Using RWE for Research-Oriented Market Access for High-Cost Therapies

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Outline

1. Uncertainty in the Regulatory/Reimbursement Landscape
2. Value of Information (VOI)
3. Reducing Uncertainty: **R**esearch **O**riented **M**arket **A**ccess
   - Principles
   - Overview
   - Methods and Outputs
4. VOI in Decision Making
5. Coding VOI in R

Learning Objectives

1. How uncertainty changes regulatory/reimbursement decisions
2. What is ROMA and the life-cycle approach to HTA
3. How we can measure and price uncertainty with VOI
4. That VOI is easier to implement than you may think

Housekeeping

Slides & Code will be available on IHE's GitHub 

IHE survey to help support our development of this workshop

Uncertainty in the Regulatory/Reimbursement Landscape

Regulatory and Reimbursement Landscape

Conditional approvals are now a common part of the regulatory and reimbursement landscape

- Health Canada Notice of Compliance with Conditions (NOC/c)
- CADTH Time limited recommendations
- NICE – managed access agreements in cancer and rare diseases
- EMA – Conditional marketing authorization
- P/T Working Group on EDRDs consultation on a supplemental process
- CanReValue - the generation and use of Real World Evidence (RWE) for cancer drug funding decisions in Canada

Regulatory and Reimbursement Landscape

Payers must answer difficult questions before listing a product

- What is the value of the product?
  - Clinical and budget impact
  - Health impact
- How confident are we about the evidence and our decision?
  - Quality of the evidence base
  - Data coverage and availability across jurisdictions
- Can we increase confidence in our decisions?
  - Use existing RWD to improve knowledge base
  - Establishing new RWD collection if needed (eg establishment of registries)

Regulatory and Reimbursement Landscape

Drug programs face increasing budgetary pressures

- Increasing number of therapies
- Increasing proportion of the covered population who are clinically indicated for one or more products
- Increasing cost of therapies coming to market
- Absence of mechanisms for reassessment and delisting therapies

Robust evidence and cost-effectiveness analysis (CEA) can support decision making

- Available evidence often leaves decision makers ***highly uncertain***, and
- Additional, on-market, evidence is ***costly to generate***.

Research-**O**riented **M**arket **A**ccess (ROMA)

- Protocol to assess the value of generating real world evidence (RWE)
- Consistent with a '**life-cycle health technology assessment**' (LCHTA) framework

Regulatory and Reimbursement Landscape

ROMA builds on existing HTA methods for assessing value of new technologies

Grounded in principles of current HTA methods

- Evidence appraisal
- Cost-effectiveness analysis / value assessment

Developed as an explicit response to **increasing volume** of promising but **high cost** and **highly uncertain** technologies

These technologies provide specific challenges to conventional health care reimbursement decision making processes and health system budgets

Focus is on **addressing uncertainty** and **minimizing risk** of making the wrong decisions

Sources of Uncertainty in HTA

Type of Uncertainty	Examples
Parameter Uncertainty	What is the effectiveness of the treatment? What resources do patients use?
Assumption Uncertainty	What is the relationship between progression free survival and overall survival?
Structural Uncertainty	What is the clinical treatment pathway? What are the relationships between parameters?
Methodological Uncertainty	What discount rate should be used? What is the most appropriate method for estimating survival curves?

The Importance of Uncertainty

Immature evidence base leads to higher uncertainty

- e.g. small n, single-arm trials, case control studies, cohort studies
- long follow-up times required may not be feasible
- Small patient populations make small-n trials more common

More uncertainty means more payer risk

- Uncertainty around product value means risky decisions
- Products may have high up-front or life-time costs

Adoption and diffusion of technology

- Whether a technology is good value depends on people both having access and being given treatment

The Importance of Uncertainty

Uncertainty has a value

- In a research context uncertainty can be valued to determine whether further research is a good use of scarce resources
- The value of the uncertainty can be used to identify an evidence based ***market access*** price
  - That is, the acceptable price when initially coming to market

On-market evidence may reduce uncertainty

- Post-market data collection can change degree of uncertainty
- If uncertainty in the evidence base ⬇ then decision uncertainty will likely ⬇
- Based on the collection of additional evidence:
  - a technology can be reappraised,
  - recommendations and listing decisions can be reconsidered, and
  - a long-term value based price identified

Reducing Uncertainty: Research Oriented Market Access

Principles

Overview

Methods and Outputs

ROMA and Uncertainty

Challenge	ROMA advantage
Immature Evidence Base	Opportunities for collection of additional data in a real-world context
High cost products	Can make estimates of value and then assess whether value proposition is met and whether decision risk is reduced
Technology diffusion/adoption	Consider the technology over the course of a longer time frame and assess whether diffusion/adoption is happening, and impact on value proposition

ROMA Principles

Feasibility & Go-No-Go

Value Predictions and Monitoring Design

Decision Rules and Value Based Procurement Contracting

ROMA Overview

HTA
- Clinical Review
- **Economic evaluation & value of information**
- **On-market evidence generation plan**

Decision
- Reimburse
- Reimburse with conditions
- **Reimburse with ROMA (ie evidence generation)**
- Do not reimburse

VBP
- Pharmacoeconomic assessment
- **Value Based Price informed by economic report**
- **Plans for review informed by On-market evidence generation plan.**

Pricing
- HTA recommendation
- **On-market evidence generation plan**

ROMA Overview

Cost-effectiveness	**Cost-effectiveness statistics** • Incremental cost-effective ratios • Net monetary benefit
Value of information	**Value of on-market evidence generation given size of population** • Can we generate post-approval evidence to inform reassessment? • Is the value of research greater than the cost? • Maximum amount efficient to pay to avoid risk of wrong decision?
On-market evidence generation plan	**Specify data collection and analysis plan** • What data to collect? • From which patients? • For how long? • How to analyze it?
Decision information	**Key information for decision making** • Cost-effectiveness statistics • Cost of additional research • Value of additional research

ROMA Methods & Process

Methodological protocol built on standard CEA and value of information (VOI) methods

- Leveraging administrative data assets for data collection, synthesis and re-analysis;
- Develop multiple research designs to allow alternative research-oriented market access agreements to be evaluated; and
- Facilitate RWE reanalysis for decision making, in three stages distinguished by continuation criteria.

ROMA Methods & Process

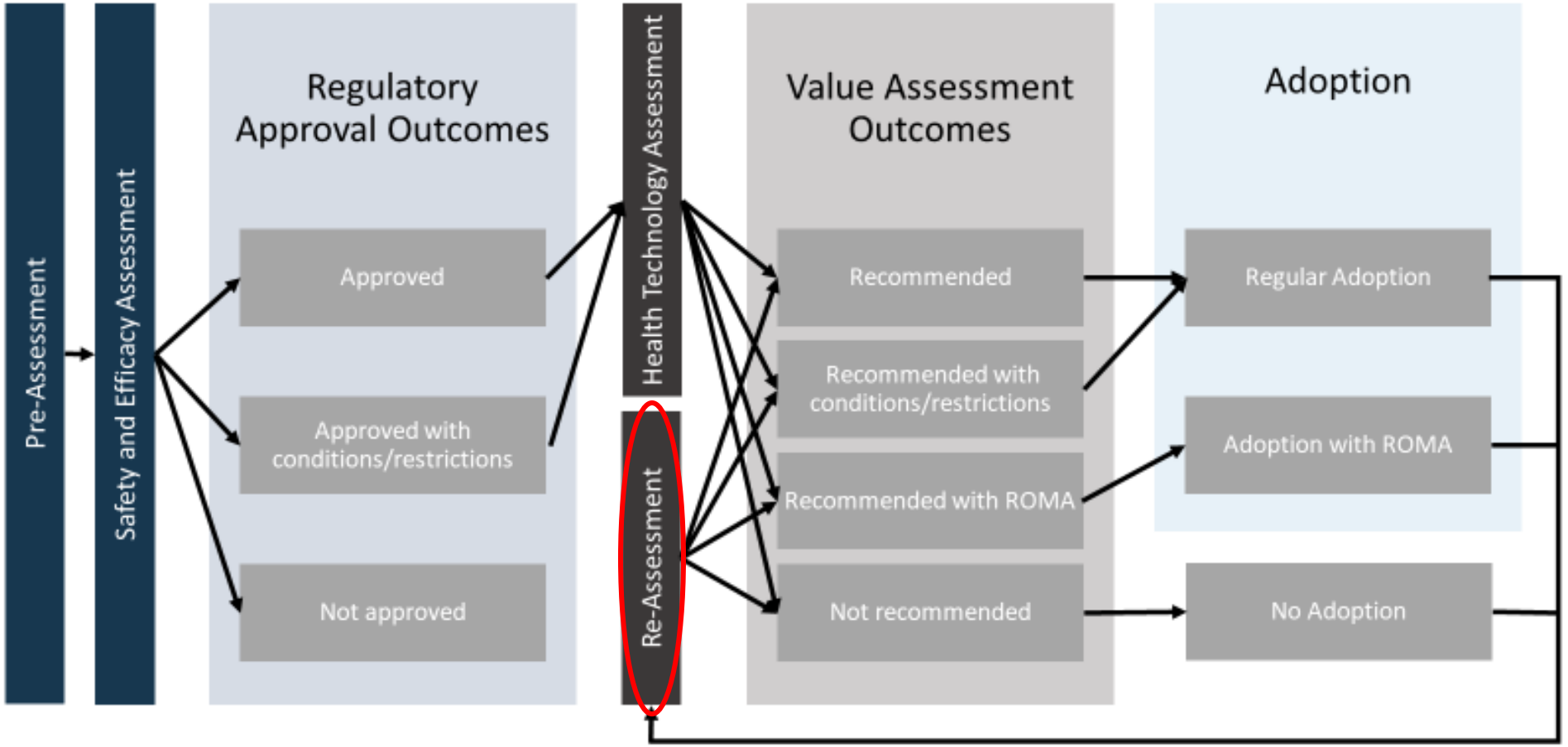
Three key stages

I. Product assessment – clinical appraisal and early VOI

II. Develop multiple research designs to allow alternative research-oriented market access agreements to be evaluated

III. Facilitate RWE reanalysis for decision making, in three stages distinguished by continuation criteria

ROMA


Pre-Assessment
Safety and Efficacy Assessment
Regulatory Approval Outcomes
Approved
Approved with conditions/restrictions
Not approved
Health Technology Assessment
Re-Assessment
Value Assessment Outcomes
Recommended
Recommended with conditions/restrictions
Recommended with ROMA
Not recommended
Adoption
Regular Adoption
Adoption with ROMA
No Adoption

ROMA Stage I: Initial Assessment

The **purpose** of this stage is to provide guidance to develop models suitable for:

- Expected Net Benefit (ENB) and PSA,
- Iterative (Bayesian) updating of model parameters, and
- Range of VOI outputs: EVPI, EVPPI, ENPVSI.

De novo model development to support:

- Reduction of structural uncertainty, alignment to care pathway,
- Efficiency of model structure for advanced methods implementation, and
- Inclusive participation of all stakeholders.

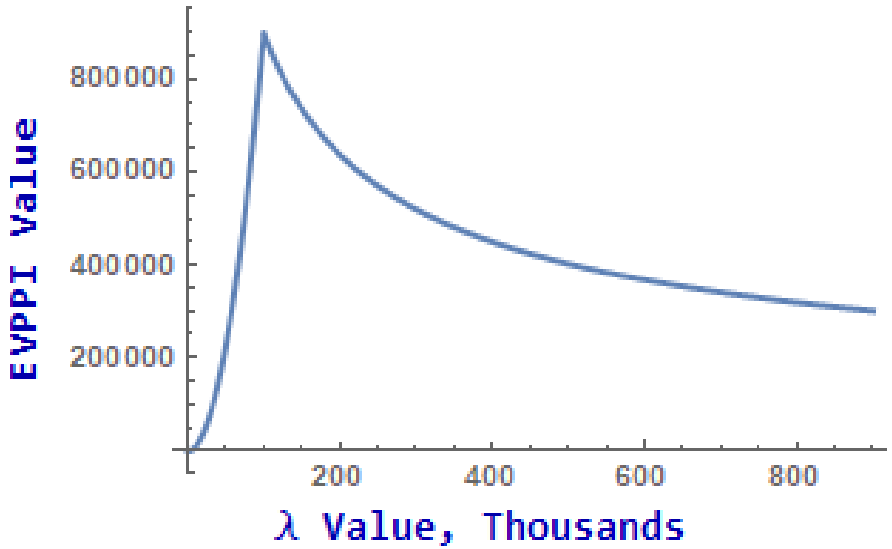
ROMA Stage I: Initial Assessment

Objectives

- Conduct scoping and evidence review, set model structure
- Develop *de novo* model, produce ENB and PSA
- Conduct rapid expected value of perfect parameter information (EVPPI) analysis

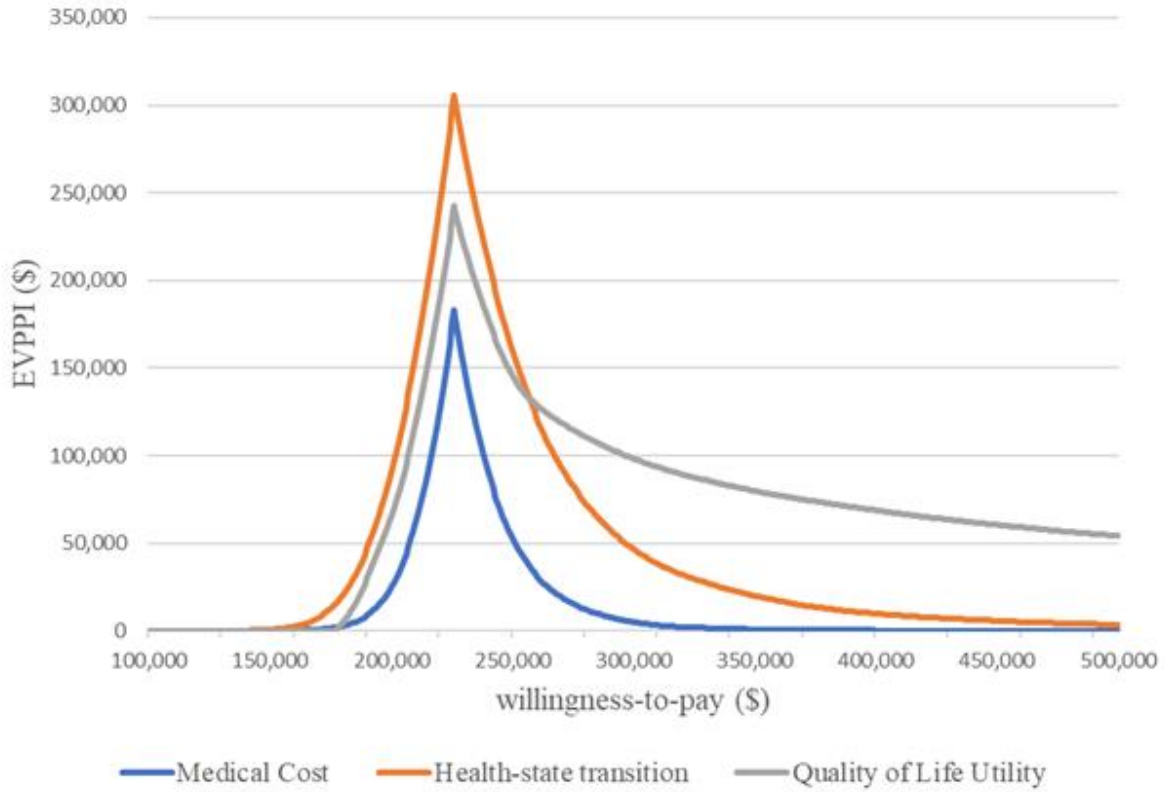
Continuation Criteria

For at least one parameter, the EVPPI is greater than the cost to generate RWE for that parameter



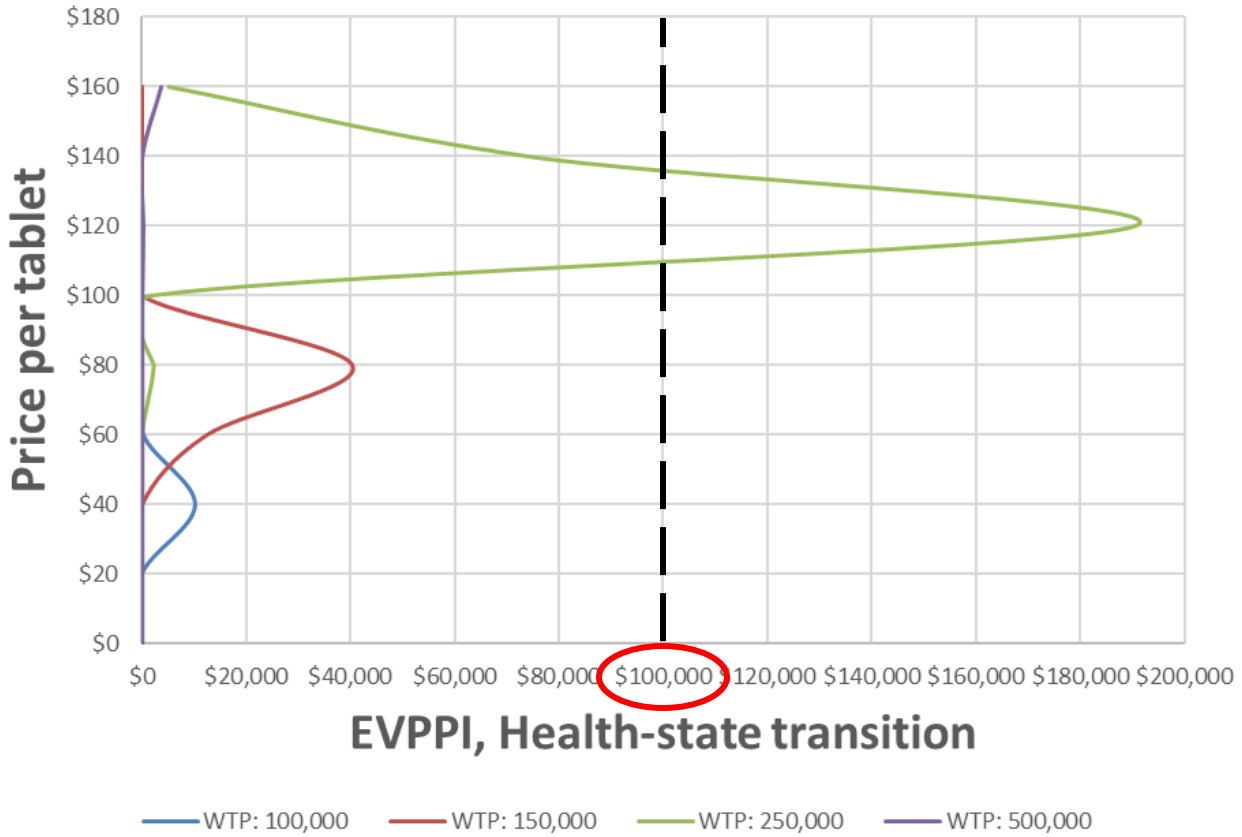
ROMA Outputs

The value of additional research depends on the **willingness to pay per additional QALY**



ROMA Outputs

The value of additional research **for a given willingness to pay** per QALY is **dependent on the price** of the product.

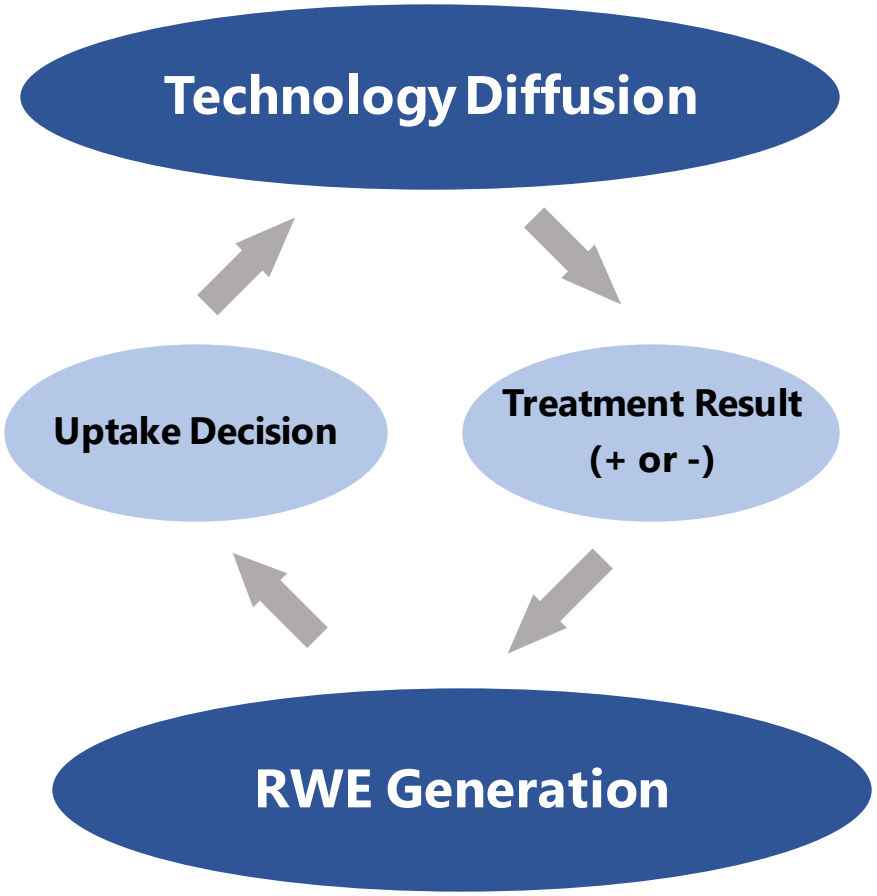


ROMA Stage II: RWE Research Design

The **purpose** of this stage is to identify the optimal research design which maximizes expected net present value of sample information (ENPVSI).

RWE development is a function of interdependent processes which must be modelled

- The diffusion of the technology
- The subsequent generation of RWE



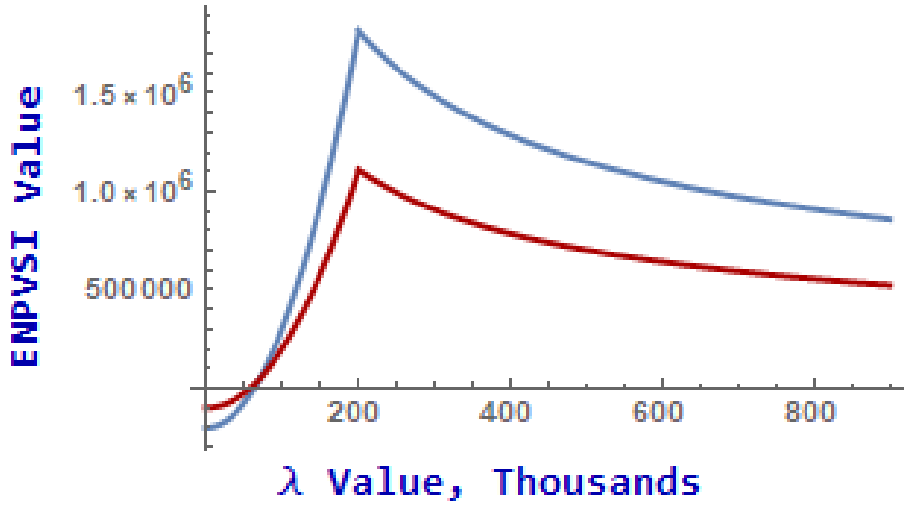
ROMA Stage II: RWE Research Design

Stage II **objectives**:

- Develop candidate research designs,
- Simulate RWE generation through technology diffusion and data generation models
- Estimate ENPVSI for each research design

Continuation Criteria

There must be a positive ENPVSI for at least one of the research designs



ROMA Stage III: Implementation

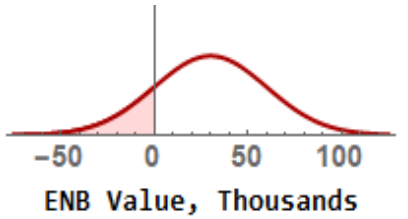
The **purpose** of this stage is to implement one of the research designs with a positive ENPVSI

Stage III **objectives**

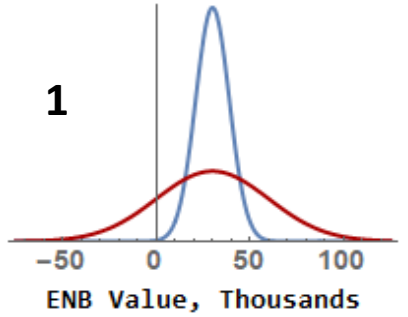
- **Implement** research design through ROMA
- **Update** ENB and ENPVSI with new information from RWE at each readout period, apply stopping condition
- **Complete** analysis and final ENB estimate at end of ROMA period, or when completion condition is met

ROMA Stage III: Implementation

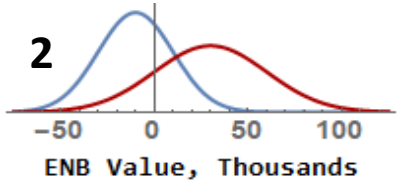
Stopping Condition: ENPVSI is less than or equal to zero.
This happens when the RWE produces:



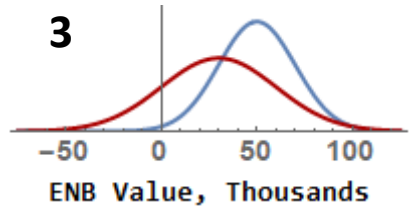
1. A consistent mean ENB but with reduced uncertainty



2. A lower mean ENB such that it is more certain that the candidate technology is not cost effective



3. A higher mean ENB such that it is more certain that the candidate technology is cost effective



Comparing ROMA & traditional HTA

Traditional HTA

Clinical and economic review

CDEC recommends that [redacted] be listed for the treatment of [redacted] in patients aged [redacted] and with [redacted] if the following clinical criteria and condition are met:

Clinical criteria

- Confirmed diagnosis of [redacted] with [redacted]
- Discontinuation criteria should be developed for [redacted] in consultation with physicians and patients who have expertise in [redacted] .

Condition

- Substantial reduction in price

ROMA

Stage 1: Clinical review and 1st VOI

- Clinical effectiveness highly uncertain
- For at least one parameter, EVPPI is > than the cost to generate RWE for that parameter.

Recommendation: Continue appraisal 

Stage 2: VOI and Research Design

- There are **viable** sampling designs to address methodological issues and reduce uncertainty
- There **is a positive** ENPVSI for at least one of the research designs

Recommendation: Reimburse with ROMA 

Stage 3: Implementation

- **Implement** RWE strategy
- **Update** outputs with new evidence
- **Complete appraisal** and make final listing assessment

Comparing ROMA & traditional HTA

Payers or reimbursement agencies make one of three reimbursement recommendations under uncertainty:

- Fund/recommend
- Do not fund/recommend
- Fund/recommend with conditions (eg managed access agreement, price reduction)

ROMA approach enhances ‘fund with conditions’

- Provides specific research design and contractual arrangements

Comparing ROMA & traditional HTA

With ROMA:

- Decision-makers gain an additional tool, and achieve optimal price-uncertainty balance at the point of recommendation
- Patients have timely access to novel therapies
- Manufacturers are ensured fair compensation
- Payers are supported to make efficient funding decisions

Value of Information

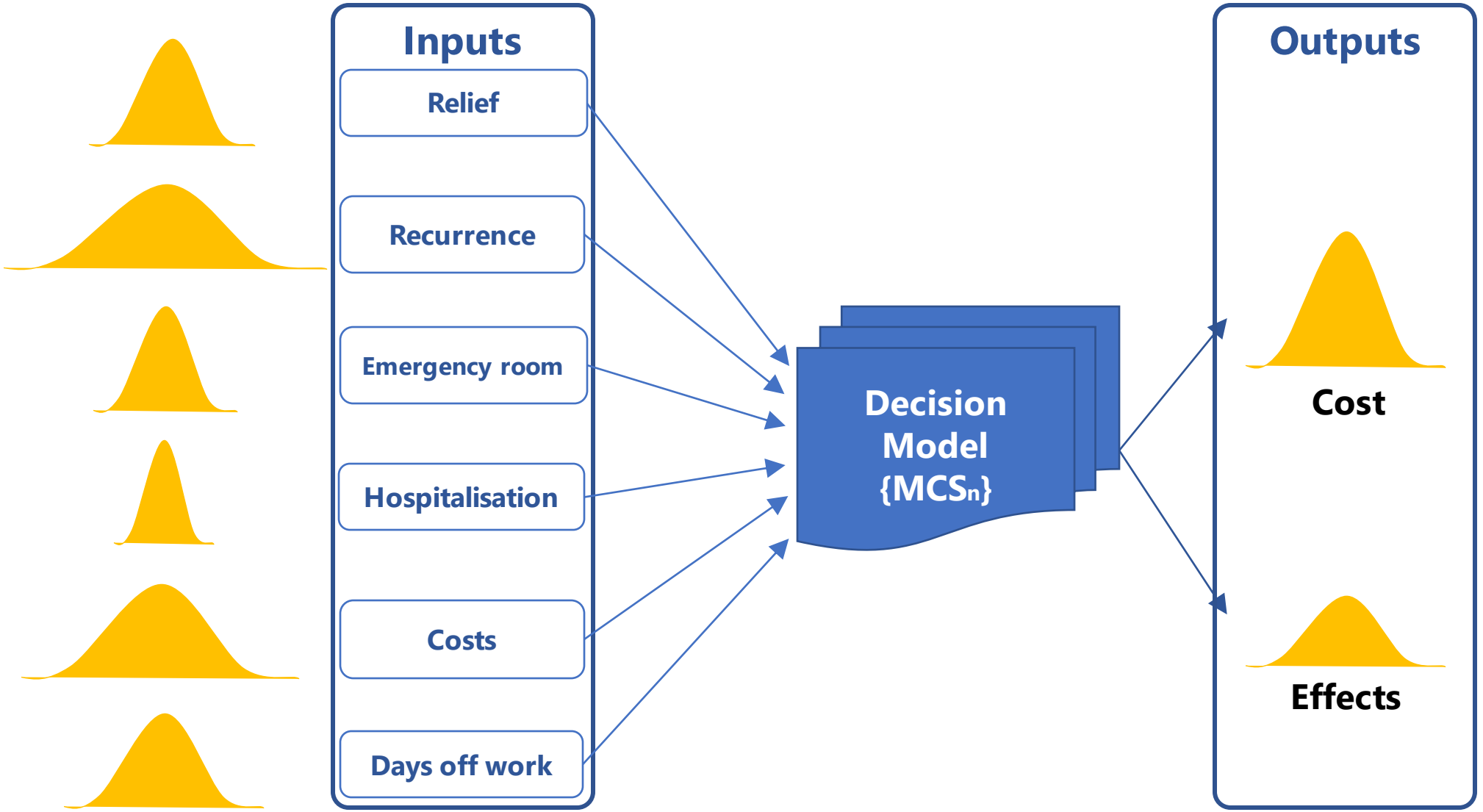
How is uncertainty quantified?

EVPI, EVPPI, EVSI

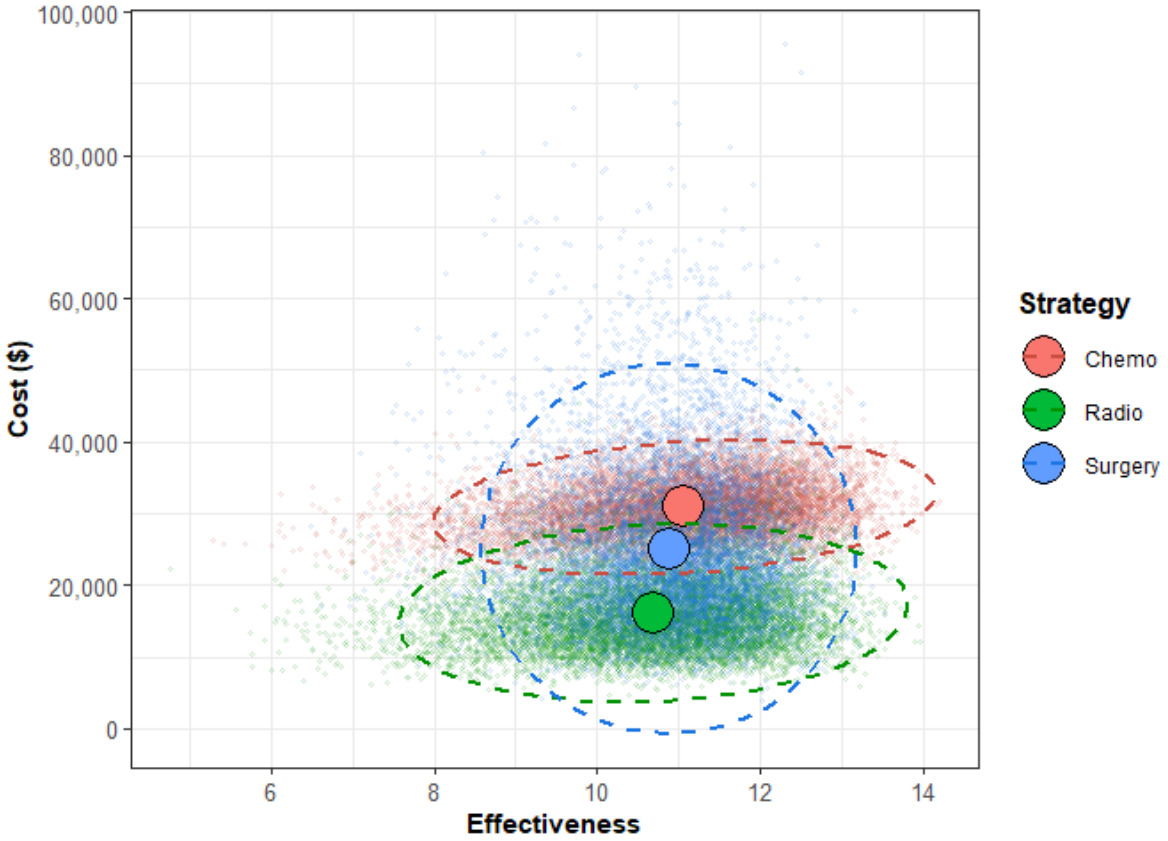
Probabilistic Sensitivity Analysis

- Most decision analytic models use some form of probabilistic sensitivity analysis (PSA)
- PSA samples from parameter distributions over many model iterations to generate outputs, tabulated as costs and benefits
- PSA helps to quantify the level of confidence in the output of the analysis, in relation to uncertainty in the model inputs

PSA: Monte Carlo Analysis

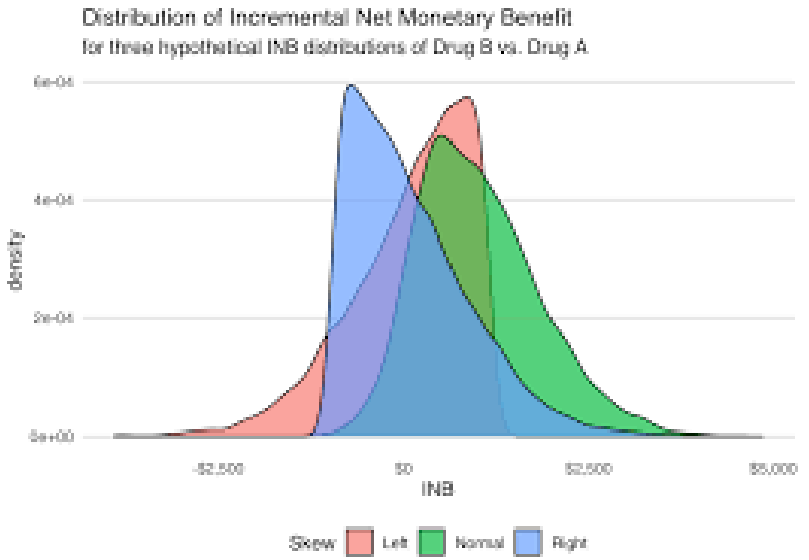


Probabilistic Sensitivity Analysis



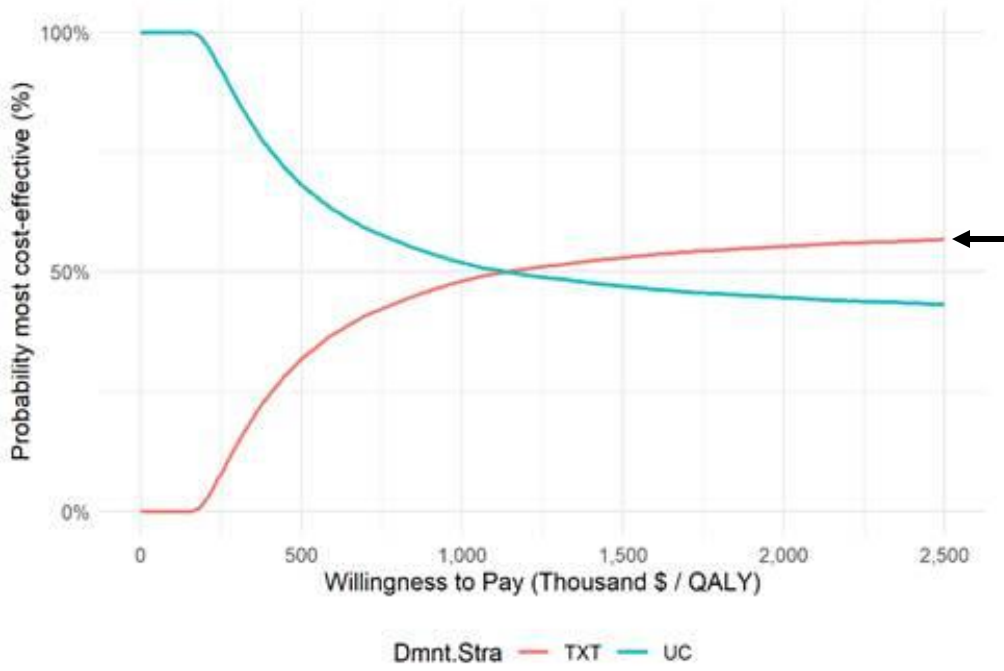
The net monetary benefit for intervention *i* is:

$$\lambda E_i - C_i$$



Sources: Dampack; Incremental Thoughts.

Value of Information



← Based on current information (θ) the probability that a product delivers the promised value never rises above 55% - no matter how much we are willing to pay for health gains

Value of Information (VOI) analysis allows us to estimate the value of gaining additional information

The Expensive Drugs for Rare Diseases Program is characterized by highly uncertain evidence at the time of adoption.

Parameter Uncertainty → Decision Uncertainty

The risk of making the wrong decision

- Probability that incremental Net Benefit is negative

The cost of making the wrong decision = The expected net benefit forgone and the additional costs incurred by the decision.

The expected cost of the wrong decision determines how much decision makers should consider uncertainty

Expected Total Cost of Wrong Decision

- Probability of making the wrong decision
- Value of Health Foregone (λ)
- Population affected by the condition

Value of Information

Value of information: a means of valuing the expected gain from reducing uncertainty through some form of data collection exercise

The **expected value of research** is the expected reduction in the probability of making the 'wrong' decision multiplied by the average consequence of being 'wrong'

Useful when making decisions under conditions of uncertainty (i.e. all decisions)

Value of Information

We can reduce uncertainty by collecting more evidence

We can estimate different **values** of collecting more evidence

i. Expected Value of Perfect Information (EVPI)

ii. Expected Value of Perfect Parameter Information (EVPPI)

iii. Expected Net Present Value of Sample Information (ENPVSI)

Value of Information

We can reduce uncertainty by collecting more evidence

We can estimate different **values** of collecting more evidence

i. **Expected Value of Perfect Information (EVPI)**
ii. Expected Value of Perfect Parameter Information (EVPPI)
iii. Expected Value of Sample Information (EVSI)

EVPI: Expected Value of Perfect Information

Aim is to choose the option that maximises net benefit (NB)

i. Maximise Expected Net Benefit for treatment *(j)* given current information *(θ)*:

$$\max_j \; E_\theta \, NB(_{j,\ \theta})$$

ii. The expected value of a decision taken with perfect information is found by averaging these maximum net benefits over the distribution of θ:

$$E_\theta \max_j NB(_{j,\ \theta})$$

iii. EVPI = Difference between ENB with perfect information and ENB with current information

$$EVPI = E_\theta \max_j NB(_{j,\ \theta}) - \max_j E_\theta \, NB(_{j,\ \theta})$$

Value of Information

There is a cost to generating additional evidence

Compare **C** with EVPI

- If **C < EVPI** then further research **is** cost-effective
- If **C > EVPI** then further research **is not** cost-effective

Example of PSA Output

	Treatment Net Health Benefit	
	A	**B**
State of the world 1	9	12
State of the world 2	12	10
State of the world 3	14	20
State of the world 4	11	10
State of the world 5	14	13
Expectation	12	**13**

The decision maker – looks at the Expectation and chooses Treatment B.

EVPI – Vignette I

	Treatment Net Health Benefit		Optimal Choice		Maximum health benefit		Health Loss
	A	B					
State of the world 1	9	12	**B**		12		0
State of the world 2	12	10	**A**		12		2
State of the world 3	14	20	**B**		20		0
State of the world 4	11	10	**A**		11		1
State of the world 5	14	13	**A**		14		1
Expectation	12	**13**			13.8		0.8

EVPI – Vignette II

	Treatment Net Health Benefit		Optimal Choice		Maximum health benefit		Health Loss
	A	B					
State of the world 1	9	12	**B**		12		0
State of the world 2	12	10	**A**		12		2
State of the world 3	14	20	**B**		20		0
State of the world 4	11	10	**A**		11		1
State of the world 5	14	13	**A**		14		1
Expectation	12	**13**			13.8		0.8

Expected health benefit with **current** information

EVPI – Vignette III

	Treatment Net Health Benefit		Optimal Choice		Maximum health benefit		Health Loss
	A	B					
State of the world 1	9	12	**B**		12		0
State of the world 2	12	10	**A**		12		2
State of the world 3	14	20	**B**		20		0
State of the world 4	11	10	**A**		11		1
State of the world 5	14	13	**A**		14		1
Expectation	12	13			**13.8**		0.8

Expected health benefit with **perfect** information

EVPI – Vignette IV

	Treatment Net Health Benefit		Optimal Choice		Maximum health benefit		Health Loss
	A	B					
State of the world 1	9	12	**B**		12		0
State of the world 2	12	10	**A**		12		2
State of the world 3	14	20	**B**		20		0
State of the world 4	11	10	**A**		11		1
State of the world 5	14	13	**A**		14		1
Expectation	12	13			13.8		**0.8**

Expected health loss from **imperfect** information

EVPI – Vignette V

	Treatment Net Health Benefit		Optimal Choice		Maximum health benefit		Health Loss
	A	B					
State of the world 1	9	12	**B**		12		0
State of the world 2	12	10	**A**		12		2
State of the world 3	14	20	**B**		20		0
State of the world 4	11	10	**A**		11		1
State of the world 5	14	13	**A**		14		1
Expectation	12	13			13.8		0.8

EVPI = Expected health loss * value of health (λ)

EVPI: Value of the Health Lost due to Uncertainty

Lambda (λ) = value of health

Q_{ci} = Expected Health Benefit under **Current** Information
= 13 QALYs

Q_{pi} = Expected Health Benefit under **Perfect** Information
= 13.8 QALYs

Health loss due to uncertainty = $(Q_{pi} - Q_{ci})$ = 0.8

EVPI: Expected Value of Perfect Information

EVPI is the price a decision maker would be willing to pay to have perfect information, such that all decision uncertainty is removed.

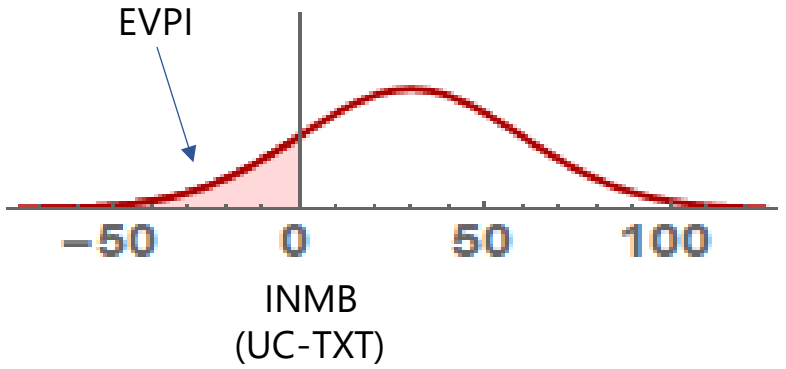
Two types of "incorrect" decisions:

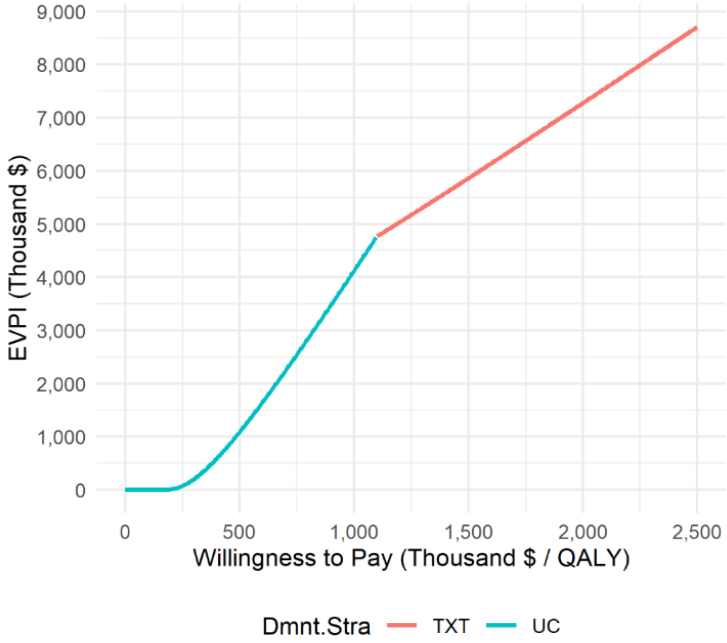
- Adopting a technology that is not cost-effective
- Failing to adopt a technology that is cost-effective

$$\underbrace{E_\theta \max_j \{NB(j,\theta)\}}_{\text{ENB with perfect information}} - \underbrace{\max_j \{E_\theta NB(j,\theta)\}, j = 1,2,\dots J}_{\text{ENB with current information}}$$

EVPI Interpretation

- If the price that a healthcare decision maker would be willing to pay to have perfect information regarding all factors that influence which treatment choice is preferred as the result of a cost-effectiveness analysis.
- The value (in money terms) of removing all uncertainty from such an analysis.
- Not directly informative for decision making!





EVPPI: Expected Value of Partial Perfect Information

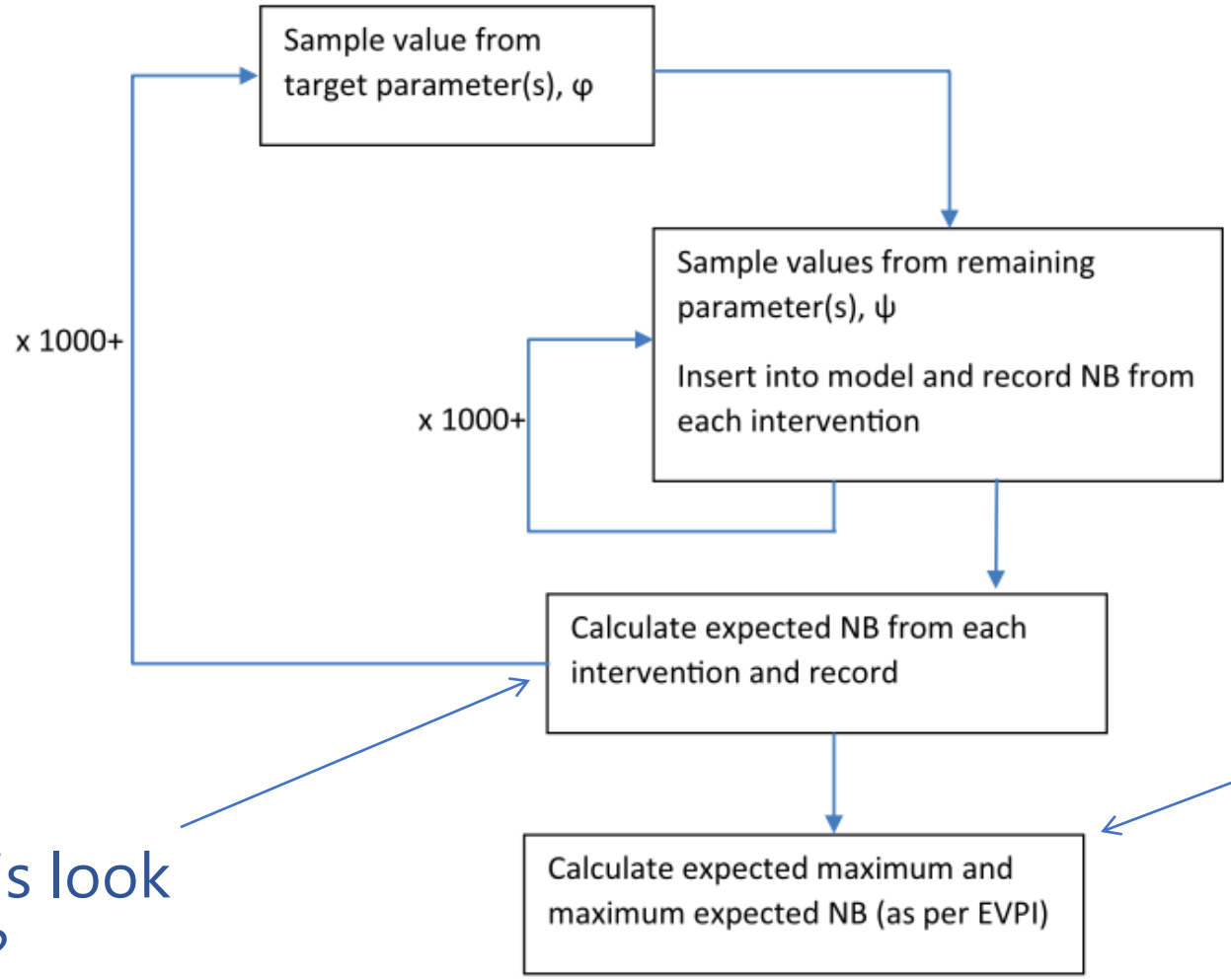
The price that a healthcare decision maker would be willing to spend in order to gain perfect information for one or more factors (i.e. inputs to an economic model).

$$\underbrace{E_\theta \max_j \left[E_{\phi\psi} NB(j,\phi,\varphi)\right]}_{\text{ENB with perfect parameter information}} - \underbrace{\max_j \{E_\theta NB(j,\theta)\}}_{\text{ENB with current information}}, j = 1,2,\ldots J$$

$$\phi = all\ parameters, \varphi = parameter\ of\ interest,$$
$$\psi = all\ other\ parameters, j = all\ strategies, \theta = current\ information$$

Calculating EVPPI

Other methods are available due to computational burden, such as SAVI, single loop approximation, quadrature.



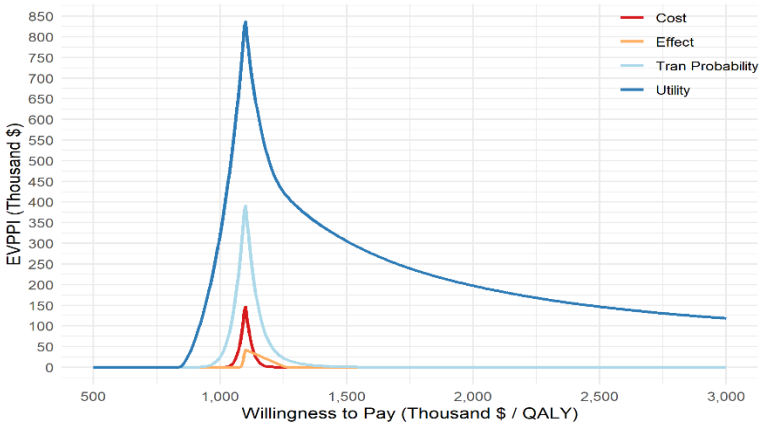
Does this look familiar?

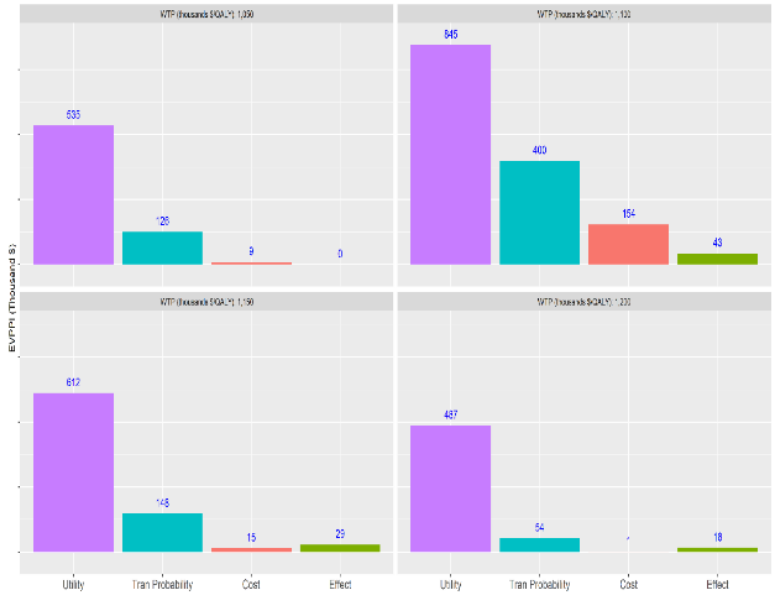
This is different!

Wilson, Pharmacoeconomics 2015

EVPPI Interpretation

- The price that a healthcare decision maker would be willing to spend in order to gain perfect information for one or more factors (i.e. inputs to an economic model).
- If the cost of research is in excess of the EVPPI for a given parameter (or set of parameters), do not proceed.
- Necessary, but not sufficient: cost of research < EVPPI





EVSI: Expected Value of Sample Information

Estimates the value of a decision to collect additional sample information. This is about reducing, but not eliminating, uncertainty.

$$\underbrace{E_D \max_j \left[E_{\theta_I} | D * NB\left(j, \theta_i\right) \right]}_{\text{ENB with new posterior/sample information}} - \underbrace{\max_j \{E_\theta NB(j, \theta)\}, j = 1,2, \ldots J}_{\text{ENB with current information}}$$

$j = all\ strategies, \theta = current\ information,$
D=simulated additional data,

Calculating EVSI

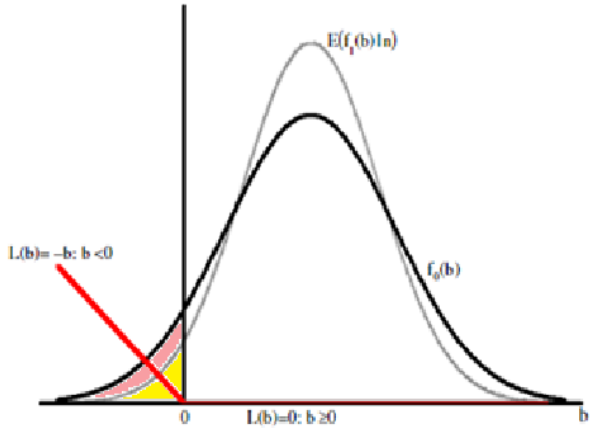
Calculating EVSI

1. Identify parameter(s) of interest θ_I
2. Simulate new data from proposed research D
3. Update θ_I with D $\theta_I|D$
4. Calculate NB for each *j* intervention (MCS) $E_{\theta_I|D} NB(j; \theta_I)$
5. Record the maximum NB $\max_j E_{\theta_I|D} NB(j; \theta_I)$
6. Repeat steps 1 – 5 *n* times $E_D\left[\max_j E_{\theta_I|D} NB(j; \theta_I)\right]$

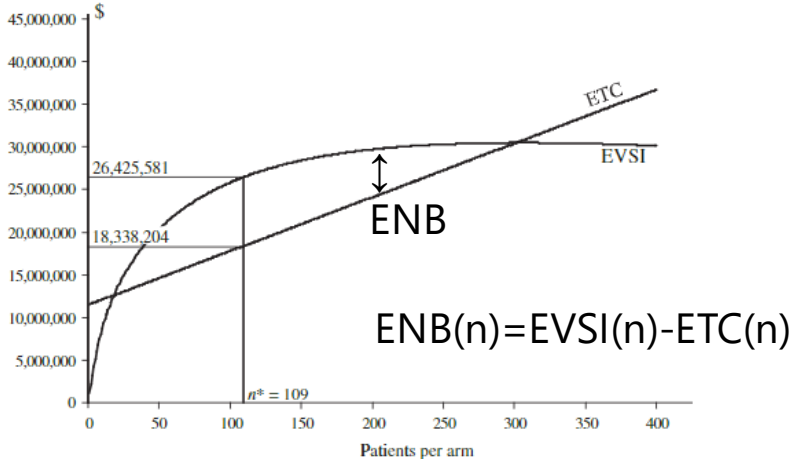
$$\text{EVSI} = E_D\left[\max_j E_{\theta_I|D} NB(j; \theta_I)\right] - \max_j E_\theta NB(j, \theta)$$

EVSI Interpretation

- EVSI can be used to help determine the optimal research design (study population, comparison to be tested, sample size) to maximize both the reduction in uncertainty and the value to the society of conducting the study.
- If the EVSI < expected total cost of sampling, proceed.



Eckermann & Willan, Health Economics 2007



ENB(n)=EVSI(n)-ETC(n)

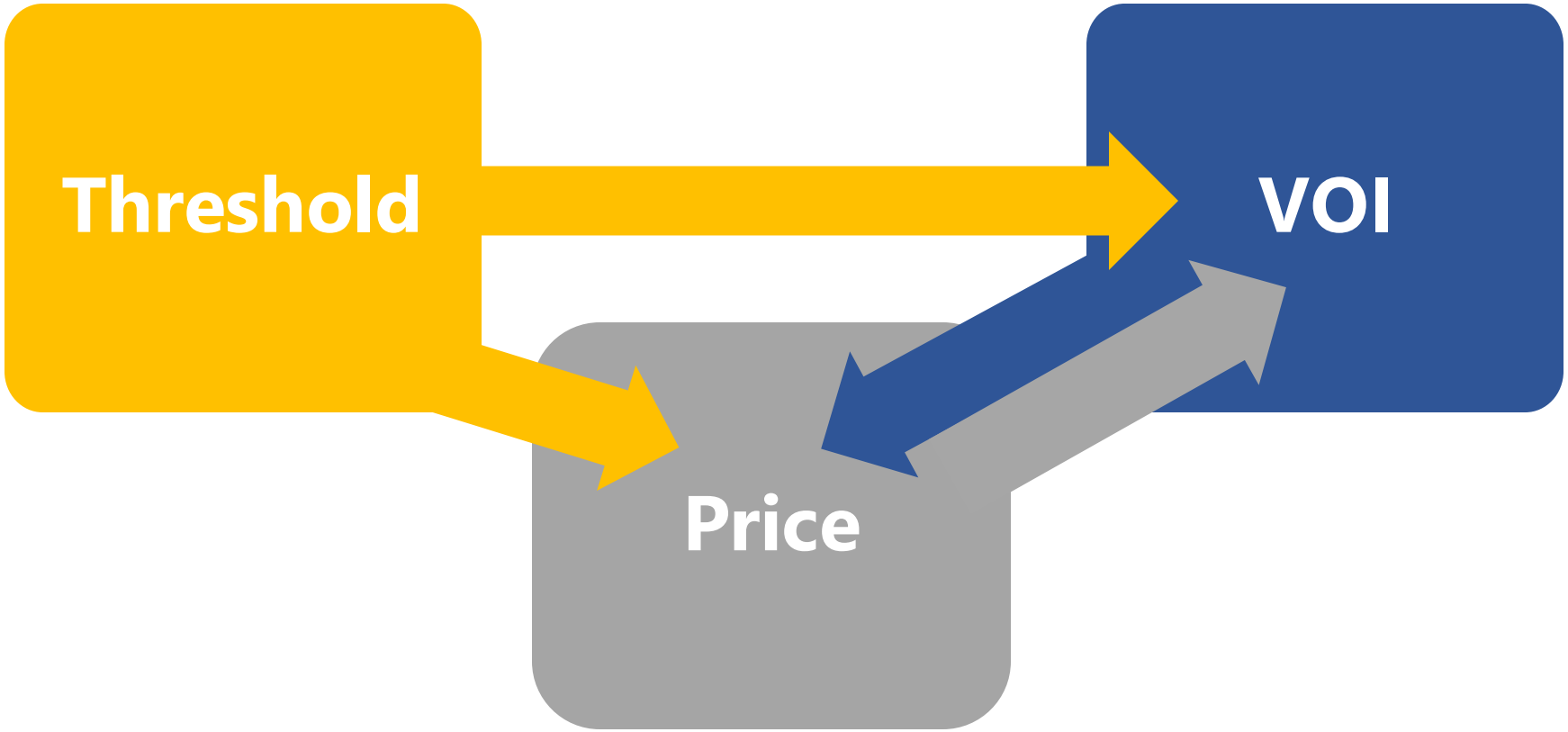
Willan &Eckermann, Health Economics 2010

How does VOI fit into Decision Making?

Literature Review

Linking ROMA

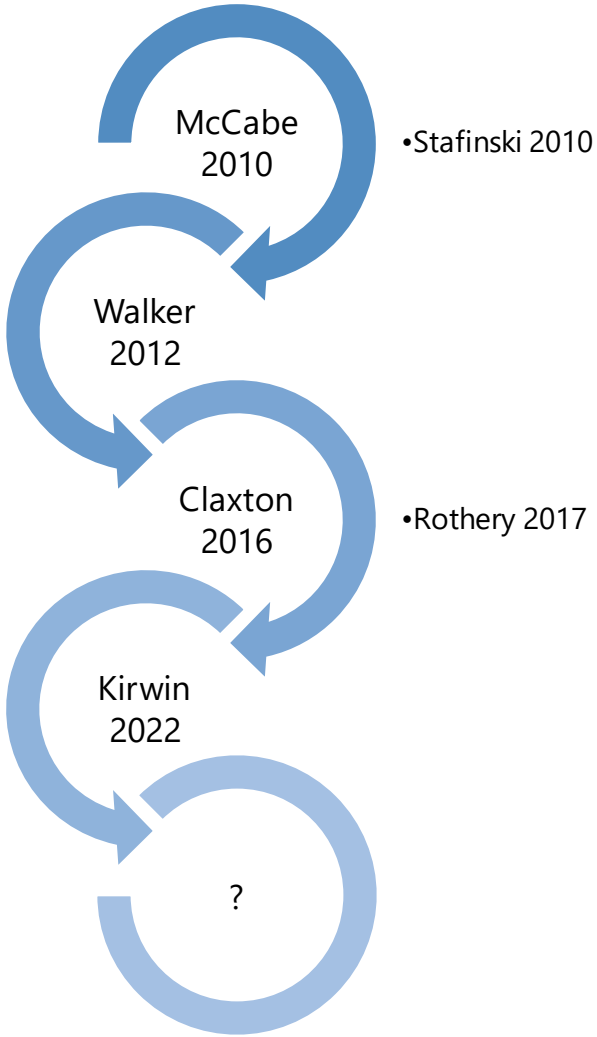
Relationships



Literature Overview Objectives

- Summarize some key papers in the development of LC-HTA and ROMA
- Focus on content rather than critique
- Highlight key developments over past 10+ years

Timeline



•Stafinski 2010

•Rothery 2017

McCabe

- Framework to classify and evaluate ROMA schemes

Walker

- Classification of tech characteristics, payer authority
- Taxonomy of schemes

Claxton

- Value of information- making the decisions explicit

Kirwin

- Lifecycle additions
- Risk-based price

McCabe 2010

CONFERENCE PAPER

Pharmacoeconomics 2010; 28 (2): 143-152
1170-7690/10/0002-0143/$49.95/0

Access with Evidence Development Schemes

A Framework for Description and Evaluation

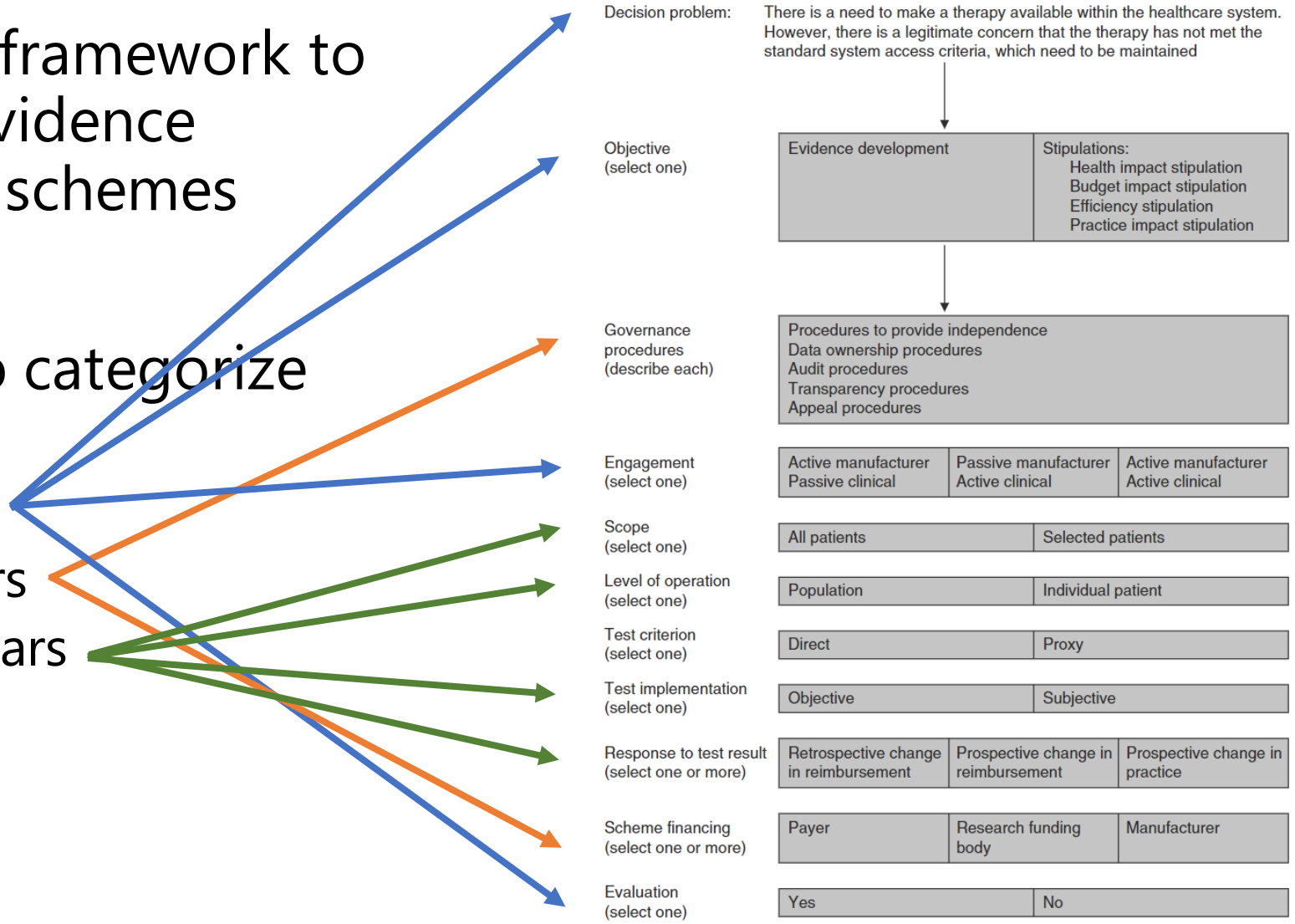
Christopher J. McCabe,[1] *Tania Stafinski,*[2] *Richard Edlin*[1] and *Devidas Menon,*[2] *for and on behalf of the Banff AED Summit*

1 Academic Unit of Health Economics, Leeds Institute of Health Sciences, University of Leeds, Leeds, UK
2 Department of Public Health Sciences, University of Alberta, Edmonton, Alberta, Canada

McCabe 2010

- Aim is to develop a framework to evaluate access w evidence development (AED) schemes

- Figure developed to categorize and design AEDs
  - System Level Chars
  - Organizational Chars
  - Research Design Chars



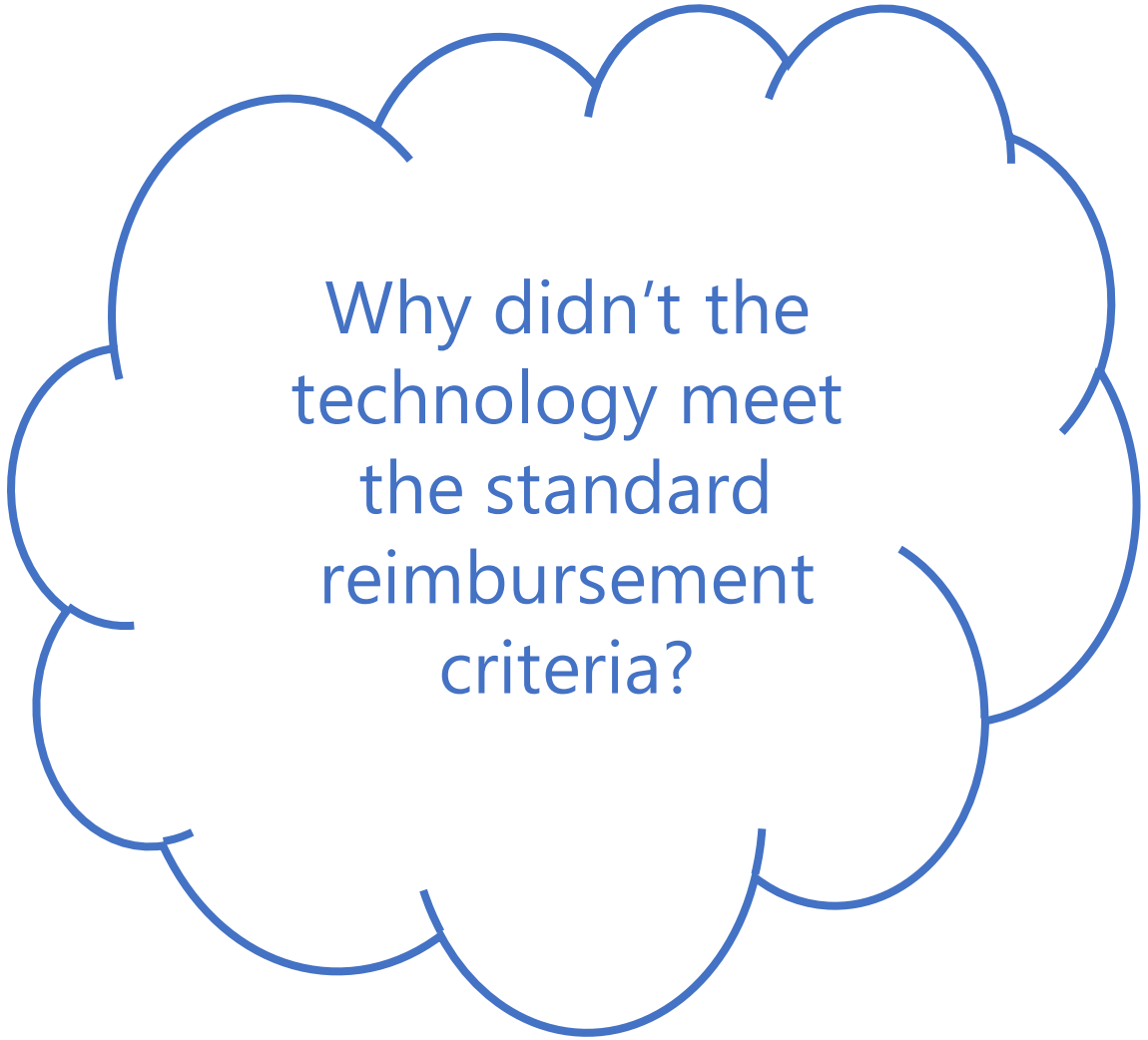
McCabe 2010: System Level Characteristics

- Decision problem
- **Objective (stipulations)**
  - **Evidence generation schemes**
  - **Health impact stipulation schemes**
  - **Efficiency stipulation schemes**
  - **Budget impact stipulation schemes**
  - **Practice stipulation schemes**
- Engagement
- Evaluation

Evidence: resolving uncertainty
Health impact: $$ to payer if no desired impact
Efficiency: is it CE? (price adjustment)
Budget impact: minimize payer risk due to uptake or patient pop
Practice: quality of care/ appropriateness, real world

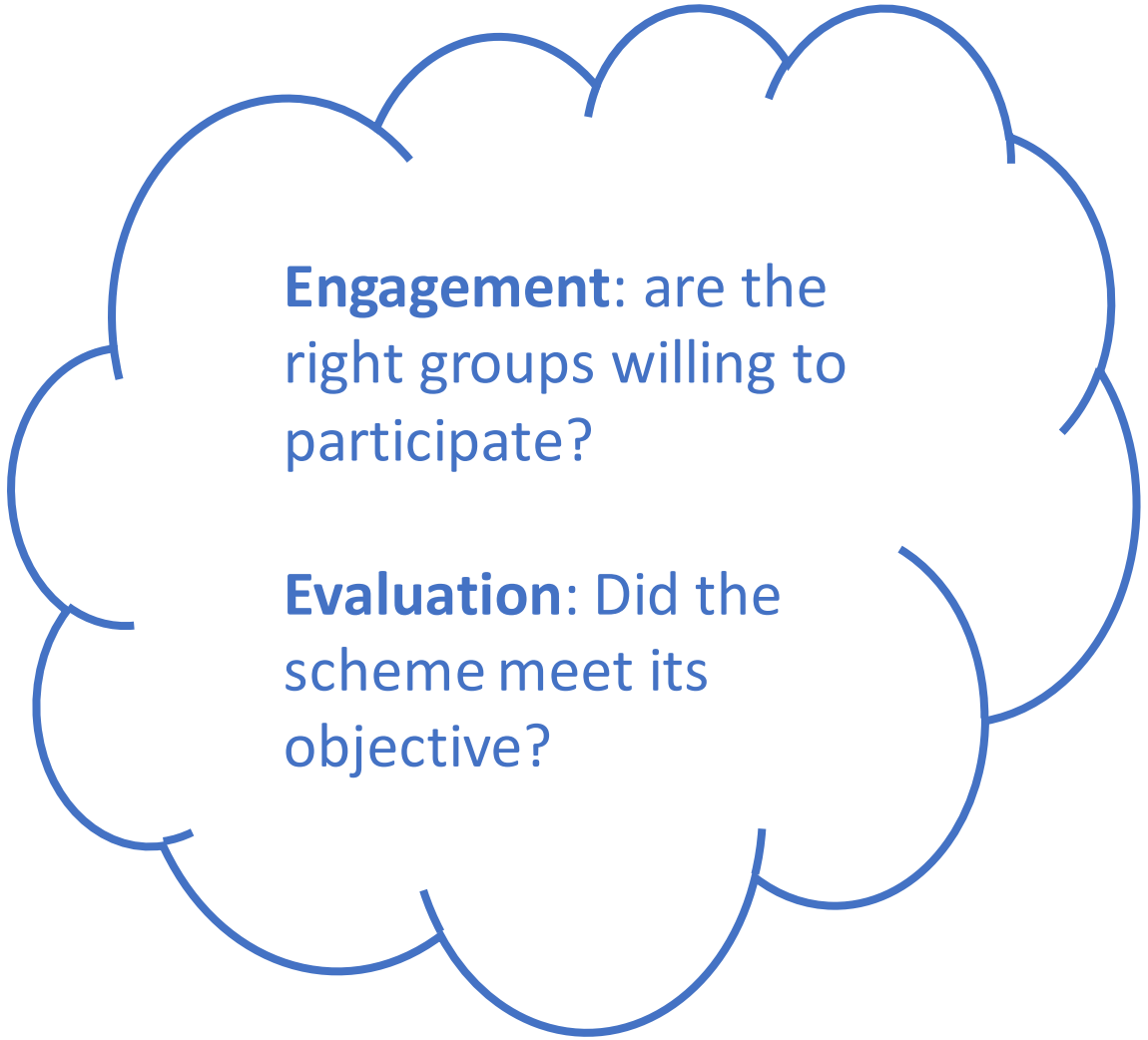
McCabe 2010: System Level Characteristics

- **Decision problem**
- Objective (stipulations)
  - Evidence generation schemes
  - Health impact stipulation schemes
  - Efficiency stipulation schemes
  - Budget impact stipulation schemes
  - Practice stipulation schemes
- Engagement
- Evaluation



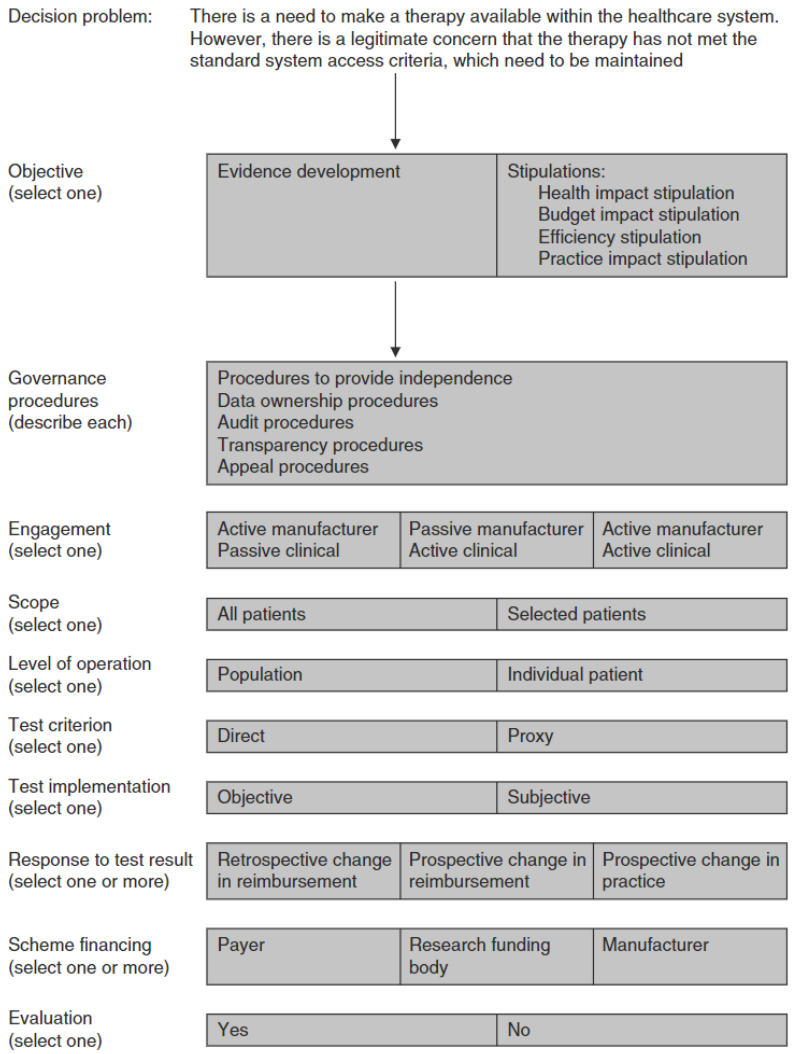
McCabe 2010: System Level Characteristics

- Decision problem
- Objective (stipulations)
  - Evidence generation schemes
  - Health impact stipulation schemes
  - Efficiency stipulation schemes
  - Budget impact stipulation schemes
  - Practice stipulation schemes
- **Engagement**
- **Evaluation**



McCabe 2010: Organization Characteristics

- Financing
  - Who is paying for it?
- Governance
  - Who is in charge?



Decision problem:	There is a need to make a therapy available within the healthcare system. However, there is a legitimate concern that the therapy has not met the standard system access criteria, which need to be maintained		
Objective (select one)	Evidence development	Stipulations: Health impact stipulation Budget impact stipulation Efficiency stipulation Practice impact stipulation	
Governance procedures (describe each)	Procedures to provide independence Data ownership procedures Audit procedures Transparency procedures Appeal procedures		
Engagement (select one)	Active manufacturer Passive clinical	Passive manufacturer Active clinical	Active manufacturer Active clinical
Scope (select one)	All patients	Selected patients	
Level of operation (select one)	Population	Individual patient	
Test criterion (select one)	Direct	Proxy	
Test implementation (select one)	Objective	Subjective	
Response to test result (select one or more)	Retrospective change in reimbursement	Prospective change in reimbursement	Prospective change in practice
Scheme financing (select one or more)	Payer	Research funding body	Manufacturer
Evaluation (select one)	Yes	No	

McCabe 2010: Research Design Characteristics

Scope

- Which patients?

Level of operation

- Individual patient outcomes? Population level outcomes?

Test Criterion

- What is the outcome that matters? Is a proxy measure used?

Test Implementation

- What are the methods?

Response to Test Result

- What happens when the results report?

After answering these questions, Access with Evidence Development Schemes can be characterized.

McCabe 2010: Discussion

- AEDs provide an important alternative to denying access or allowing open use of the technology.
- Article attempted to provide a framework both to stimulate debate about the methodology of existing schemes and to aid the design of future schemes.
- The framework includes characteristics about the general system in which the scheme exists, as well as specific characteristics relating to both the scheme organization and research design.
- Also apply the scheme to the UK Multiple Sclerosis Risk-Sharing Scheme
- Must evaluate the schemes themselves – does not make sense to go so far in improving evidence without evaluating if the process to do so is efficient

Walker 2012

VALUE IN HEALTH 15 (2012) 570–579

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POLICY PERSPECTIVES

Coverage with Evidence Development, Only in Research, Risk Sharing, or Patient Access Scheme? A Framework for Coverage Decisions

Simon Walker, MSc[1,], Mark Sculpher, PhD[1], Karl Claxton, PhD[1,2], Steve Palmer, MSc[1]*

[1]*Centre for Health Economics, University of York, York, UK;* [2]*Department of Economics and Related Studies, University of York, York, UK*

Walker 2012

Aim: develop a conceptual framework outlining the decisions available to payers

Prior decisions were approve/ do not approve

It's not just value, it's uncertainty – how do we incorporate this into decisions?

- Only in Research
- Only with Research (aka Allow with Research/ AWR)
- Authority over effective price

OIR vs OWR

- Reversal cost
- Health of patients in/ outside of research
- Who bears the cost of research
- Degree of uncertainty

Walker 2012: X & Y Axis

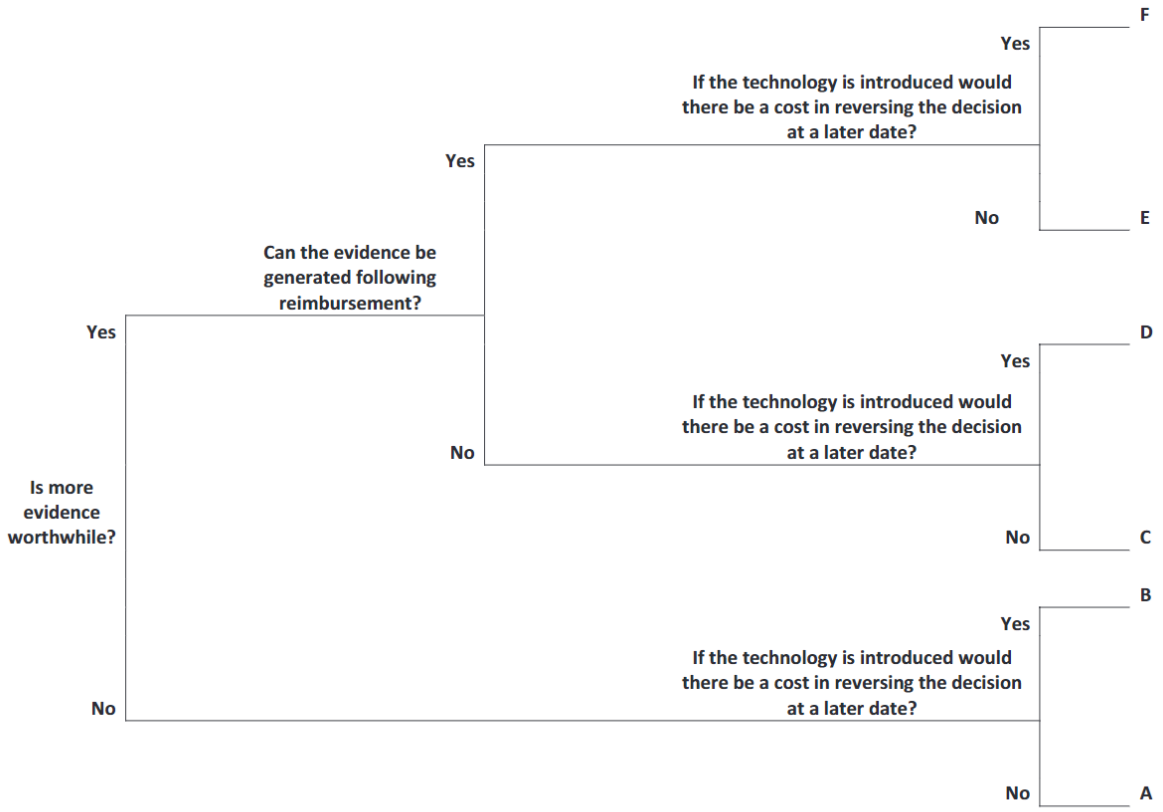

Fig. 1 – The technology's characteristics.

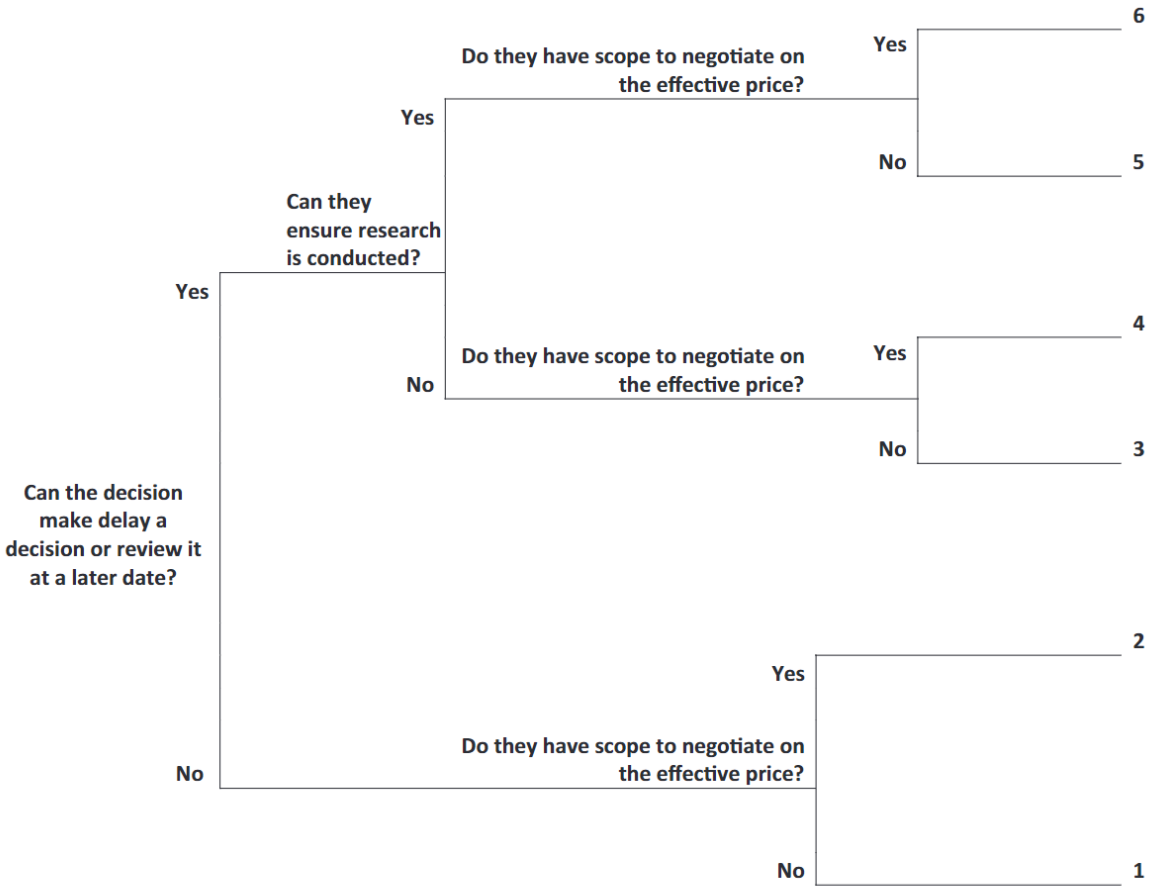

Fig. 2 – The purchaser's range of authority.

Walker 2012: Options Inventory

Expected to be Cost Effective

Table 1 – Coverage options when the treatment is expected to be (i.e., on average) cost-effective given existing evidence.

E(NHB)<0		Technology characteristics					
		A	B	C	D	E	F
	Range of authority	No cost of reversal/ Evidence not worthwhile	Cost of reversal/ Evidence not worthwhile	No cost of reversal/ Evidence worthwhile/ Cannot get evidence with approval	Cost of reversal/ Evidence worthwhile/ Cannot get evidence with approval	No cost of reversal/ Evidence worthwhile/ Can get evidence with approval	Cost of reversal/ Evidence worthwhile/ Can get evidence with approval
1	Cannot delay/reconsider No influence over effective price Cannot ensure research is conducted	Accept	Accept	Accept	Accept	Accept	Accept
2	Cannot delay/reconsider Influence over effective price Cannot ensure research is conducted	Accept	Accept	Accept	Accept	Accept	Accept
3	Can delay/reconsider No influence over effective price Cannot contract for research	Accept	Accept	Accept OIR	Accept OIR	Accept OIR	Accept OIR
4	Can delay/reconsider Influence over effective price Can ensure research is conducted	Accept	Accept Price influence	Accept Price influence OIR	Accept Price influence OIR	Accept Price influence OIR	Accept Price influence OIR
5	Can delay/reconsider No influence over effective price Can ensure research is conducted	Accept	Accept	Accept OIR	Accept OIR	OWR	OIR OIR
6	Can delay/reconsider Influence over effective price Can ensure research is conducted	Accept	Accept Price influence	Accept Price influence OIR	Accept Price influence OIR	Price influence OWR	Price influence OIR OWR

E(NHB), expected(net health benefit); OIR, only in research; OWR, only with research.

Not Expected to be Cost Effective

Table 2 – Coverage options when the treatment is not expected to be (i.e., on average) cost-effective given existing evidence.

E(NHB)<0		Technology characteristics					
		A	B	C	D	E	F
	Range of authority	No cost of reversal/ Evidence not worthwhile	Cost of reversal/ Evidence not worthwhile	No cost of reversal/ Evidence worthwhile/ Cannot get evidence with approval	Cost of reversal/ Evidence worthwhile/ Cannot get evidence with approval	No cost of reversal/ Evidence worthwhile/ Can get evidence with approval	Cost of reversal/ Evidence worthwhile/ Can get evidence with approval
1	Cannot delay/reconsider No influence over effective price Can ensure research is conducted	Reject	Reject	Reject	Reject	Reject	Reject
2	Cannot delay/reconsider Influence over effective price Can ensure research is conducted	Reject Price influence	Reject Price influence	Reject Price influence	Reject Price influence	Reject Price influence	Reject Price influence
3	Can delay/reconsider No influence over effective price Can ensure research is conducted	Reject	Reject	Reject OIR	Reject OIR	Reject OIR	Reject OIR
4	Can delay/reconsider Influence over effective price Can ensure research is conducted	Reject Price influence	Reject Price influence	Reject Price influence OIR	Reject Price influence OIR	Reject Price influence OIR	Reject Price influence OIR
5	Can delay/reconsider No influence over effective price Can ensure research is conducted	Reject	Reject	Reject OIR	Reject OIR	Reject OIR	Reject OIR
6	Can delay/reconsider Influence over effective price Can ensure research is conducted	Reject Price influence	Reject Price influence	Reject Price influence OIR	Reject Price influence OIR	Reject Price influence OIR OWR	Reject Price influence OIR OWR

E(NHB), expected(net health benefit); OIR, only in research; OWR, only with research.

Tables included for illustration – you are not supposed to be able to read the text!

Walker 2012: Taxonomy of Decision Options

Evidence Generation	Outcome-Based Schemes	Non-Outcome Based Schemes
- **Only in Research (OIR)** - Only for patients in the research - **Only with Research (OWR)** - All patients have access, but evidence is generated	- **Money Back Guarantees** (Payer reimbursed if patient target not met) - **Conditional Treatment Continuation** (Sponsor paid only for continuation) - **Price Linked to Outcome** (Price linked to specific outcomes by patient).	- **Different price by patient** • Discounted initiation, full price continuation • Individual volume agreements • Fixed cost per patient (irrespective of course) • **Population Level** • Price negotiation • Expenditure Caps • Volume discounts

Walker 2012: Taxonomy of Decision Options

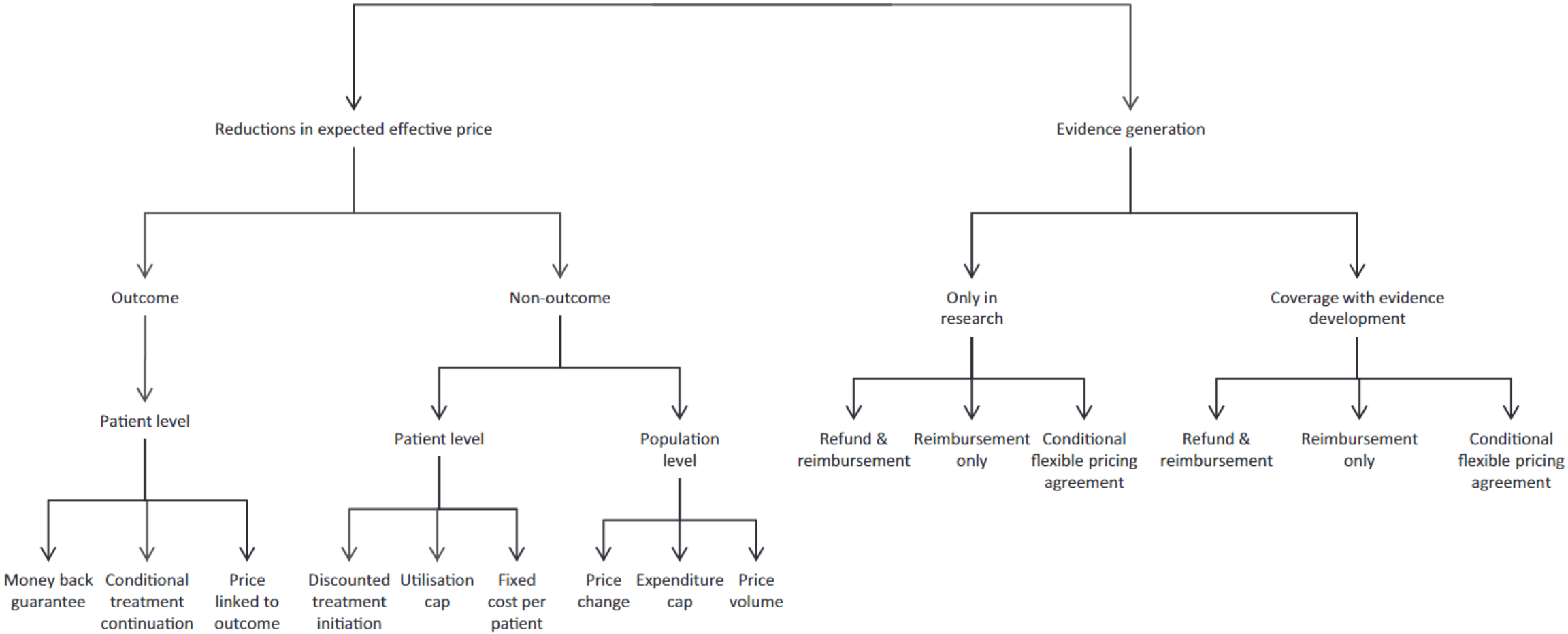

Fig. 3 – A new taxonomy of coverage options.

Walker 2012: Discussion

- Purchasers should weigh the expected benefits of coverage against the possibility that the decision may need to be reversed and the chance that adoption will hinder evidence generation.
- Based on the purchaser's range of authority over access, research, and price and on the characteristics of the technology with regard to reversibility and evidence, different decisions may be appropriate.
- The framework clarified the assessments needed to establish the appropriateness of different decisions.
- A taxonomy of coverage decisions was suggested.

Claxton 2016

VALUE IN HEALTH 19 (2016) 885–891

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journal homepage: www.elsevier.com/locate/jval

METHODOLOGY

A Comprehensive Algorithm for Approval of Health Technologies With, Without, or Only in Research: The Key Principles for Informing Coverage Decisions

Karl Claxton, PhD[1,2], Stephen Palmer, MSc[1], Louise Longworth, PhD[3], Laura Bojke, PhD[1], Susan Griffin, PhD[1], Marta Soares, MSc[1], Eldon Spackman, PhD[1], Claire Rothery, PhD[1,]*

[1]*Centre for Health Economics, University of York, York, UK;* [2]*Department of Economics and Related Studies, University of York, York, UK;* [3]*Health Economics Research Group, Brunel University, London, UK*

Claxton 2012, 2016

- A report to NICE (2012), ViH (2016)
- Outlines circumstances in which AWR and OIR are appropriate
- Reduces factors to seven questions
- Provide series of flow charts with four outcomes:
  - Approve
  - OIR
  - AWR
  - Reject

1. Is the technology expected to be cost-effective?
2. Are there significant irrecoverable costs?
3. Does more research seem worthwhile?
4. Is the research possible with (without) approval?
5. Will other sources of uncertainty resolve over time?
6. Are the benefits of research greater than the costs?
7. Are the benefits of approval greater than the opportunity costs?

Claxton 2016: Algorithm without significant irrecoverable costs

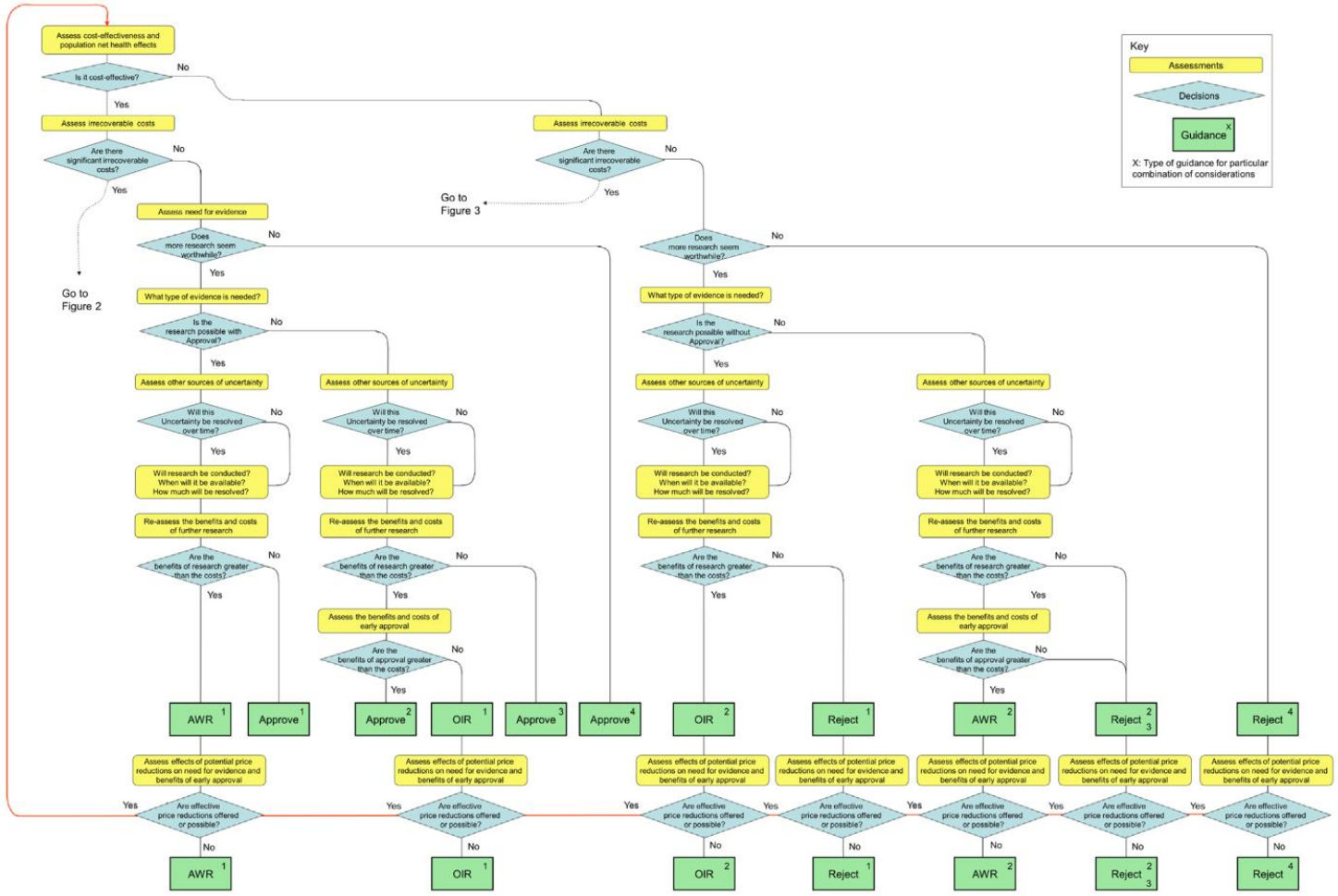


Fig. 1 – An algorithm for OIR and AWR decisions—technologies *without* significant irrecoverable costs. AWR, approval with research; OIR, only in research.

Claxton 2016: Algorithm with significant irrecoverable costs, by expected CE

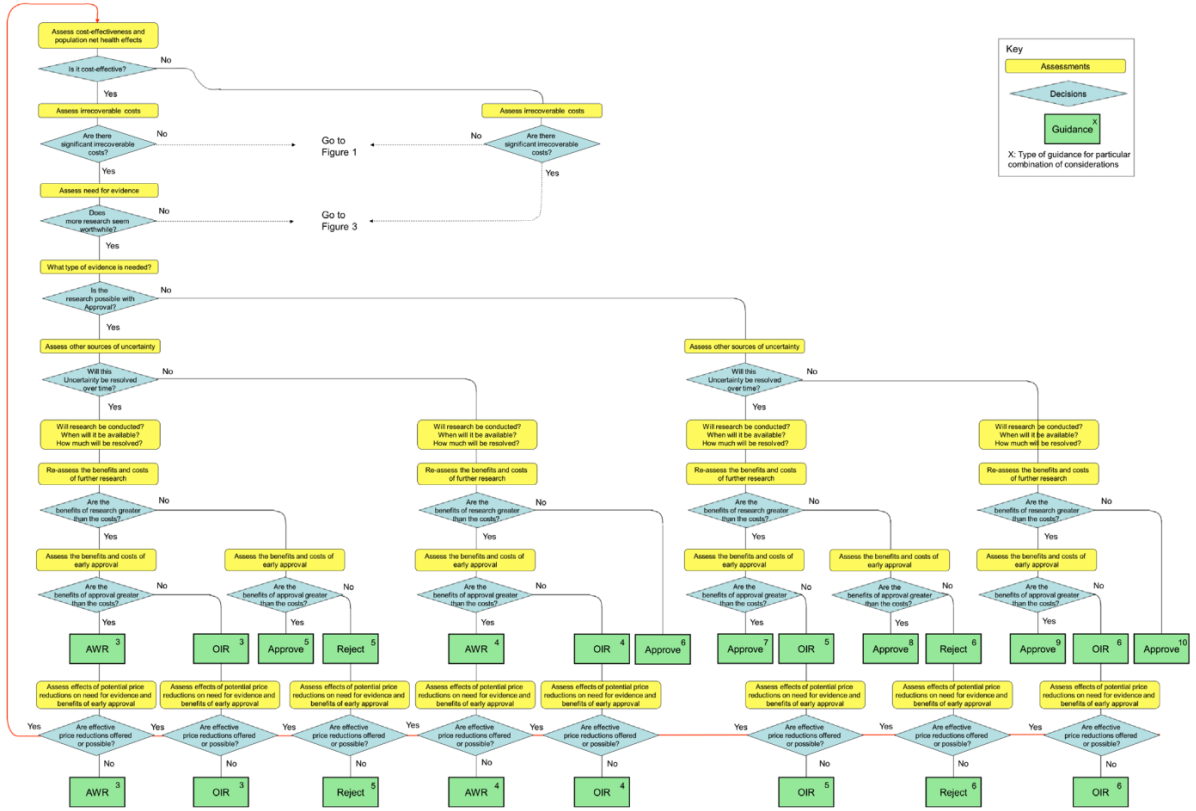


Fig. 2 – An algorithm for OIR and AWR decisions—technologies *with* significant irrecoverable costs, *expected* to be cost-effective and research is needed. AWR, approval with research; OIR, only in research.

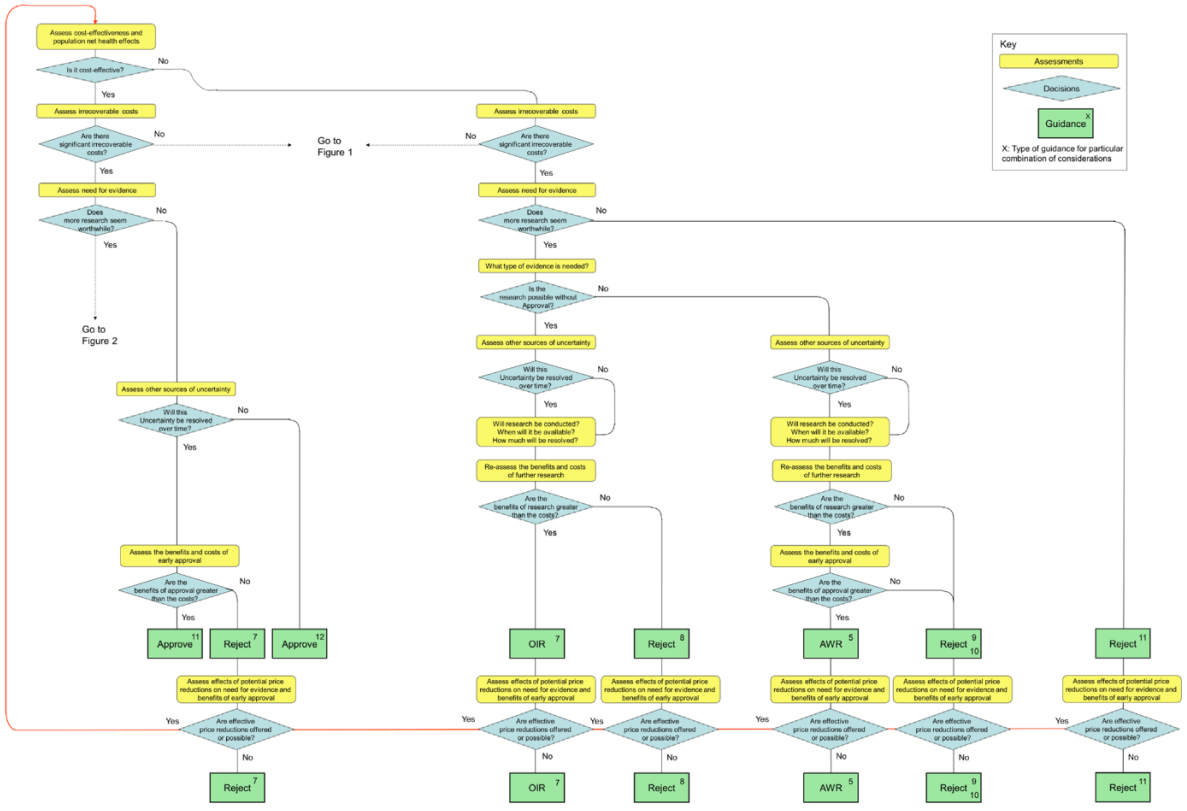


Fig. 3 – An algorithm for OIR and AIR decisions—technologies *with* significant irrecoverable costs, *not* expected to be cost-effective and research is *not* needed. AWR, approval with research; OIR, only in research.

Claxton 2016: Discussion

- Determining expected cost-effectiveness is only a first step.
- In addition to AWR for technologies expected to be cost-effective and OIR for those not expected to be cost-effective, there are other important circumstances when OIR should be considered.
- Principles demonstrate that cost-effectiveness is a necessary but not sufficient condition for approval.
- Even when research is possible with approval, OIR may be appropriate when a technology is expected to be cost-effective due to significant irrecoverable costs.

Rothery 2017

HEALTH ECONOMICS
Health Econ. **26**(Suppl. 1): 109–123 (2017)
Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/hec.3467

CHARACTERISING UNCERTAINTY IN THE ASSESSMENT OF MEDICAL DEVICES AND DETERMINING FUTURE RESEARCH NEEDS

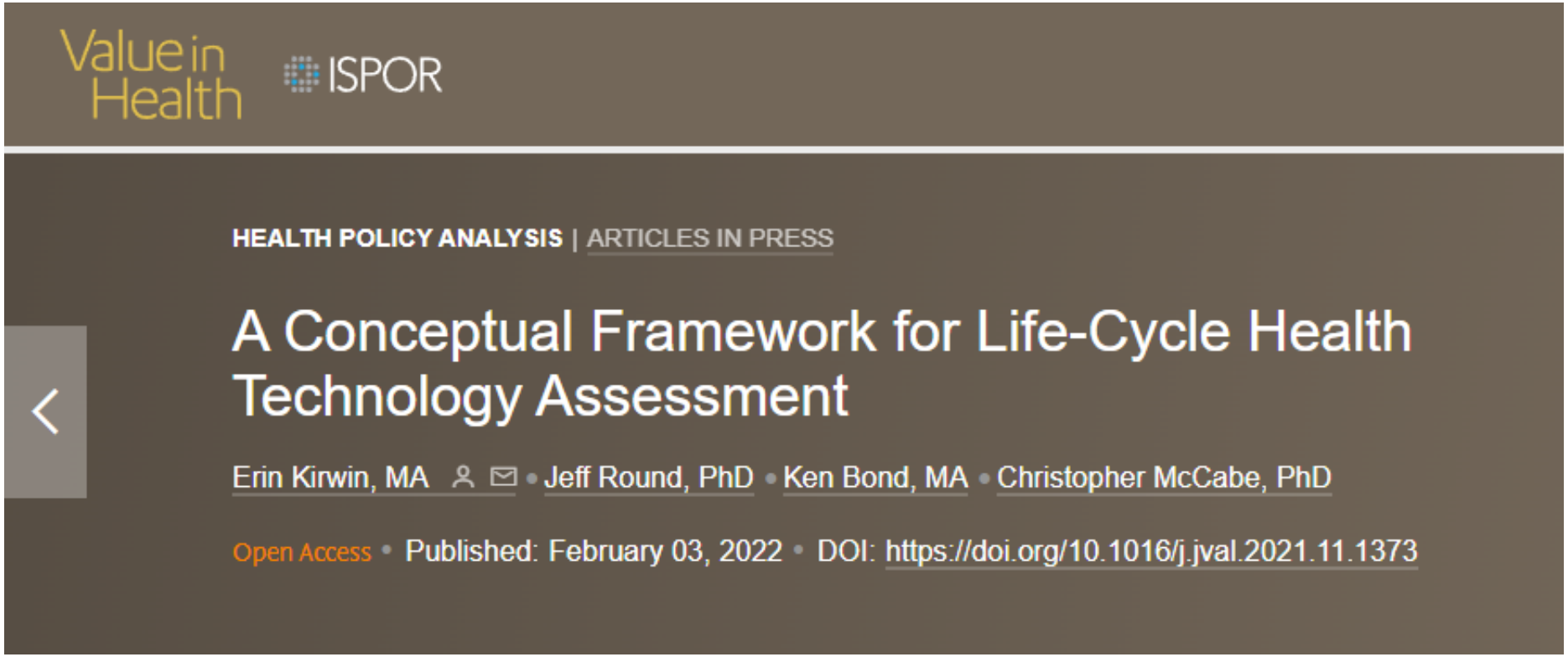
CLAIRE ROTHERY[a*], KARL CLAXTON[a,b], STEPHEN PALMER[a], DAVID EPSTEIN[c], ROSANNA TARRICONE[d,e] and MARK SCULPHER[a]

[a]*Centre for Health Economics, University of York, York, UK*
[b]*Department of Economics and Related Studies, University of York, York, UK*
[c]*Department of Applied Economics, University of Granada, Granada, Spain*
[d]*Centre for Research on Health and Social Care Management, Bocconi University, Milan, Italy*
[e]*Department of Policy Analysis and Public Management, Bocconi University, Milan, Italy*

Rothery 2017

- Aim: Extend the ideas from Claxton 2016 and apply to medical devices
- Devices are different because of:
  - learning curve,
  - incremental innovation,
  - capital costs,
  - different/dynamic pricing horizon

Kirwin 2022


Value in Health
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HEALTH POLICY ANALYSIS | ARTICLES IN PRESS
A Conceptual Framework for Life-Cycle Health Technology Assessment
Erin Kirwin, MA • Jeff Round, PhD • Ken Bond, MA • Christopher McCabe, PhD
Open Access • Published: February 03, 2022 • DOI: https://doi.org/10.1016/j.jval.2021.11.1373

Kirwin 2022: Standard HTA Procedures

- In most cases, standard HTA happens after or concurrent to regulatory approval (safety and effectiveness).
- Assessment: Review sponsor evidence dossier, clinician and patient input, HTA agency commissions or conducts a review of the clinical evidence. Often review economic evaluation.
- Appraisal: results are reviewed and discussed by recommendation body. Can also consider issues such as equity, acceptability, as well as input from stakeholders.
- Recommendations typically take the form of (i) recommend, (ii) recommend with conditions/restrictions, or (iii) do not recommend.

Kirwin 2022: Challenges w/ Standard HTA

- Health System Sustainability
  - Without de-adoption, approval at threshold value implies budgets will continually expand
- Evolving Evidence
  - Evidence for new and existing technologies is continually evolving, impacts other technologies (complements or substitutes).
  - No formal mechanisms for review.
- Uncertainty
  - Structural/Parameter/Methodologic
  - Characteristics of a technology, care pathway, future events
  - Risk of wrong decision

Kirwin 2022: Aim and Objectives

- "We aim to address these challenges through our conceptual framework for life-cycle health technology assessment (LC-HTA), designed to improve outcomes for patients, payers, and sponsors."
- Essentially, we are developing a framework to address these three issues.
- Builds upon Walker 2012, Claxton 2016, Rothery 2017, but with a process oriented set of decision rules, and specific conditions for when reassessment is required, and a lesser focus on OIR vs AWR

LC-HTA Framework: ROMA

Research-Oriented Market Access (ROMA)

- Contractual agreements for technologies with a lot of uncertainty regarding cost-effectiveness.
- Contract defines a research protocol that will be implemented (incl. duration, data sources that will be used, and re-assessment terms)

LC-HTA Framework: Prices & Risks

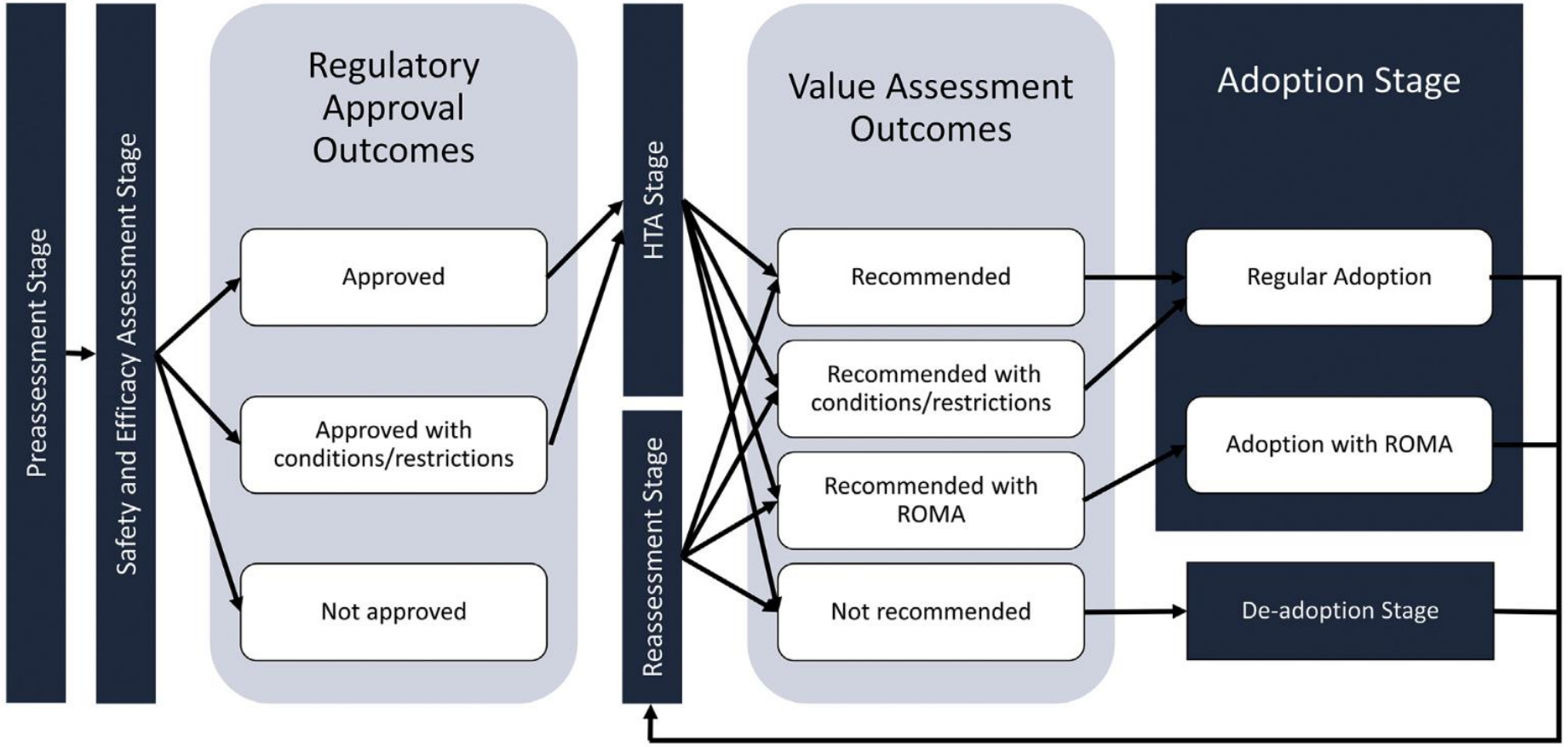
- A theoretic max acceptable price for each tech is the **Value-Based Price**, the price at which the ICER = CET, or NMB = 0. Problem is, this implies indifference between technologies that have different uncertainty but same NMB.

- Alternative is the **Risk-Based Price**, based on the payer risk tolerance: max monetary risk the payer is willing to accept for a wrong decision. The risk-based price is the price at which, for any given value threshold, the EVPI is equal to payer risk tolerance. Finally, the critical price is defined as the lesser of the value-based price and the risk-based price.

- For risk-averse decision makers, the **Critical Price** is defined as the lesser of the value-based price and the risk-based price.

Kirwin 2022

Figure 1. The LC-HTA framework. Dark shaded square boxes represent LC-HTA stages as introduced in the section The LC-HTA Framework; lighter shaded rounded boxes represent outcomes. White rounded boxes represent statuses within stages and outcomes.



LC-HTA indicates Life-cycle health technology assessment; HTA, health technology assessment; ROMA, research-oriented managed access.

LC-HTA Framework: Regulatory Stage

- Small changes relative to standard HTA
  - Regulatory and HTA agencies engage in greater information sharing relating to analyses regarding technologies, and communication regarding likely timelines and outcomes of regulatory processes. (ie R2D2 in Canada)
  - This improves the efficiency of the overall regulatory and review process.

Outcomes

i. Allow market access,
ii. Allow market access with conditions/ restrictions, or
iii. Do not allow market access.

LC-HTA Framework: HTA Stage

- Formulating the Decision Problem
  - Clearly articulate the decision problem, critical to ensure consistency in analyses and decisions
- Evidence review and synthesis
  - Full systematic review, not limited to submitted evidence dossier
  - Analysis of relevant care pathways, patient and clinician engagement/consultation
  - Identification of real-world evidence (RWE) sources that capture care-related information (diagnosis, treatment, outcomes)

LC-HTA Framework: HTA Stage

- De-novo Model development and VOI analysis
  - Develop a de-novo health economic model, reflecting care pathway in jurisdiction and designed to accommodate RWE (reduces structural uncertainty, could reduce parameter uncertainty)
  - Structured to allow efficient VoI

Outputs:

- The expected NMB should be estimated, with a PSA to quantify uncertainty
- EVPI
- The value-based price
- The risk-based price
- The Expected Value of Perfect Parameter Information (EVPPI) for key model parameters

LC-HTA Framework: HTA Stage Outcomes

i. When no conditions or restrictions are required, and the sponsor submitted price is less than or equal to the critical price, HTA agencies should recommend adoption.

ii. When the evidence indicates that adoption of the technology should only be made for specific indications or patient groups (e.g. patients with specific genetic mutations, or only following unsuccessful treatment with other technologies), OR when the sponsor submitted price is greater than the critical price, AND the value-based price is less than the risk-based price, the HTA agency should recommend adoption with conditions/ restrictions.

iii. When the sponsor submitted price is greater than the critical price, AND the risk-based price is less than the value-based price, the HTA agency should recommend ROMA. Under ROMA, on-market research will be undertaken to reduce uncertainty.

iv. When the evidence indicates that the technology will not have a positive NMB at any price that is acceptable to the sponsor, the HTA agency should not recommend adoption.

LC-HTA Framework: Adoption Stage

- Regular Adoption:
  - Contractual agreement describes the inputs, process and decision rules of re-assessment
- Re-assessment under one of four conditions:
  - Regulatory changes
  - Health system activities
  - New evidence
  - HTA method changes

LC-HTA Framework: ROMA

Protocol Development:

- Candidate ROMA protocols should be developed based on EVPPI results, using the risk-based price
- Either only-in-research or only-with-research designs, later more likely
- Two additional simulation components:
  - RWE generation model and
  - Technology diffusion model
- Use these models to simulate evidence generated over time for each design
- Estimate the Expected Net Benefit of Sampling (ENBS, given optimal duration for each design)

Protocol Implementation:

- If at least one protocol has a positive ENBS, ROMA possible
- Design with highest ENBS should be prioritized
- Contractual agreement must include data read-out periods and stopping conditions
- RWE analyzed at each read-out period to evaluate if stopping conditions have been met.
- Once met or at end of ROMA term, the same 4 HTA-Stage Outcomes are available: approve, approve with conditions, approve with (more) ROMA, do not approve.

LC-HTA Framework: No Adoption Stage

- Technologies are not adopted under two circumstances:
  - If tech will not have a positive ENB at any price that is acceptable to the sponsor
  - When prices that are acceptable to both the sponsor and the payer cannot be negotiated

- Same re-assessment criteria as regular adoption!
  - Regulatory changes
  - Health system activities
  - New evidence
  - HTA method changes

LC-HTA Framework: Re-assessment Stage

- With ROMA
  - When research reports, new evidence is synthesized with same outcomes as before

- Without ROMA
  - Triggered when any of the four contracted conditions arises (Regulatory changes, health system activities, new evidence, HTA method changes)
  - Submissions for re-evaluation can be made by any party (sponsor, patients, clinicians). Must indicate the basis for re-assessment (ie new evidence or new submitted price).

Discussion: Challenges Addressed

Challenge	Solution
Sustainability	- Fair prices through value-based and risk-based prices - Sponsor benefit: faster access to market - Payer benefit: protection from incorrect decision - Patients: access for those tech is indicated for, others benefit by preservation of budget
Evolving Evidence	- Responsive to evolving evidence - Contributes to the generation of new evidence
Uncertainty	- Structural: resolved by aligning the model to the relevant care pathway and jurisdiction - Parameter: addressed by including evidence outside of dossier, updating information through ROMA (efficient using VOI) - Linkage of uncertainty to risk, decision rules which are responsive to risk, and mechanisms to share the burden of risk between payers and sponsors.

Discussion: Implementation

- Challenge of adjusting current processes – evidence from NICE show that incremental approaches have not been successful

- Resource implications: methods proposed are complex and there are a small number of skilled/qualified people to implement them.
  - Long term efficiencies (updating de-novo models when developed) could mitigate this, as could information sharing between regulatory and HTA bodies, as well as between HTA agencies internationally.

Wrap-Up

1. How uncertainty changes regulatory/reimbursement decisions
2. What is ROMA and the life-cycle approach to HTA
3. How we can measure and price uncertainty with VOI

4. That VOI is easier to implement than you may think

VOI Implementation

https://github.com/IHECA/Roma-Workshop-2023

R Demonstration