THE UNIVERSITY OF MELBOURNE

Faculty of Medicine, Dentistry and Health Sciences

Economic evaluation alongside clinical trials:

principles of study design and decision analysis

Dr An Duy Tran
Email: an.tran@unimelb.edu.au
@antranduy1

Methods and Implementation Support for Clinical and Health research Hub (MISCH)
Melbourne School of Population and Global Health

Website:- https://clinicalresearch.mdhs.unimelb.edu.au/
Email: misch-info@unimelb.edu.au
@MISCHHub

THE UNIVERSITY OF MELBOURNE

Faculty of Medicine, Dentistry and Health Sciences

The Hub

- **MISCH**: Methods and Implementation Support for Clinical and Health research
- Aim: To provide support on core research methods to researchers and affiliated researchers of the University of Melbourne in health research
- Scope of support: Biostatistics and Clinical Epidemiology, Health Economics, Clinical Trials, Implementation Effectiveness and Co-Design and Health Informatics (REDCap).

Health Economics

https://clinicalresearch.mdhs.unimelb.edu.au/#our-people

MISCH MANAGER
Shaie O'Brien

HEALTH
ECONOMICS LEAD
An Duy Tran

MISCH OPERATIONS
MANAGER
An Nguyen

DIRECTOR OF MISCH
Julie Simpson

HEALTH ECONOMIST
Kim Dalziel

HEALTH ECONOMIST
Ting Zhao

HEALTH ECONOMIST
Paul Amores

https://clinicalresearch.mdhs.unimelb.edu.au/about-us/health-economics

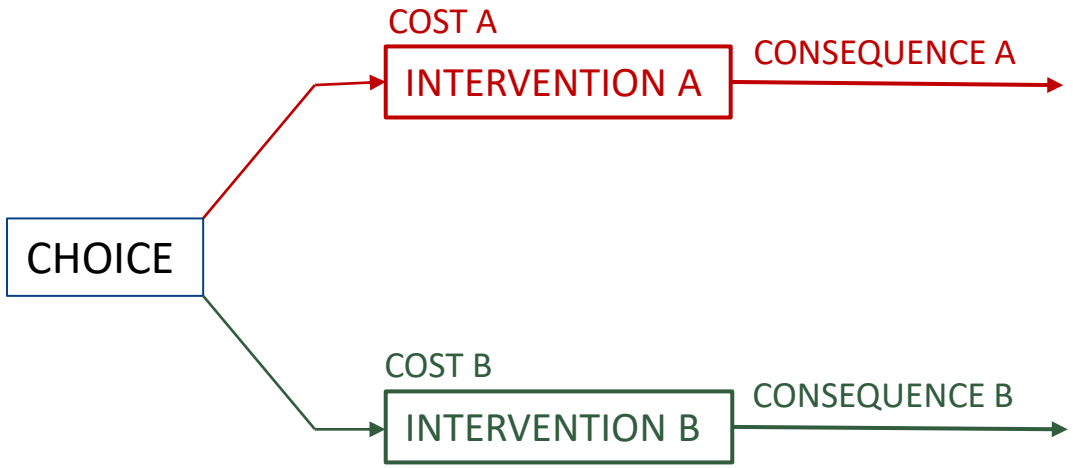
Housekeeping

- Please keep your microphone switched off during the presentation.
- You are welcome to leave your video on or off as you prefer.
- If you have any questions, please feel free to enter them in the chat box. We will review and answer them throughout the presentation.
- This presentation is being recorded and a link will be provided after the webinar.
- A copy of the slides will also be provided.

What is economic evaluation of health care interventions?

Comparative analysis of alternative interventions in terms of both costs and consequences (e.g., changes in blood glucose level, incidence of cardiovascular events)

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



General rule:
Difference in cost is compared with difference in consequences

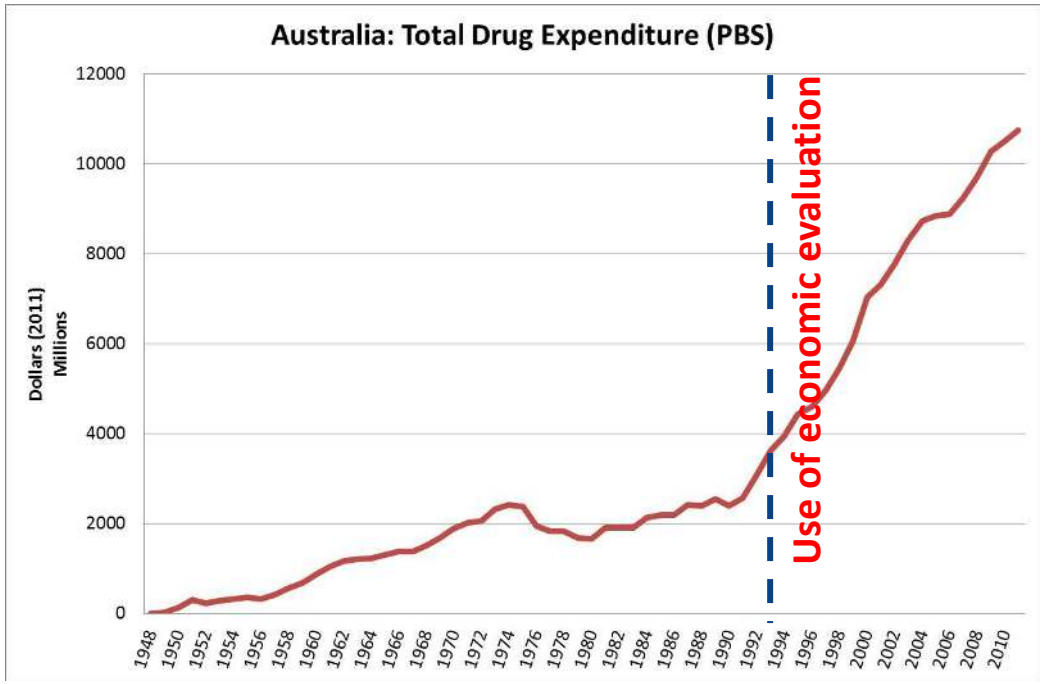
Note: A study that measures costs only does not necessarily constitute an economic evaluation.

Why economic evaluation?

- Health care resources are scarce
- Health care providers and receivers face continual questions about allocation of health care resources, for examples:
  - Should the hospital purchase a new diagnostic equipment?
  - Should a new, expensive drug for treatment of diabetes be reimbursed?
- Economic evaluation seeks to inform decisions in health care on how the available resources should be used to maximise health gain
- Economic evaluation helps to make the criteria explicit for making choices

Health Technology Assessment in Australia

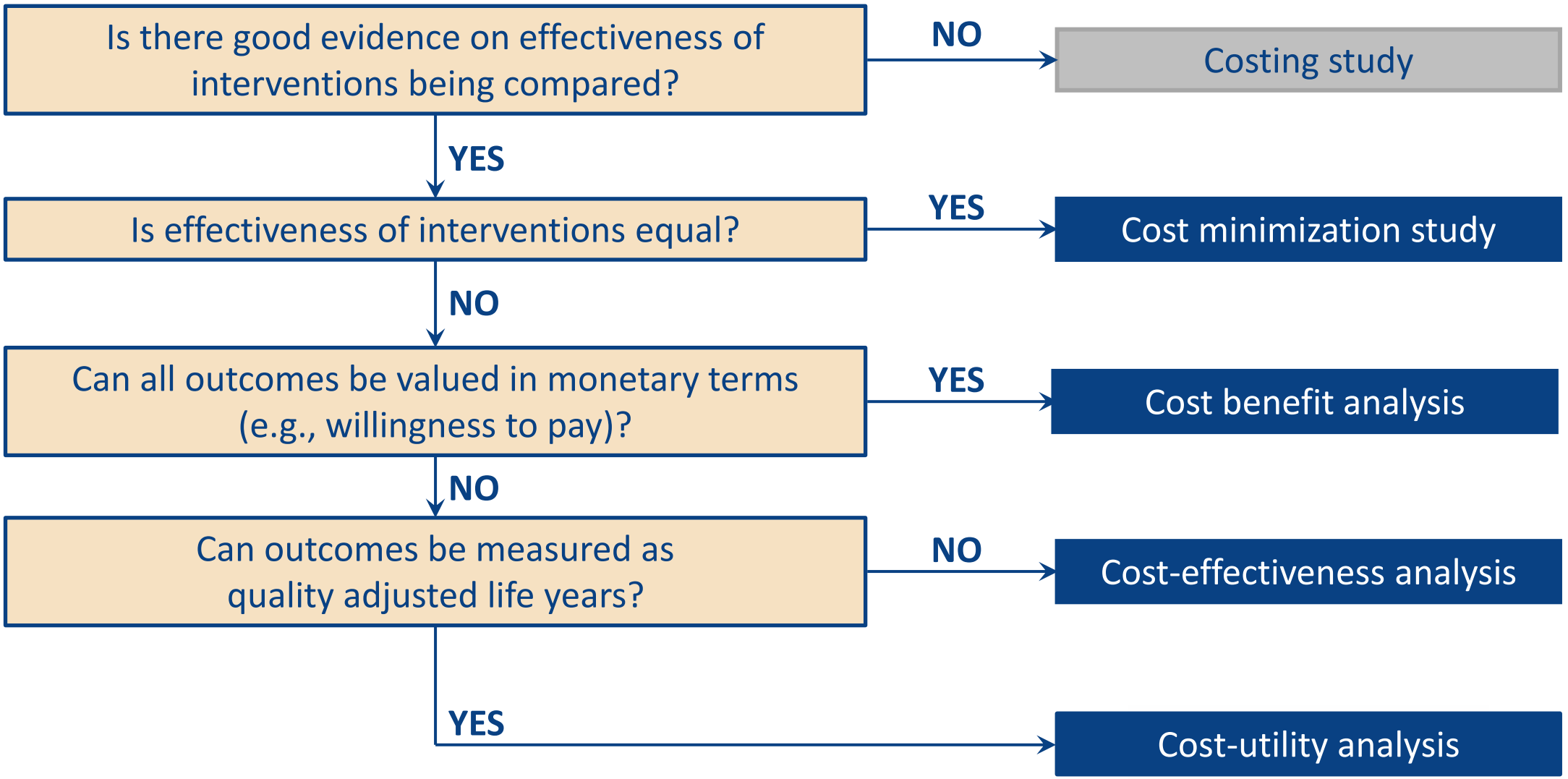
- Applications for medicines to be subsidized by the PBS are assessed by the Pharmaceutical Benefits Advisory Committee (PBAC). PBAC gives advice to the Minister about which drugs should be made available as pharmaceutical benefits
- The committee takes into account clinical effectiveness, safety and **cost-effectiveness**
- Since 1993, it has been mandatory for sponsors to provide economic evaluation in submissions to PBAC



Types of economic evaluation analysis

TYPE	COSTS	OUTCOMES	DECISION
Cost-consequences	Dollars	Various health outcome measures, reported in a disaggregated way	At discretion of decision makers
Cost-minimisation	Dollars	Not compared, assumed identical in all aspects	Least cost alternative
Cost-effectiveness	Dollars	Comparison based on a common measure on health, e.g. LY's gained, blood pressure reduction	Cost per natural unit of consequence, e.g. cost per 10 mmHg reduction in systolic blood pressure
Cost-utility	Dollars	A summarised measure of impacts on health-related quality of life, valued as "utility", used to estimate quality-adjusted life years (QALYs)	Cost per preference-based unit of consequence, e.g. per QALY
Cost-benefit	Dollars	A summarised measure of impacts on health and non health benefits valued in monetary term (i.e., Dollars)	Net financial cost Cost/benefit ratio

Choice of an appropriate analysis for economic evaluation



Cost minimisation

- Special form of cost effectiveness analysis
- Compare at least two treatments
- Outcomes measured using same measure (e.g. number of a cardiovascular event)
- Outcomes statistically equivalent
- With sufficient power to say that they are the same; not just to say that there is no evidence of difference

Cost-effectiveness analysis (CEA)

- Most commonly used method of economic evaluation
- Compares costs and outcomes
- Requires a common, unambiguous outcome measure
- Outcomes measured in natural units
  - cases detected
  - deaths prevented
  - life years gained

Cost-utility analysis

- A variant of cost-effectiveness analysis (often referred to as such)
- A generic measure of health is used for consequences
- Can be used to compared interventions in different clinical areas to assess the opportunity cost of adopting a program
- Utility in this type of analysis refers to individuals or society's preference for any set of health outcomes (health states)

Twins may rank "having a broken arm" on a scale 0 (death) to 1 (perfect health) differently

Compare two alternatives

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)

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

- In cost-utility analysis, ICER typically represents incremental cost per QALY gained
- What is the threshold for an ICER to be acceptable in a society?
- The willingness-to-pay threshold in Australia is in the range $45,000-$60,000 per QALY gained

Cost-utility analysis example

Journal of the American Heart Association

ORIGINAL RESEARCH

Cost-Effectiveness of Combination Therapy for Patients With Systemic Sclerosis–Related Pulmonary Arterial Hypertension

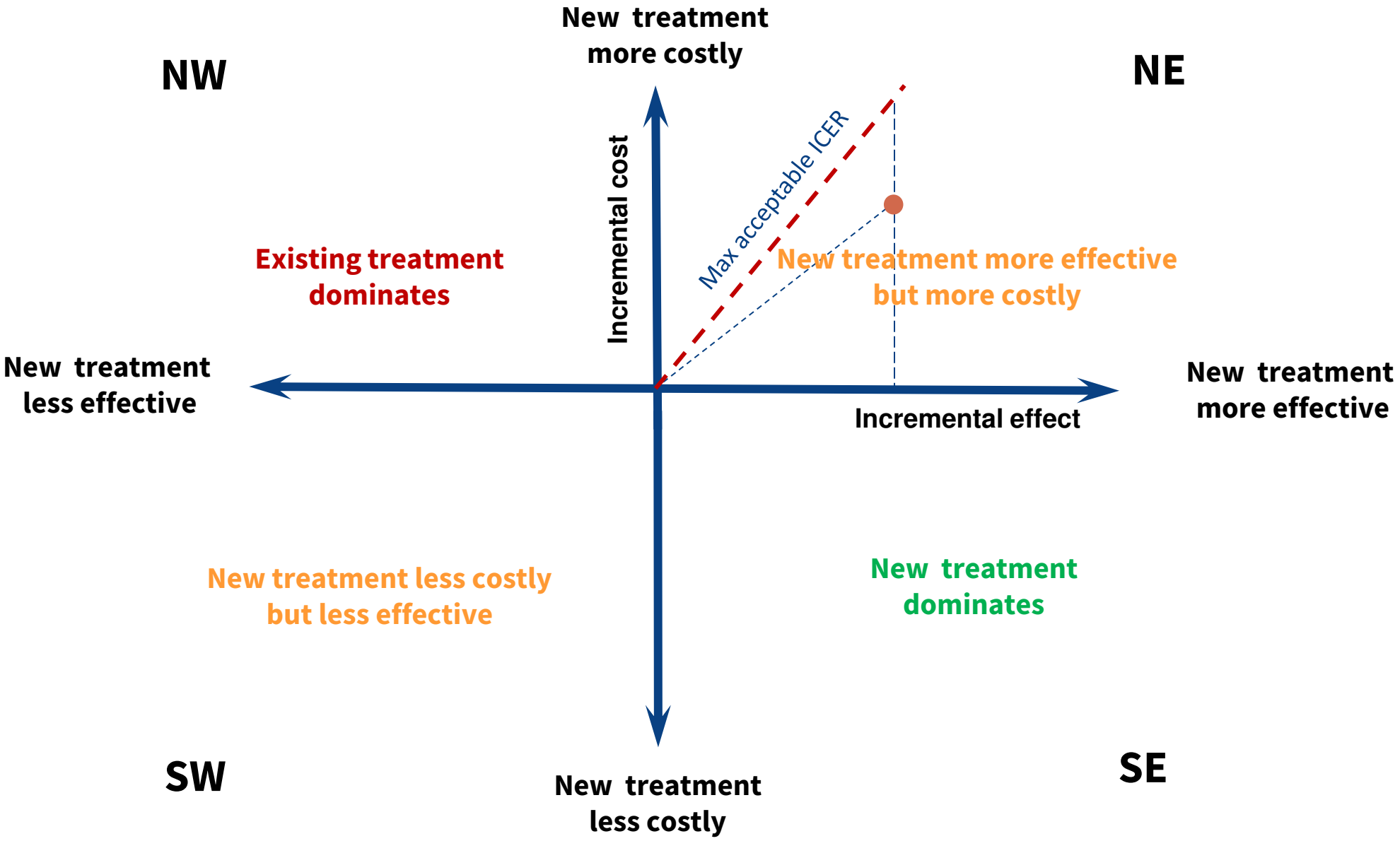
An Tran-Duy, PhD†; Kathleen Morrisroe, MBBS, PhD†; Philip Clarke, PhD; Wendy Stevens, MBBS; Susanna Proudman, MBBS; Joanne Sahhar, MBBS; Mandana Nikpour, MBBS, PhD; Australian Scleroderma Interest Group (ASIG)*

Table 5. Base Case Analysis (Sampling Drugs Based on Distributions)

	Combination Therapy*	Monotherapy†	Incremental
Drug cost (95% CI), AU$	255 983 (252 354 to 259 679)	155 179 (152 596 to 157 816)	100 804 (99 750 to 101 863)
Nondrug cost (95% CI), AU$	6556 (6477 to 6635)	7934 (7824 to 8045.45)	–1378 (–1419 to –1339)
Total cost (95% CI), AU$	262 539 (258 865 to 266 300)	163 113 (160 462 to 165 819)	99 426 (98 394 to 100 441)
Life years	9.19 (3.84 to 3.96)	7.11 (2.97 to 3.08)	2.07 (0.87 to 0.88)
QALYs	3.90 (9.02 to 9.36)	3.02 (6.97 to 7.26)	0.87 (2.05 to 2.09)
ICER, AU$ per life year gained			47 989 (47 897 to 48 084)
ICER, AU$ per QALY gained			113 823 (113 302 to 114 364)

ICER indicates incremental cost-effectiveness ratio; and QALY, quality-adjusted life year.
*Combination therapy is treatment with two specific PAH agent from different classes at one time.
†Monotherapy is treatment with a single PAH-specific therapy.

Cost-effectiveness plane



Identifying resource use

- 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

Possible resources in broad 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				

Measuring and valuing resource use

- 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- S	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									

Notes on MBS/PBS data

- Require consent of the patients for their data to be released
- MBS/PBS allow access to a maximum 5-year window of data.
- Takes time and costs money to extract data (from $10k to $20k, depending on number of patients and time window)
- MBS/PBS data do not contain data related to hospital admissions
- MBS and PBS data rely on Medicare claims and patients filing a prescription; health care that is no claimed through Medicare or unfilled prescriptions is not captured in these datasets

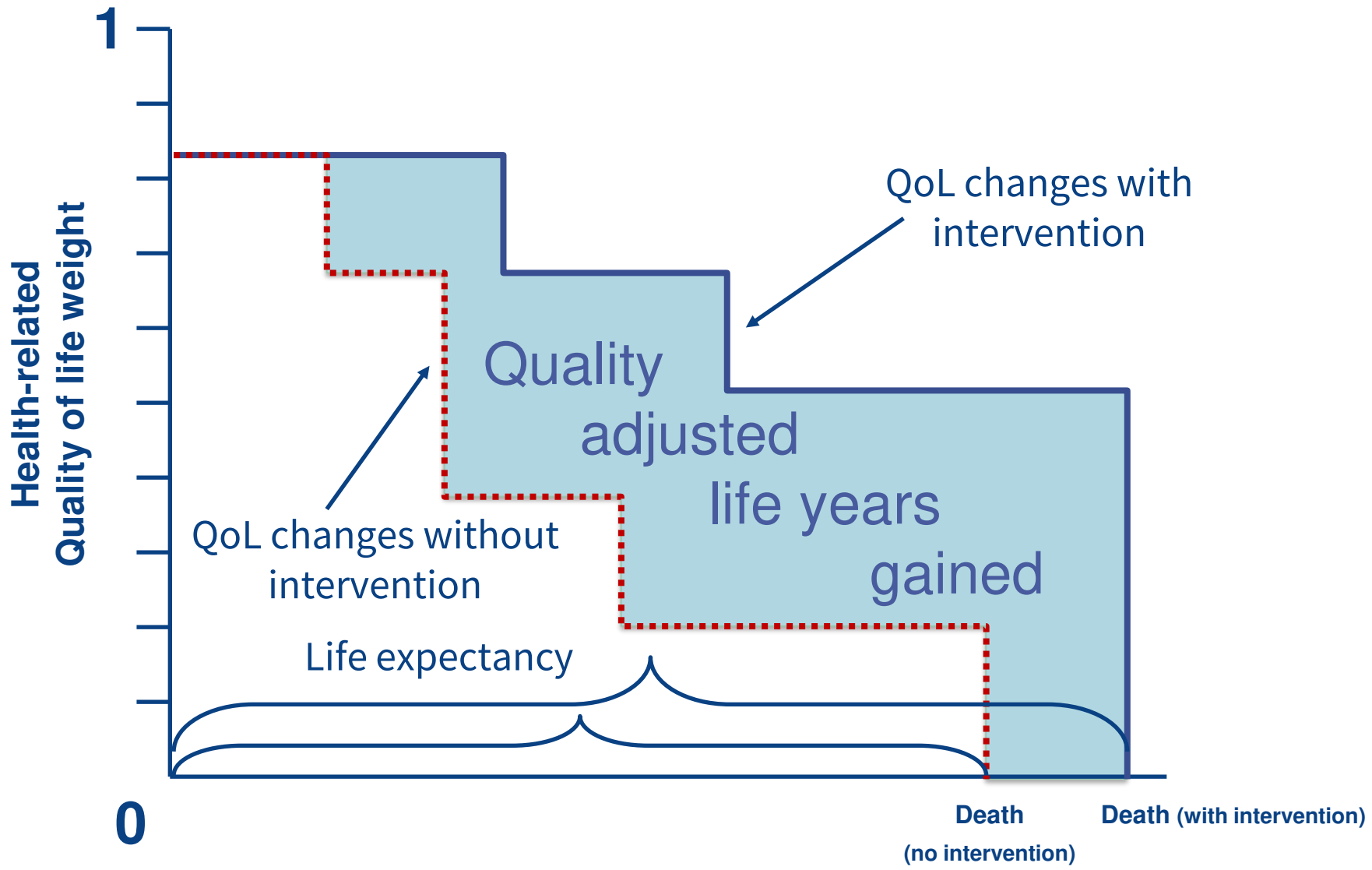
Micro-costing using hospital data

- Hospital records are normally generated on discharge for billing purposes and normally contain:
  - Primary/ principle diagnosis (main reason the patient is in hospital)
  - Secondary/ other diagnoses (can be many fields – other things that happened while in hospital)
  - Date of admission / date of discharge
- Data linkage of hospital records is possible in some Australian states (e.g. WA and NSW) and requires:
  - Consent of the patient needed especially if it is being linked with other data;
  - Under some circumstances de-identified data can be linked and made available following protocol to ensure patient confidentiality

Health outcomes in economic evaluation

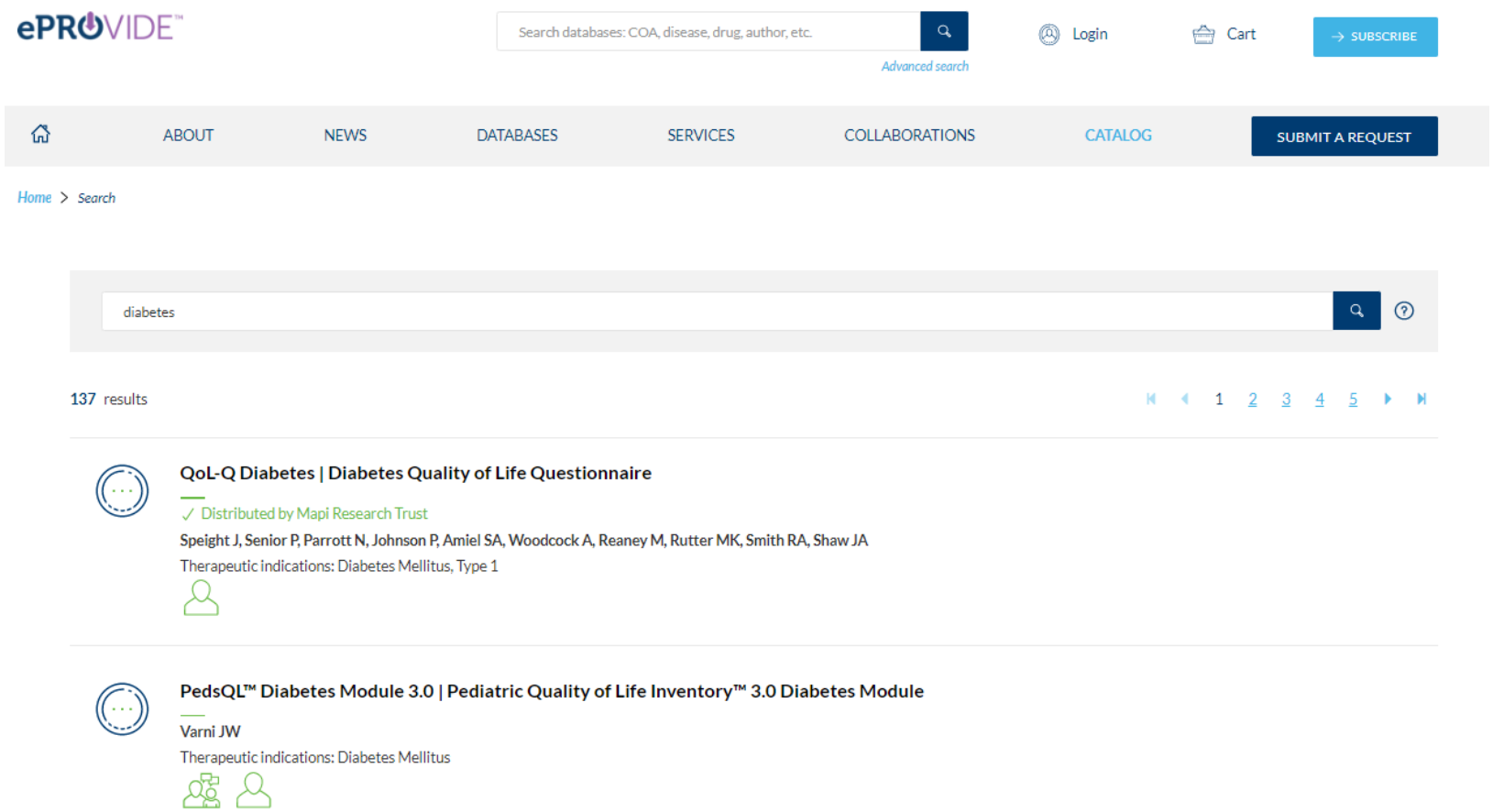
- Clinical outcomes
  - appropriate only when there is only one major objective of the intervention
  - specific to the health condition concerned *(not allow comparisons of treatments for different diseases)*
  - difficult to make decision if the clinical outcome is the final endpoint
- Patient-reported 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).

Using QALYs to measure outcomes



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)



Examples of health utility instruments

	No. questions/ No. dimensions	No. levels for each dimension	No. unique health states	Costs
EQ-5D-3L	5/5	3	243	Varies
EQ-5D-5L	5/5	5	3,125	Varies
SF-6D (based on SF-36)	11/6	4-6	18,000	Free for publicly funded research
HUI-2	7/7	3-5	24,000	Free/ fees for proprietary materials
HUI-3	8/8	5-6	251,942,400	Free/ fees for proprietary materials
AQoL-8D	35/8	4-7	217,728	Free
PedsQL (2-18 years old)	23/4	5-8	1,000	Varies
CHU9D (7-17 years old)	9/9	5	1,953,125	Free for non-commercial use

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

Recommendations for use of utility instruments

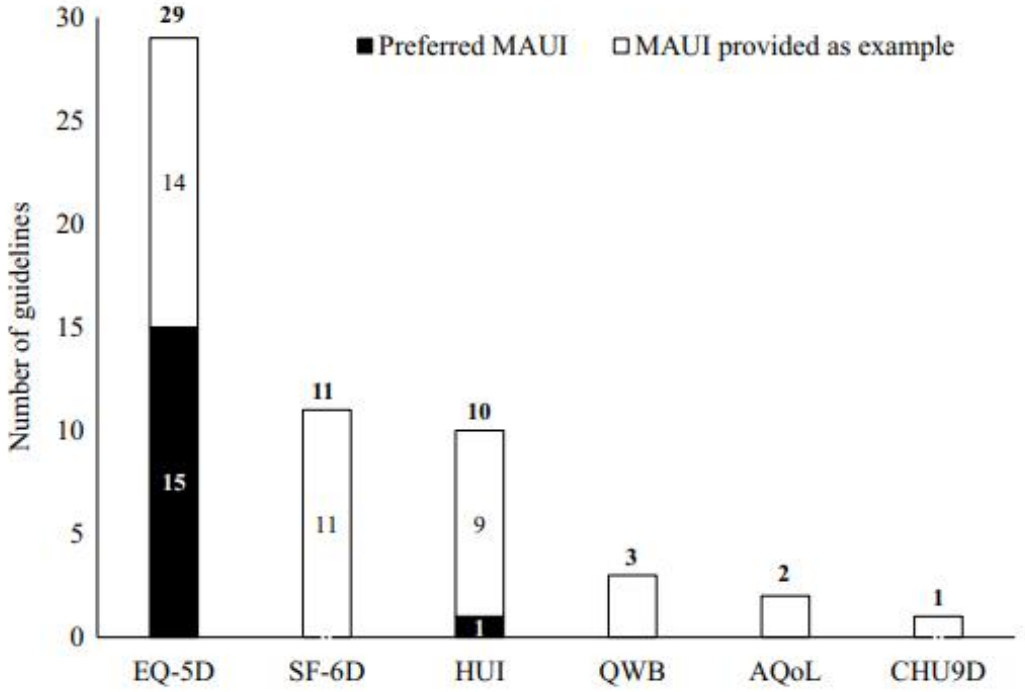


Fig. 2 MAUIs preferred or provided as an example across identified official PE guidelines. *AQoL* Assessment of Quality of Life, *CHU9D* Child Health Utility 9D, *HUI* Health Utility Index, *MAUI* multi-attribute utility instrument, *QWB* quality of well-being, *SF-6D* Short-Form 6-Dimension. Numbers sum to more than 34 because some guidelines cite more than one MAUI

Source:

The European Journal of Health Economics (2020) 21:1245–1257
https://doi.org/10.1007/s10198-020-01195-8

ORIGINAL PAPER

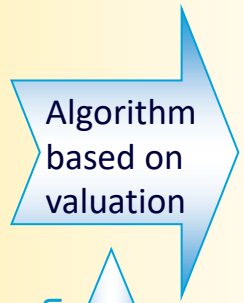
Check for updates

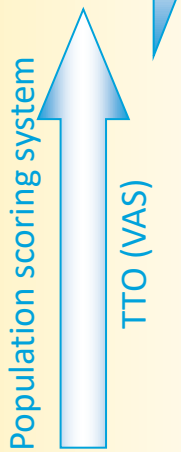
Which multi-attribute utility instruments are recommended for use in cost-utility analysis? A review of national health technology assessment (HTA) guidelines

Matthew Kennedy-Martin[1] · Bernhard Slaap[2,3] · Michael Herdman[4] · Mandy van Reenen[3] · Tessa Kennedy-Martin[1] · Wolfgang Greiner[5] · Jan Busschbach[2] · Kristina S. Boye[6]

EQ-5D-3L

		Health state profiles (patients)	Value for health (society)
Mobility	[1] no problems [2] some problems [3] confined to bed	1 1 1 1 1	1.00
Self-care	[1] no problem [2] some problem [3] unable to wash or dress	1 2 2 1 1	0.79
Usual activities	[1] no problems [2] some problems [3] unable to perform	2 2 1 2 2	0.55
Pain/discomfort	[1] no pain or discomfort [2] some pain or discomfort [3] extreme pain	2 2 3 2 3	0.02
Anxiety/depress.	[1] no anxiety/depression [2] moderate anxiety/depression [3] extreme anxiety/depression	3 3 3 3 3	-0.59





Value sets for EQ-5D are summarized at https://euroqol.org/publications/key-euroqol-references/value-sets/

EQ-5D-5 Levels

- Launched in 2009
- Improve the instrument sensitivity and reduce the ceiling effect of the EQ-5D-3L
- 5 levels of response: no problem, slight, moderate, severe , extreme
- Wording has changed
- Available in more than 130 languages
- A valuation set (tariff) is still being developed for a number of countries including the UK
- Cross walk values are available

Decision analytic modelling: Why?

- 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

Decision analytic model

- 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

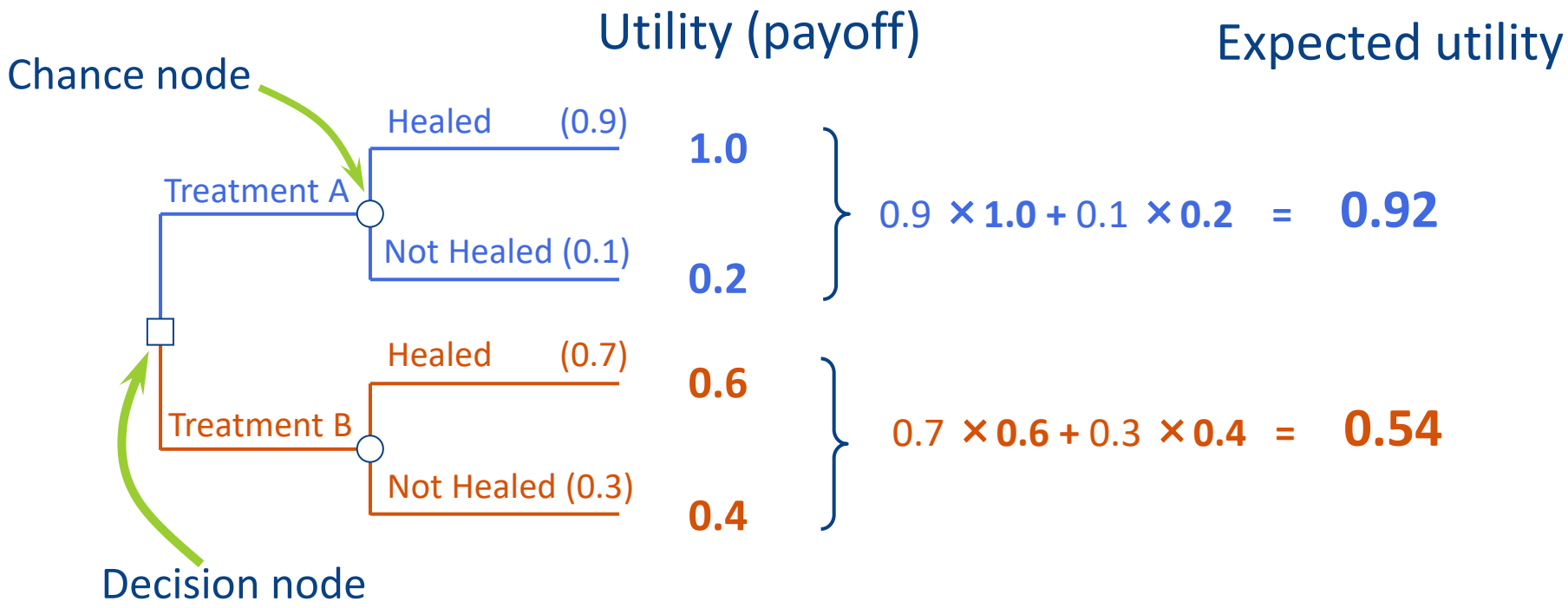
Model types

		Cohort level		Individual level	
		Continuous state	Discrete state	Markovian	Non-Markovian
No interaction among objects	Implicit time	**-**	**Decision tree**	**Patient-level decision tree (sampling individuals)**	
	Explicit time	**-**	**Markov model**	**Patient-level Markov model (sampling individuals)**	
Interaction among objects	Discrete or continuous time	**System dynamics**	**Markov chain model**	**Individual event history model (e.g., discrete time simulation 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.

Decision tree concepts

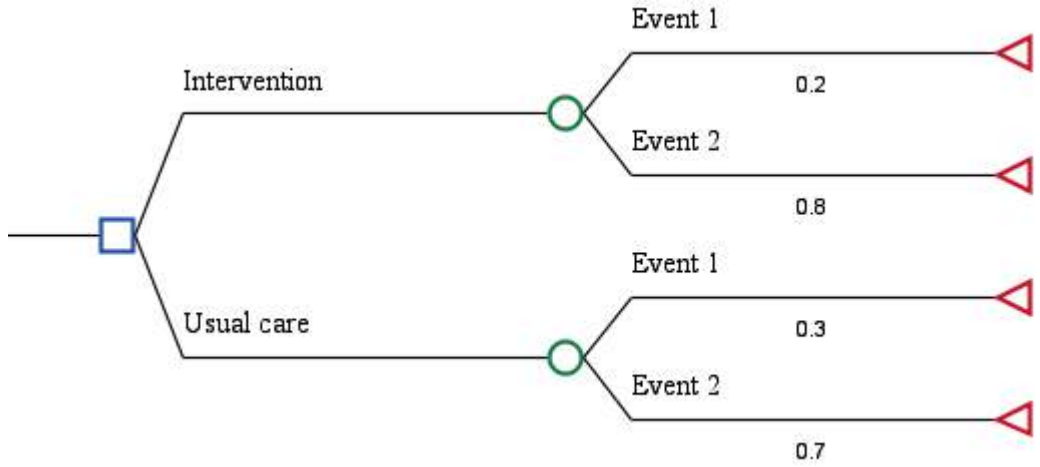
- Represents possible prognoses following each of the interventions under consideration for a patient over a short period of time
- Requires development of health states and assignment of probabilities and payoffs (e.g., utilities, costs)
- Time elapsed in <u>not explicitly</u> modelled

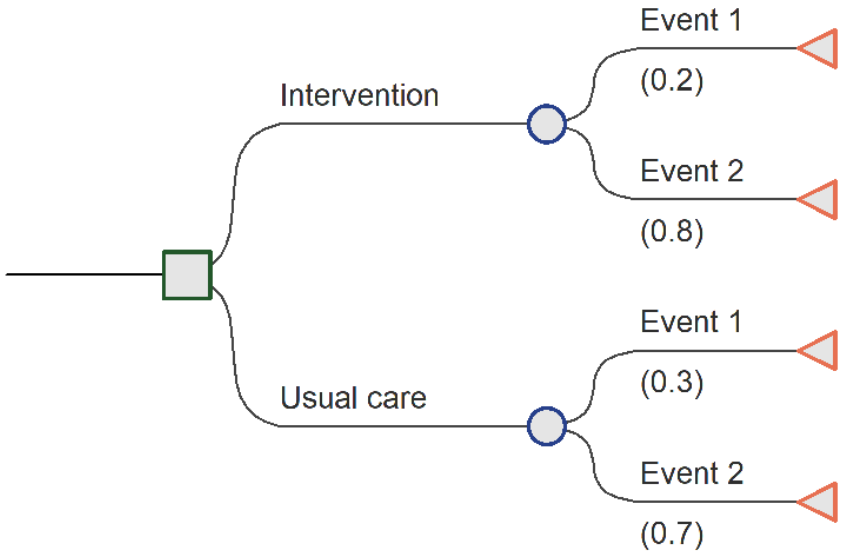


Time horizon: 6 months

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$1,800 for academic use and AU$2,500 for commercial use)
- DARE (Decision Analysis in R for health economic Evaluation)
  - Developed by Dr 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/





Case study: building a decision tree using DARE

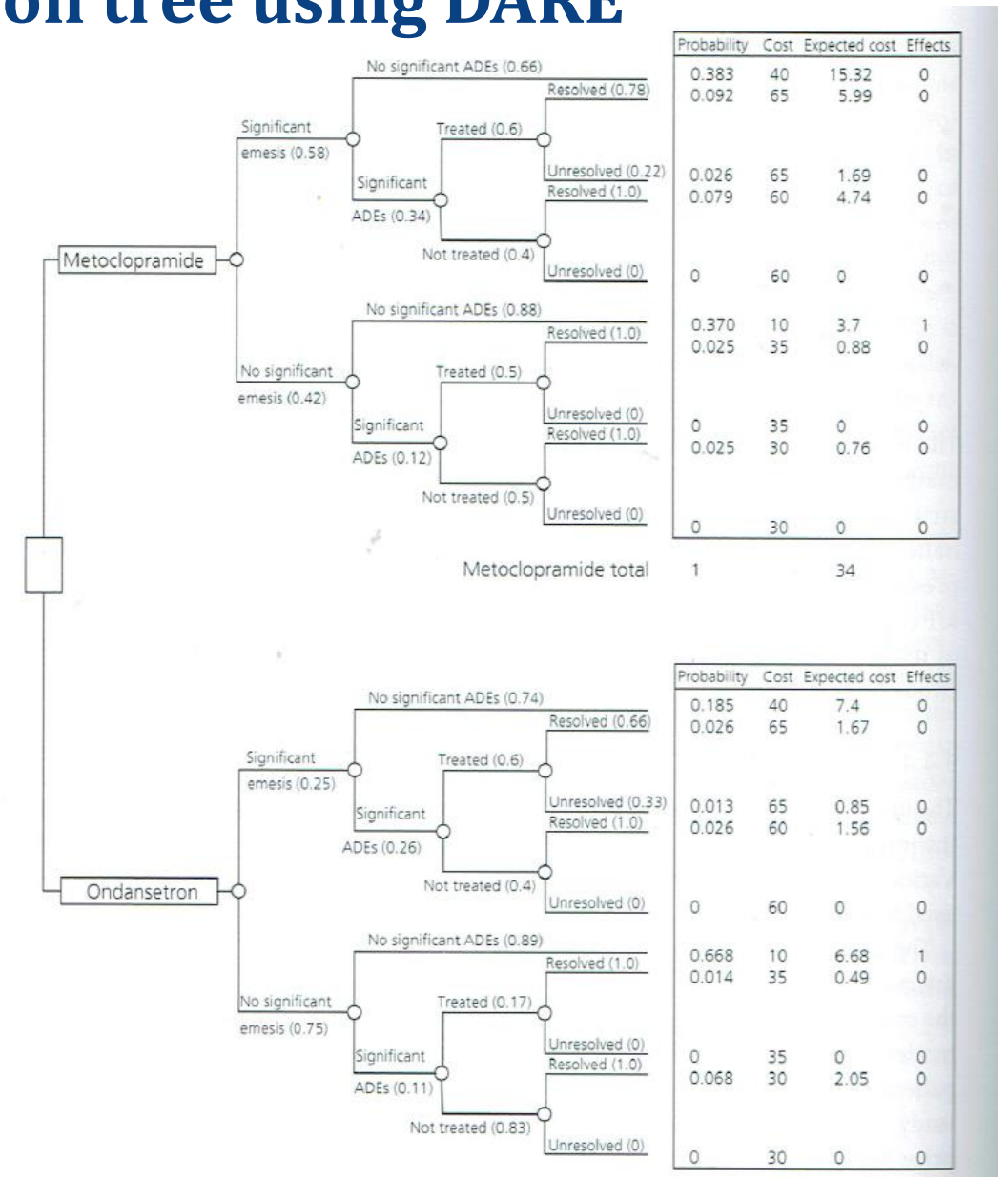
Br. J. Cancer (1992), **66**, Suppl. XIX, S64–S67

Economic evaluation of ondansetron: preliminary analysis using clinical trial data prior to price setting

M.J. Buxton[1] & B.J. O'Brien[2]

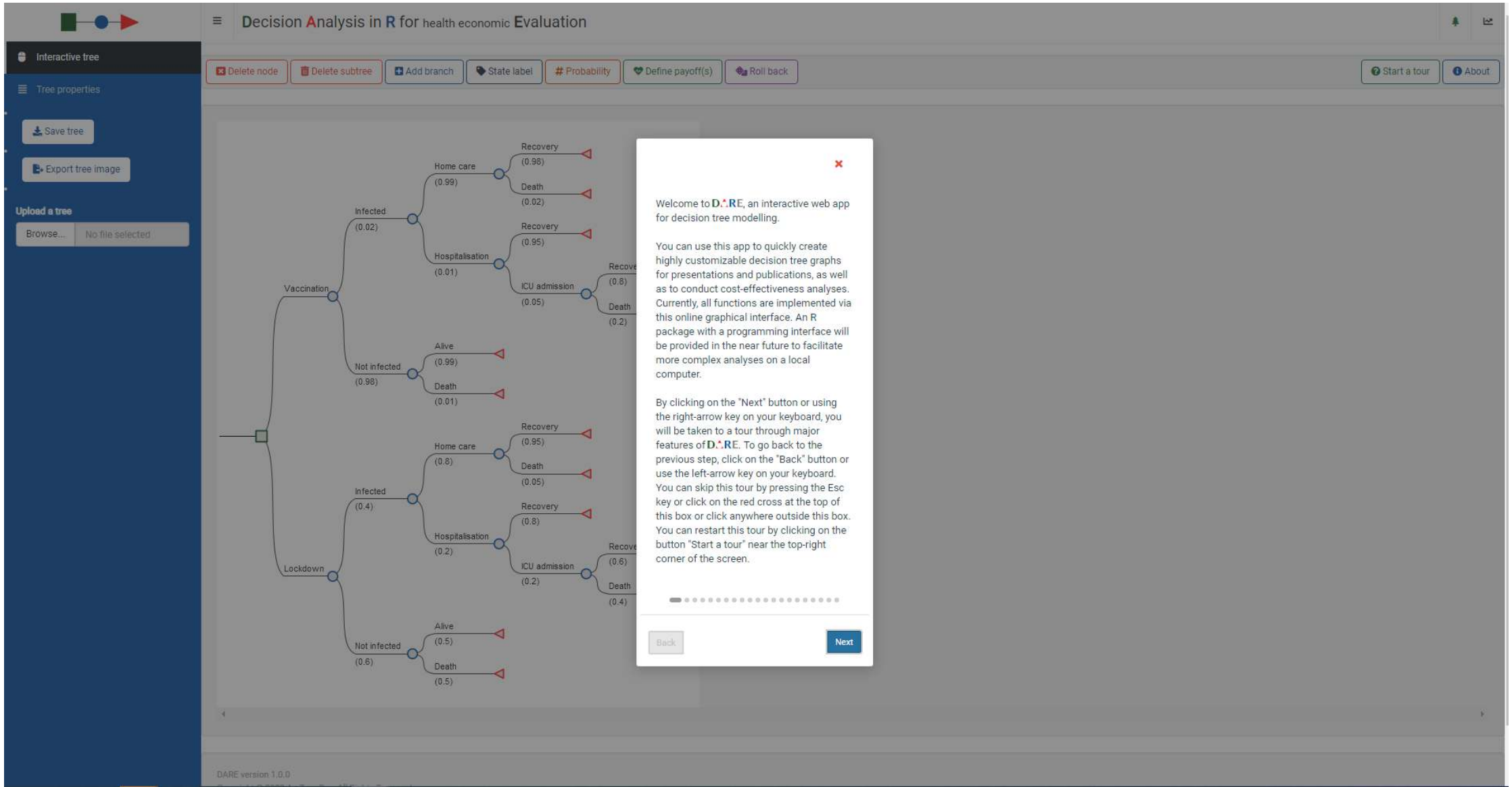
[1]*Health Economics Research Group, Brunel University, Uxbridge, Middlesex, UB8 3PH, UK;* [2]*Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada L85 3Z5.*

Summary This study combines secondary analysis of efficacy and side-effect data from a randomised controlled trial with estimates of resource use to evaluate the likely economic effects of the new antiemetic agent ondansetron. Costs, effects and cost-effectiveness of ondansetron in the prophylaxis of acute nausea and vomiting induced by chemotherapy are assessed relative to antiemetic therapy with metoclopramide. Superior efficacy of ondansetron is quantified both in terms of significant emesis avoided and emesis management costs avoided. A simple cost analysis, with the metoclopramide dosage priced at £10, indicates that therapy with ondansetron would give equivalent net treatment costs, at a price ratio (ondansetron/metoclopramide) of 2.3 to 1. If therapeutic success is defined as the avoidance of emesis and antiemetic side-effects, then the two therapies would be equally cost-effective at a drug price ratio of 5 to 1. We conclude that, (i) economic evaluation prior to price setting is feasible and informative; (ii) such models can indicate prospective data collection priorities.

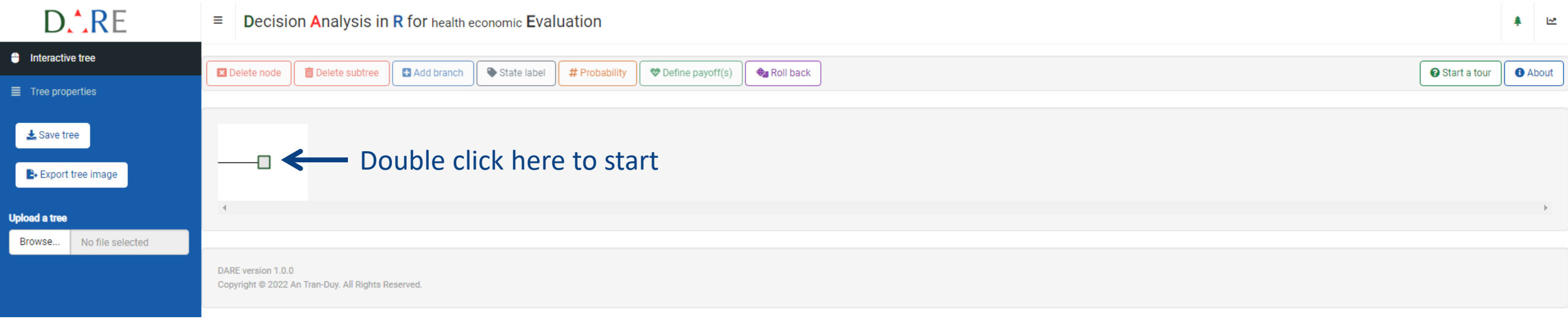


- Treatment cost: £10
- Cost of an episode of emesis: £ 30
- Cost of side-effects: £20
- Cost of treating side-effects: £ 5

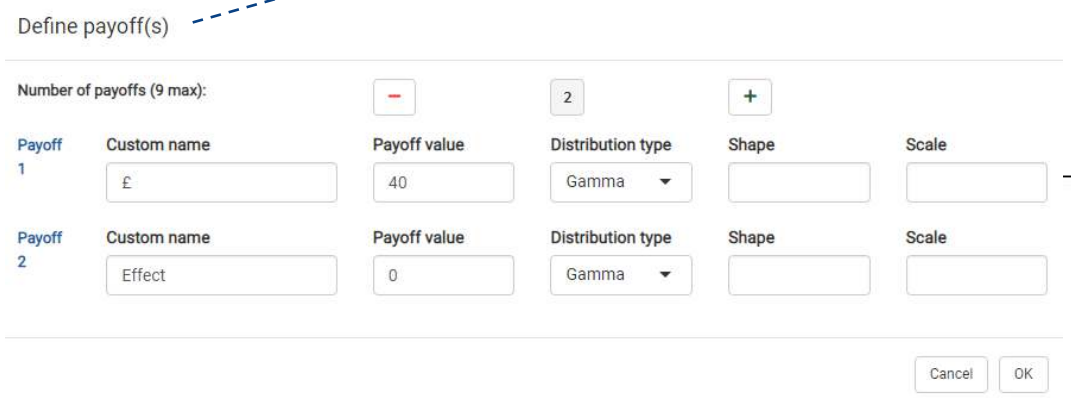
DARE interface – Tour through major features

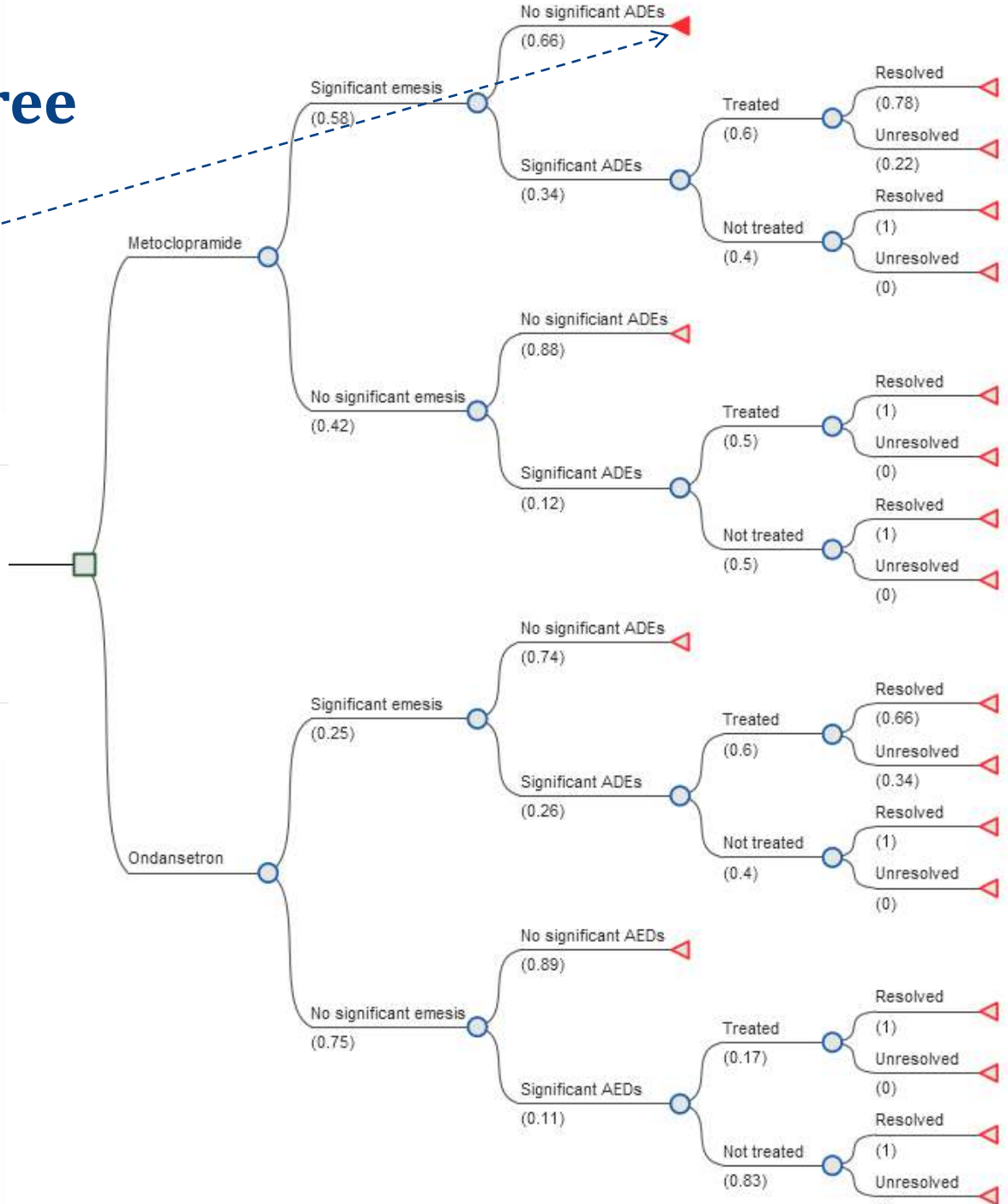


Start at the decision node



The target decision tree

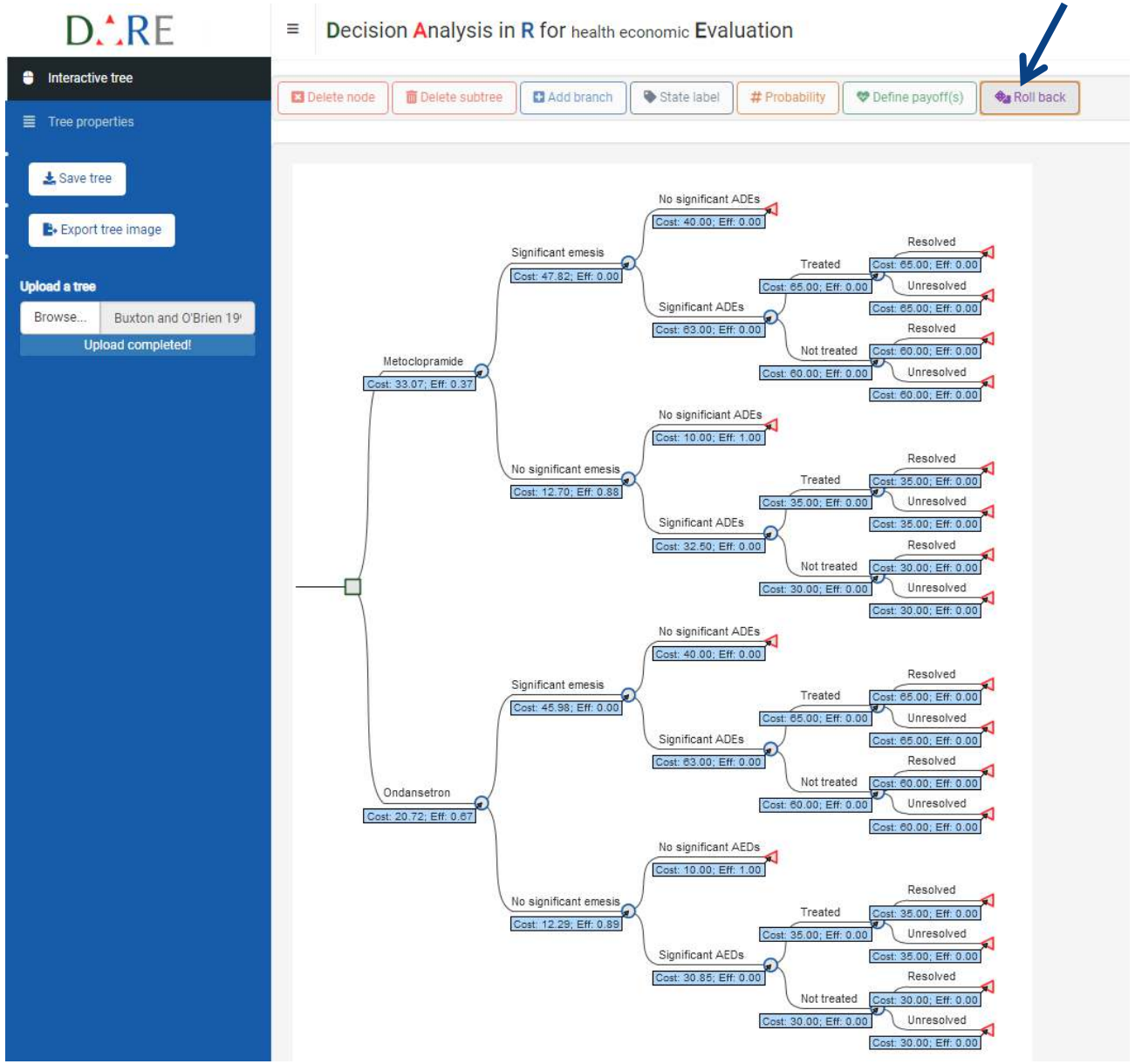




Rolling back

DARE will show an error if:

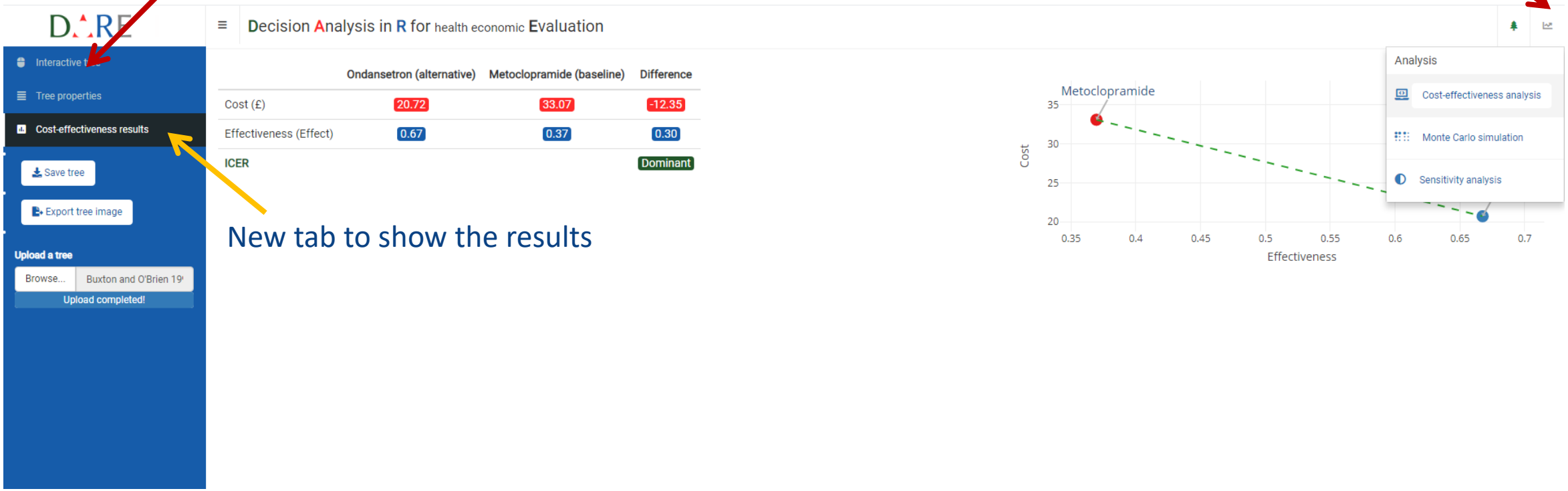
- There is one or more missing values for payoffs or probabilities
- If the probabilities of the children of a node are not valid (e.g., more than one hashtag (#) for probability, the sum of the probabilities of all children of a chance node is larger than 1)



Running cost-effectiveness analysis

Click here to go back to the interactive tree for updates

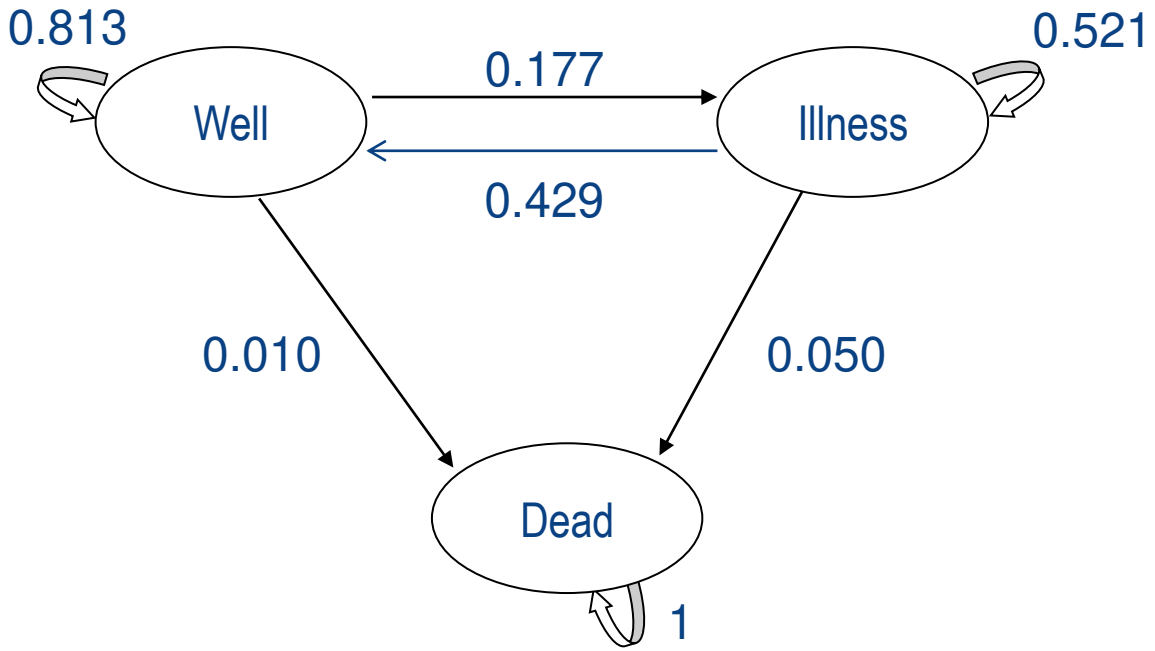
Menu to run cost-effectiveness analysis



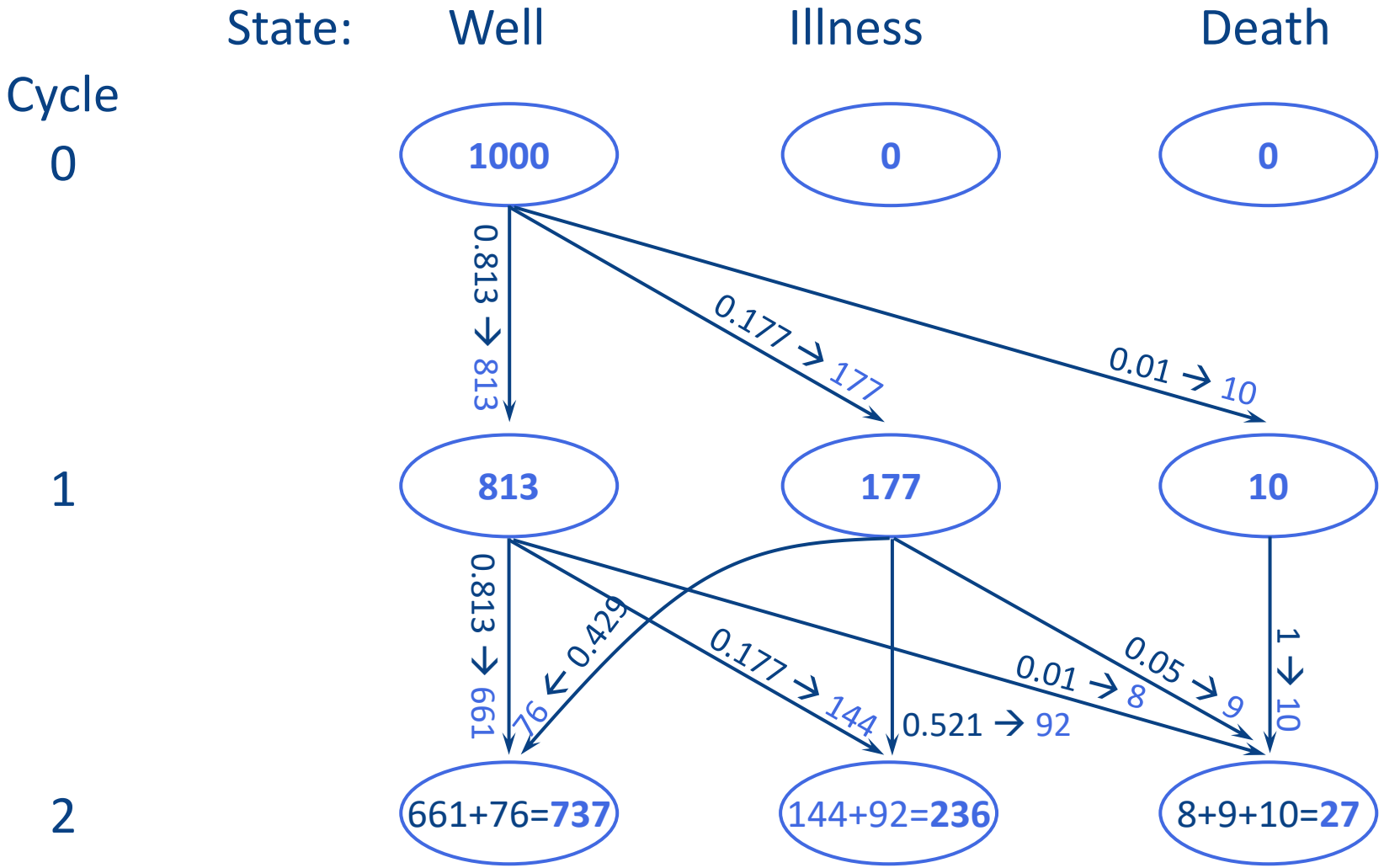
New tab to show the results

Markov (state-transition) model concepts

- 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



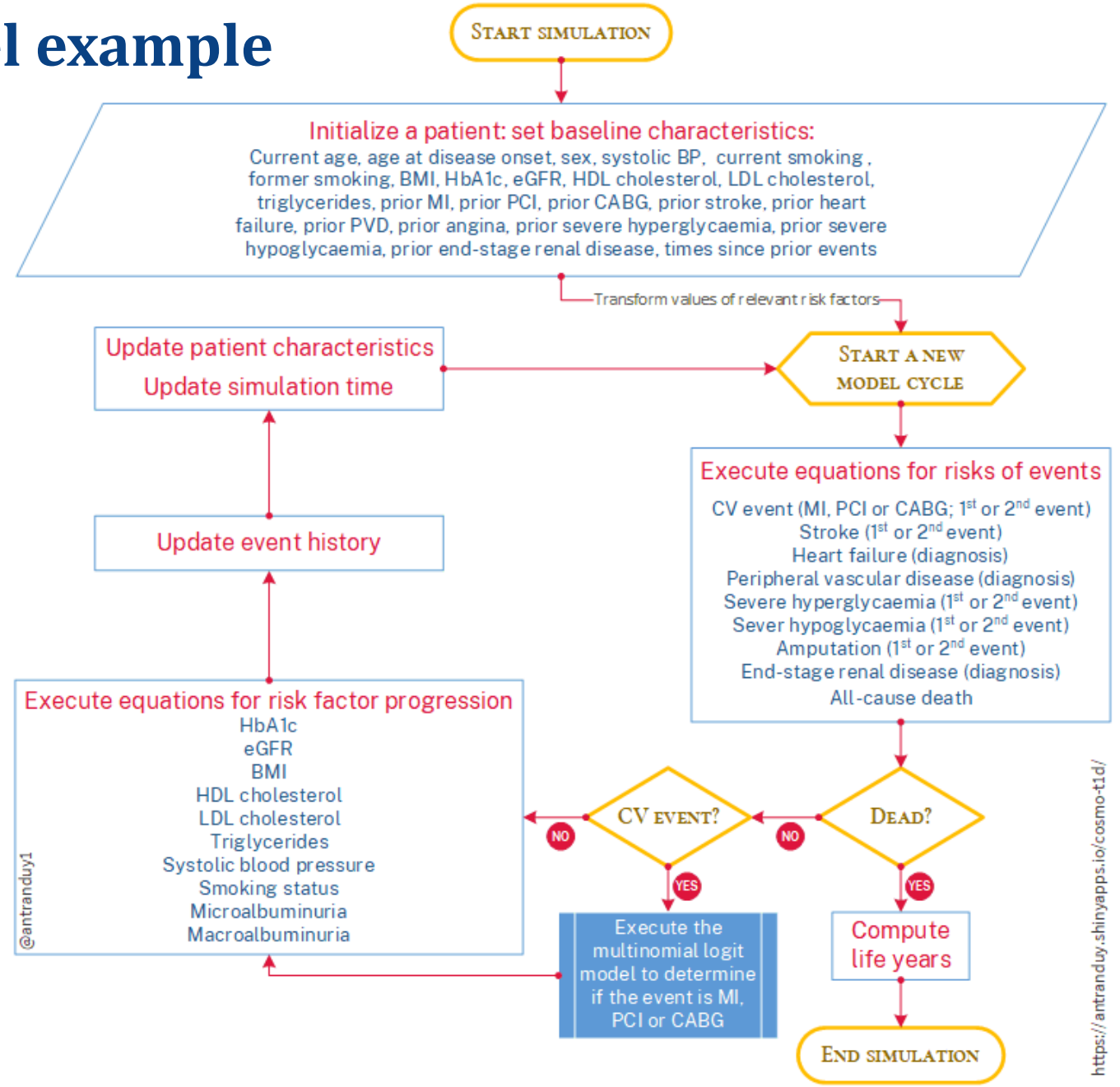
Markov model implementation



42

Patient-level model example

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



Health economics short courses

- https://mspgh.unimelb.edu.au/centres-institutes/centre-for-health-policy/research-group/health-economics/study/short-courses-in-health-economics
- Introduction to Cost-Effectiveness Analysis in Health (one day)
- Practical Methods for Health Economic Evaluation (three day)
- Designing Health Economic Evaluation Alongside Clinical Studies (one day)
- Evaluating Public Health Interventions using Economic and Epidemiologic Methods (one day)

Quiz – Questions 1 and 2

An RCT was conducted in patients with type 2 diabetes to compare the effects of two drugs on reducing risk of fatal cardiovascular complications. Based on available funding, 100 patients were recruited and followed up for 24 months in each treatment arm. Health-related quality of life was measured using EQ-5D-5L at baseline at the end of the follow-up period. The results showed no statistically significant difference in survival rates between the two treatments.

1. Because the survival rates were not significantly different, a cost-minimisation should be conducted.

   a. TRUE b. FALSE

2. With the measurements of health-related quality of life, we can accurately calculate QALYs and conclude which drug produces a better health outcome.

   a. TRUE b. FALSE

Quiz – Questions 3 and 4

An RCT is designed to compare a novel lipid-lowering therapy with the traditional drug. The primary health outcome is a reduction in LDL-cholesterol at 3 months and the secondary outcome is quality of life measured on a simple visual analogue scale with 0 indicating death and 1 indicating perfect health. No other health outcomes are measured. All costs related to the treatments and health care resource utilisation are captured.

3. This study design is adequate for a cost-utility analysis.
   a. TRUE b. FALSE

4. By conducting a trial-based cost-effectiveness, one can provide the policy makers with results that can directly be used to conclude if the novel therapy is cost-effective compared with the traditional drug.
   a. TRUE b. FALSE

Thank you

THE UNIVERSITY OF MELBOURNE

Faculty of Medicine, Dentistry and Health Sciences

MACH Melbourne Academic Centre for Health

- Recording:- **https://machaustralia.org/**
- MISCH Newsletter:- **https://clinicalresearch.mdhs.unimelb.edu.au/collaborate/contact-us/misch-newsletter-sign-up**
- Website:- https://clinicalresearch.mdhs.unimelb.edu.au/
- Email:- misch-info@unimelb.edu.au
- @MischHub