theta

Toronto Health Economics and
Technology Assessment Collaborative

# Economic evaluations using real world data

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# Today's confusion

**Health Economics…. A New Toxicity?**


*"The drug itself has no side effects - but the number of health economists needed to prove its value may cause dizziness and nausea"*

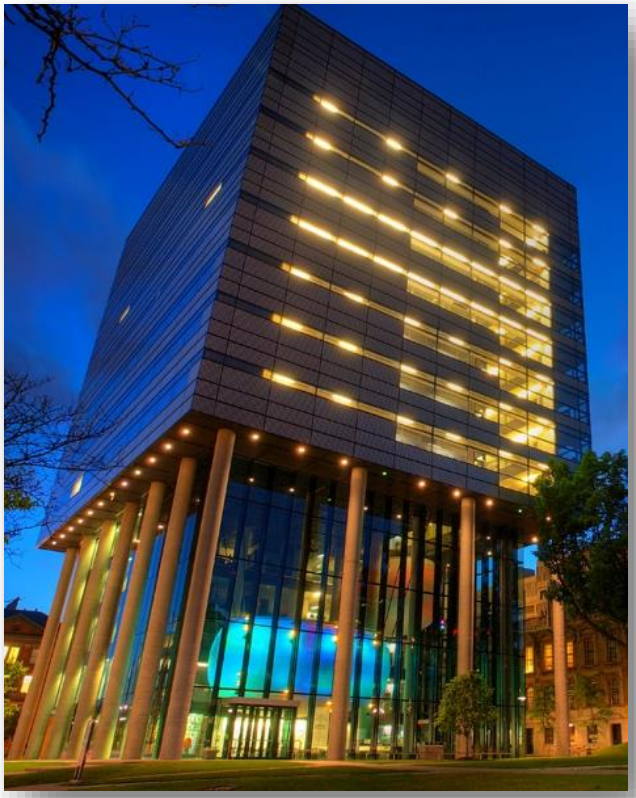
# Acknowledgments


- Dr Murray Krahn and THETA staff /collaborators

- SAS Group
  - Ruth Croxford
  - Matt Malczewski

No conflict of Interests to declare (I think)


# THETA Collaborative



Multi-disciplinary research collaborative supporting evidence-based policy decision-making regarding new health technologies in Ontario & advancing the science of health technology assessment

- Established in 2007
- Funded by the HQO (2007-2017)
- Received Canada Foundation for Innovation (CFI) award for future growth (2014-2017)
- Projects and collaborations with MaRS EXCITE, CIHR, pCODR , CADTH…..

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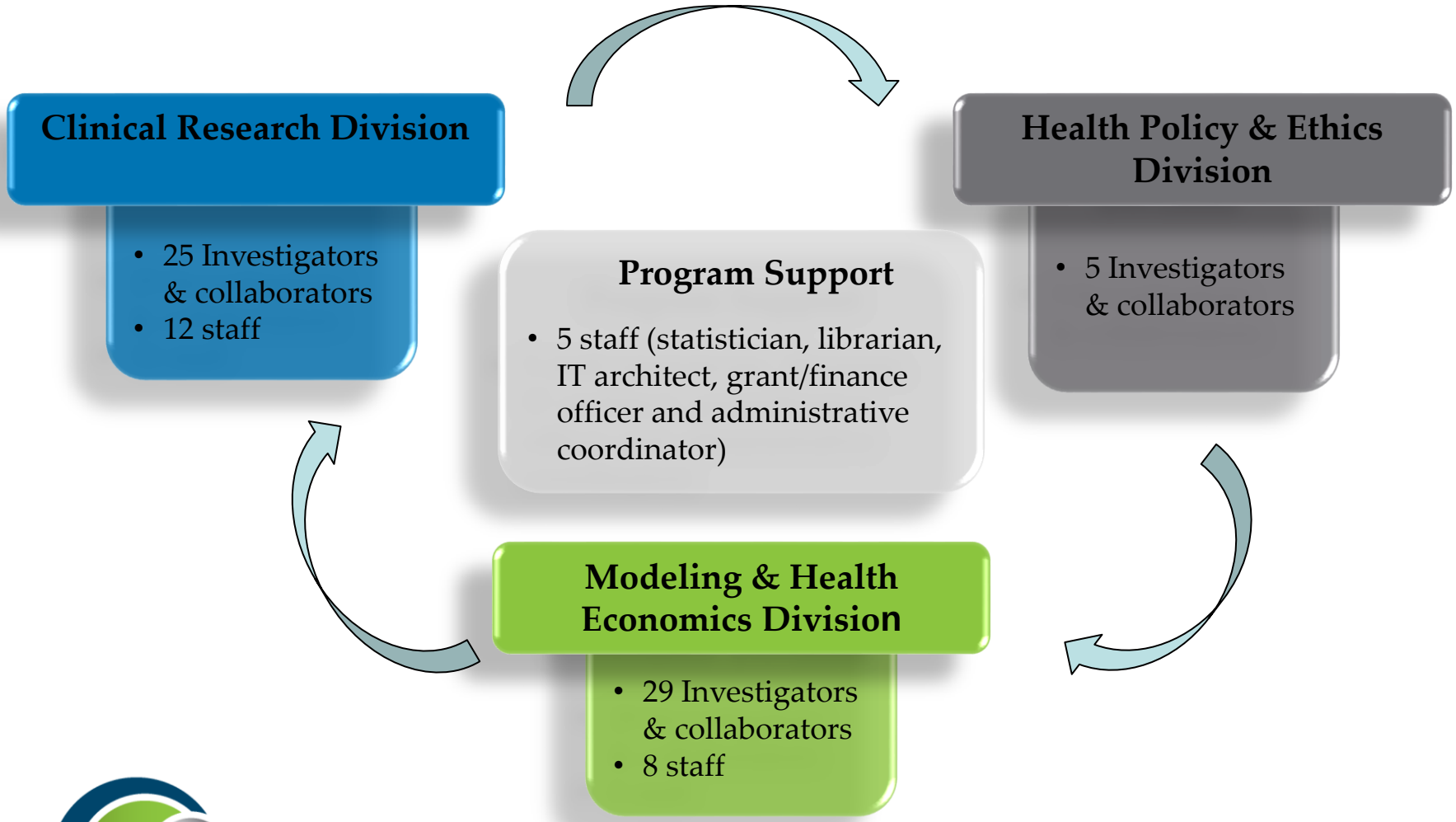
# THETA Composition & Function

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# THETA Areas of Expertise

## 1. Evaluation of Complex Interventions

- Community-based research (e.g., field evaluations, clinical trials)
- Mixed methods (combined quantitative and qualitative)

## 2. Economic Evaluations

- Population-based health policy models
- Trial based & model-based economic evaluations
- Comprehensive evidence synthesis methods
- Other: Early HTA, budget impact analysis, health utility elicitation

## 3. Ethics & Health Policy

- Incorporate ethics and social values in HTA
- Need assessment for user communities for HTA (industry, government) within and across jurisdictions and industry sectors

# Evaluating Health Technologies

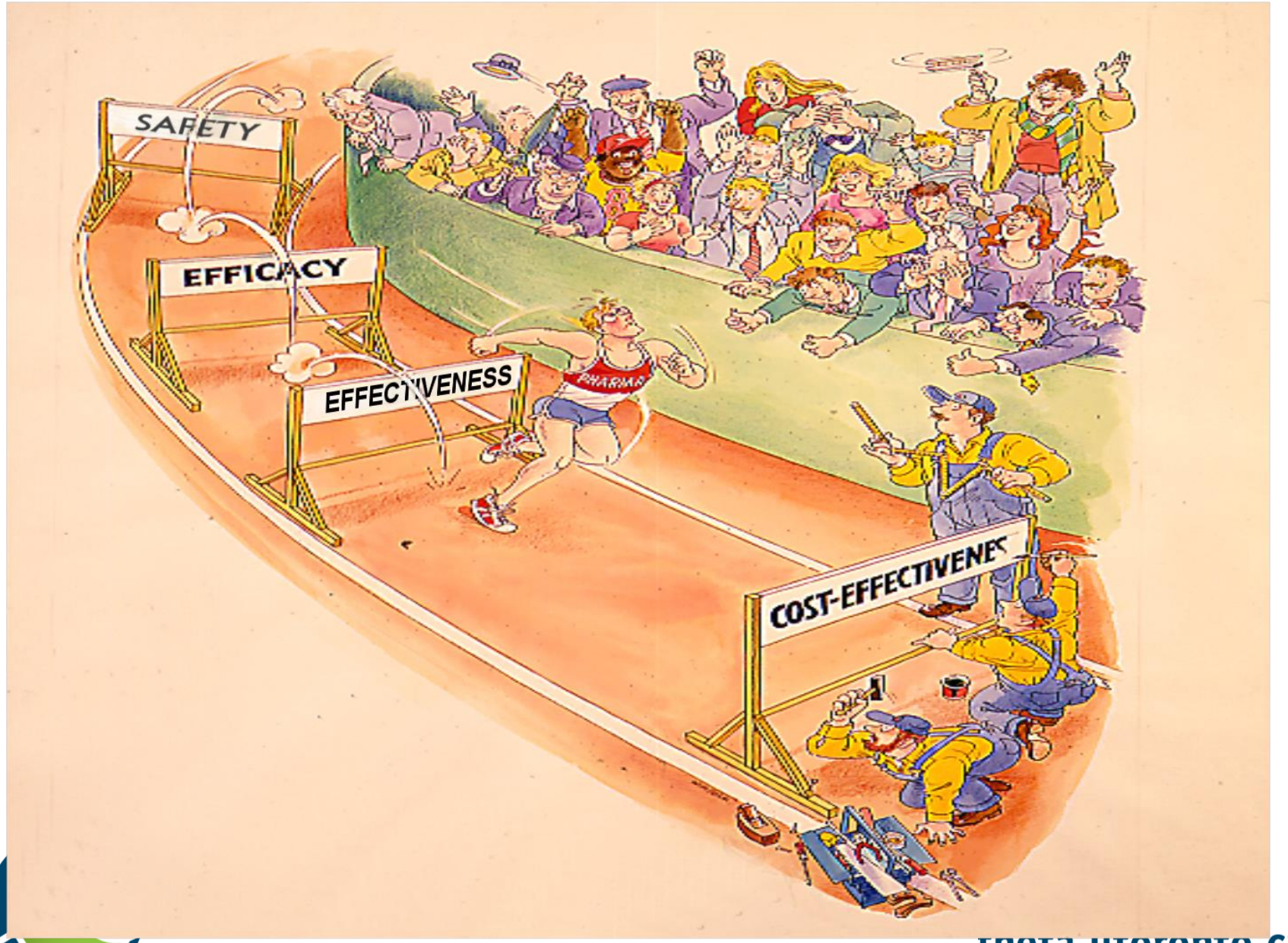
**Safety:** Does it do harm?

**Efficacy:** Can it work under ideal circumstances?

**Effectiveness:** Does it work under real-world circumstances?

**Efficiency:** Is it worth doing? What is the "value for money"?

**Access:** Is it reaching those who need it?


SAFETY
EFFICACY
EFFECTIVENESS
PHARMA
COST-EFFECTIVENES

# HTA and the Efficiency Question

Why is this question important?

- High price of new health technologies
- Number of potential users (e.g., antilipidemics) could mean high aggregate cost even for moderately priced drugs

# Decisions, Decisions

Is it worthwhile to pay for a new drug to treat Multiple Sclerosis (MS) ?

- Patients with MS will relapse about once every 2 years.
- Tx effect: decrease the frequency of relapses by one-third
- $15,000 per patient per year, injected twice a week
- 50% of patients experience debilitating flu-like symptoms that may lasting several months or more.

# Decisions, Decisions

Is it worthwhile for a provincial Ministry of Health to reimburse pharmacists at a rate of $300 per patient for a disease management program in congestive heart failure?

Is it worthwhile to pay $56,000 per treatment course for a 2nd line cancer chemotherapy drug that delays tumour growth but is not known to extend lives?

# Economic Foundations of the Evaluation of Efficiency

**Fundamental Problem:** Scarcity of resources

**Economics:** The study of the allocation of limited (scarce) resources among alternative uses to satisfy unlimited need

**Efficiency:** Achieving the maximal health benefit for a fixed amount of resources (or using the minimal amount of resources to achieve a specified health objective)

# Overarching concept: Opportunity cost

# Opportunity cost

- the health benefits that could have been achieved had the money been spent on the next best alternative intervention or healthcare programme
- A broader concept of cost, extending beyond the costs related to health service alone
  - Burden falling on patients (travelling costs, parking fees, time lost from work)
  - Burden falling on caregivers

# Economic Evaluation

The comparative analysis of alternative courses of action in terms of their costs and consequences

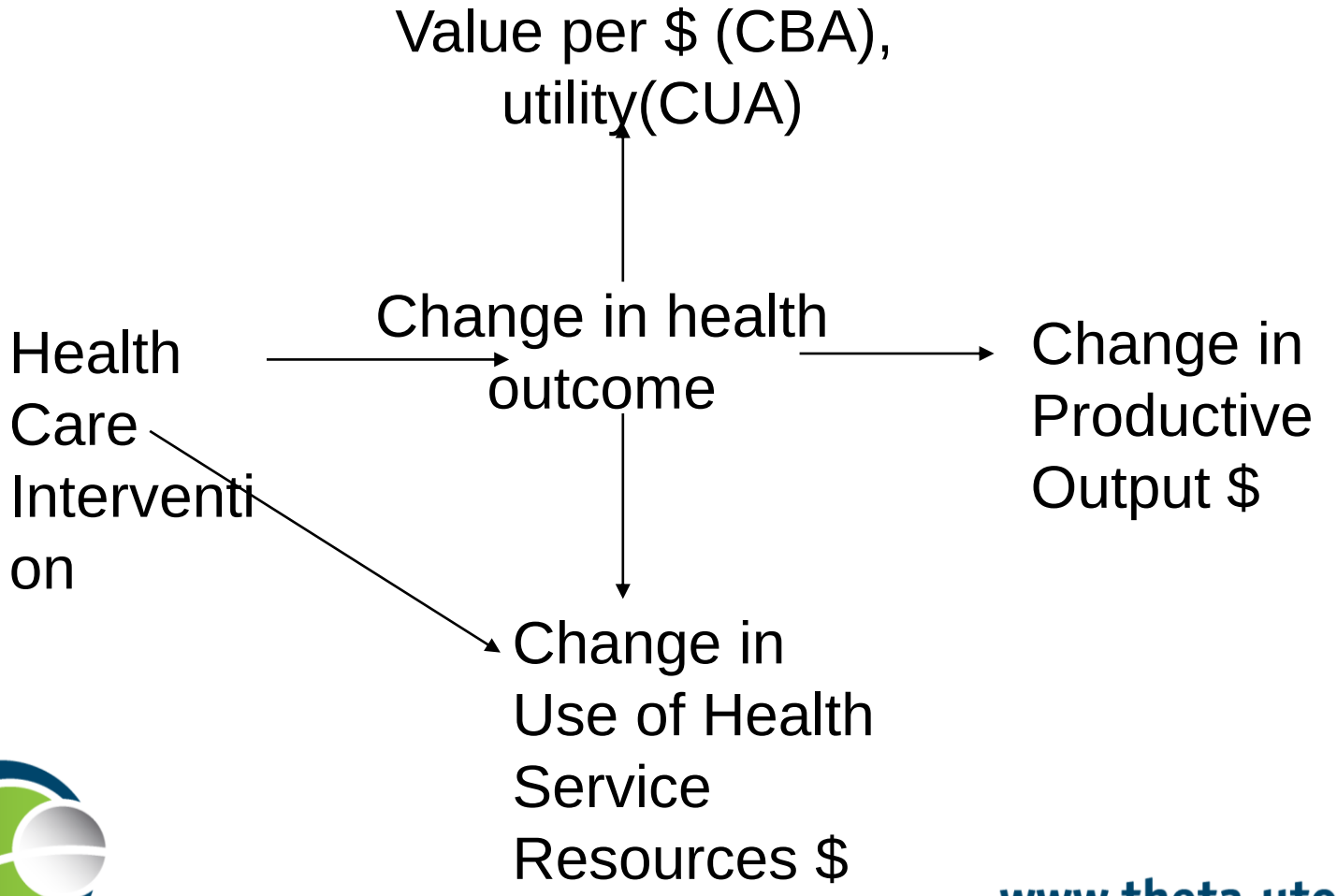
The systematic framework that underlies EE helps to bring transparency and objectivity to policy making

# Types of Economic Evaluation

- Cost Effectiveness Analysis (CEA)
- Cost Utility Analysis (CUA)
- Cost Benefit Analysis (CBA)
  - Cost Minimization (CMA)

*Differentiated by whether and how <u>health</u> consequences are valued.*

# Valuation of Health Consequences



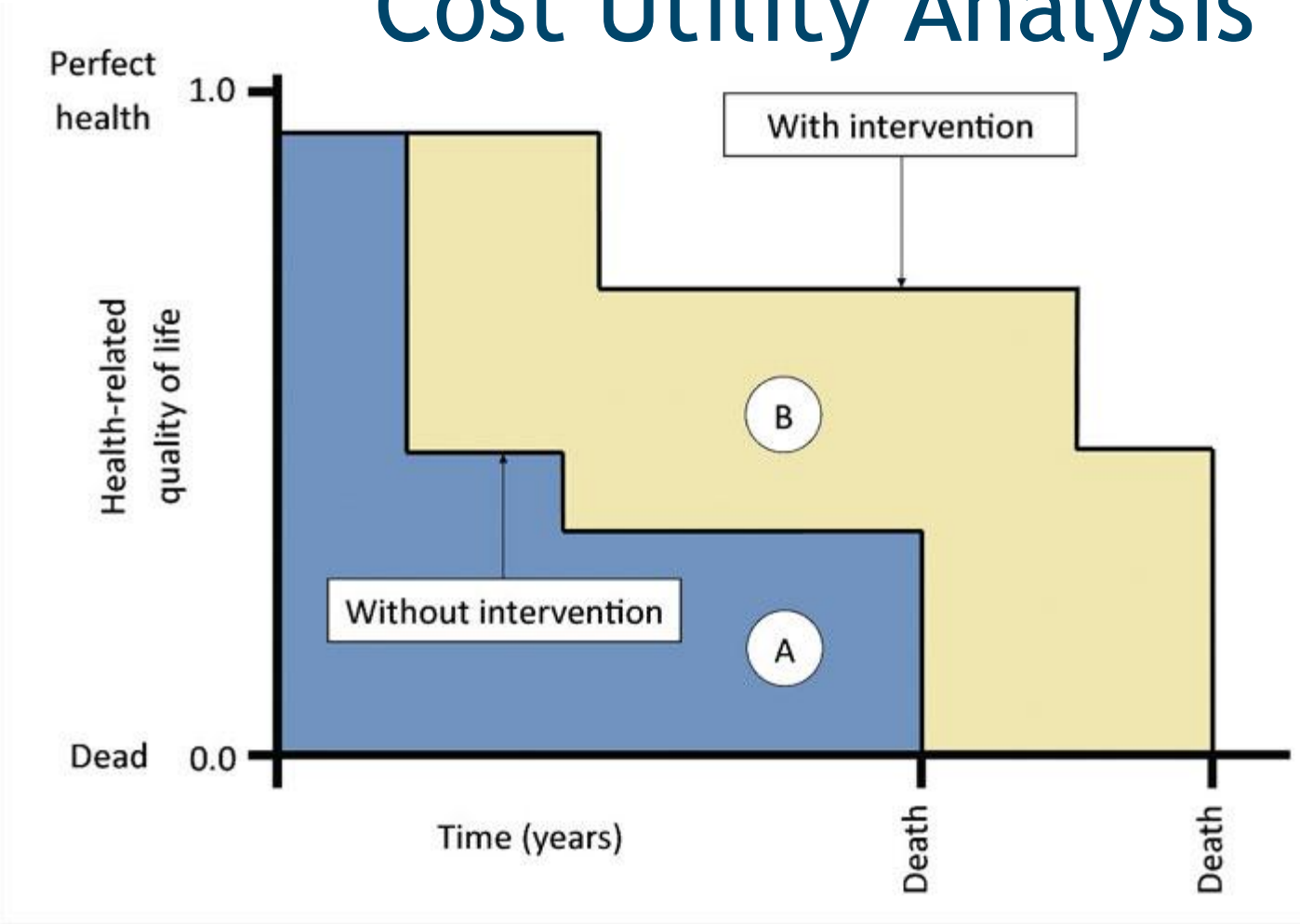
# Cost-Effectiveness Analysis

- Health consequence measured in natural units of health effect (e.g., life saved, life-year gained, case cured, disability day avoided)
- Costs comprise the total direct/indirect, medical/non-medical costs incurred over the study time horizon (depending on the perspective)
- Decision index is a cost-effectiveness ratio, e.g., cost per life year gained

# Cost-Utility Analysis

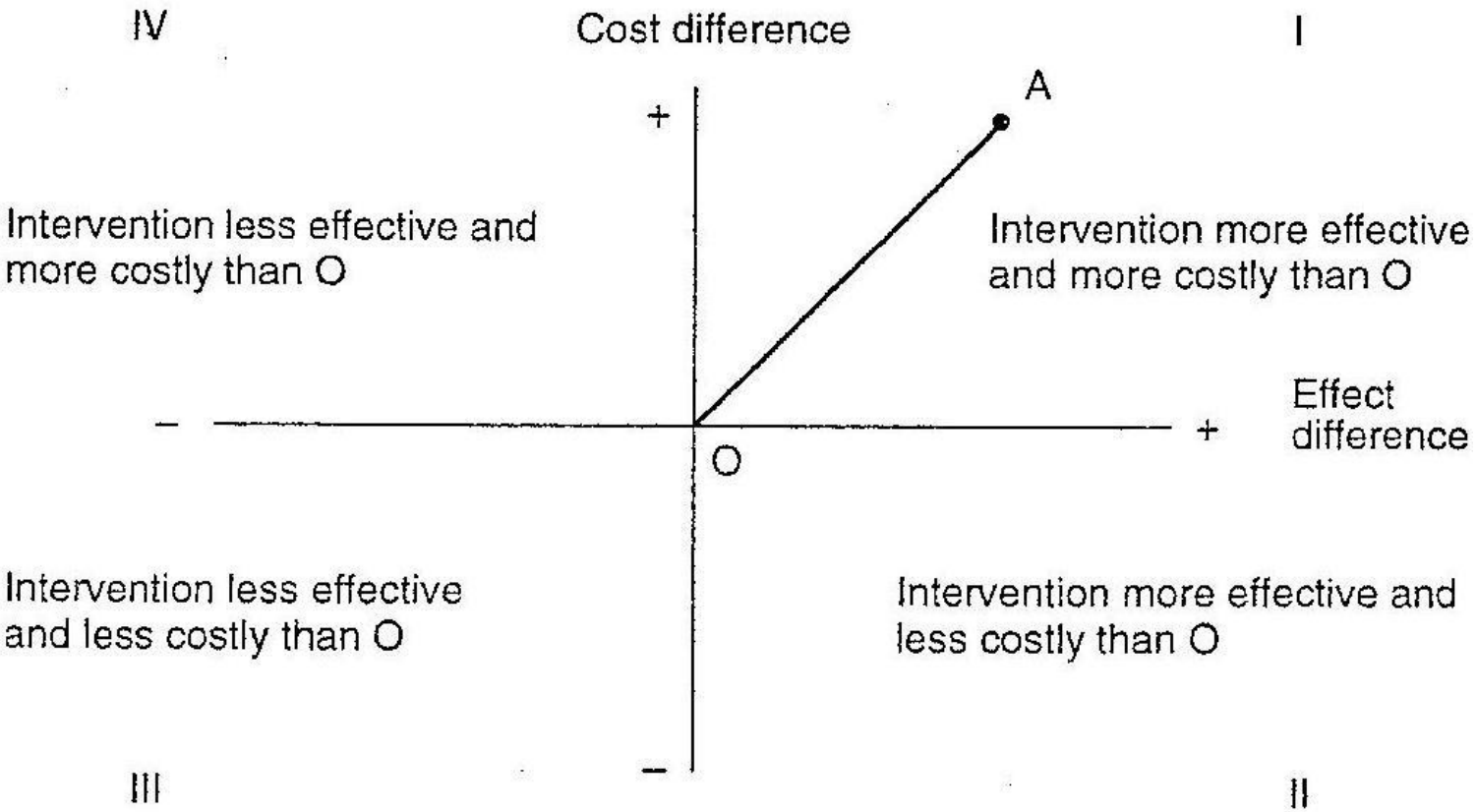
- A variation of CEA in which ALL health outcomes are valued using a metric called a quality-adjusted life year (QALY)
- Each year of life is weighted by its quality of life using a "utility" weight [scale of 0 (dead) to 1 (excellent health)] and these weighted life years are summed over all years of life.
- Decision index is a cost-utility ratio, cost per QALY

# Cost Utility Analysis




A: Number of QALYs with the control group
A+B: Number of QALYs with the intervention group
B: Number of QALYs gained with the intervention

# CE Quadrants

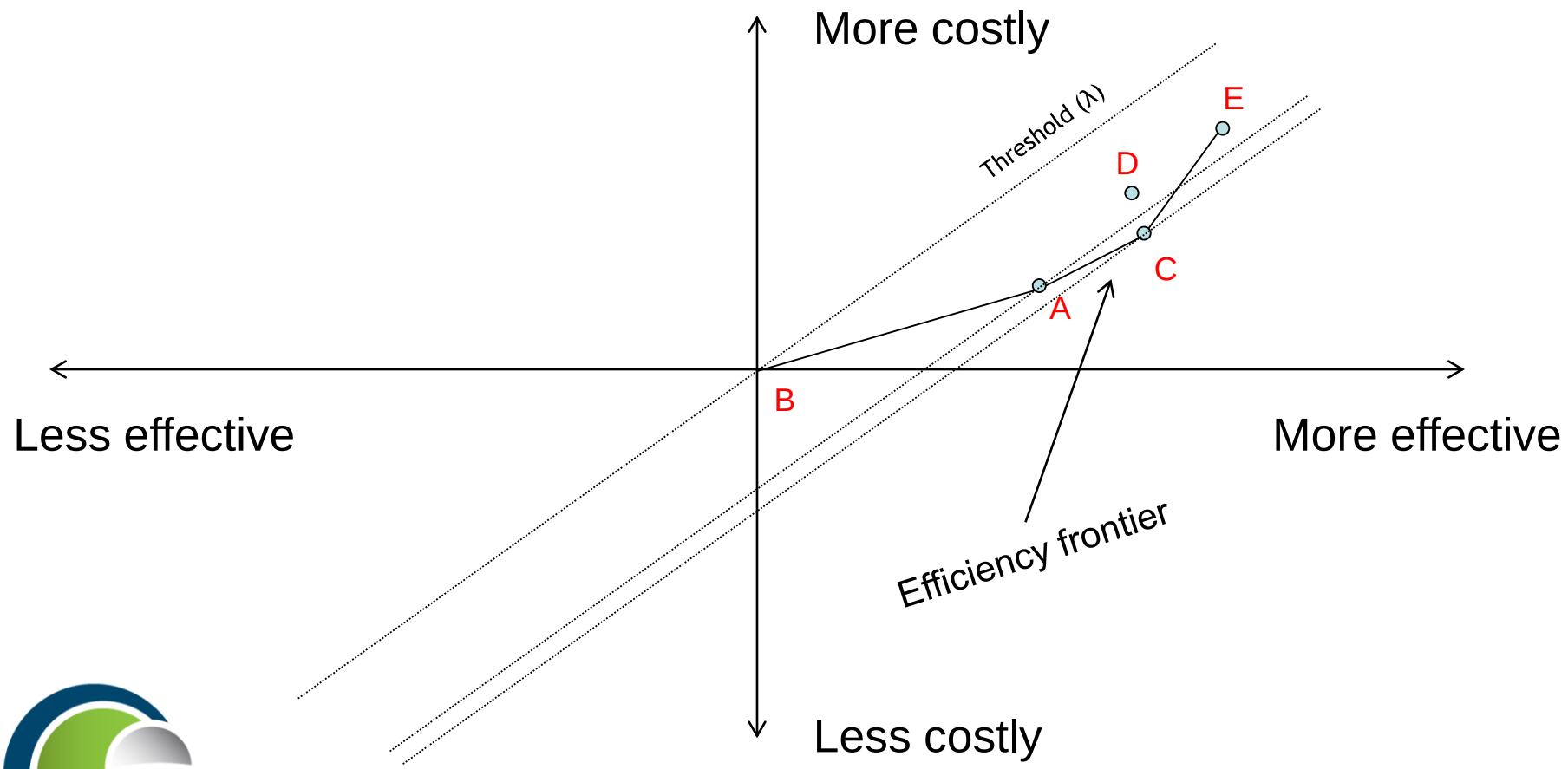



d from Black (1990)

# Calculating incremental CE ratios (ICERs)

- Rank order alternatives treatment options from lowest to highest total cost
- Calculate <u>incremental</u> ratio between least costly and next more costly alternative
  - Incremental $costs_{A-B}$/incremental health $effect_{A-B}$
- If there are more than 2 alternatives, proceed to next more costly alternative (C) and calculate an incremental ratio between B and C, and so on.

# The CE Plane


More costly
Threshold (λ)
E
D
C
A
B
Less effective
More effective
Efficiency frontier
Less costly

# How to use ICERs to decide on value for money?

- Ideally: A threshold that defines "value for money".

Below the threshold → Approve, Above the threshold →Reject

- Thresholds proposed so far are based on:
  - Arbitrary or almost arbitrary values
  - Society's willingness to pay for a unit of health
  - the notion of opportunity cost
  - the country's GDP

# Thresholds based on opportunity costs- the empirical threshold

- The opportunity cost of a new intervention in the health care system as it functions currently
- The UK first to attempt an empirical estimation of the threshold using administrative data (Claxton, 2013)
- Estimate marginal cost per QALY using changes on budget sizes and QALYs generated across Primary Care Trusts over time.
- £18,317/QALY, but likely an overestimation

# What is RWE?

- Extensions of RCT\observation studies
  - long term follow up after breaking randomization/non-randomized studies.
- Patient Registries
  - Disease-specific patient registries (OCR, OSN, ORN etc)
- Administrative data
  - Health care claims data, diagnosis\lab data, drug utilization etc
- Health surveys
  - QoL questionnaires, Surveys alongside RCTs



1.RAND group. Health and Healthcare: Assessing the Real-World Data Policy Landscape in Europe .2014

# What is RWE?

- Electronic health records
  - (e.g. CMS databases, e-Health Ontario)
- Medical chart reviews
- Population health data
  - E.g. health-related information in a national Census
- Resource utilization data
  - Healthcare Costs, inpatient/outpatient resource use
- Sales/claims data
  - Claims data from insurance companies etc.

# How can RWE help with efficiency questions?

- Real-world long term evidence of costs and effects (mortality, hospitalization, resource utilization)
- Lifecycle evaluation of technology efficiency using patient level data/large policy models
- Validation of economic evaluation by comparing their output with real-world data
- A platform to estimate economic burden of disease

# Example: Admin data in EE

- EEs based on patient-level Admin data
  - Retrospectively done through linking admin data with registries
  - Linked admin and RCT data
- Admin data as input for decision models
  - Discrete state transition/ agent-based models.
  - Continuous time multi-state models
- Help estimating an empirical threshold in EE

# Example: Admin data in EE

- Allow policy makers to iteratively evaluate the efficiency of technologies over their lifecycle using policy models
- Validate economic models by comparing their output with real-world data (e.g. disease prevalence, resource use intensity).
- Provide the platform to estimate economic burden of disease

# 1. Patient-level EE

- <u>EE alongside RCTs (piggyback EE)</u>
  - +Patient-level (adjust for heterogeneity)
  - +Strong internal validity (good quality control)
  - +Tailored approach in data collection
  - + Relatively less expensive collection of cost and resource utilization data

  - Choice of comparison therapy
  - Efficacy instead of Effectiveness
  - Ignoring available literature evidence
  - Short term follow up/surrogate outcomes.
  - Statistical power.

# 1. Patient-level EE

- EE using patient-level admin data
  - + Real-world evidence of effectiveness
  - + Long term follow up on hard outcomes (mortality, hospitalization, resource utilization)
  - + More complete follow-up of resource utilization
  - + Real-world comparators
  - + Large numbers

  - - Lack of randomization (sol: matching, propensity/regression models)
  - - Absence of important for EE outcomes (e.g. QoL) limited to the already collected data
  - - More complex disease pathways (e.g treatment changes)
  - - Statistical challenges (Censoring, Skewness, Missing data)

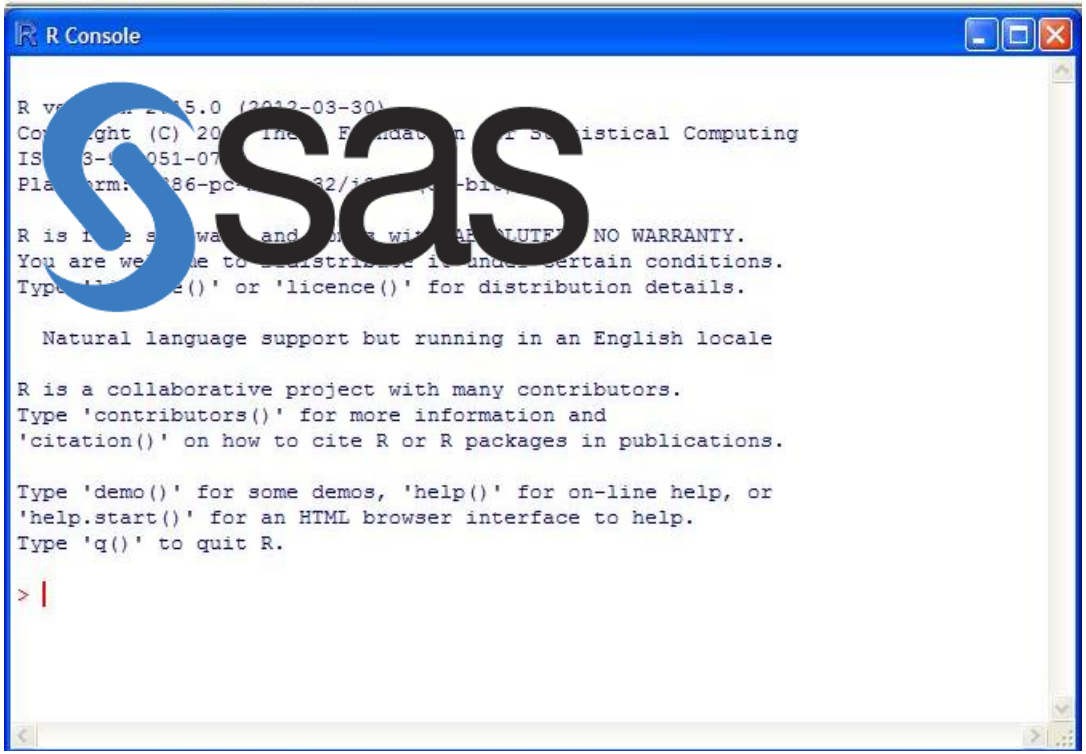
# 1. Patient level EE

- Statistical models that deal with the limitations of patient-level EE:
  - Inverse-probability weighting method (Lin,2003; Willan,2006)
  - Two part generalized linear models (Basu, 2010)
  - Linear Mixed Models (Liu, 2008)
  - Multivariate seemingly unrelated models (Gomes,2012)

# 1.Patient level EE

Very convenient to implement in SAS

- Can also easily be done in R (…or the other way round)




Code available in R on demand…

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# Example: Cost-effectiveness of Stroke Units in Ontario

- Stroke Unit (SU) post-stroke care has been shown to improve health outcomes and increase healthcare costs.
- Its real-world cost-effectiveness in Ontario is unknown
- 1-,2-,5-year CE of SUs vs general wards (GW) in providing post-stroke care using administrative and registry data.



(Pechlivanoglou et al OSN Report 2015). Please do not cite!

# CE of Stroke Units in Ontario (methods)

- Administrative data (e.g NACRS, CIHI DAD, ODB), data from four Ontario Stroke Audits (OSA) linked at ICES and published literature
- SU matched to GW patients using hard matching and propensity score matching.
- Inverse probability weighting to adjust for censoring. QoL linked to mRS severity at discharge.
- Outcomes: Total cost, Life expectancy, QALYs, ΔCost/ΔQALY

# CE of Stroke Units in Ontario (Results)

- 3,743 patients receiving SU care, 1,989 (53%) able to be matched.

Significant gain in

- life expectancy (SU:3.50 LYs vs GW:3.25LYs, LYG: 0.249 [0.120 0.379])
- QALYs (1.943vs 1.814 QALYs , QALYs gained: 0.129 [0.033 - 0.224])

- Non significant differences in costs ($103,508 vs $102,835. Diff = $673 [-$7,155, $8,500]).

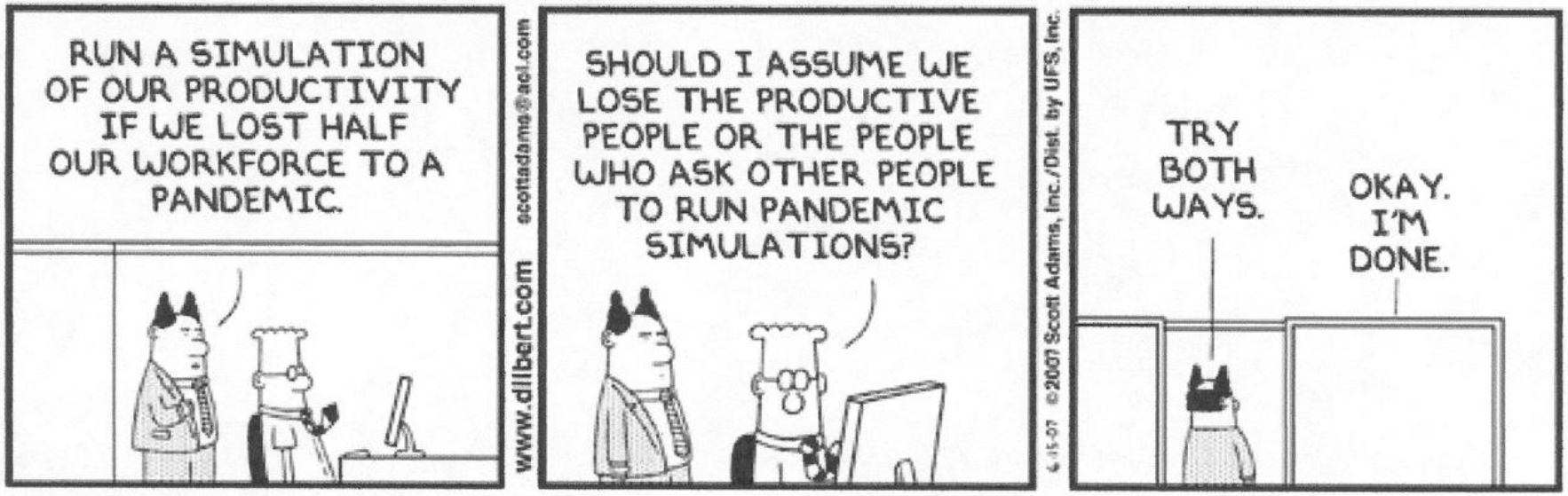
# CE of Stroke Units in Ontario (Results)

- ICER: $5217/QALY
- PSA: 43% chance that SUs are simultaneously reducing costs and increasing QALYs

BUT

"SUs considerably less cost effective when using the 2010 cohort compared to the 2004/2008 cohorts."

# Decision models in EE



# Decision models in EE

Study time in EE:

as long as there is a treatment effect - usually significantly longer than RCT data

EE should reflect reality (e.g. discontinuation)

Such RCT/admin data are rarely available

Solution: Mathematical modelling of natural history of the disease

- State transition models (e.g. Markov models)
- Agent-based/Discrete event simulation models

# Decision models in EE

State transition models:

- Based on states an individual can occupy over lifetime (e.g. healthy, sick, stable, progressed, dead)
- Each state associated with a cost and a health outcome ($’s, LYs or QALYs)
- Transition between states with some probability
- Transitions occur in cycles (months, years etc)
- Markov assumption: no “memory” within states (the duration of stay in state)

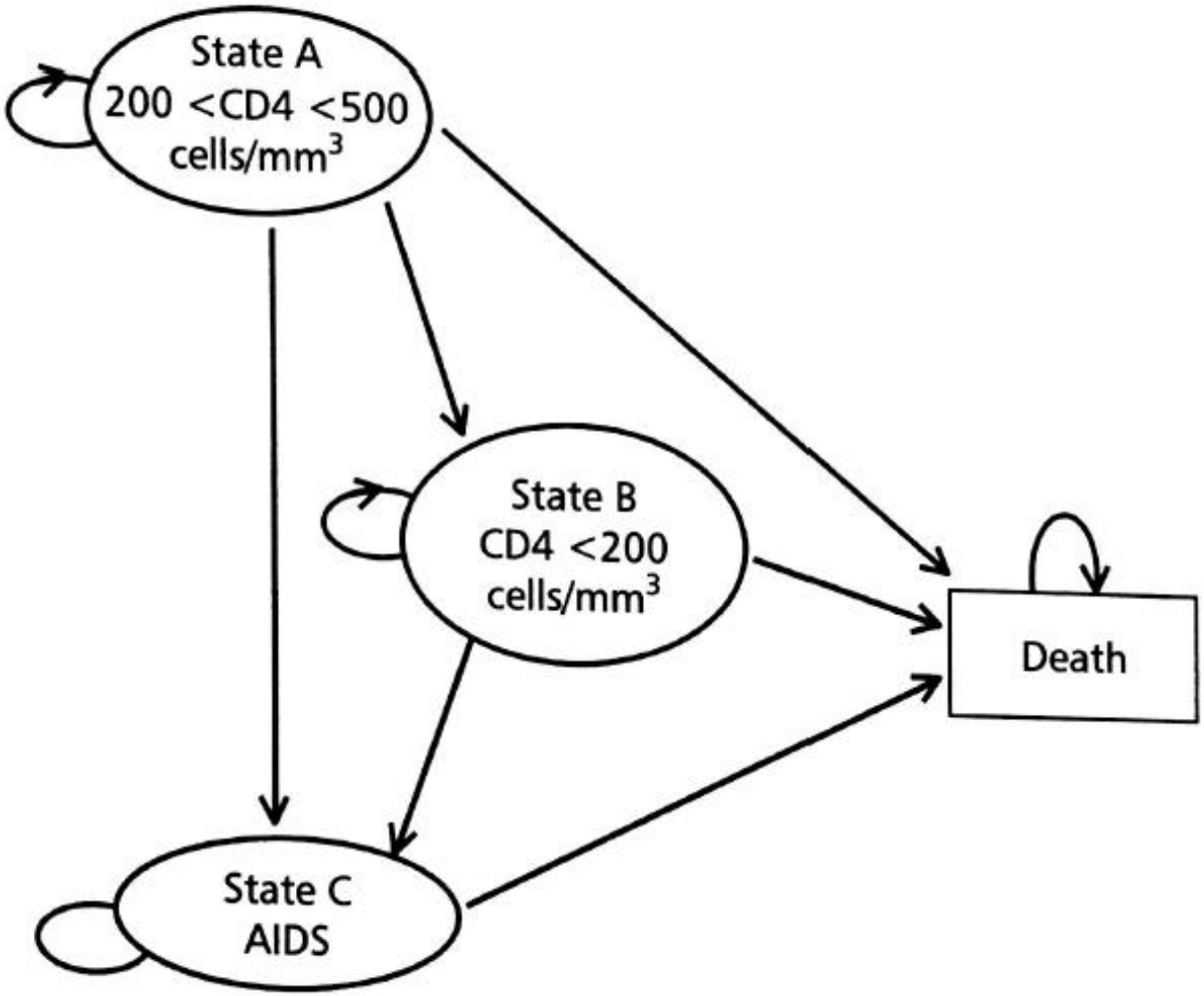
# Decision Models and SAS

- Here a switch to R\Matlab\Excel or specialized software is needed.

- Workshops\Courses in R \TreeAge provided by THETA annually

# Markov Model

- Fig



# Admin data and decision modelling

Admin data can provide:

- the vehicle of input parameter estimation (e.g. cost of care, long-term survival, probability of (re) hospitalization)
- Risk prediction equations that allow long-term projection of RCT results to hard enpoints
- The transition probabilities upon which the decision model will be based

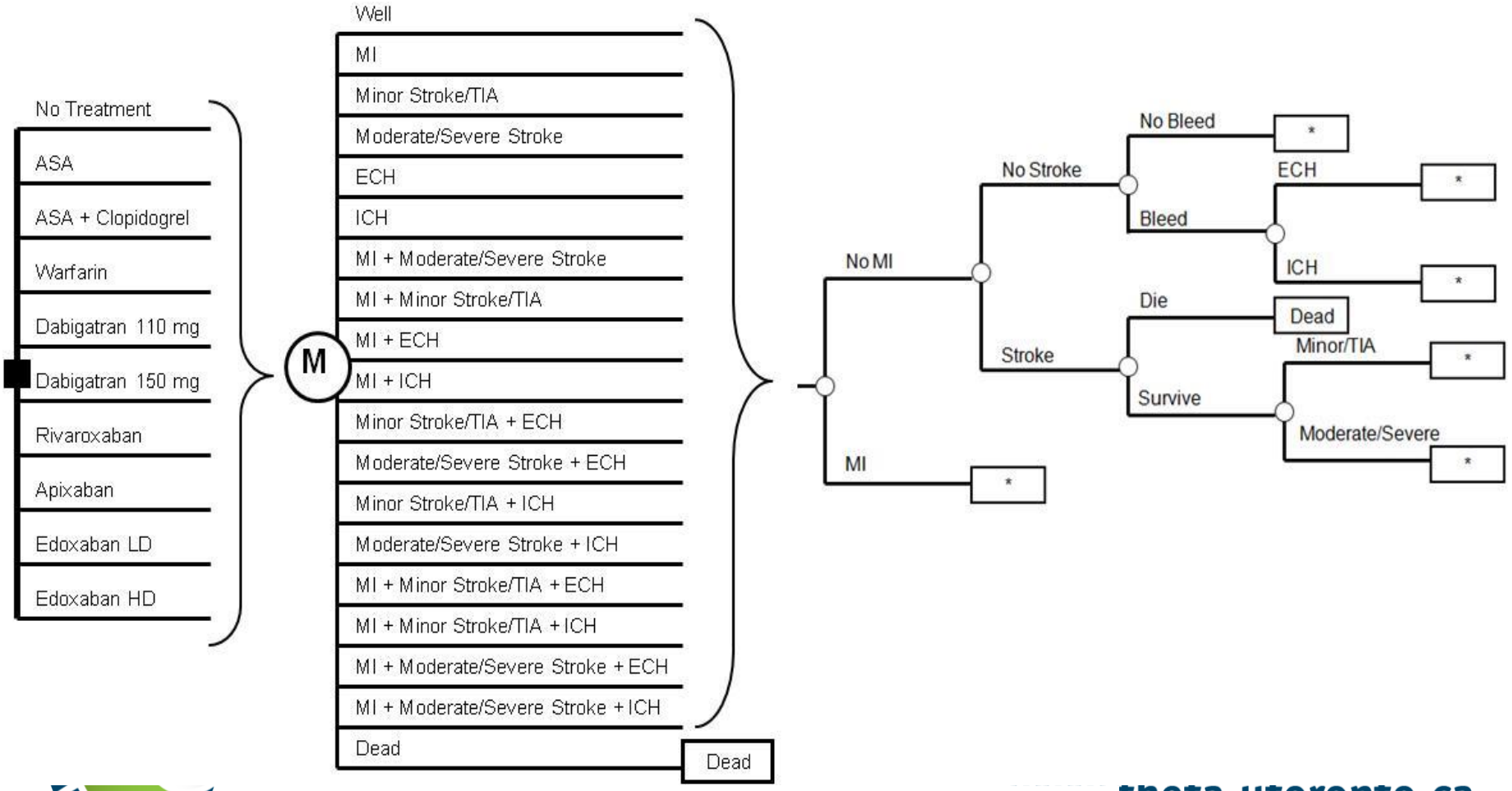
# Input parameters based on admin data

- Estimation of cost per state per cycle

  E.g. CE of Atrial Fibrillation prophylaxis (Tawfik et al 2015)

  - direct health care costs of AF using ICES:
    - identify all resources utilized by patients in AF cohort
    - Phase-based (i.e. initial diagnosis, continuing care, and final) and event-based costing (e.g. minor/moderate/severe stroke, ICH, bleeding)
    - Average over phases and events per cycle

# Input parameters based on admin data

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Tawfik et al Cost-effectiveness of stroke prevention treatments in atrial fibrillation patients: A new generation of drugs, 2015

# Risk prediction models using admin data

- Decision models often populated by regression-based prediction models when:
  - RCTs provide surrogate endpoints
  - RCTs or prospective observational studies end long before average life expectancy of the population(e.g Minimum residual disease – MRD- testing)

# Risk prediction models using admin data

- Admin data can help constructing risk predictions models for predictions

  Examples:

  - Framingham risk model most often used model in EEs of CVD interventions (SBP -> CHD, Stroke, Death)
  - Models to predict survival from pathologic complete response in breast cancer
  - Models for ESRD progression (based on albuminuria GFR etc)

# Estimation of transitions using admin data

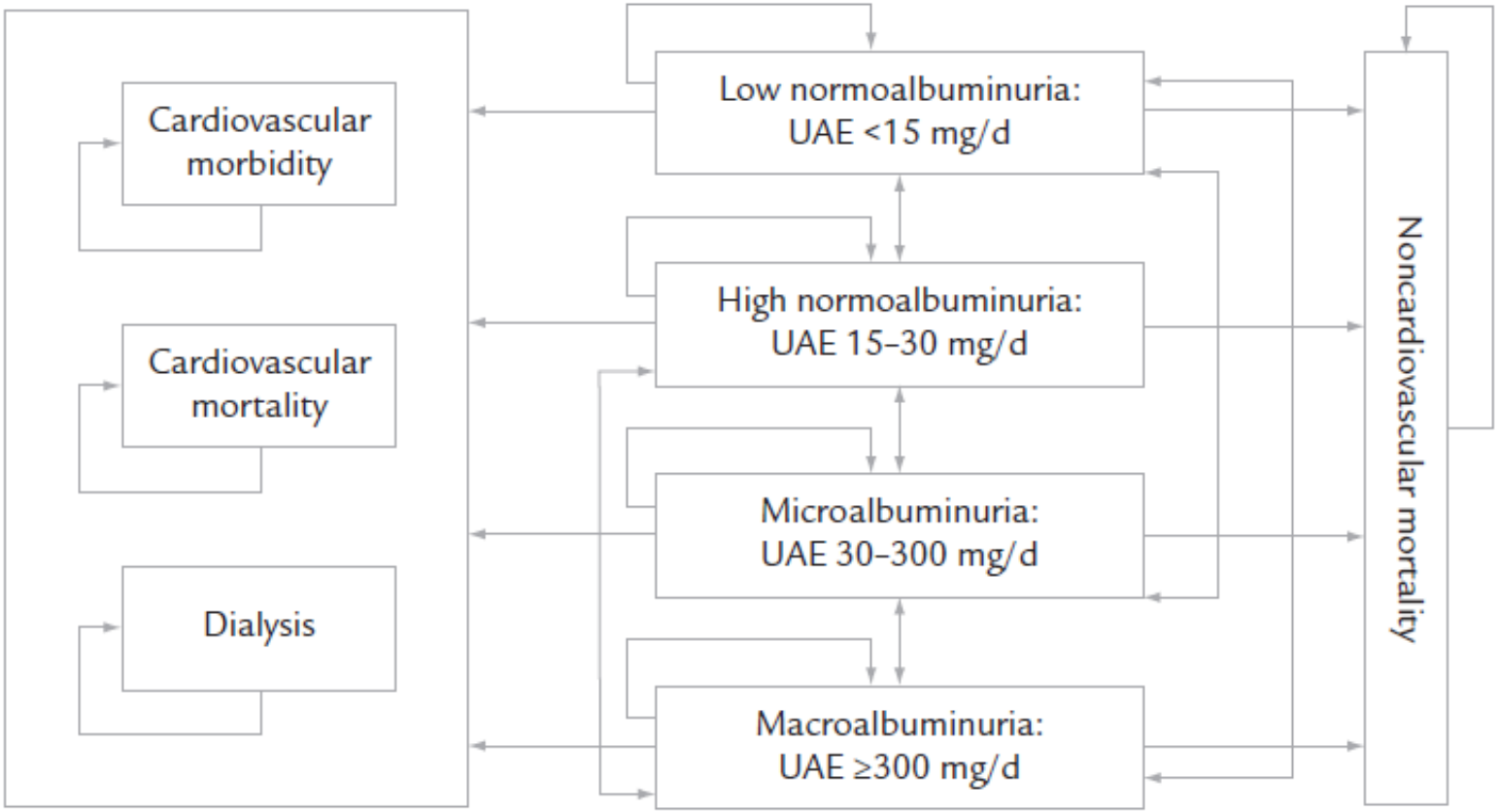
- Multi-state Markov (MSM) model: a process in which an individual moves through a series of states in continuous time
- MSM can deal with observational data were:
  - Patients seen at intermittent follow-up visits
  - exact time of disease onset is unknown
  - Censoring and death interrupt disease pathway
  - Transition between states is affected by (time-dependent) covariates
  - Possible misclassification
  - Individuals occupy multiple states over time

# CEA of Screening for Albuminuria to Prevent CVD and ESRD in the Netherlands

- Data from the observational Prevention of Renal and Vascular End Stage Disease (PREVEND) study

- Disease progression/mortality: annual transition probabilities, representing the disease progression or mortality estimated using the PREVEND data

# CEA of Screening for Albuminuria to Prevent CVD and ESRD in the Netherlands




# CEA of Screening for Albuminuria to Prevent CVD and ESRD in the Netherlands

- Transition probabilities estimated based on patient-level, time-to-event data
  - First a transition intensity matrix was calculated
  - Transitions between states were assumed to occur at any time (discrete events in continuous time) within the observed time intervals
  - subjects were allowed to progress, regress or remain in the state at any time
  - Misclassification was allowed

# Conclusion

- Current Shift to RWE – for a good reason!
  - Understanding effectiveness and cost-effectiveness in real-world clinic practice
  - >2 arm comparisons
  - When RCT is difficult/unethical
  - Long term effects etc
  - Evaluation over lifecycle
  - Invaluable input source for EE and economic burden studies

# Conclusion

- Administrative data is an invaluable source for EE
- Health economists and data analysts together are slowly becoming aware of it
- THETA and ICES have so far demonstrated that this marriage is feasible
- EE using admin data is an evolving field
- Methods are new, with few applications in the literature, no standardized code functions etc.

# Thank you!!

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