HRQoL measurement

Aspect	Component
Practicality *(acceptable to the patients and stakehoders*	Time taken to complete; response rate; completion rate
Reliability *(can reproduce similar results over repeated measurements on the same population)*	Stability over time; agreement between raters; agreement between scores from different places of administration
Validity *(extent to which an instrument measures the value placed on health)*	Content validity: Coverage of health dimensions; sufficient sensitivity Face validity: relevance and appropriateness for the population Construct validity: ability to reflect differences in health

Source: Brazier J and Deverill M. A checklist for judging preference-based measures of health-related quality of life: learning from psychometrics. Health Econ 1999;8:41-51

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Trial-Based CEAs and Decision-Making

- **Characteristics:**
  - Use data directly from an RCT (or other clinical trial)
  - Typically focus on **short-term outcomes** and a **limited set of comparators**
  - Less complex, fewer assumptions, high internal validity
- **Implications for decision-making:**
  - Decisions are **highly evidence-driven**, based on observed trial results
  - Good for interventions where **short-term outcomes and direct comparisons** are sufficient
  - Limitation: may **not generalize** well to other populations, settings, or long-term outcomes
  - Can lead to **conservative decisions**, because uncertainty beyond trial conditions is not fully explored

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RCT limitations and the need for modelling

- An RCT might not compare all relevant alternatives
  - Need modelling costs and effects of interventions not included in the RCT
- Information from an RCT might not be sufficient
  - Need to synthesize evidence
- Follow-up period in an RCT might not be long enough
  - Need to extrapolate the results
- Final endpoint is not measured in an RCT
  - Need to link intermediate outcomes to the final outcome
- RCTs often provide evidence specific to a particular setting or cohort
  - Need generalization
- Modelling helps to evaluate uncertainty in the results obtained from the RCTs

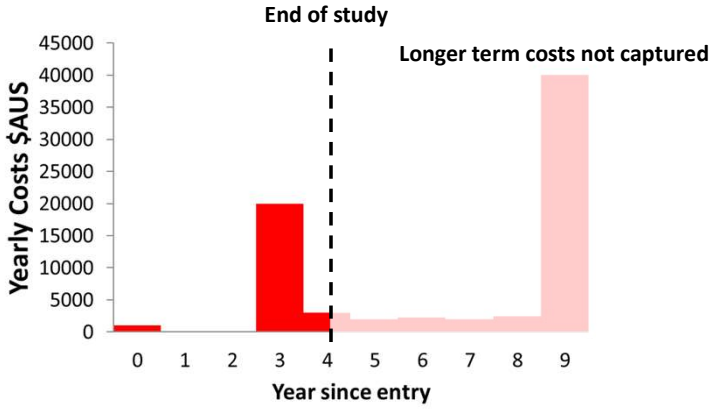
Modelling for CEAs

- **A model**: a simplified representation of the real world that is designed to capture the essential elements of a system, problem, or decision

- **Modelling**: the process of constructing and using these simplified representations to understand, predict, or evaluate the consequences of different choices, policies, or interventions

Extrapolation: costs

Within-study versus long-term costs



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Example: Extrapolation in CEAs

	Within study	Within study + modelling	Difference
Costs	$502	$502	-
Life years gained	0.03	0.05	-40%
QALYs gained	0.02	0.03	-33%
Incremental cost per life years gained	$16,733	$10,040	67%
Incremental cost per QALY gained	$25,100	$16,733	50%

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Transformation

- Indigenous Australians have a life expectancy about 10 years lower than non-Indigenous population
- Cardiovascular disease (CVD) is the leading cause of death
- It is suggested that blood pressure of the Indigenous Australians should be controlled. What is the long-term implications of this?

→ Prediction model that links blood pressure and other risk factors to 5-year or 10-year risk of CVD

→ Prediction that links blood pressure and other risk factors to life expectancy

5-year CVD risk equation

- Model based on a Cox proportional hazard model: $p = 1 - S(5)^{\exp\left\{\sum_{i=1}^{n} \hat{\beta}_i (x_i - \overline{x}_i)\right\}}$

ORIGINAL ARTICLE

Development and Use of Prediction Models for Classification of Cardiovascular Risk of Remote Indigenous Australians

An Tran-Duy, PhD [a,*], Robyn McDermott, PhD [b,c], Josh Knight, PhD [a], Xinyang Hua, PhD [a], Elizabeth L.M. Barr, PhD [d,e], Kerry Arabena, PhD [f], Andrew Palmer, MD, PhD [a,g], Philip M. Clarke, PhD [a,h]

Table 2 Estimated coefficients and hazard ratios from Cox proportional hazard models.

Variable	Primary model		Reduced information model	
	Coefficient (p-value) [95% CI]	Hazard ratio [95% CI]	Coefficient (p-value) [95% CI]	Hazard ratio [95% CI]
Men	0.272 (0.074) [−0.029, 0.573]	1.328 [0.925, 1.731]	0.261 (0.076) [−0.031, 0.552]	1.312 [0.927, 1.697]
Age, years	0.050 (<0.001) [0.038, 0.063]	1.052 [1.039, 1.065]	0.048 (<0.001) [0.036, 0.061]	1.050 [1.037, 1.062]
Systolic BP, mmHg	0.010 (0.012) [0.002, 0.018]	1.010 [1.002, 1.018]	0.014 (<0.001) [0.006, 0.022]	1.014 [1.006, 1.022]
Waist circumference, cm	0.009 (0.110) [-0.002, 0.020]	1.010 [0.999, 1.020]	0.009 (0.09) [−0.001, 0.020]	1.010 [0.998, 1.020]
Diabetes*	0.268 (0.104) [−0.015, 0.592]	1.325 [0.974, 1.755]	0.405 (0.009) [0.101, 0.709]	1.517 [1.055, 1.980]
Triglycerides, mg/dL	0.001 (0.142) [0.000, 0.001]	1.001 [1.000, 1.001]	–	–
ACR	0.003 (0.001) [0.001, 0.005]	1.003 [1.001, 1.004]	–	–

Generalisation

- A trial-based economic evaluation found that cholesterol-lowering therapy (statin) is cost-effective compared to no cholesterol lowering therapy
- Should policy makers fund a national program for cardiovascular prevention in the general population using cholesterol lowering therapy?
- We know:
  - There are many risk factors for cardiovascular disease (CVD), for example history of myocardial infarction, history of stroke, diabetes, age
  - Efficacy of and adherence to the therapy in an RCT can be different from the effectiveness of the therapy in the real-world setting
- What do we need to investigate?
  - To what extent the cardiovascular risk profile of the cohort in the RCT differ from the general population?
  - How did the treatment effect vary across patient characteristics?

Decision analytic modelling

- Development of mathematical relationships to define possible outcomes of interest resulting from different alternative options
- Purpose:
  - Integrate evidence on clinical and economic outcomes into a consistent framework to inform decisions about clinical practices and healthcare resource allocations
  - Allow for variability and uncertainty associated with all decisions

Model types

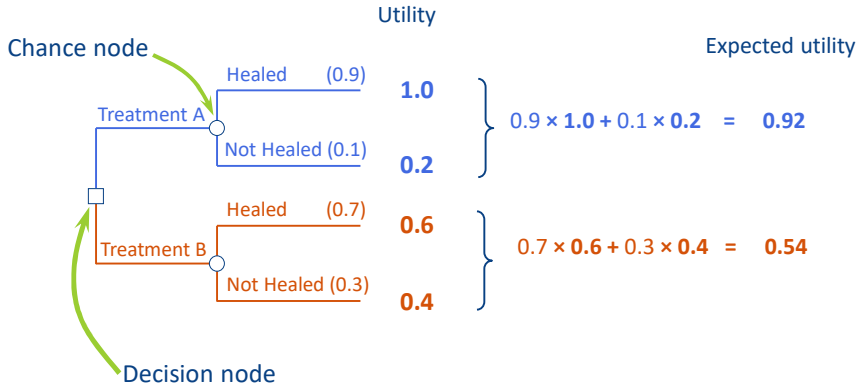
		Cohort level		Individual level	
		Continuous state	Discrete state	Markovian	Non-Markovian
No interaction among objects	Implicit time	-	• **Decision tree**	• **Patient-level decision tree**	
	Explicit time	-	• **Markov model**	• **Patient-level Markov model**	• **Discrete time simulation** • **Discrete event simulation**
Interaction among objects	Discrete or continuous time	**System dynamics**	• **Markov chain model**	• **Individual event history model**	• **Discrete event simulation** • **Individual-based simulation**

Source: Brennan A et al. A taxonomy of model structures for economic evaluation of health technologies. Health Economics. 2006;15:1295-310.

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Decision tree

- Represents possible prognoses following each of the interventions under consideration for a patient over a short period of time
- Requires development of health states and assignment of probabilities and payoffs (e.g., utilities, costs)
- Time elapsed in not explicitly modelled

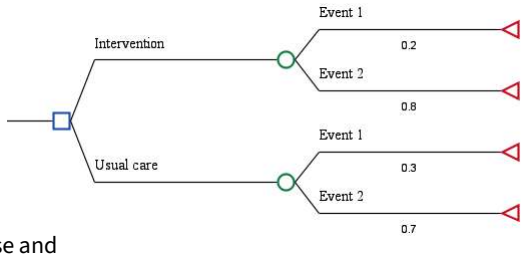


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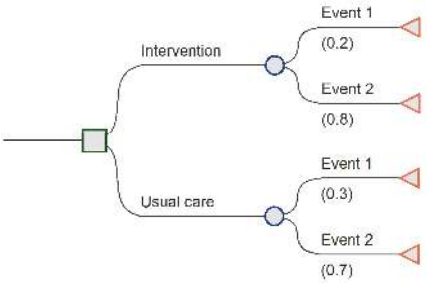
Time horizon: 6 months

Tools for building decision trees

- TreeAge Pro
  - Developed by TreeAge Software LLC in USA
  - Many features
  - Visualisation is suboptimal;
  - Customisation of the tree diagrams is very limited
  - Expensive (a standard license costs AU$3,100 for academic use and AU$3,500 for commercial use)



- DARE (Decision Analysis in R for health economic Evaluation)
  - Developed by A/Prof An Duy Tran at University of Melbourne
  - Currently fewer features compared to TreeAge Pro, but is growing
  - Elegant visualisation
  - Tree diagrams are highly customisable
  - Freely available at https://dare.shinyapps.io/tree/

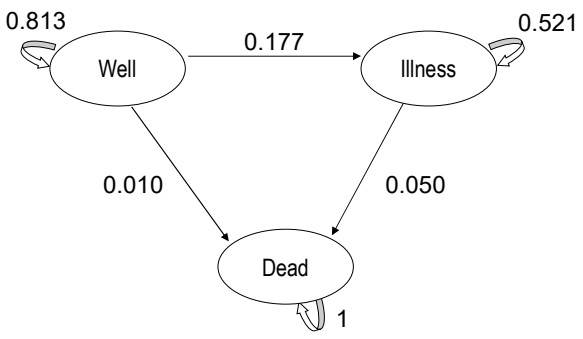


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Markov (state-transition) models

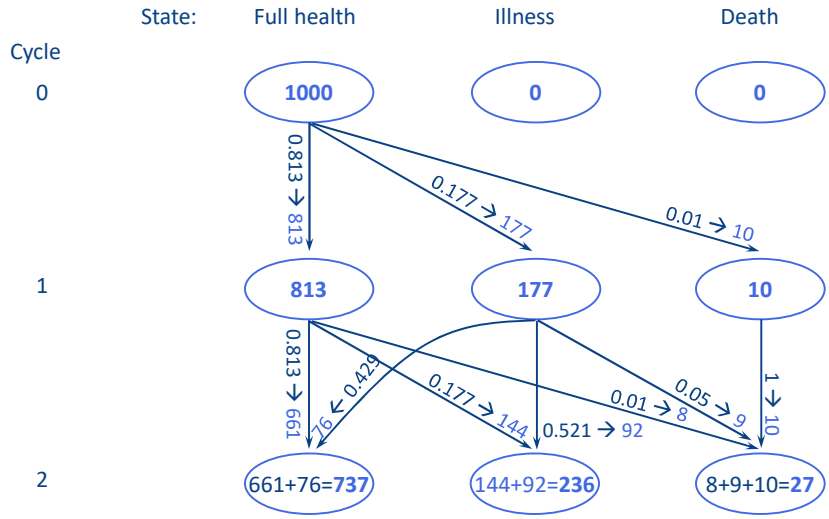
- Represents a series of possible health states over a long period of time that a patient can occupy at a given point in time
- Time elapse is explicitly modelled



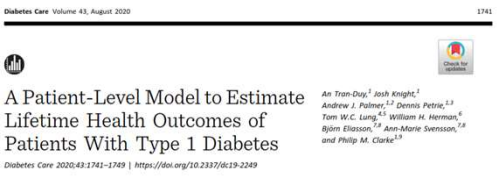
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Markov model – state membership



Discrete-time simulation



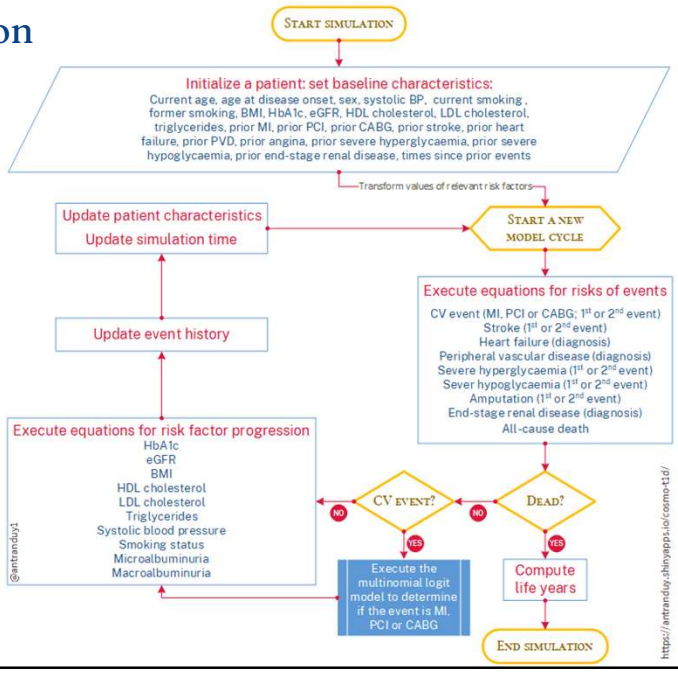
Diabetes Care Volume 43, August 2020 1741

A Patient-Level Model to Estimate Lifetime Health Outcomes of Patients With Type 1 Diabetes

An Tran-Duy, Josh Knight, Andrew J. Palmer, Dennis Petrie, Tom W.C. Lung, William H. Herman, Björn Eliasson, Ann-Marie Svensson, and Philip M. Clarke

Diabetes Care 2020;43:1741–1749 | https://doi.org/10.2337/dc19-2249

For more information, see:
https://antranduy.shinyapps.io/cosmo-t1d/



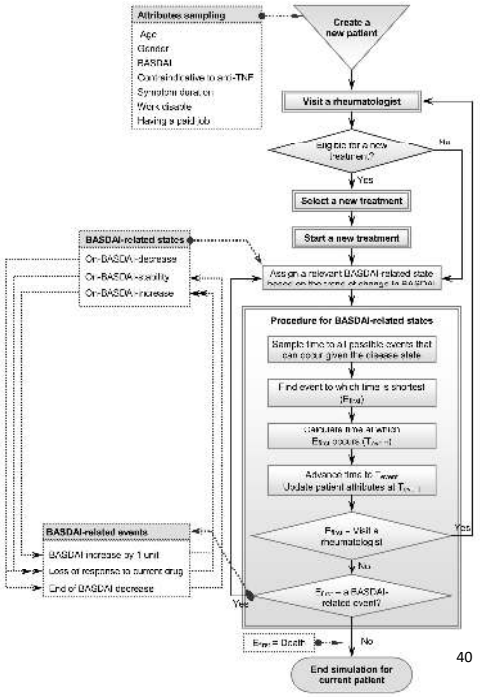
Discrete-event simulation

Downloaded from ard.bmj.com on November 17, 2011 - Published by group.bmj.com

Extended report

A discrete event modelling framework for simulation of long-term outcomes of sequential treatment strategies for ankylosing spondylitis

An Tran-Duy,[1] Annelies Boonen,[2] Mart A F J van de Laar,[3] Angelinus C Franke,[4] Johan L Severens[5]

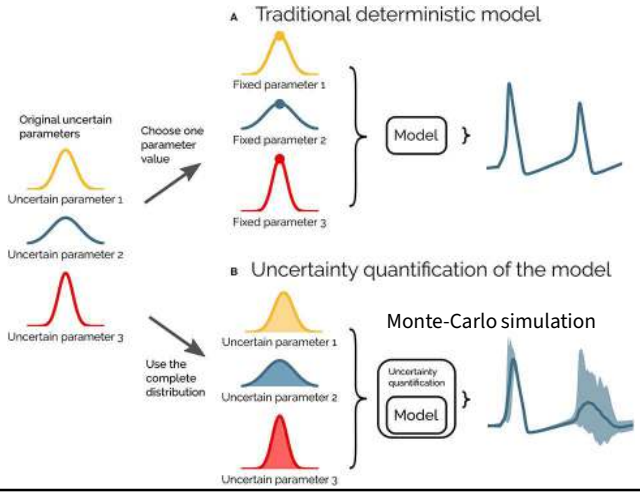


Dealing with uncertainty

- We are rarely 100% confident that a particular decision is the ‘right’ one
- So often our decisions are made under uncertainty
- Uncertainty analysis is important because in general we prefer more certain outcomes (benefits) over less certain ones
- We need to present and explain the level of uncertainty to decisions makers so they can take this into account when making their decisions
- Uncertainty is everywhere – we need to capture it, reduce it where possible (but not ignore it)

Example: Parameter uncertainty analysis

- How does uncertainty around the model parameters impact on the overall robustness of the results?
- Uncertainty analysis aims to quantify the uncertainty in the model output that arises from the uncertainty in the model parameters

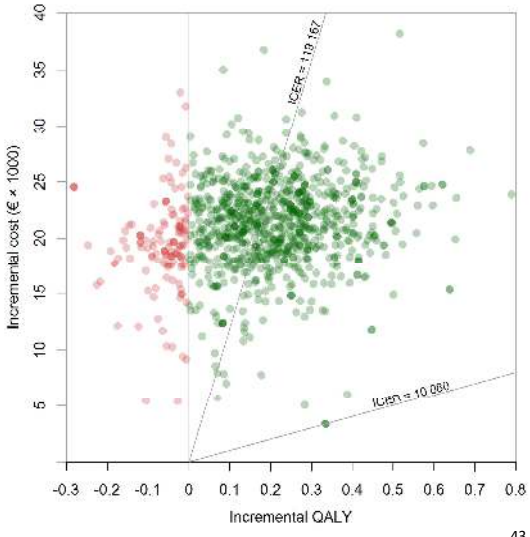


Source: Tennøe et al. Uncertainpy: a Python toolbox for uncertainty quantification and sensitivity analysis in computational neuroscience. Frontiers in neuroinformatics. 2018 Aug 14;12:49.

Probabilistic sensitivity analysis

Cost-effectiveness plane

Scatter plot of incremental mean costs against incremental mean QALYs of treatment strategy including biological agents compared with conventional treatment strategy for patients with rheumatoid arthritis.



Source: Tran-Duy A *et al*. Modelling outcomes of complex treatment strategies following a clinical guideline for treatment decisions in patients with rheumatoid arthritis. *Pharmacoeconomics* 2014;32:1015-28.

Model-Based CEAs and Decision-Making

Characteristics:

- Use a **mathematical model** (Markov, microsimulation, etc.) to integrate multiple data sources
- Can **extrapolate long-term outcomes** and **simulate multiple comparators**
- Account for **uncertainty** and population variability

Implications for decision-making:

- Allow decision-makers to evaluate **long-term cost-effectiveness** even when trial data are incomplete
- Support **policy decisions** that consider lifetime costs, benefits, and multiple alternatives
- Can identify **key drivers of uncertainty** and **inform decision on collecting further data**
- Because they rely on assumptions, results may be **less certain than trial-based CEAs**, requiring careful interpretation

Concluding remarks: Comparing the approaches

Aspect	Trial-based CEAs	Model-based CEAs
Scope of comparison	Limited to interventions directly compared in the RCT	Can include **multiple interventions** and **comparators** not included in a single trial
Time horizon	Restricted to the trial's **follow-up period**.	Can **extrapolate beyond** trial duration to estimate lifetime costs and effects
Outcomes	Often focus on **intermediate or short-term outcomes**	Can **link intermediate outcomes** (e.g., HbA1c, BP) to **final outcomes** (e.g., QALYs, life-years).
Evidence base	Relies primarily on **one source of evidence** (the trial)	**Synthesizes multiple data sources** — RCTs, registries, literature, and expert opinion.
Uncertainty and Generalizability	Enables **probabilistic sensitivity analysis** and **scenario exploration**	• Enables **probabilistic sensitivity analysis** and **scenario exploration** • Also allows **generalization** to different settings or populations
Technical Complexity and Resource Requirements	• Simpler analytic methods (e.g., descriptive statistics, bootstrapping) • Quicker to implement, fewer assumptions	• Requires **modelling techniques** (Markov models, microsimulation, etc.) • **Time-consuming**, data-intensive, and involves many **assumptions** • Demands greater expertise in **modelling, programming, and validation**

Thank you

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