Markov Modelling for Health Technology Assessment

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Synopsis

- What is Markov modelling?
- How is it used in health technology assessment (HTA)?
- 2-state models
  - inputs & outputs
- 3-state models
  - quality of life and sensitivity analysis
- Multi-state models
- Demo: modelling software (*TreeAge Pro*)

What is Markov modelling?

- A **Markov model** is a stochastic **model** used to **model** randomly changing systems where it is assumed that future states depend only on the current state not on the events that occurred before it (that is, it assumes the **Markov** property of *historical independence*)

  - Developed in nuclear physics to describe the random motion of nuclear particles
  - In healthcare: usually follows one or more hypothetical cohorts of people
    - e.g. compare vaccinated vs unvaccinated birth cohorts over their lifetime
  - Non linear, e.g. doubling an input won't double the output

Markov models in health technology assessment

- Used to predict *future* costs and benefits of interventions
  - Compares an intervention with ‘usual care’ or another intervention
    - In 2+ identical cohorts
  - Extends the results of clinical trial(s) to the patient’s lifetime or another time horizon
  - Calculates the cost per event prevented or cost per QALY gained (ICER)
  - Can include competing risks
    - E.g. Death from CVD or other causes
  - Can have time varying inputs
    - E.g. costs or mortality rates that change over time

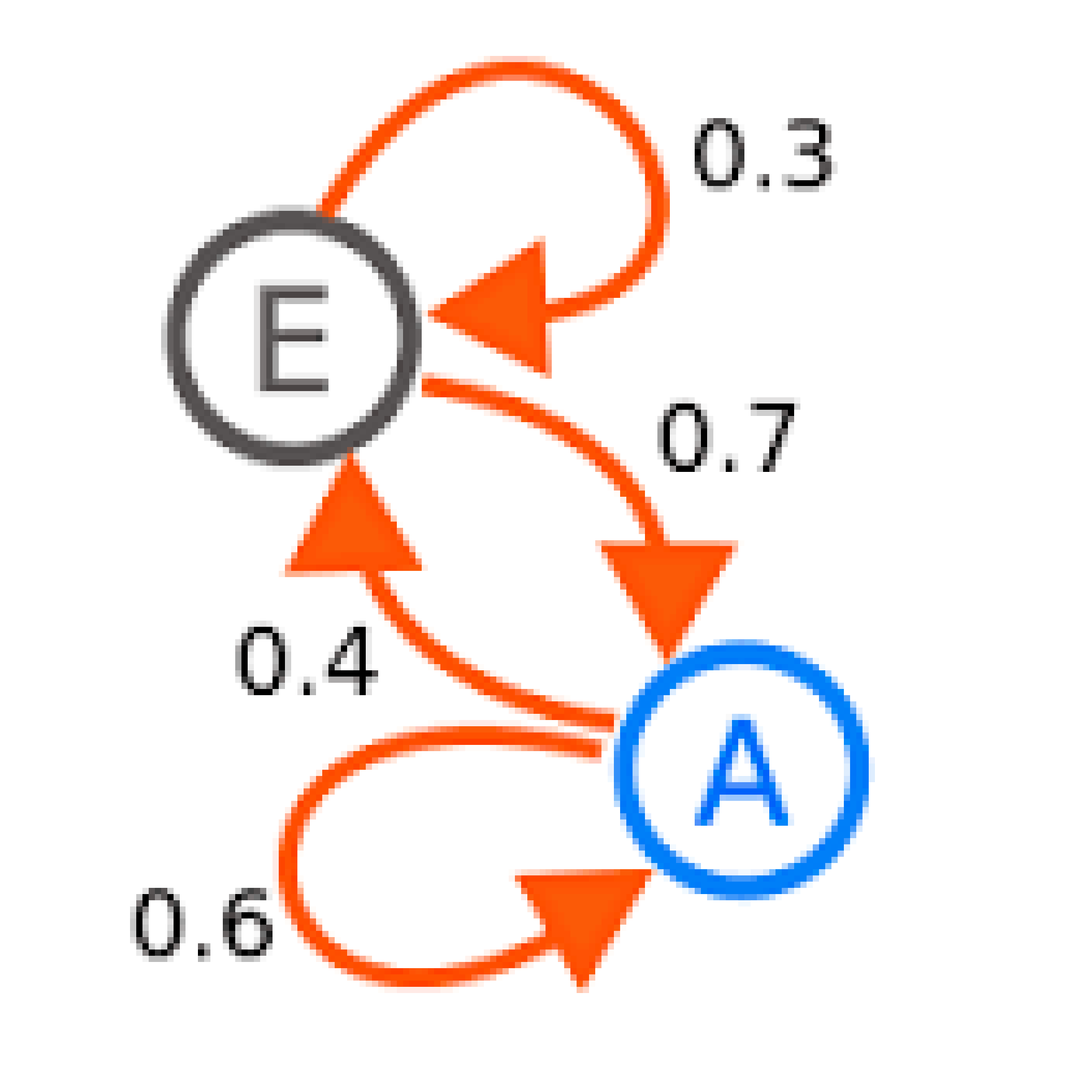
Markov models are used for prediction:

- **“it is very difficult to predict anything— especially the future.”**
  - ***Neils Bohr, 1956***

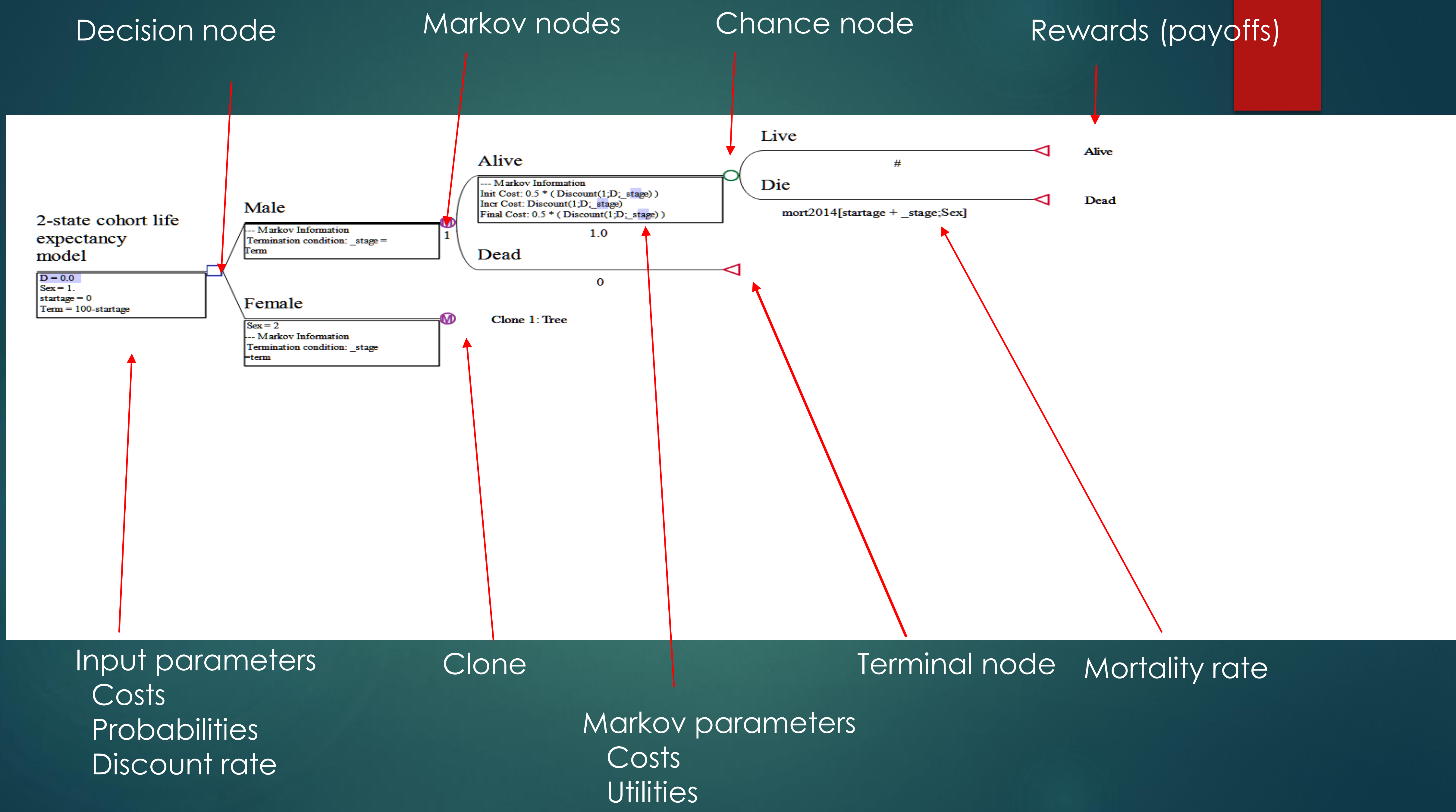
The 2-state Markov model

- Based on local mortality tables (life tables)
  - These reflect recent mortality, not future mortality
- 2 states:
  - Alive
  - Dead
- Considers how a *cohort* of individuals progresses over its lifetime
  - OR how discrete individuals progress over time
- Compares *life expectancy* under 2 or more different circumstances
- Can calculate life years gained by an intervention
- Can run sensitivity analyses *('alternative facts?')*

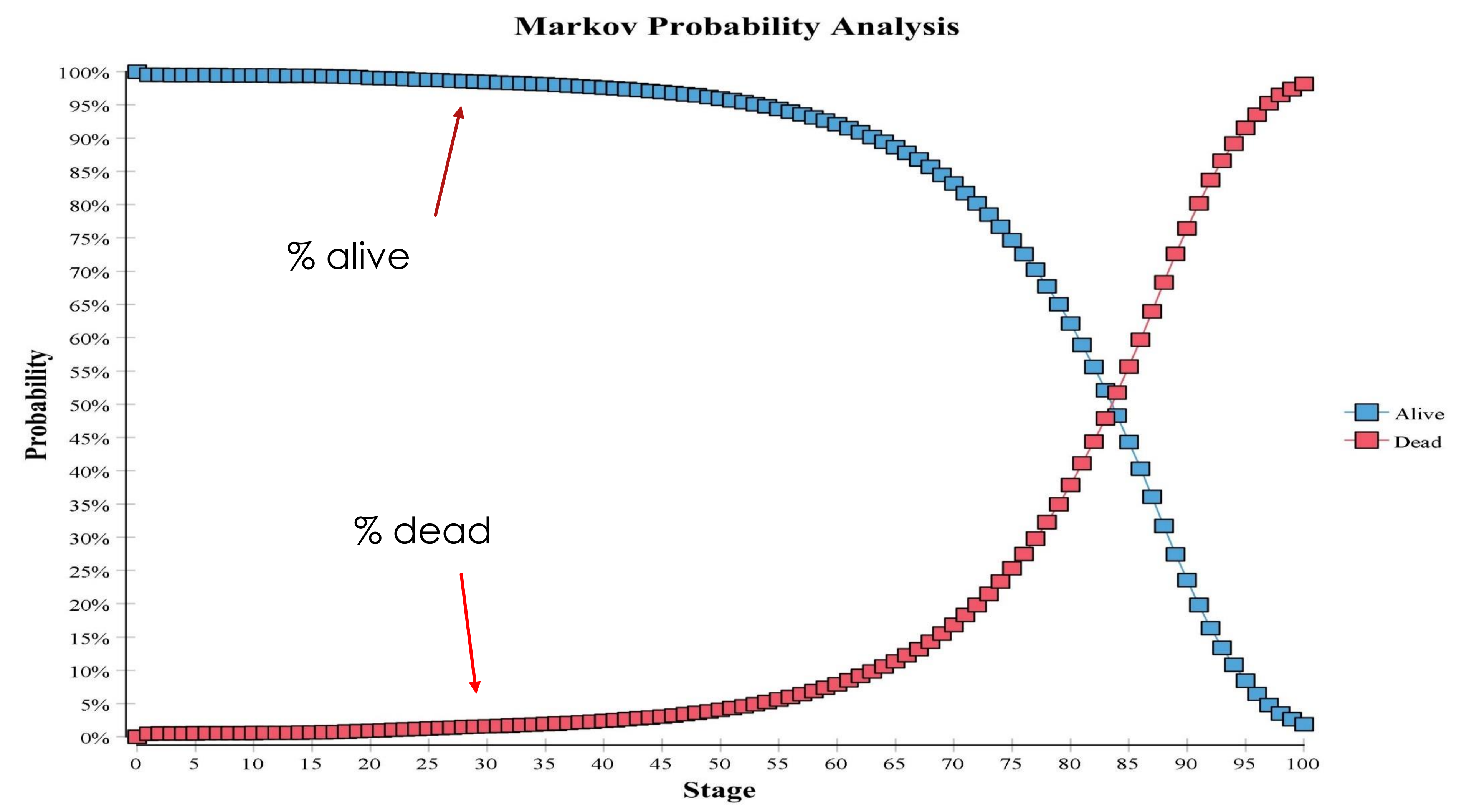
Health state E



Health state A


Decision node
Markov nodes
Chance node
Rewards (payoffs)
2-state cohort life expectancy model
D = 0.0
Sex = 1.
startage = 0
Term = 100-startage
Male
--- Markov Information
Termination condition: _stage = Term
1
Female
Sex = 2
--- Markov Information
Termination condition: _stage =term
Alive
--- Markov Information
Init Cost: 0.5 * (Discount(1;D;_stage))
Incr Cost: Discount(1;D;_stage)
Final Cost: 0.5 * (Discount(1;D;_stage))
1.0
Dead
0
Clone 1: Tree
Live
#
Die
mort2014[startage + _stage;Sex]
Alive
Dead
Input parameters
Costs
Probabilities
Discount rate
Clone
Markov parameters
Costs
Utilities
Terminal node
Mortality rate

The ‘Markov trace’ for a 2-state model



Birth

Age 100y

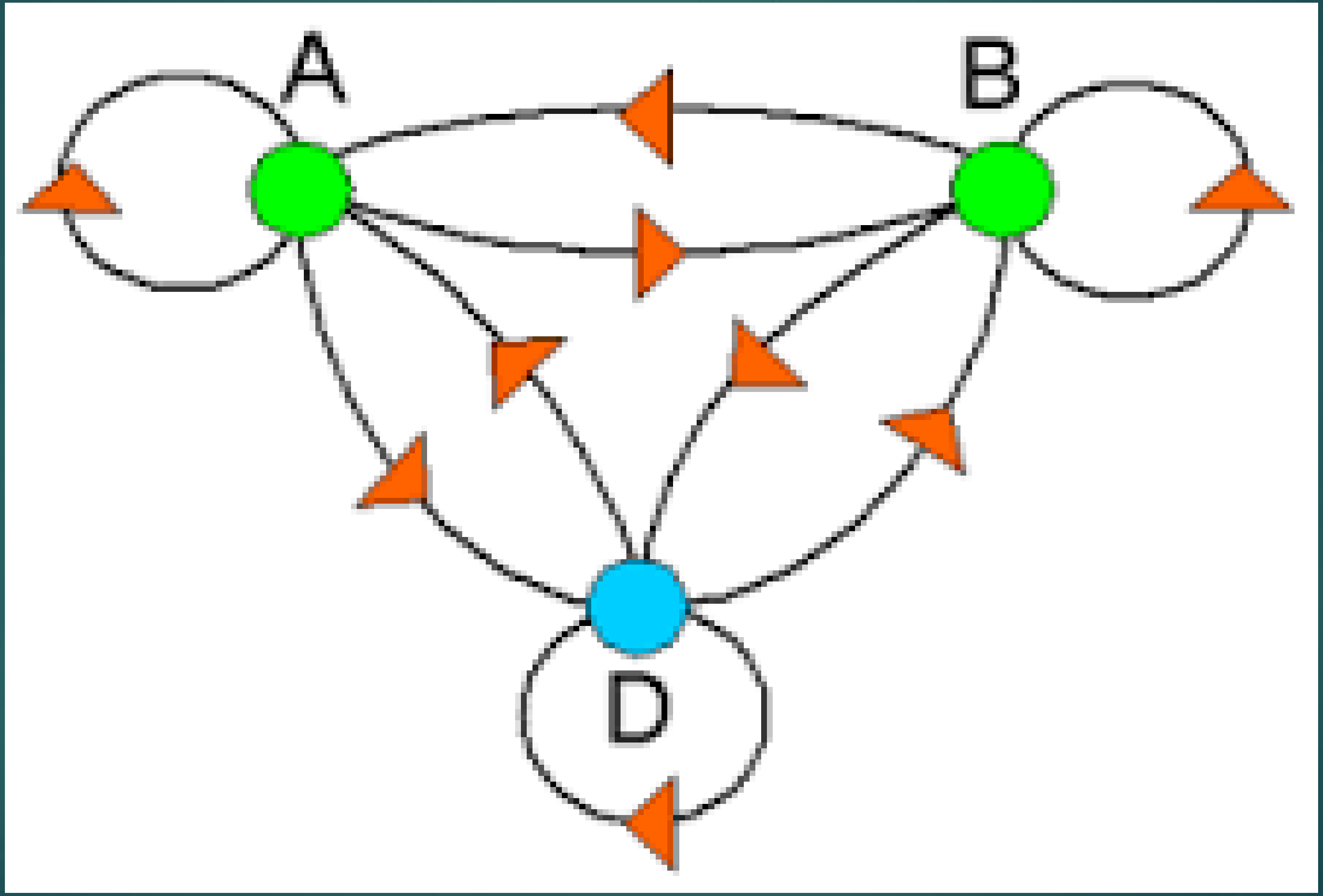
The 3-state Markov model

- Based on disease progression, quality of life and mortality
- Only 3 states:
  - Well
  - Unwell
  - Dead
- Compares *quality-adjusted* life expectancy under different circumstances
- Can calculate *lifetime* costs and QALYs gained by an intervention
- Requires sensitivity analyses on uncertain parameters (e.g. risk of an event)
- Easily expanded to a multi-state model

3-state Markov model

Well

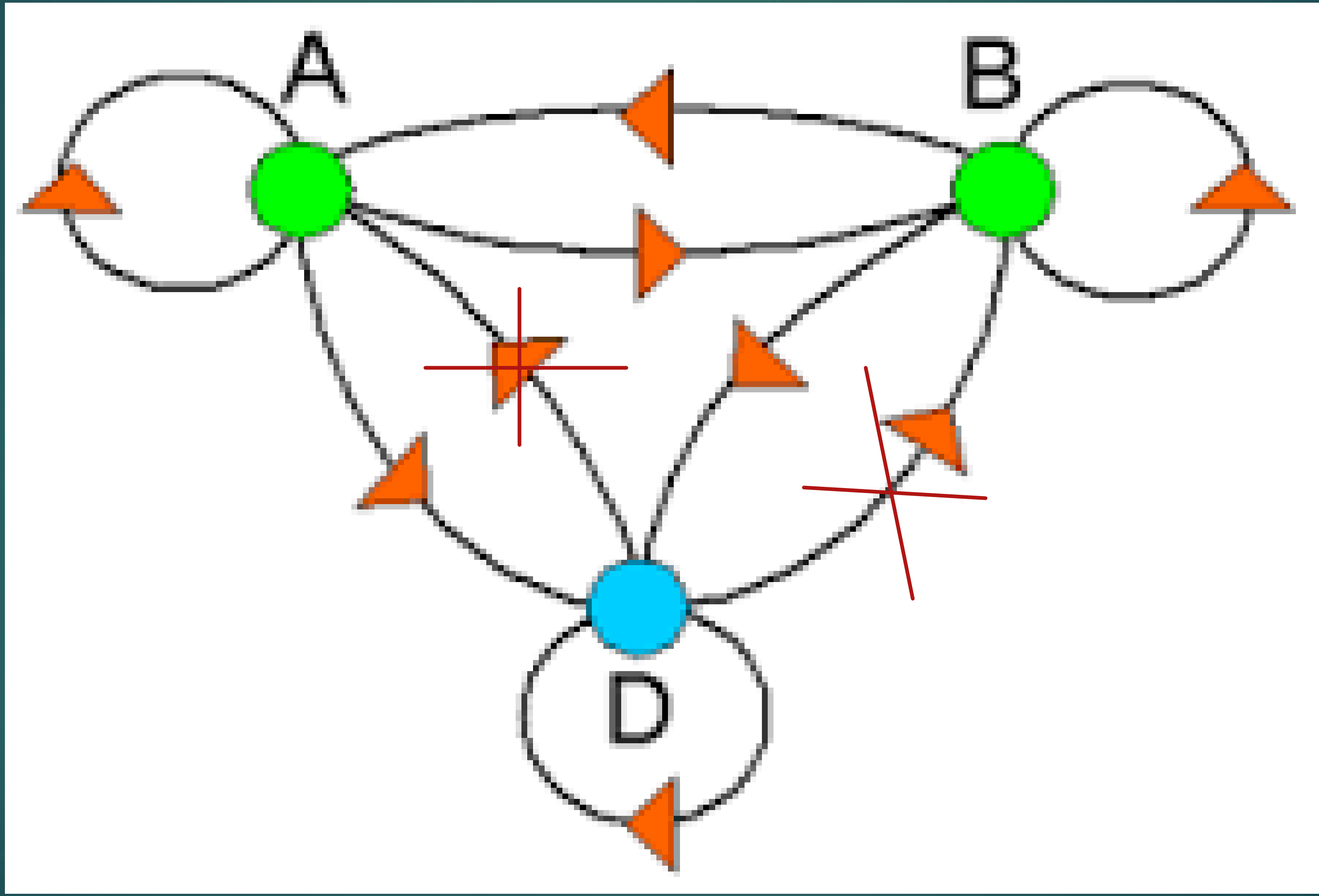
Unwell



Dead

3-state Markov model, corrected

Well



Unwell

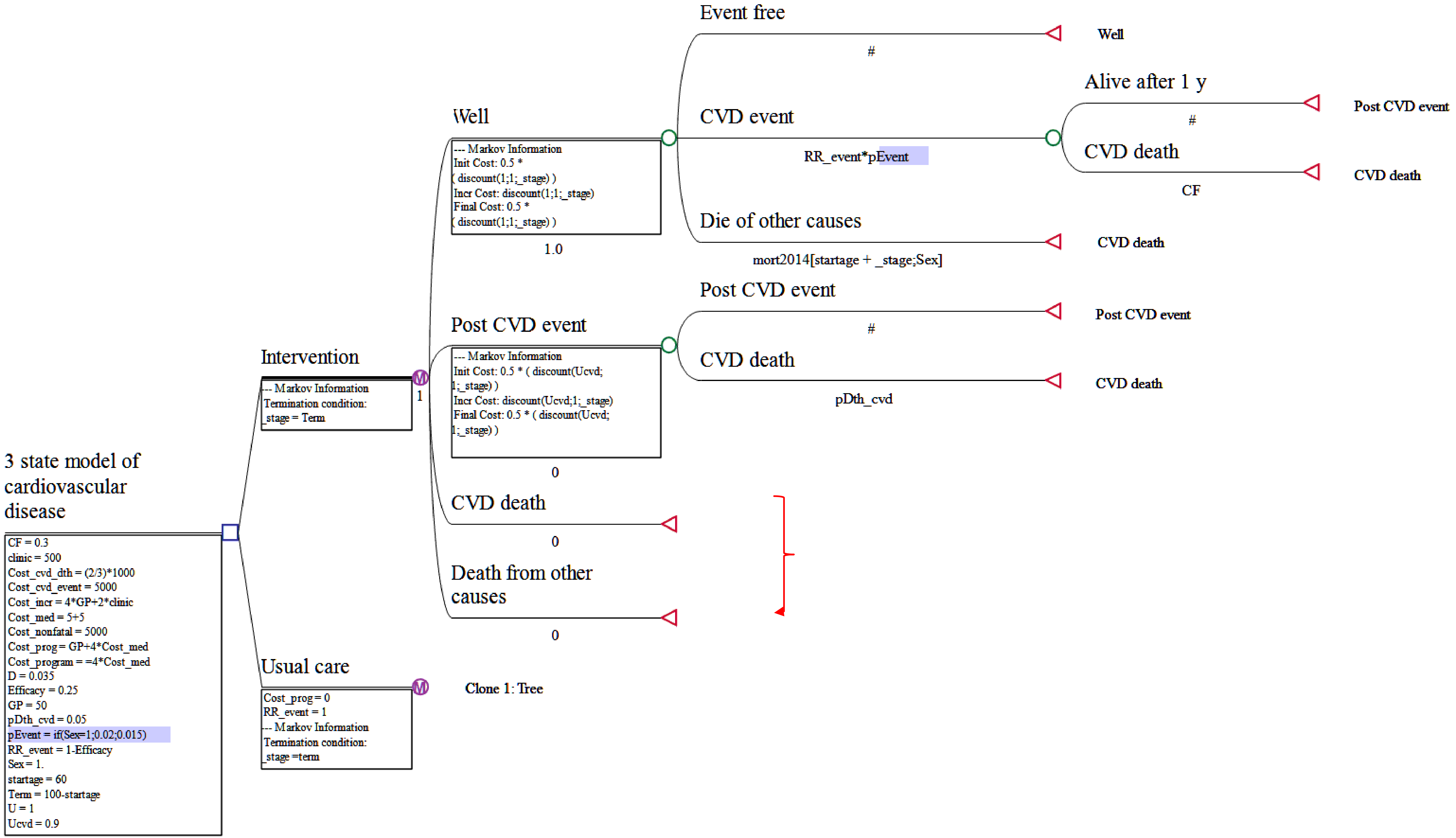
Dead

Example

- A new intervention is available for reducing cardiovascular risk
- Is it likely to be cost effective compared to 'usual care?'

Example

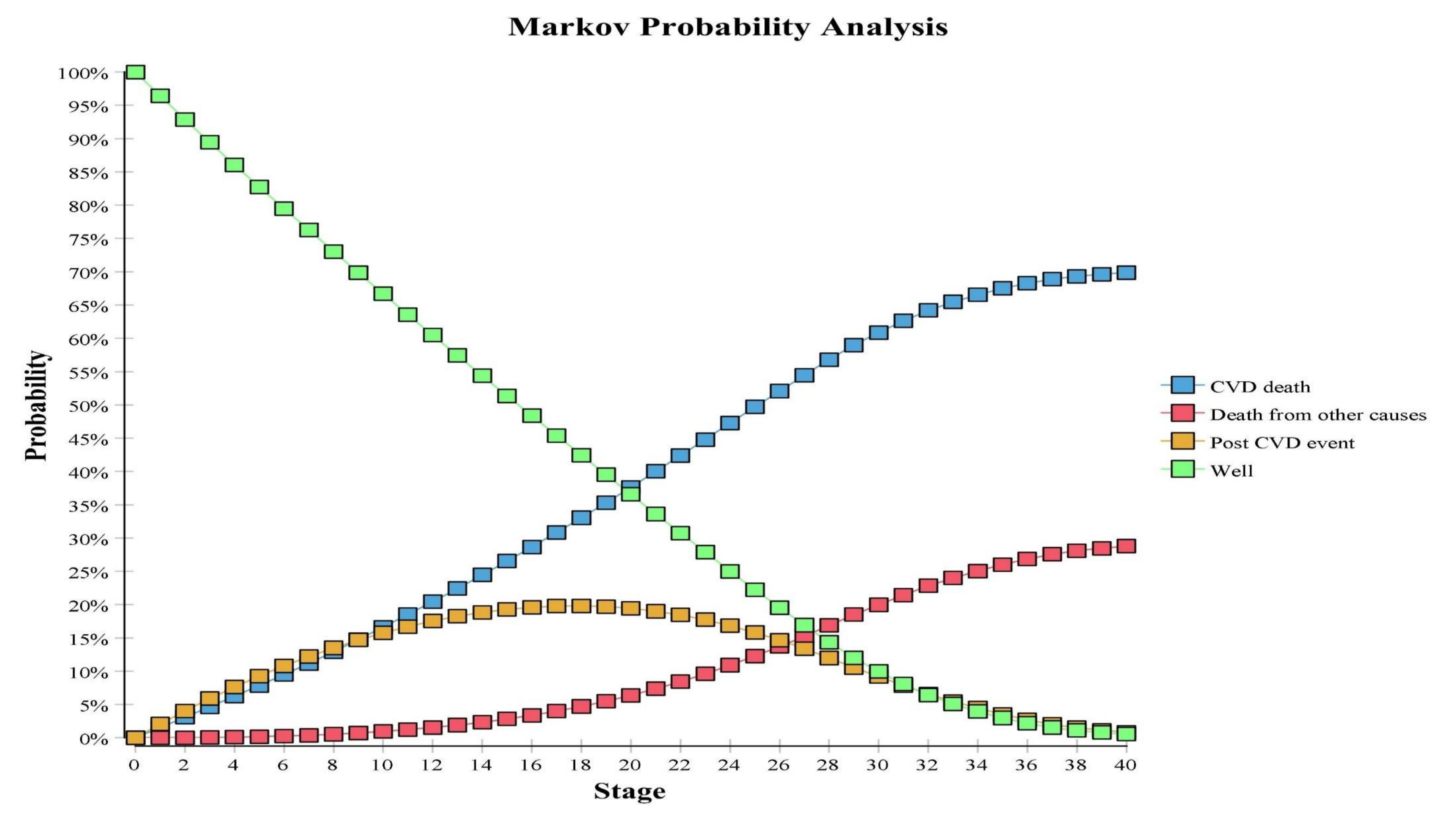
- Information required:
  - Epidemiology
    - Baseline risk of *specified target group*, for men and women age 60+ (= annual prob. of CVD event)
    - Case fatality of CVD events (age/sex dependent)
    - Effectiveness of the new programme (includes efficacy and adherence)
    - CVD risk after first CVD event
    - Mortality from other causes
  - Costs
    - Annual cost of novel programme or medicine
    - Cost of healthcare for a CVD event (stroke or AMI)
    - Annual costs of maintenance therapy after CVD event
  - Quality of life
    - Mean quality of life (utility) of target group
    - Mean quality of life post-CVD event (stroke or AMI)


Event free
Well
#
Alive after 1 y
Post CVD event
#
Well
CVD event
CVD death
CVD death
--- Markov Information
Init Cost: 0.5 * (discount(1;1;_stage))
Incr Cost: discount(1;1;_stage)
Final Cost: 0.5 * (discount(1;1;_stage))
RR_event*pEvent
CF
1.0
Die of other causes
CVD death
mort2014[startage + _stage;Sex]
Post CVD event
Post CVD event
Post CVD event
#
Intervention
--- Markov Information
Init Cost: 0.5 * (discount(Ucvd; 1;_stage))
Incr Cost: discount(Ucvd;1;_stage)
Final Cost: 0.5 * (discount(Ucvd; 1;_stage))
CVD death
CVD death
--- Markov Information
Termination condition:
_stage = Term
1
pDth_cvd
0
3 state model of cardiovascular disease
CVD death
0
CF = 0.3
clinic = 500
Cost_cvd_dth = (2/3)*1000
Cost_cvd_event = 5000
Cost_incr = 4*GP+2*clinic
Cost_med = 5+5
Cost_nonfatal = 5000
Cost_prog = GP+4*Cost_med
Cost_program = =4*Cost_med
D = 0.035
Efficacy = 0.25
GP = 50
pDth_cvd = 0.05
pEvent = if(Sex=1;0.02;0.015)
RR_event = 1-Efficacy
Sex = 1.
startage = 60
Term = 100-startage
U = 1
Ucvd = 0.9
Death from other causes
0
Usual care
Cost_prog = 0
RR_event = 1
--- Markov Information
Termination condition:
_stage =term
Clone 1: Tree

A 3-state CVD Markov model

Name	Description	Root Definition	Low	High
Cost_GP	Annual cost of GP visits	200	0	0
CF	CVD case fatality	0.3	0.2	0.6
clinic	Cost of CV clinic	500	300	500
Cost_cvd_dth	Cost of CVD death	1000	500	1000
Cost_med	Annual cost of new medicine	200	0	0
Cost_nonfatal	Cost of non fatal CVD event	Cost_cvd_gamma	4000	8000
Cost_post_cvd	Annual cost after CVD event	750	0	0
D	Discount rate	0.035	0	0.05
Efficacy	Efficacy of novel therapy	Efficacy_normal	0.2	0.3
Event	CVD event	discount(1;D;_stage)	0	0
GP	Annual cost of GP (quarterly)	200	0	0
pDth_cvd	Prob of cvd death	0.01	0.005	0.015
pEvent	Annual prob of CVD event	prob_event_beta	0.02	0.05
RR_event	Relative risk of CVD event	1-Efficacy	0.75	1
Sex	Male=1, Female=2	1	1	2
startage	Age at start	60	50	70
Term	Time horizon	100-startage	10	40
Ucvd	QoL post CVD	0.9	0.8	1
X		1	0	0

3-state Markov model trace

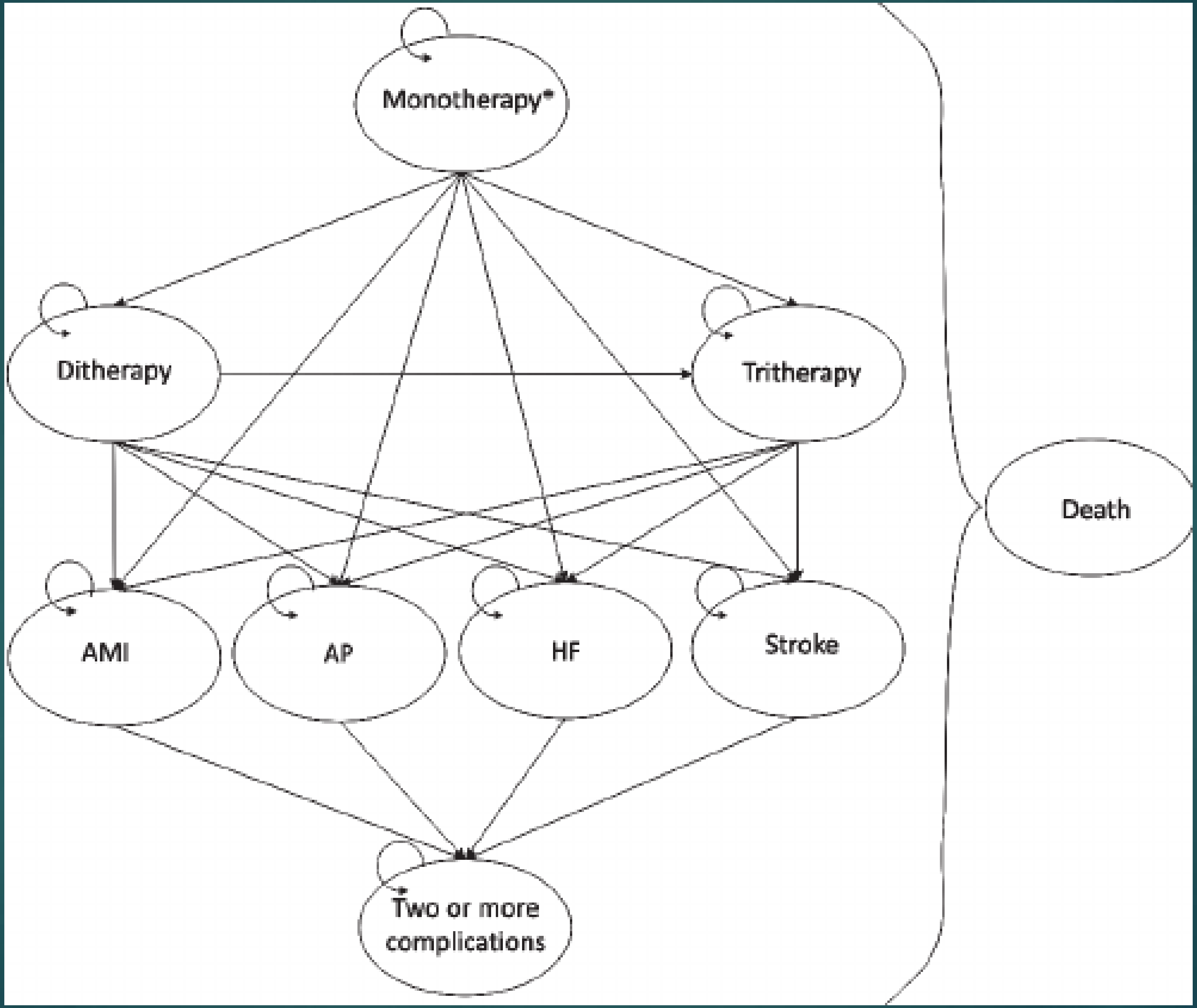


Age 60 y

Age 100y

The multi-state model

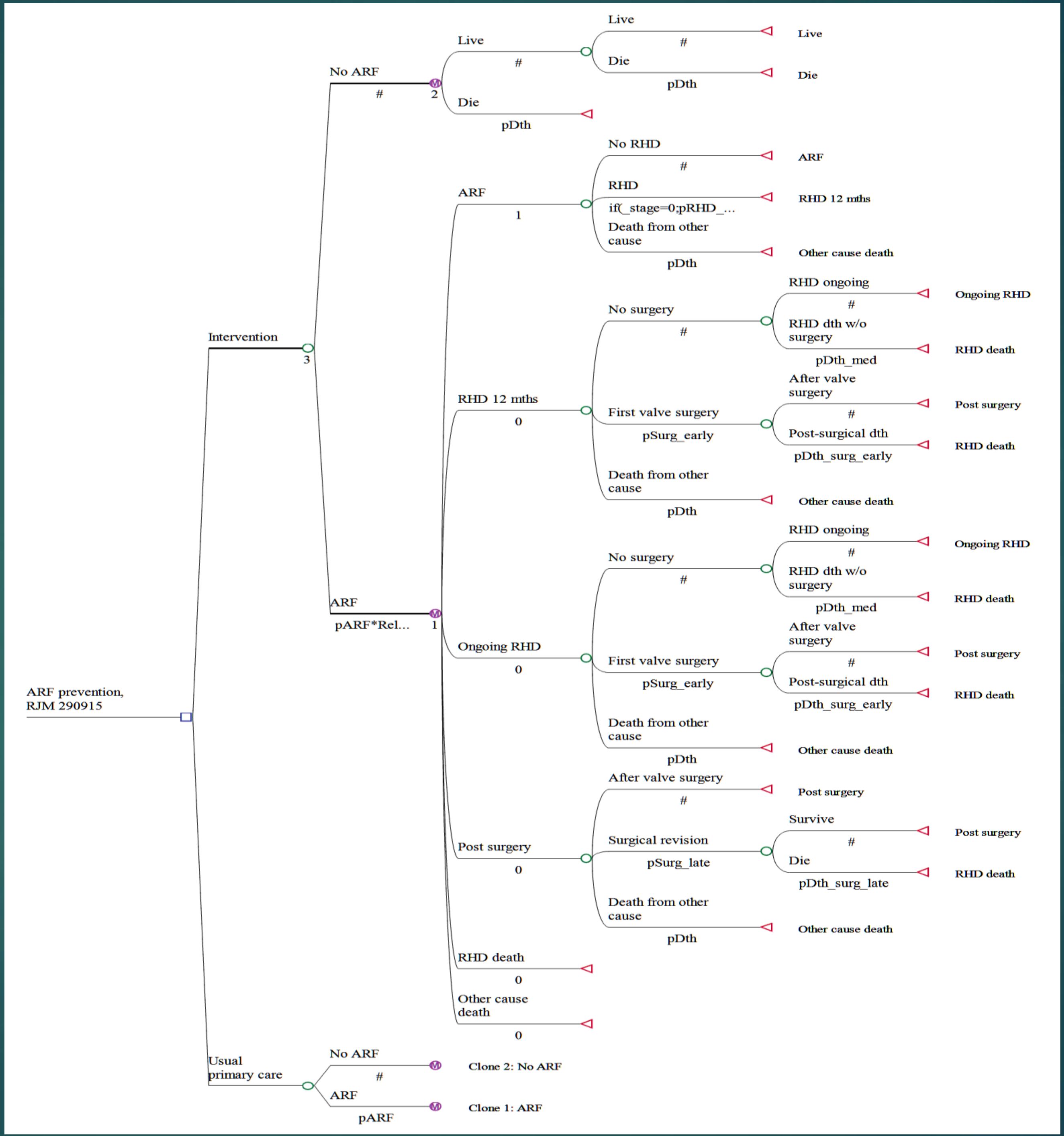
- Useful when chronic disease *progression* is well characterised clinically
  - e.g. CVD, cancer, respiratory disease, rheumatic heart disease
- One disease with several disease states:
  - Well
  - Disease State 1,   Disease State 2,   Disease State 3 …. etc.
  - Dead
- Based on mortality, disease progression & quality of life in each health state
- Compares quality-adjusted life years (QALYs) under many different circumstances
- Calculates *lifetime* cost and QALYs gained by an intervention
- Calculates the cost per QALY gained (ICER= incremental cost effectiveness ratio)
- Requires sensitivity analyses on uncertain parameters
- Powerful, flexible, useful


Monotherapy*
Ditherapy
Tritherapy
Death
AMI
AP
HF
Stroke
Two or more complications

Progression from well to:
- acute rheumatic fever;
- rheumatic heart disease;
- valve surgery;
- surgical revision;
- death from RHD or other

School intervention

No school intervention



Never ARF

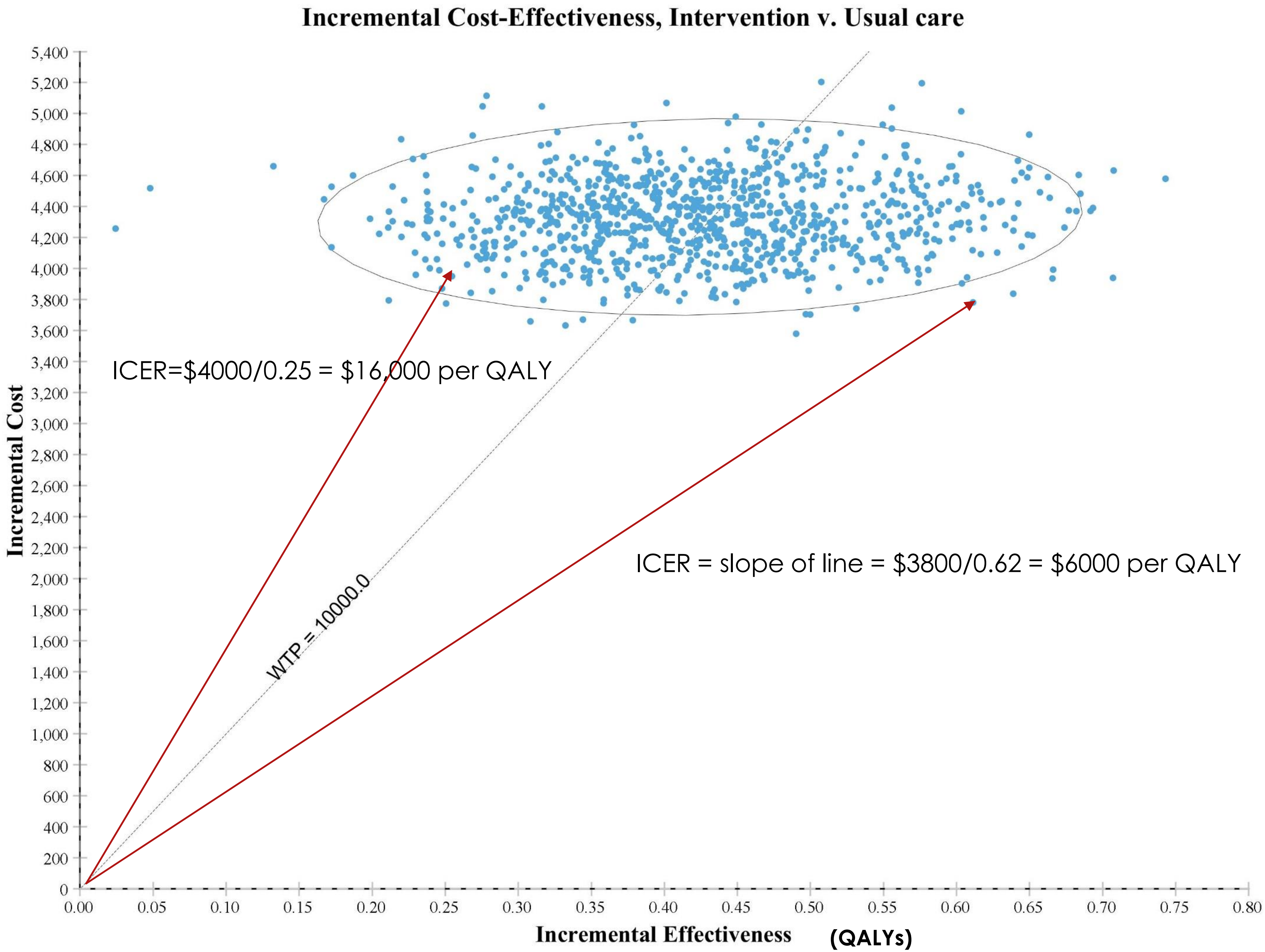
ARF

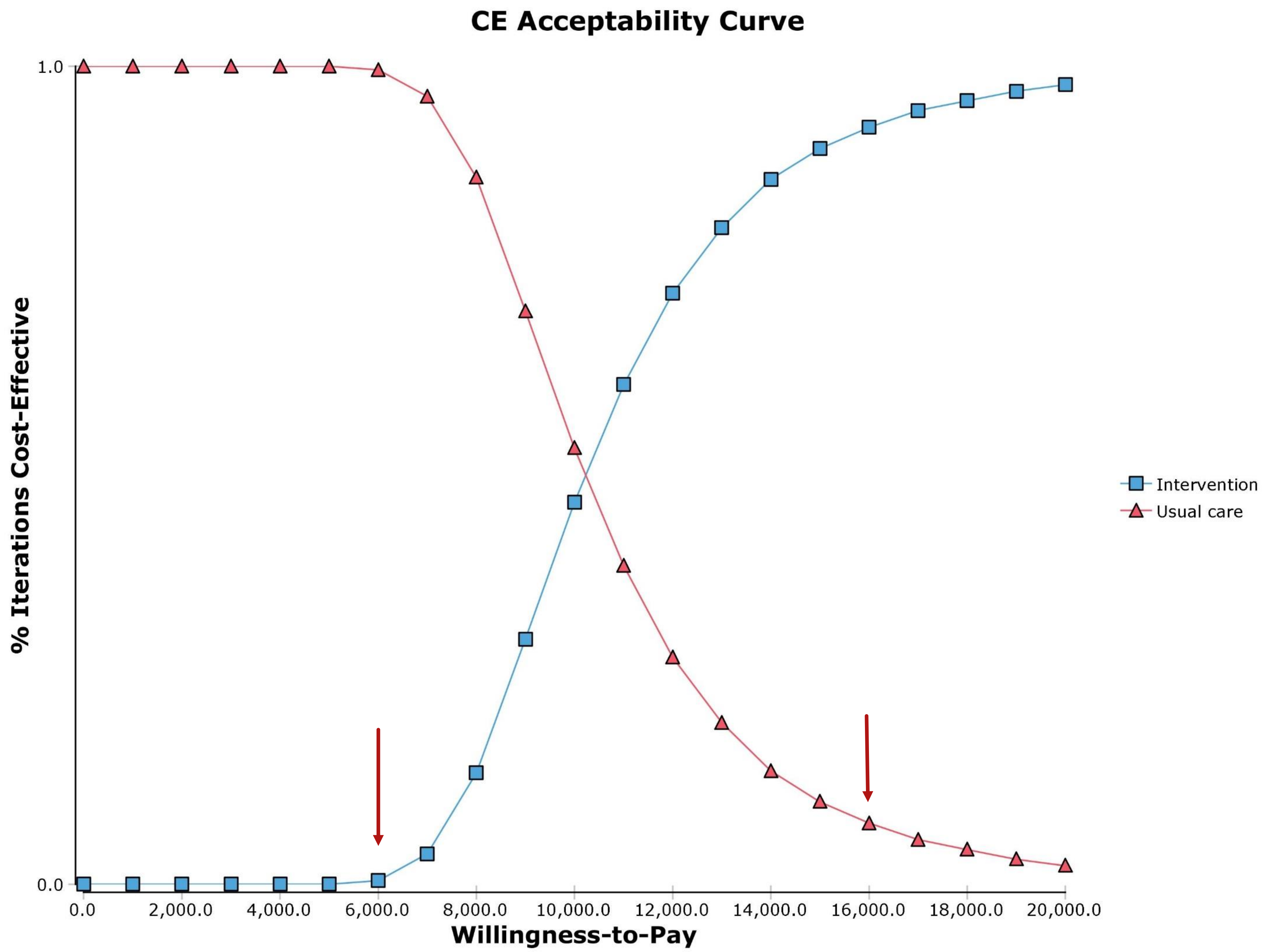
RHD, some with surgery

Valve surgery

Surgical revision

Death


Incremental Cost-Effectiveness, Intervention v. Usual care
Incremental Cost
Incremental Effectiveness
(QALYs)
ICER=$4000/0.25 = $16,000 per QALY
ICER = slope of line = $3800/0.62 = $6000 per QALY
WTP = 10000.0
5,400
5,200
5,000
4,800
4,600
4,400
4,200
4,000
3,800
3,600
3,400
3,200
3,000
2,800
2,600
2,400
2,200
2,000
1,800
1,600
1,400
1,200
1,000
800
600
400
200
0
0.00
0.05
0.10
0.15
0.20
0.25
0.30
0.35
0.40
0.45
0.50
0.55
0.60
0.65
0.70
0.75
0.80


CE Acceptability Curve
1.0
0.0
% Iterations Cost-Effective
0.0
2,000.0
4,000.0
6,000.0
8,000.0
10,000.0
12,000.0
14,000.0
16,000.0
18,000.0
20,000.0
Willingness-to-Pay
Intervention
Usual care

Analysis of Markov models

- Base case analysis uses the most probable value of each variable
  - Cost per clinical outcome averted (e.g. cost per premature death prevented)
  - Cost per life year gained
  - Cost per QALY gained
- Sensitivity analyses
  - One-way , e.g. vary the cost of the intervention *or* baseline risk
  - Two-way, e.g. vary the cost *and* the baseline risk
  - Multi-variate, vary all important variables (Tornado diagram)
  - Probabilistic, present in a Cost Effectiveness Acceptability Curve (CEAC)
    - Run the model many times, sampling from distributions of variables

Populating the Markov model

- Costs
  - MoH (admissions)
  - PHARMAC dispensing (medicines)
  - Suppliers (medicines, medical devices)
  - DHBs
- Incidence rates and efficacy
  - Pivotal RCTs and meta=analyses
- Adherence/uptake
  - Publications or naturalistic trials
- Quality of life
  - RCTs or specific QoL publications
- Mortality
  - Statistics NZ
- Many of the above
  - IDI

TreeAge Pro modelling software

- Has been available since about 1995
- Continually upgraded (for a price!)
- Visual, flexible, dynamic, powerful
- Can be linked to a spreadsheet for inputs and outputs
- Can be converted to a spreadsheet model
- Requires multiple inputs
- Used by Industry and PHARMAC
- Moderately good ‘Help’ file and U tube training
- Remote support via email or phone
- Moderately expensive

- *Disclaimer: I have no commercial interest in this or any other modelling software*

Supplementary Notes

- QALYs
- Discounting

Health related quality of life

- Patient reported outcomes (PROs):
  - Patient satisfaction surveys
  - Health related-quality of life (HRQoL or QoL)
    - Disease-specific questionnaire (e.g. St. Georges asthma QoL scale)
    - Generic questionnaire (e.g. Short Form 36)
    - Health state index: EQ-5D, HUI3, Visual analogue scale (VAS)
    - Range: full health = 1 to death =0

Quality of Life (QoL) – EuroQol EQ-5D

- **Mobility**
- 1. No problems walking around
- 2. Some problems walking around
- 3. Confined to bed
- **Self-Care**
- 1. No problems with self care
- 2. Some problems with self care
- 3. Unable to wash or dress
- **Usual activities**
- 1. No problems with performing usual activities
- 2. Some problems with performing usual activities
- 3. Unable to perform usual activities
- **Pain/Discomfort**
- 1. No pain or discomfort
- 2. Moderate pain or discomfort
- 3. Extreme pain or discomfort
- **Anxiety/Depression**
- 1. Not anxious or depressed
- 2. Moderately anxious or depressed
- 3. Extremely anxious or depressed

Ordinary health

Health State: 11111

Utility: 1.000

Severe Bipolar Disorder

Health State: 11212

Utility: 0.690

Moderate Arthritis

Health State: 2(1-2)221

Utility: 0.592

Defining a Quality Adjusted Life Year (QALY)

- The quality-adjusted life-year (**QALY**) is a generic measure of disease burden, including both the quality and the quantity of life lived. It is used in economic evaluation to assess the value for money of medical interventions.

- One **QALY** equates to one year in perfect health.
- 0.5 QALYs =
  - 6 mths in perfect health
  - 12 mths in 50% health (health state index 0 to 1)

  - https://en.wikipedia.org/wiki/Quality-adjusted_life_year

Discounting of future costs and benefits

- Expenditure in the future is valued lower than current expenditure
- Distant health benefits are valued less highly than immediate benefits
- *Future costs* should always be reduced= 'discounted to present value'
  - And the rate justified
- *Future health outcomes* may also be discounted
  - Debated by economists, who often do it both ways
- Discount rates are country-specific
  - US: 3% pa, UK 6%, NZ 3.5% (PHARMAC)
- Often use 5% pa and vary in a sensitivity analysis