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Improving healthcare decisions

Introduction to HTA

Educational Seminar

ISPOR Dubai – September 19, 2018

Educational Seminar: Introduction to HTA

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Educational Seminar: Introduction to HTA

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Health Technology Assessment and international collaboration

ISPOR Dubai 2018

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What is HTA ?

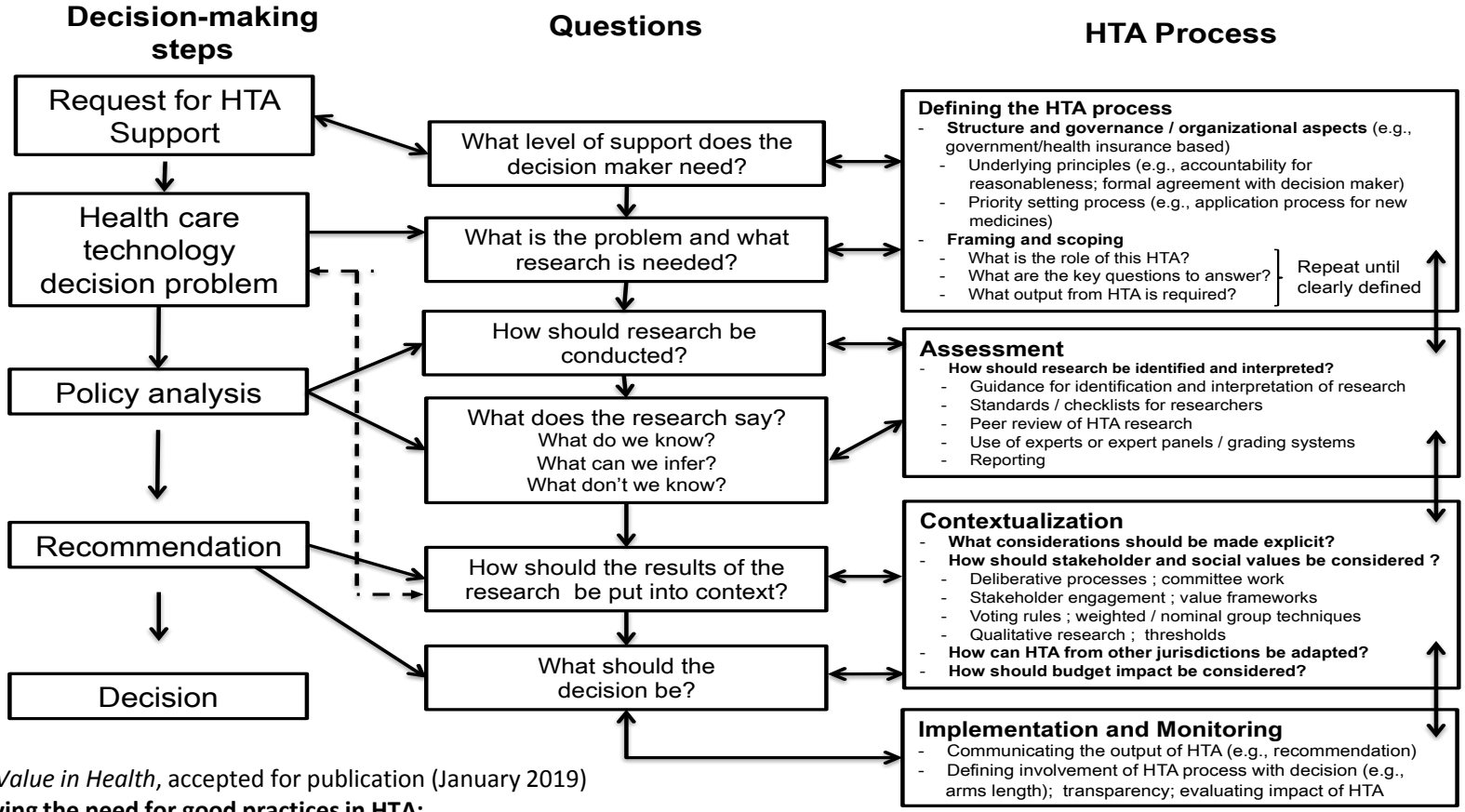
What is Health Technology Assessment?

ISPOR HTA CENTRAL (web resource) explains HTA this way:

> "an evidence-based, **multidisciplinary process** intended to **support healthcare decision making** by **assessing** properties and effects of one or more new or existing health technologies **in comparison** with a current standard. Aiming at **determining added value**, HTA uses **explicit analytical frameworks** based on research and the scientific method in a **systematic, transparent, unbiased** way"

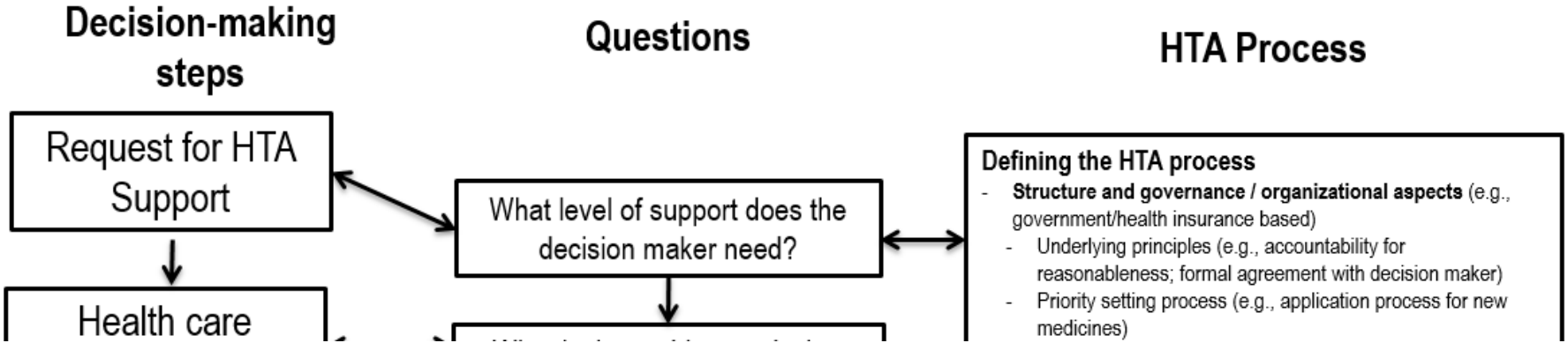
Source: ISPOR HTA Central
www.ispor.org/strategic-initiatives/hta-central

Components of HTA within the healthcare decision-making process



Source: *Value in Health*, accepted for publication (January 2019)
"**Identifying the need for good practices in HTA: Summary of the ISPOR HTA Council Working Group Report**"

Request for HTA



Source: *Value in Health*, accepted for publication (January 2019)
"**Identifying the need for good practices in HTA: Summary of the ISPOR HTA Council Working Group Report**"

Defining the HTA process

- **Structure and governance / organizational aspects** (e.g., government/health insurance based)
  - Underlying principles (e.g., accountability for reasonableness; formal agreement with decision maker)
  - Priority setting process (e.g., application process for new medicines)

Source: *Value in Health*, accepted for publication (January 2019)
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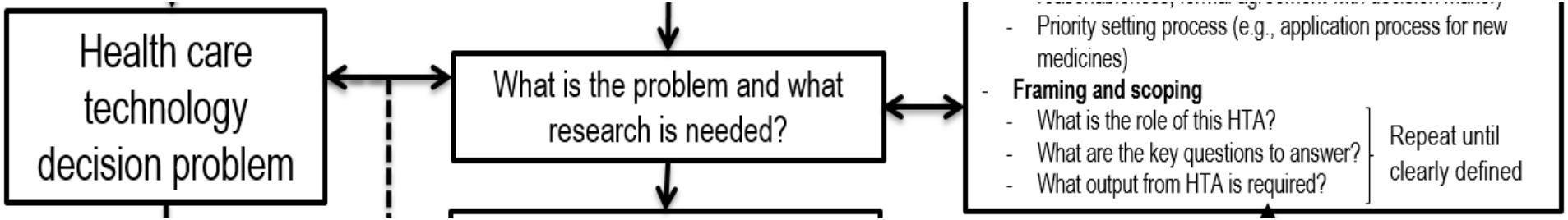
Healthcare technology decision problem



Source: *Value in Health*, accepted for publication (January 2019)
"**Identifying the need for good practices in HTA: Summary of the ISPOR HTA Council Working Group Report**"

Defining the HTA process

- **Framing and scoping**
  - What is the role of this HTA?
  - What are the key questions to answer?
  - What output from HTA is required?

} Repeat until clearly defined

Source: *Value in Health*, accepted for publication (January 2019)
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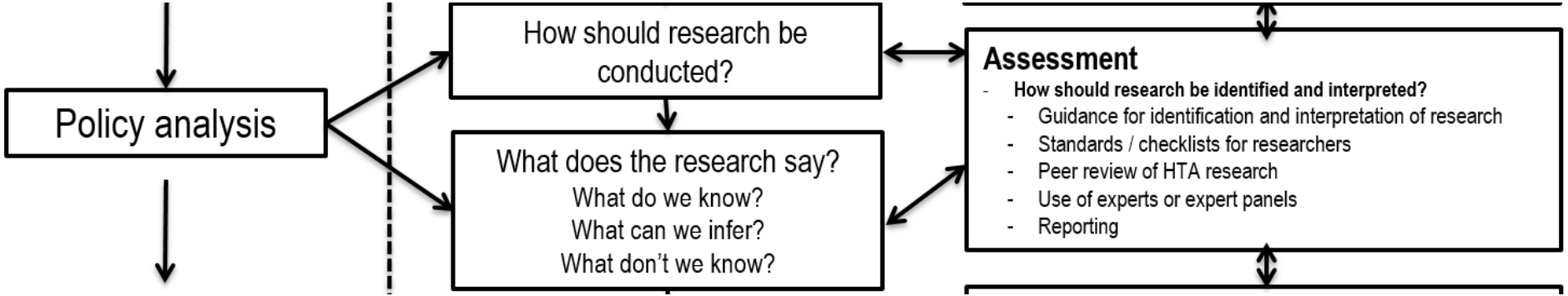
Policy analysis and assessment



Source: *Value in Health*, accepted for publication (January 2019)
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Assessment

Assessment

- **How should research be identified and interpreted?**
  - Guidance for identification and interpretation of research
  - Standards / checklists for researchers
  - Peer review of HTA research
  - Use of experts or expert panels
  - Reporting

Source: *Value in Health*, accepted for publication (January 2019)
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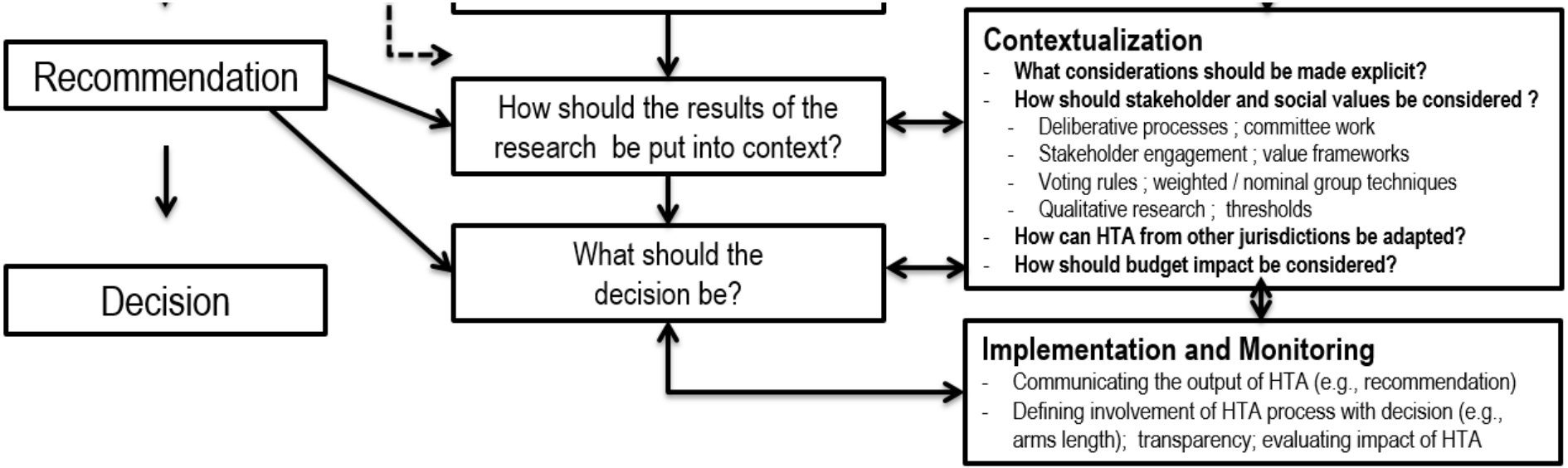
Informing recommendations and decisions



Source: *Value in Health*, accepted for publication (January 2019)
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Contextualization (appraisal)

Contextualization

- **What considerations should be made explicit?**
- **How should stakeholder and social values be considered ?**
  - Deliberative processes ; committee work
  - Stakeholder engagement ; value frameworks
  - Voting rules ; weighted / nominal group techniques
  - Qualitative research ; thresholds
- **How can HTA from other jurisdictions be adapted?**
- **How should budget impact be considered?**

Source: *Value in Health*, accepted for publication (January 2019)
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Implementation

Implementation and Monitoring

- Communicating the output of HTA (e.g., recommendation)
- Defining involvement of HTA process with decision (e.g., arms length); transparency; evaluating impact of HTA

Source: *Value in Health*, accepted for publication (January 2019)
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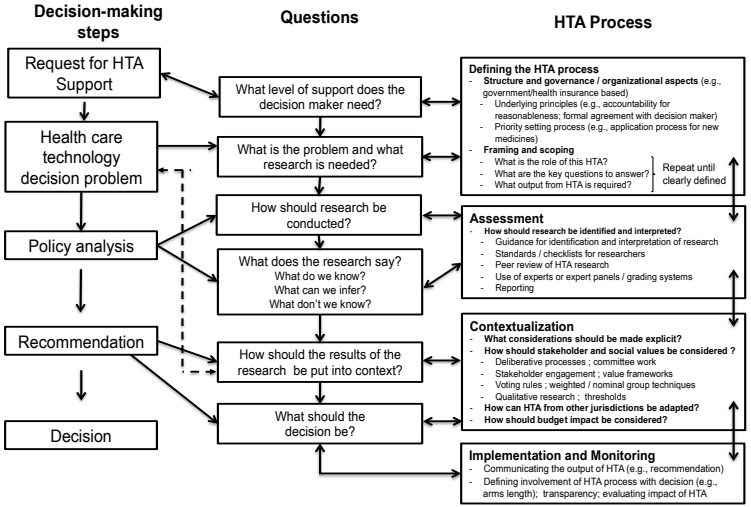
Scientific and technical cooperation in HTA – with a view to EUnetHTA, European network for HTA

Using results of research and applying scientific methodology

"HTA uses **explicit analytical frameworks** based on research and the **scientific method*** in a systematic, transparent, unbiased way"

* **Definition of scientific method: principles and procedures** for the **systematic pursuit of knowledge** involving the recognition and formulation of a **problem**, the collection of **data** through **observation and experiment**, and the **formulation and testing of hypotheses** (MERRIAM-WEBSTER DICTIONARY)

Components of HTA within the healthcare decision-making process



Source: Value in Health, accepted for publication (January 2019)

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National / local context

Globalize the evidence, localize the decision

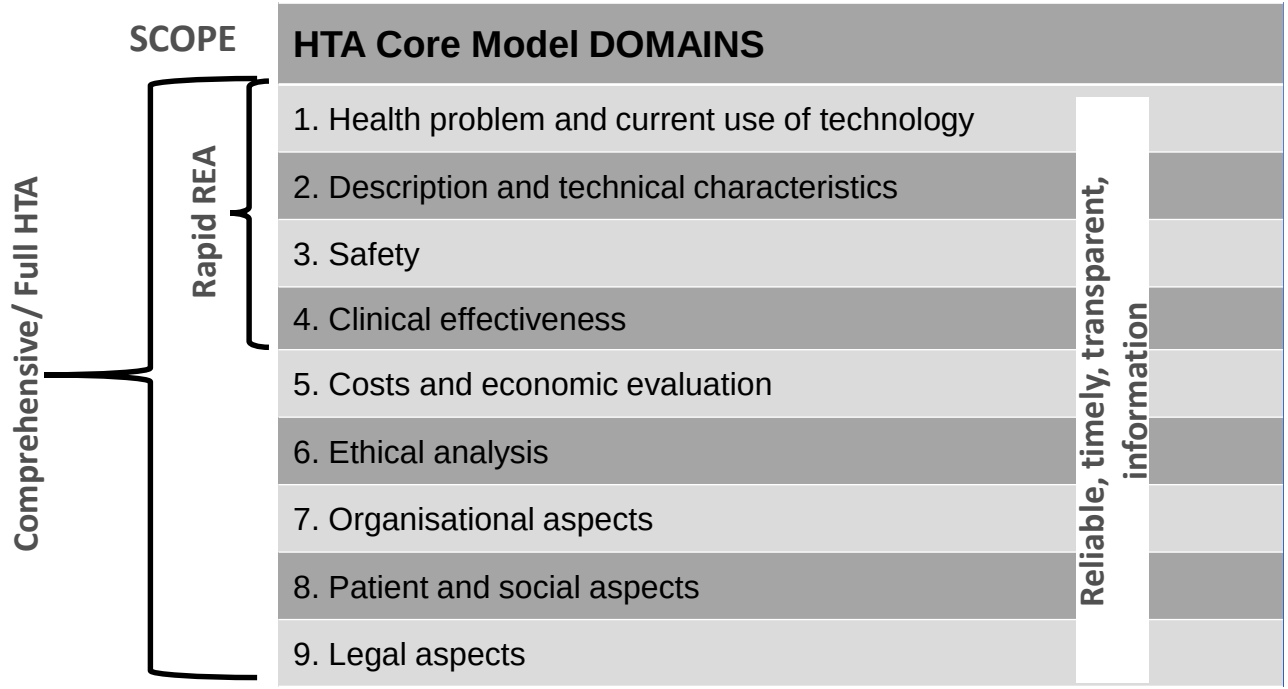
J.M. Eisenberg

Locate the decision, globalize the evidence, localize the reporting

EUnetHTA

National / local context

The Domains of the HTA Core Model® - assessing dimensions of value



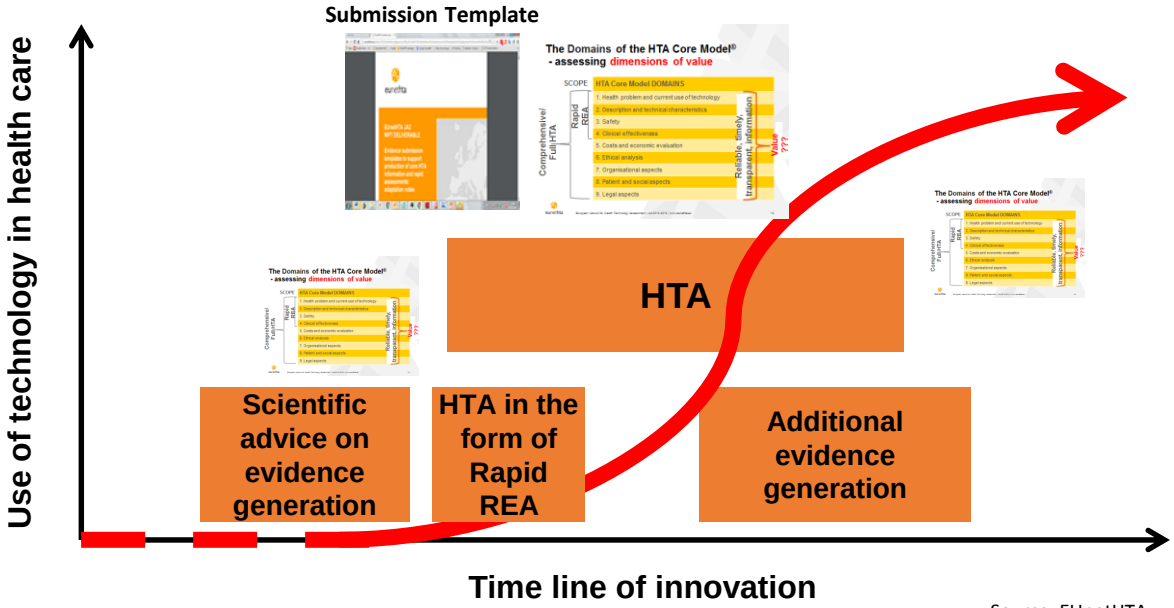
Source: EUnetHTA
www.eunethta.eu

LEGO® the obvious analogue of the HTA Core Model®

EUnetHTA → → → → → → → → → → →
Project JA1 JA2 JA3

Source: EUnetHTA
www.eunethta.eu

HTA along the Health Technology Life-cycle – the HTA Core Model provides framework



Source: EUnetHTA
www.eunethta.eu

Educational Seminar: Introduction to HTA

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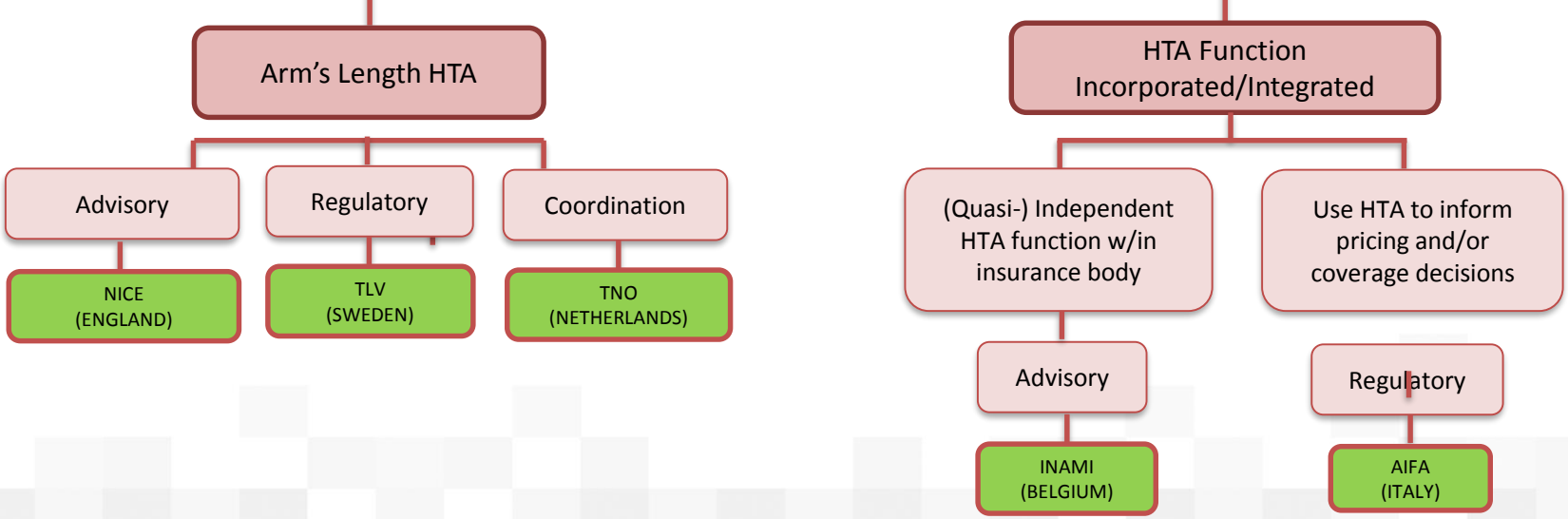
Approaches to HTA Implementation

Panos Kanavos, PhD
London School of Economics
ISPOR Dubai, September 2018

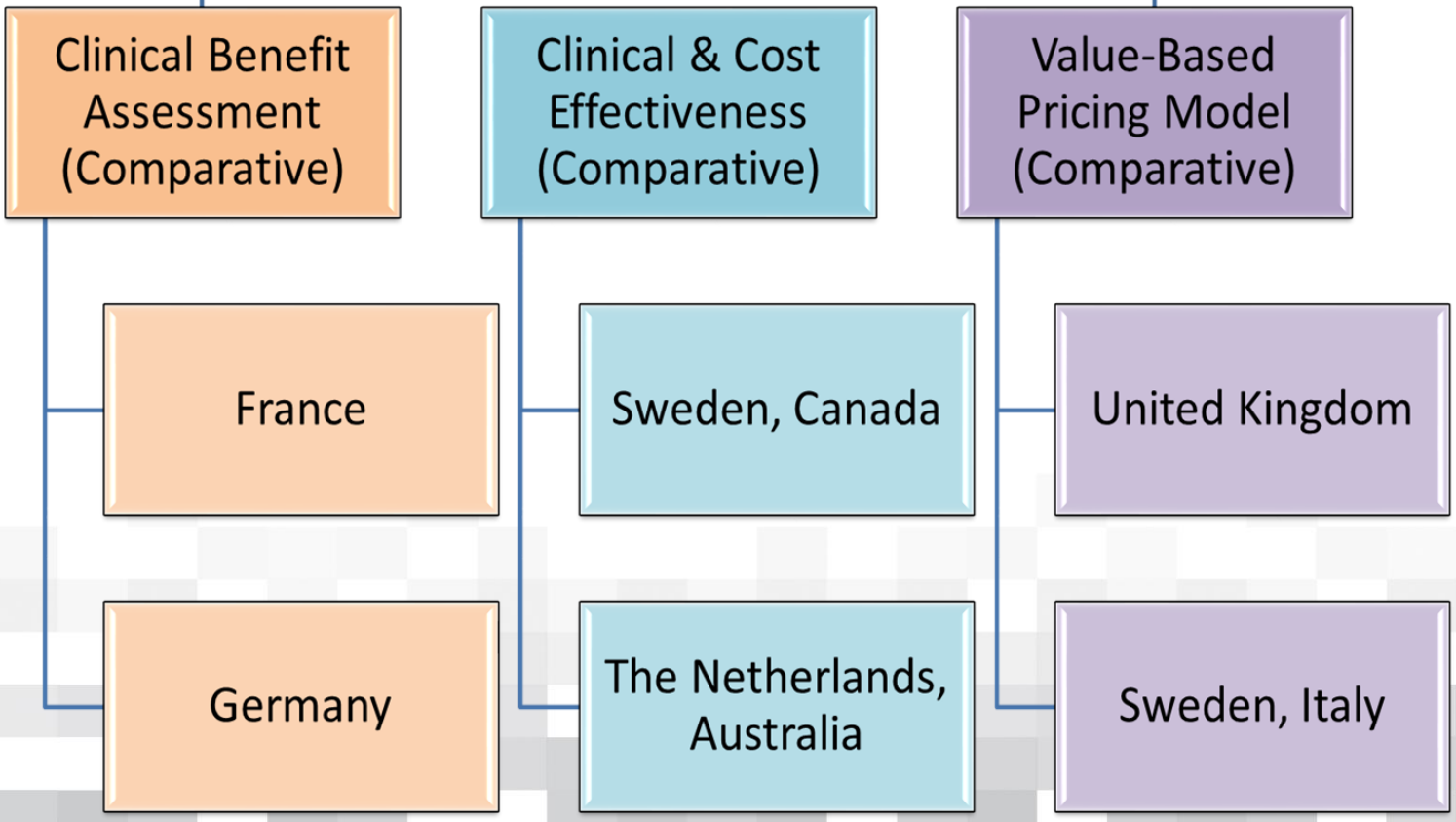
LSE THE LONDON SCHOOL OF ECONOMICS AND POLITICAL SCIENCE

A Taxonomy of HTA Systems



HTA systems are not the same in more dimensions than one: (a) Governance (system); (b) Model of HTA; (c) Topic selection; (d) Evidence and data requirements; (e) Type of evidence considered; (f) Analytical design; (g) Assessment Methods; (h) Perspective adopted; (i) How do we deal with affordability and budget impact; (j)Role of stakeholders; (k) Balancing Efficiency (utilitarianism) and Fairness (egalitarianism); (l) Dissemination; and (m) Implementation.

A taxonomy of HTA models



Clinical and Cost Effectiveness Seeks to Answer Two Questions

Question 1

1a) Is the particular technology, in comparison to the current standard of care:

- Less effective?
- Just as effective?
- More effective?

1b) If it is more effective – by how much?

- Longevity?
- Quality of life?

Clinical effectiveness

Question 2

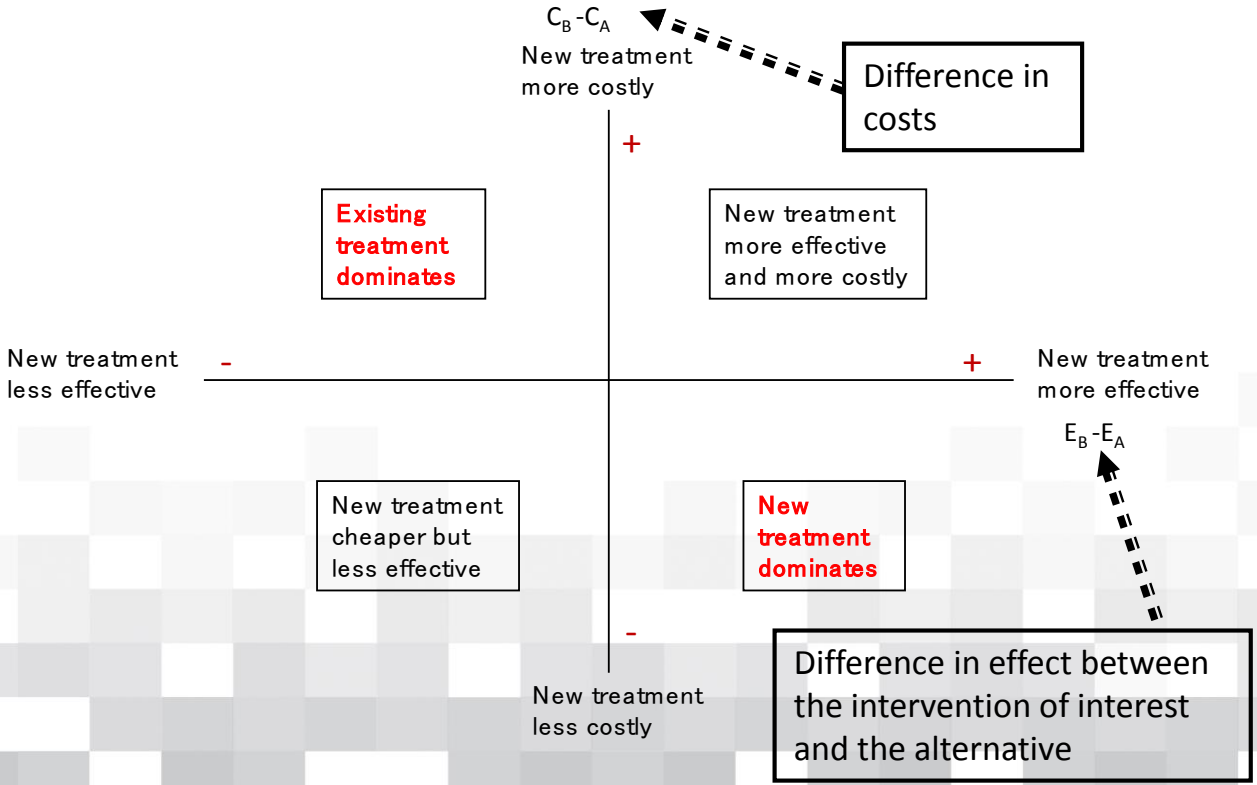
2) Does the cost of the particular technology provide:

- No value-for-money?
- Poor value-for-money?
- Good value value-for-money?

Cost effectiveness

Incremental cost-effectiveness ratio (ICER)

Cost-effectiveness plane



Incremental cost-effectiveness ratio (ICER)

$$ICER = \frac{\Delta \text{costs}}{\Delta \text{effectiveness}} = \frac{Cost_{\text{int}} - Cost_{comp}}{Eff_{\text{int}} - Eff_{comp}}$$

- Higher *ICERs* indicate lower cost-effectiveness
- But what does this *ICER* tell the decision makers?
- A new intervention is found to be more effective and more expensive but…..
- It is necessary to have further information to determine whether society considers this additional benefit to be worth the additional cost involved

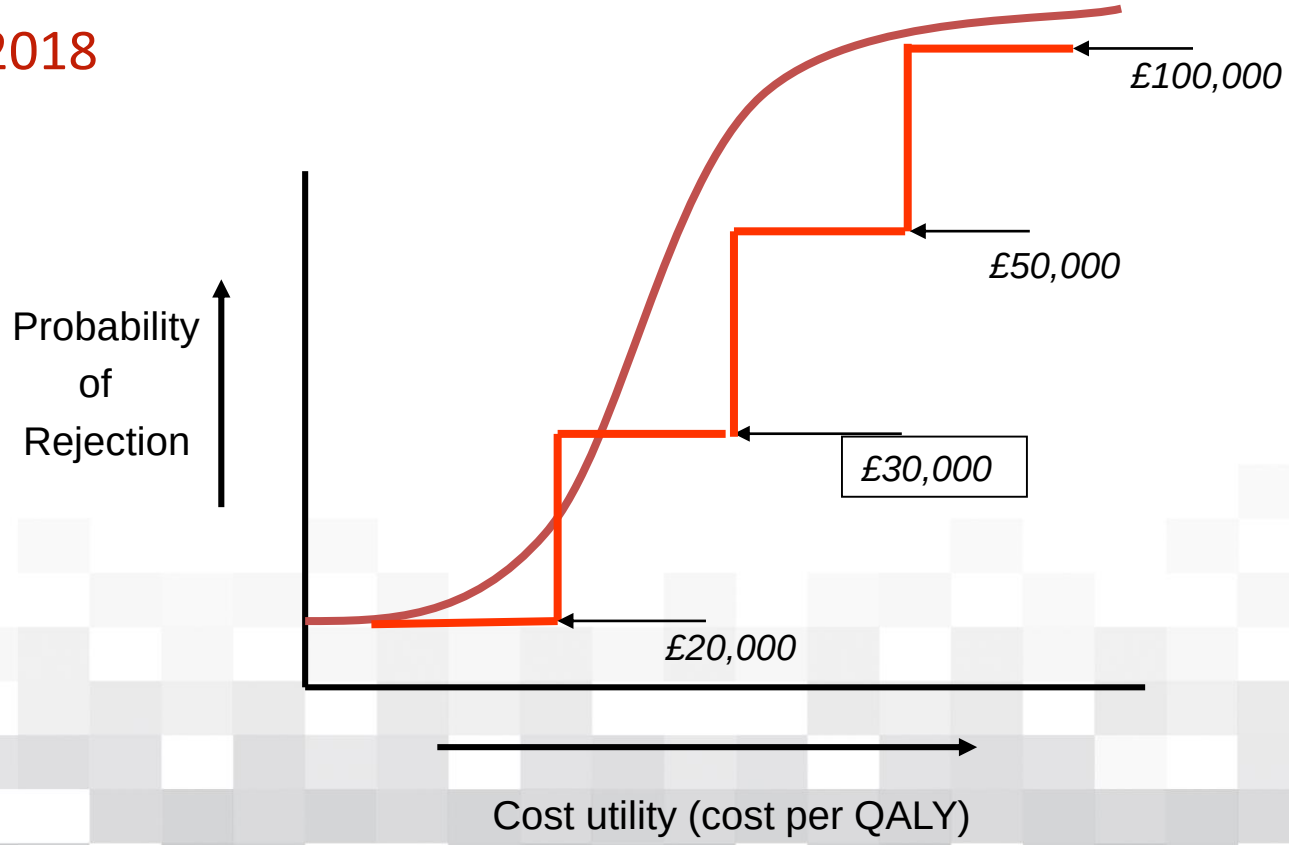
- To do this, an **external value** system is needed - something to compare the *ICER* to:
  - 'Cut-off point' , 'ceiling value', threshold (λ) for the *ICER*
  - λ represents the maximum amount society is willing to pay for a unit increase in health benefits (**maximum price or shadow price of a unit increase in the health benefits**)

$$ICER = \frac{Cost_{\text{int}} - Cost_{comp}}{Eff_{\text{int}} - Eff_{comp}} < \lambda$$

UK thresholds: NICE (England) (1)

- Current UK threshold set at £20,000 per QALY to £30,000 per QALY
- Plus £50,000 per QALY for end-of-life treatments (QALYs valued at 2.5 times the standard QALY)
- Plus £100,000 per QALY for rare disease treatments
- Plus if budget impact exceeds £20 million per annum, for each of the first three years of adoption commercial negotiation triggered between NHS England and company
  - Negotiation covers affordability, price or introduction via various payment mechanisms (e.g. patient access schemes)

The Cost Effectiveness (WTP) Threshold and how NICE works it out in 2018



UK Thresholds: SMC (Scotland)

- £20,000 - £30,000 per QALY threshold
- Plus:
  - Evidence of a substantial improvement in life expectancy (with sufficient quality of life to make the extra survival desirable.
    - Normally be a median gain of 3 months but the SMC assesses the particular clinical context in reaching its decision
  - Evidence of a substantial improvement in quality of life (with or without survival benefit)
  - Evidence a sub-group of patients may derive specific or extra benefit and medicine can be targeted at this sub-group
  - Absence of other therapeutic options of proven benefit for the disease in question and provided by the NHS
  - Possible bridging to another definitive therapy (eg bone marrow transplantation or curative surgery) in a defined proportion of patients
  - Emergence of a licensed medicine as an alternative to an unlicensed product that is established in clinical practice in NHS Scotland as the only therapeutic option for a specific indication

What kind of questions are we trying to address with HTA through Comparative Clinical Benefit Assessment? (demonstrate with example: France)

Comparative Clinical Benefit Assessment:
Indicator 1: Actual Medical Benefit (SMR)

Definition

- "***Service Médical Rendu***" (SMR, medical service rendered or actual medical benefit)
- **Assesses the intrinsic value of the drug**
- 4 levels: important, moderate, light, insufficient
- SMR is a driver for reimbursement rate:
  - Important: 65%
  - Moderate: 30%
  - Low: 15%
  - Insufficient: no reimbursement

How is actual medical benefit set?

Takes into account 5 criteria, as follows:

- Severity of the disease and its impact on morbidity and mortality
- Clinical efficacy/effectiveness and safety of the medicine
- Aim of the drug: preventive, symptomatic or curative
- The therapeutic strategy with regards to therapeutic alternatives
- Impact in terms of public health (burden of disease, health impact at the community level, transposability of clinical trial results)

Comparative Clinical Benefit Assessment
Indicator 2: Improvement in clinical benefit (ASMR)

- 5 levels: major (ASMR I), important (ASMR II), moderate (ASMR III), low (ASMR IV) and no improvement (ASMR V)
- ASMR is a driver for pricing
- Assessment of the therapeutic or diagnostic progress provided by the new drug in terms of efficacy and tolerability compared to existing therapies
- Need for the appropriate identification of the pertinent comparator(s) -> no comparator allowed if other drug development took place in the same period of time (3 years)
- Results of comparison take into account
  - Clinical pertinence of the main criteria
  - The evidence
  - The quantity of effect and its clinical significance
- Indirect comparisons are acceptable if done following local (HAS) guidelines
- ASMR I or V: easy case
- Non inferiority demonstrated: ASMR V
- In case of demonstration of superiority the *importance of the difference* quantifies the ASMR
  - A major therapeutic progress (ASMR I) is for drugs that have a demonstrated effect on mortality in a severe disease
  - Minor, moderate or important ASMR qualifies the additional clinical effect in terms of efficacy and tolerance
  - New modalities of administration, new galenic can be considered as a progress if its clinical interest is demonstrated
- ASMR II; III and IV -> experience of the commission/history of the decision taken
- One drug can be given different levels of ASMR depending on:
  - Their indication: breast cancer/pancreas cancer
  - The population targeted: RAS mutant/wild type
- Ensuring equity of treatment from one appraisal to another: Experience; Past decisions; Re-assessment of all drugs in the same therapeutic strategy

Comparative Clinical Benefit Assessment: Link to Pricing

Added value	ASMR	Pricing consequences
Major	**I**	Possibility of a higher price as compared to comparators Faster access (price notification instead of negotiation) and price consistency with European ones.
Important	**II**	Possibility of a higher price as compared to comparators Faster access (price notification instead of negotiation) and price consistency with European ones.
Moderate	**III**	Possibility of a higher price as compared to comparators Faster access (price notification instead of negotiation) and price consistency with European ones.
Minor	**IV**	Possibility of a higher price as compared to comparators. For other ASMR IV, depends on the target population • If same target population as the comparator: no price advantage (but advantage in terms of market share) • Situation is different if ASMR is focused on a restricted population
No clinical improvement	**V**	The drug can be listed only if the costs are less than the comparators: • Lower price Or induces cost saving

What constitutes “evidence”?

1. Randomised controlled trials
2. Observational studies
3. Systematic reviews
4. Clinician-based evidence and advice
5. Patient evidence

Avoiding “hierarchies” of evidence

But this argument resonates differently in different settings

Decision-making

- What kind of judgements are we making (irrespective of the model of HTA)?

Scientific judgements

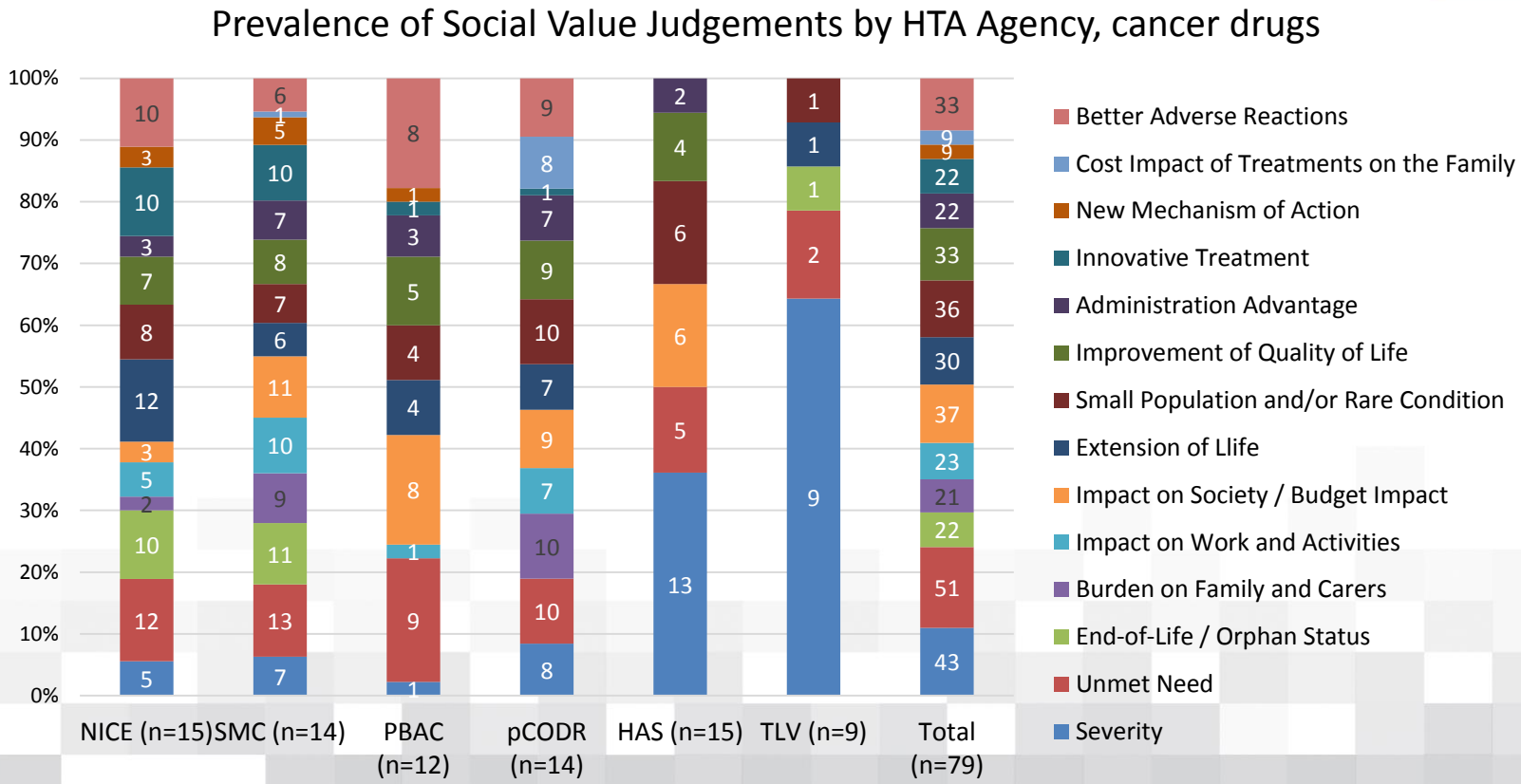
- Reliability/Quality of the evidence-base
- Appropriateness of sub-groups and the associated analysis
- Generalisability in population
- Capturing quality of life adequately
- Handling uncertainty

Social value judgements (SVJs)

- Severity of disease
- End of life interventions ("rule of rescue")
- Age
- Health inequalities

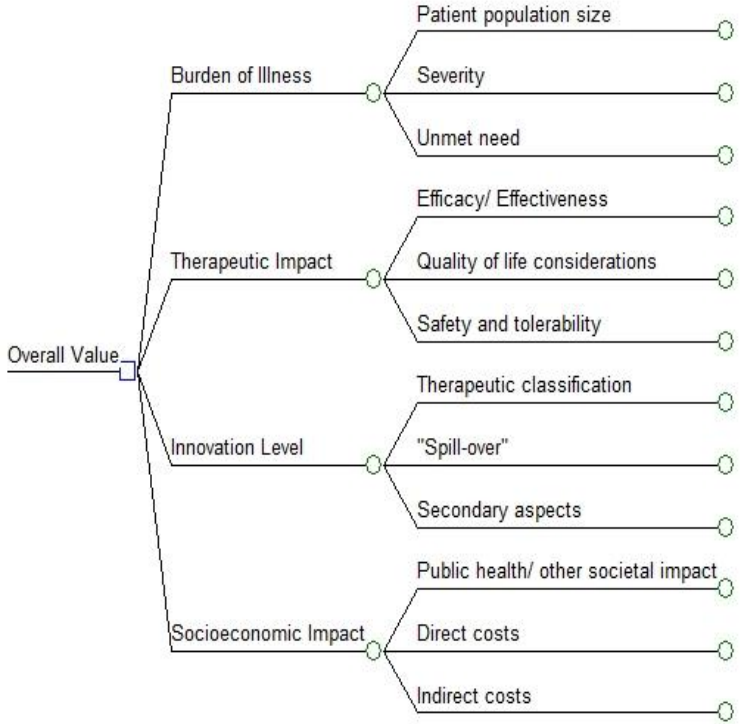
- SVJs are taken into account, but there is lack of appropriate metrics
- SVJs can be 'revealed' (e.g. 'rarity' or 'end of life criteria') but can also be 'implicit' judgements based on treatment characteristics or the disease profile

Social value judgements across 7 HTA agencies, cancer drugs



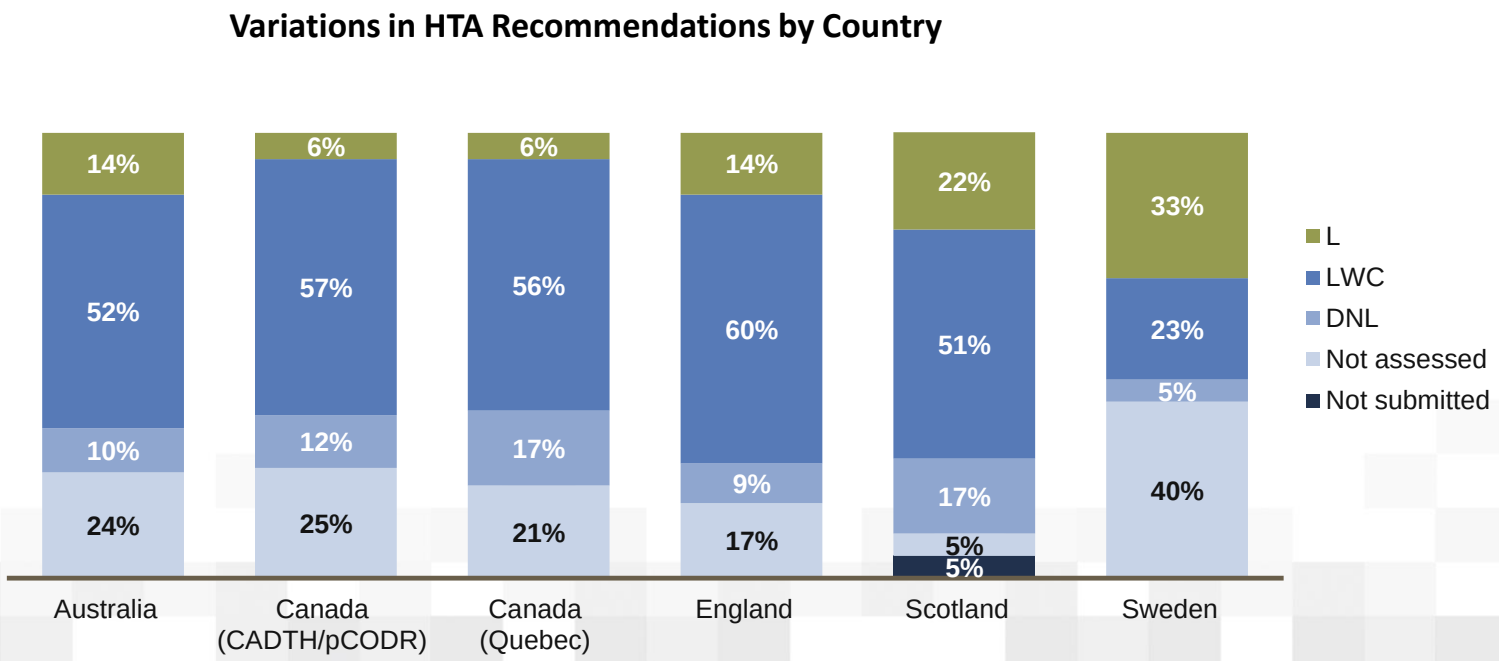
From Cost-effectiveness to Value-Based Pricing: Analytical Design and MCDA

- Countries employ several different criteria to guide assessments.
- While almost all countries firstly consider therapeutic benefit, other factors frame the analysis and shape coverage decisions
- Back to Social Value Judgements
  - Disease burden
  - Patient quality of life (QoL)
  - Budget impact
  - Availability of alternative treatments
  - Level of Innovation
  - Societal perspective and impact on individual, carer, family
- To some extent, level of innovation, equity, and social and ethical implications are considered.
- As a result, multiple criteria are used, but not clear how individual parameters of value contribute to decision-making; rise of MCDA



Source: Kanavos and Angelis, 2016.

There are significant variations in HTA recommendations across countries (N=606)

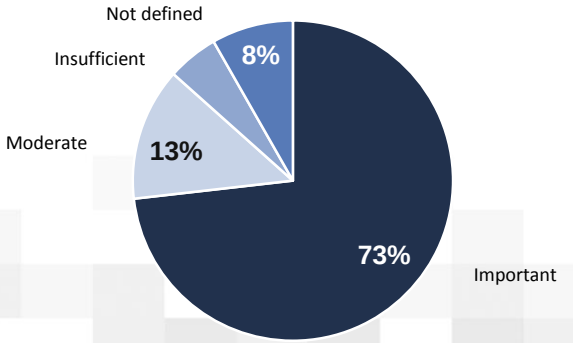


Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; DNL, do not list; L, list; LWC, list with criteria; pCODR, pan-Canadian Oncology Drug Review.
N=606 drug-indication pairs across Australia, Canada, England, Scotland, and Sweden (2012-2017).
Source: LSE, September 2017.

Assessment of Comparative Benefits Designation is Critical for Pricing in France

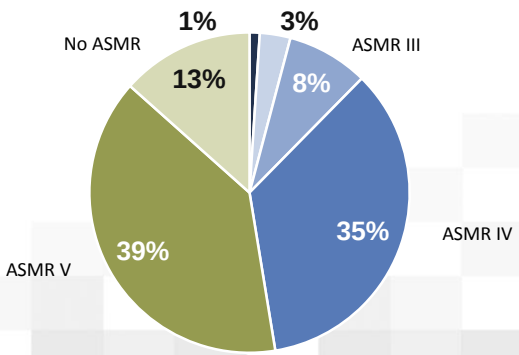
- The Transparency Commission's SMR rating is the first hurdle in demonstrating clinical benefit to society. The greater challenge is demonstrating improvement over current standard of care therapies through ASMR rating.
- The SMR rating determines reimbursement level, while the ASMR rating is the basis for pricing negotiations.

Variations in SMR (Actual Medical Benefit) Recommendations



N=97 drug-indication pairs (2012-2017).

Variations in ASMR (Improvement in Actual Medical Benefit) Recommendations

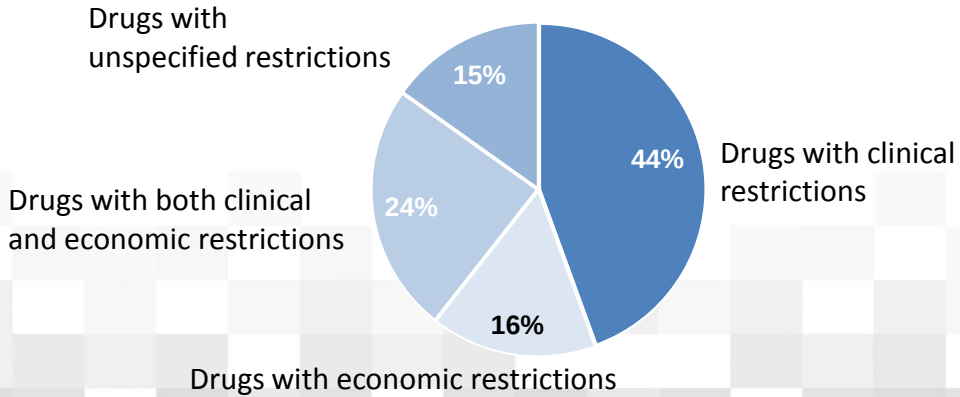


Note: ASMR I, Major; ASMR II, Important; ASMR III, Moderate; ASMR IV, Minor; ASMR V, Non-Existent.
N=97 drug-indication pairs (2012-2017).
Source: LSE, September 2017.

HTA Agency Restrictions to Protect Budgets From New Drugs with Clinical/Economic Uncertainties

- Over 53% of the drug-indication pairs analyzed across seven countries achieved List With Criteria recommendations, subject to various clinical and economic restrictions on product usage and taking into account budget impact.
- Most of the restrictions placed on drugs receiving LWC recommendations are clinical in nature rather than economic, highlighting the importance of high quality clinical evidence (e.g., trial design, evidence on hard endpoints, comparators) that HTA agencies place on new evidentiary submissions.

Variations in Restricted Recommendations



Abbreviation: LWC, List with criteria.
N=502 data points across Australia, Canada, England, France, Germany, Scotland, and Sweden (2012-2017).
Source: LSE, September 2017.

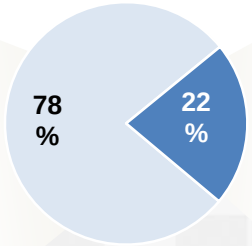
Restricted Recommendations on Product Utilization Emphasize HTA Agency Focus on Quality Clinical Evidence

Variations in Restricted Recommendations

Clinical restrictions

Economic restrictions

Clinical restrictions	
Limited to specific patient subgroup	59%
Limited to use within therapeutic pathway	13%
Restricted to specialist prescribing	9%
Special monitoring required	7%
Subject to special status/exception list	5%
Subject to dosing regimen restrictions	4%
Restrictions similar to other drugs in same class	2%



Economic restrictions	
Subject to managed entry agreement	53%
Funding conditional to improved cost-effectiveness	13%
Limited reimbursement	12%
Cost similar to other drugs in same class	10%
Funding conditional to drug price reduction	7%
Subject to duration/administration restrictions	4%

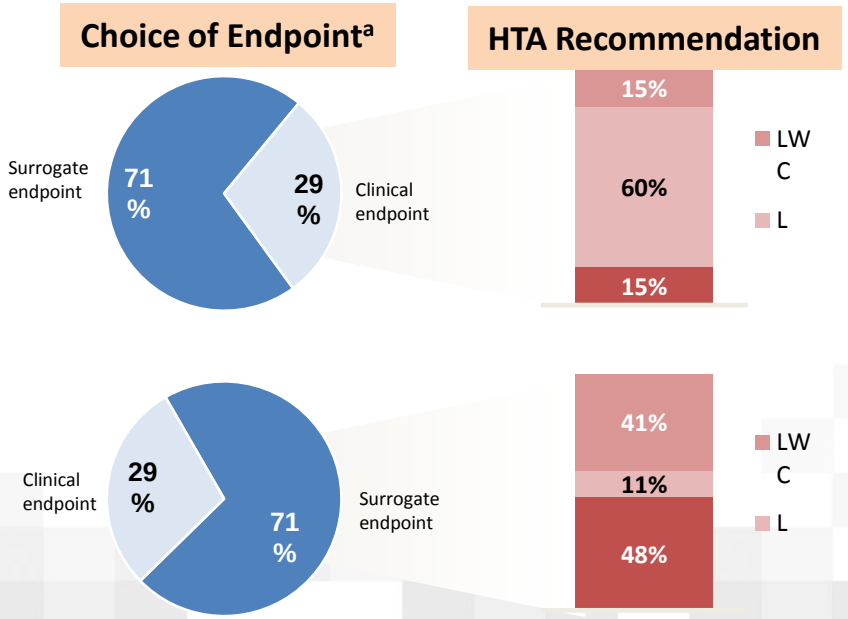
Abbreviation: LWC, List with criteria.
N=814 restrictions across Australia, Canada, England, France, Germany, Scotland, and Sweden (2012-2017).
Source: LSE, September 2017.

Use of Clinical Endpoints Increase the Probability of Positive HTA Recommendations

Use of surrogate endpoints is far more likely to lead to negative appraisals (i.e., either do not list or list with criteria). Dependence on surrogate endpoints must be properly validated in appropriate therapeutic context to avoid outright HTA rejections.

[The National Authority for Health] is quite tough on criteria, they prefer to have actual clinical endpoints and not surrogate endpoints and outcomes. – France

No manufacturer has ever properly validated its surrogate endpoints, so we don't use it. Our decision is always based on clinical endpoints. – Germany



Abbreviations: DNL, do not list; L, list; LWC, list with criteria.
[a] Clinical endpoint, overall survival; surrogate endpoint, progression-free survival.
N=24 cancer drug-indication pairs across Australia, Canada, England, France and Scotland (2012-2016).
Source: LSE Database, September 2017.

Underlying Reasons for 'Reject' Recommendations

- Study design is the most cited reason for a Do Not List recommendation across markets. HTA agency reservations over study design can foster reservations over clinical benefit and evidence, highlighting the need for companies to have unimpeachable study designs.
  - Inferior study design includes one or more of: choice of inappropriate comparators, lack of required patient subgroups, non RCTs, non-validated endpoints, and studies being atypical of standard clinical guidelines.

Variations in 'Reject' Recommendations by Country and reasons cited

	Limited/poor clinical benefit	Study design	Lack of clinical evidence	Economic model and modelling	Lack of cost-effectiveness	Other[a]
Australia	◔	◑	◔	◔	○	○
Canada (CADTH/pCODR)	◑	◕	◕	●	◔	◔
Canada (Quebec)	◕	●	◔	◔	◔	◔
England	◔	●	◔	◕	◑	○
France	◔	◔	◔	○	○	○
Scotland	◔	●	◔	●	◔	○
Sweden	◔	◑	◔	◔	◔	◔

○ = Never ◔ = Rarely ◑ = Sometimes ◕ = Often ● = Very Often

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; pCODR, pan-Canadian Oncology Drug Review.
[a] Other includes computation and submission errors, and country-specific statutory criteria.
Note: There are no DNL decisions in Germany.
N=77 drug-indication pairs across Australia, Canada, England, France, Scotland, and Sweden (2012-2017).
Source: LSE, September 2017.

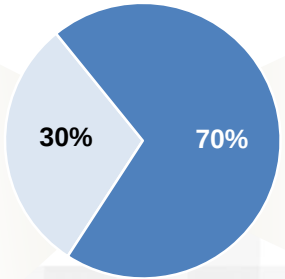
Oncology Agents Often Receive 'Reject' Recommendations For Economic Uncertainties

- Affordability remains a critical consideration for oncology agents across individual HTA settings. Most HTA agencies will aggressively challenge the economics of new oncology agents to protect their national budgets.
- Oncology agents receive Do Not List recommendations most often for economic reasons, primarily for lack of cost-effectiveness and poor modeling. When rejected for clinical reasons, it is generally prompted by problematic yet perhaps unavoidable trial designs (e.g. non-validated surrogate endpoints, non-inferiority margins, open label studies).

Clustered Reasons for 'Reject' Recommendations: Oncology

Clinical reasons for DNL recommendation Economic reasons for DNL recommendation

Contributing clinical uncertainties	
Poor study design	31%
Limited clinical benefit	24%
Lack of clinical evidence	20%
Non-representative of clinical practice	8%
Choice of comparators	6%
Non-generalizable population	4%
Adverse events	4%
No clinical outcomes	2%



Contributing economic uncertainties	
Lack of cost-effectiveness	36%
Poor modelling	32%
Misrepresentation of utility values	13%
Choice of economic comparator	13%
Other[a]	6%

Abbreviation: ICER: incremental cost-effectiveness ratio.
[a] Other includes computation and submission errors, and country-specific statutory criteria.
N=10 reasons for DNL recommendations across Australia, Canada, England, France, Germany, Scotland, and Sweden (2012-2017).
Note: Please see Appendix for additional category-specific reasons for DNL recommendations.
Source: LSE, September 2017.

Concluding remarks

- Multiple HTA systems, which differ in a variety of dimensions
- Different models of value assessment have different data and evidence requirements and take into account different dimensions of value
- What constitutes evidence is very often setting-specific
- Decision-making relies on scientific as well as social value judgements (the latter often taken on an *ad hoc* basis)
- MCDA endeavours to capture all dimensions of value explicitly
- Based on the above, there are significant variations in HTA recommendations across settings
- Robust evidence on clinical (rather than surrogate) endpoints is critical in achieving positive HTA recommendations (and resulting in coverage)

THANK YOU!

شكرا

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SECTION

1

Q&A Session

Introduction to HTA: Q&A Session

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Educational Seminar: Introduction to HTA

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Transferability of Health Technology Assessment

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Professor of Health Economics

ISPOR Dubai 2018

syreon Research Institute

Today's research for tomorrow's health

Pragmatic approach to evidence based health policy

- Too complicated and time-consuming to rank all available health care technologies according to their cost-effectiveness → cost-effectiveness criteria are assessed mainly for new and expensive therapies
- For innovative pharmaceuticals, the mandatory economic evaluation represents the fourth hurdle to market access, as registration already includes assessment of the efficacy, safety and quality.
- In addition to considering the health gain, the risk-benefit ratio and cost-effectiveness, public payers take into account several other factors in their decisions, including unmet medical need, budget impact, equity, incidence and prevalence of the disease.
- All these factors are incorporated into a formal health technology assessment process in several countries, prior to the reimbursement and formulary listing of new pharmaceutical therapies

Importance of NICE

- National Institute for Health and Clinical Excellence (NICE) in England and Wales is one of the most prominent public institutions to incorporate economic evaluation and health technology assessment into its recommendations
- As NICE publishes health technology assessment reports that are considered to be unbiased references, public decision-makers in many other countries implicitly take into account the NICE recommendations in their own decisions.

References:

- *O'Donnell JC, Pham SV, Pashos CL, Miller DW, Smith MD. Health technology assessment: lessons learned from around the world--an overview. Value Health. 2009. 12 Suppl 2:S1-5.*
- *Lopert R, Ruiz F, Chalkidou K. Applying rapid 'de-facto' HTA in resource-limited settings: experience from Romania. Health Policy. 2013. 112. 3. 202-8.*

Welte's knock-out criteria for HTA transferability

- **"General knock-out"** criteria preclude transferability of cost-effectiveness results when either the investigated technology or the comparator are irrelevant, or the methodological quality of the cost-effectiveness study does not meet local standards, meaning that the starting points of the study are irrelevant to local decision-makers.
- **"Specific knock-out criteria"** apply when cost-effectiveness results are only transferable after adjustment for differences in treatment patterns, in unit costs, or other aspects for which adjustment may be required.

Ref: Welte R, Feenstra T, Jager H, Leidl R. A decision chart for assessing and improving the transferability of economic evaluation results between countries. 2004. 22. 13. 857–876.

Policy vs data driven HTA determinants in the transferability of international HTA recommendations

- Policy-driven determinants:
  - If the local policy is similar to the international policy, there is no need for local adjustment of that particular determinant
  - If the local policy is different from the international policy, the transferability of recommendations becomes more limited.
- Data-driven determinants:
  - require local adjustment, when the data is different.

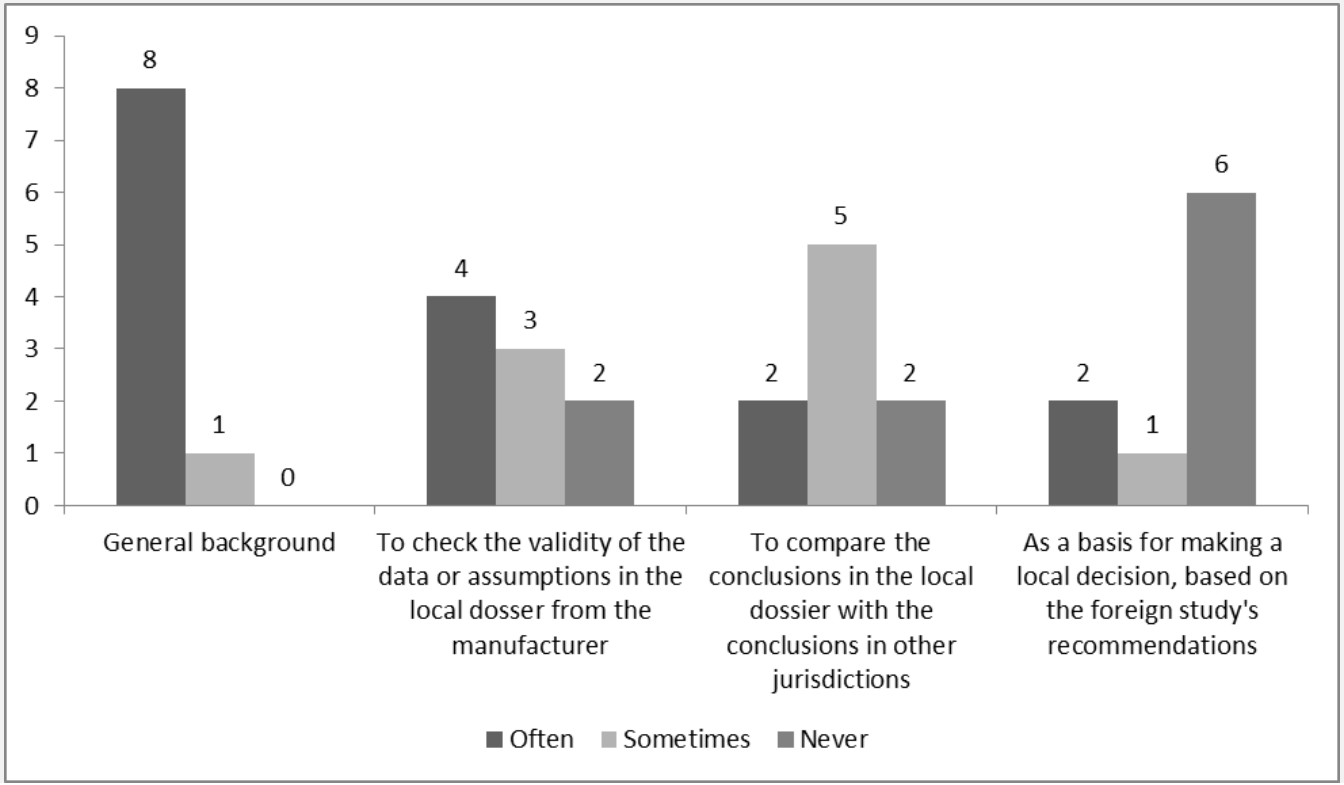
Ref: Kaló Z, Landa K, Doležal T, Vokó Z. Transferability of NICE recommendations for pharmaceutical therapies in oncology to Central-Eastern European countries, European Journal of Cancer Care, 2012. 21. 4. 442-449.

Determinants influencing the transferability of economic evaluations

	Determinant	Policy driven	Measure
comparator	positioning of therapy in local therapeutic guidelines	yes	first line, second line, etc.
	relevance of the comparator	yes	reimbursement status; local practice for standard therapy
health gain	baseline risk	no	mortality; risk of clinical endpoints
	relative efficacy	no	relative risk reduction
	efficacy	yes	absolute risk reduction
	real world benefit	no	adherence / compliance
	health state valuation	partly	utility estimates
costs	unit cost	no	production function of health care services; relative prices of medical technologies; **confidential discounts**
	resource utilization	no	local treatment practices and patient routes
methodology of economic evaluation	time horizon	yes	projection of health gain and cost (in years)
	discount factor	yes	%
	perspective	yes	health care or societal perspective; inclusion of indirect costs
	CE threshold	yes	explicit or implicit threshold

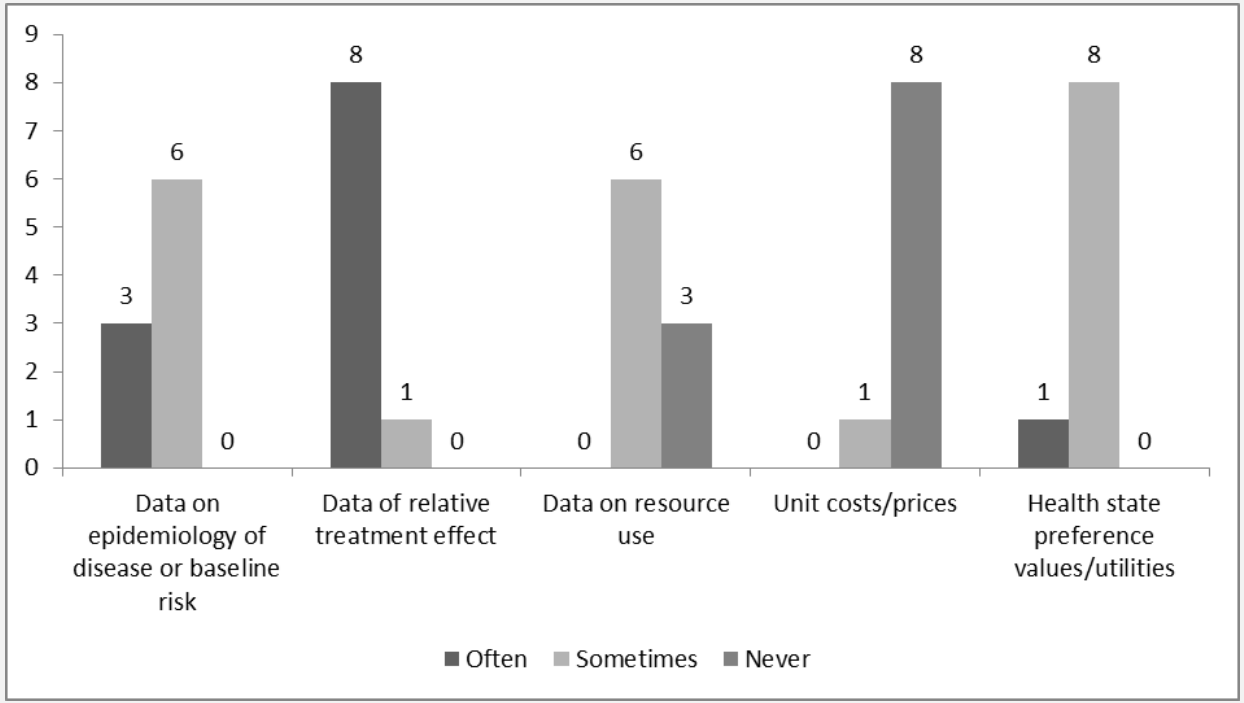
Ref: Kaló Z, Landa K, Doležal T, Vokó Z. Transferability of NICE recommendations for pharmaceutical therapies in oncology to Central-Eastern European countries, European Journal of Cancer Care, 2012. 21. 4. 442-449.

Survey of HTA agencies in LatAm / EE / Asia:
In what ways are results from studies conducted in other jurisdictions used?



Ref: Drummond M, Augustovski F, Kaló Z, Yang BM, Pichon-Riviere A, Bae EY, Kamal-Bahl S. Challenges faced in transferring economic evaluations to middle income countries. Int J Technol Assess Health Care. 2015. 31. 6. 442-

Survey of HTA agencies in LatAm / EE / Asia: Which categories of foreign data do you consider to be transferable?



Ref: Drummond M, Augustovski F, Kaló Z, Yang BM, Pichon-Riviere A, Bae EY, Kamal-Bahl S. Challenges faced in transferring economic evaluations to middle income countries. Int J Technol Assess Health Care. 2015. 31. 6. 442-

Survey of HTA agencies in LatAm / EE / Asia: Obstacles to transferring economic evaluations from other jurisdictions

OBSTACLE	Number of times mentioned
Other practice patterns, or the availability of facilities, are often different in my jurisdiction	10
The current standard of care/ relevant comparator is often different in my jurisdiction	9
Studies are often conducted in countries with a higher GDP, so results do not apply in my jurisdiction	8
Studies are often badly reported, or not enough details are given	8
It is often difficult or impossible to obtain an electronic copy of the model	7
The patient population is often different in my jurisdiction	6
Often, it is not possible to find local data to re-populate the model	6
Studies often have methodological deficiencies	5
Decision-makers in my jurisdiction much prefer a locally designed study	5
Studies often use methods that are too advanced for decision-makers in my jurisdiction	4
Other obstacles (please list and rank)	3
Lack of local technical capability	1
Decision-makers in my jurisdiction much prefer non-data driven arguments	1
Different resources & costs used in other jurisdictions	1

Ref: Drummond M, Augustovski F, Kaló Z, Yang BM, Pichon-Riviere A, Bae EY, Kamal-Bahl S. Challenges faced in transferring economic evaluations to middle income countries. Int J Technol Assess Health Care. 2015. 31. 6. 442-

Relationship of budget impact analysis and economic evaluation

- Argument: “there is no need for both”, as they are both dealing with economic aspects
- Objective of
  - economic evaluation: what is the fair price
  - budget impact analysis: affordability
- If we limit the budget without controlling the price, from the same public pharmaceutical budget
  - we can treat less patients
  - we generate less health gain

Pragmatic value assessment: light HTA system without need for local cost-effectiveness evidence

- Motto: *"you do not need to repeat what is already done by other prestigious HTA agencies"*
- Romanian HTA scorecard:
  - France HTA evaluation from HAS SMR: 15 points for SMR levels 1 or 2 (major/important) and 7 points for SMR levels 3 or 4 (moderate/low);
  - UK HTA evaluation from NICE or SMC: 15 points for a positive evaluation without any restrictions, 7 points for a positive evaluation with restrictions;
  - Germany HTA evaluation from IQWiG or G-BA: 15 points for a positive evaluation without any restrictions, 7 points for a positive evaluation with restrictions
  - Number of EU countries with a positive reimbursement status: 25 points for at least 14 EU countries, 20 points for at least 8 to 11 EU countries, 10 points for at least 3 EU countries, and 0 points for fewer than 3 EU countries;
  - Real-world data (RWD) study: 45 points if the manufacturer provides the real data collected for a period of at least 1 year in Romania
  - Budget impact analysis (only direct costs): 30 points for >5% savings; 15 points for neutral budget impact (±5%).

Ref: Radu CP, Chiriac ND, Pravat AM. The Development of Romanian Scorecard HTA System, ViHRI. 2016. 10. 41-47.

Conclusion

- Duplication of efforts in HTA research should be avoided. Transferring good quality HTA reports could be beneficial and save resources for local HTAs.
- However, making decisions based on international HTA recommendations without considering limitations of transferability makes more harm than good.
- Certain elements of HTA reports are transferable, but adjustment to local data is absolutely necessary.

Globalize methods

↓

Evaluate the transferability of international evidence

↓

Localize decisions

Educational Seminar: Introduction to HTA

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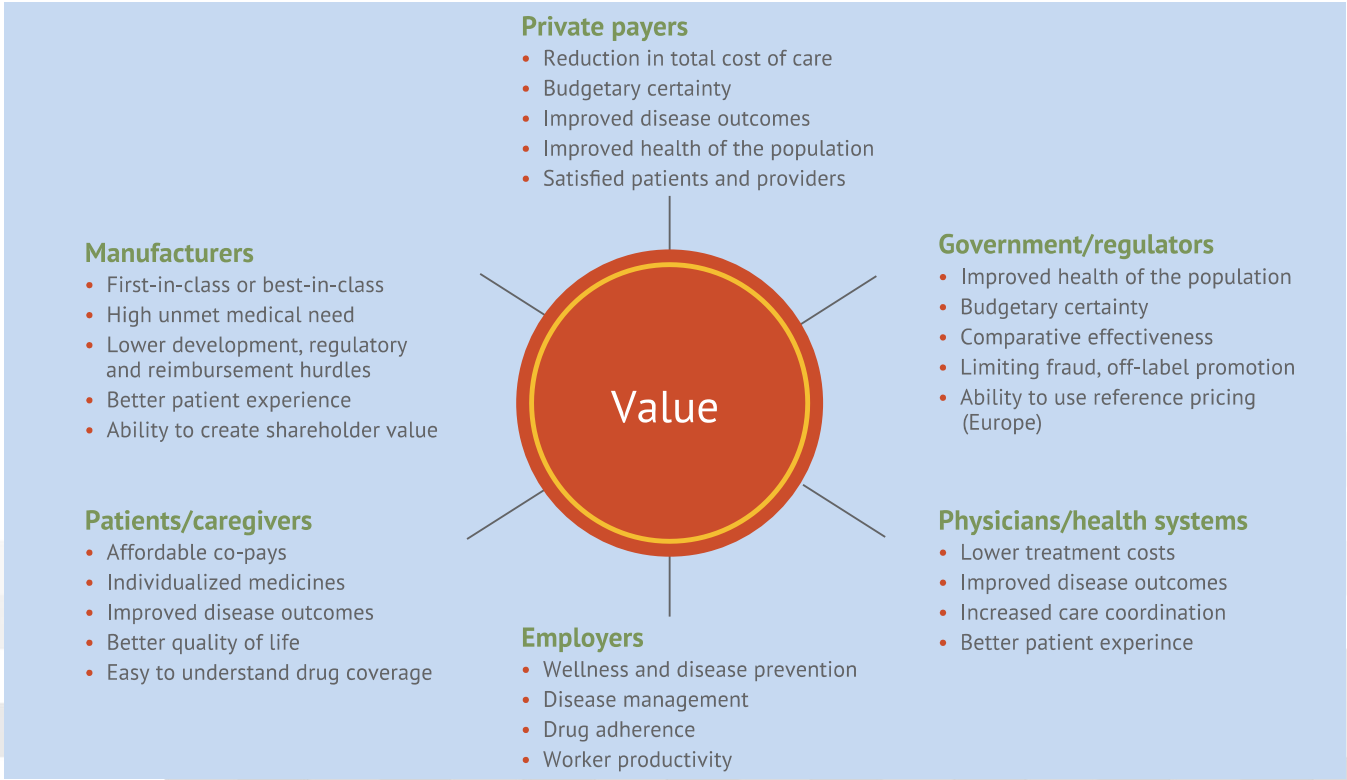
LSE Health and Medical Technology Research Group (MTRG)
London, United Kingdom

Value Frameworks

Panos Kanavos, PhD
London School of Economics
ISPOR Dubai, September 2018

LSE THE LONDON SCHOOL OF ECONOMICS AND POLITICAL SCIENCE

Whose ‘Value’ are we talking about? Value is in the eyes of the beholder



Traditional payer value assessment frameworks

Traditional Payer Value Assessment Frameworks (VAFs)

- *Strong preference for "QALYs"/cost-utility analysis*
  - England/Wales, Scotland, Ireland, the Netherlands, Norway
- *"QALYs"/cost-utility analysis mentioned as one possible approach*
  - Belgium, Portugal, Slovakia, Sweden, Switzerland,
- *"QALYs"/cost-utility analysis not encouraged (clinical benefit assessment)*
  - France, Germany.

Comparative Clinical benefit assessment: France and Germany

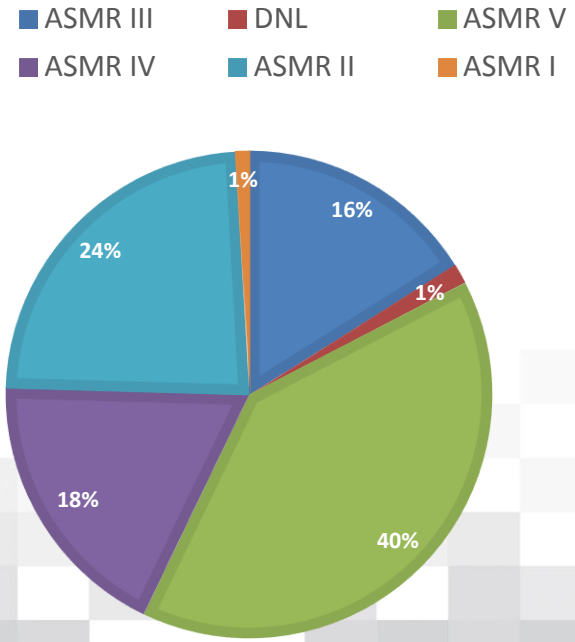
- ***France***
  - primarily uses an assessment of 'overall value' (SMR) and 'added value' (ASMR), made by an expert committee
  - This 'added value' assessment then guides the price negotiation
  - Manufacturers are asked to submit a cost-utility analysis 'for information' if they are requesting an ASMR of I, II or III

- ***Germany***
  - Primarily uses an approach comparable to France
  - In the absence of an agreement of price in the first year, the manufacturer or the regulator (G-BA) can request an economic evaluation conducted by IQWiG

Value Assessment - The case of France

France (HAS): Evidence on product ranking

(N drugs=445), 2012-2016



Source: LSE Database, 2018.

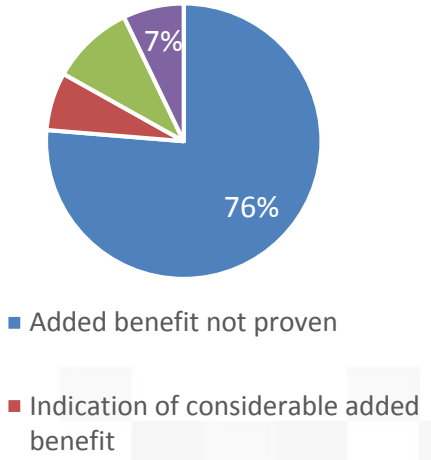
Added value	ASMR	Pricing consequences
Major	I	Possibility of a higher price as compared to comparators Faster access (price notification instead of negotiation) and price consistency with European ones.
Important	II	Possibility of a higher price as compared to comparators Faster access (price notification instead of negotiation) and price consistency with European ones.
Moderate	III	Possibility of a higher price as compared to comparators Faster access (price notification instead of negotiation) and price consistency with European ones.
Minor	IV	Possibility of a higher price as compared to comparators. For other ASMR IV, depends on the target population • If same target population as the comparator: no price advantage (but advantage in terms of market share) • Situation is different if ASMR is focused on a restricted population
No clinical improvement	V	The drug can be listed only if the costs are less than the comparators: • Lower price Or induces cost saving

Reimbursement rate	
Important	65%
Moderate	30%
Mild	15%
Insufficient	not reimbursed/included in the positive list

Value Assessment - The case of Germany

Germany (IQWIG)

(N drugs=149; N indications=321), 2012-2016



The number of indications in Germany is significantly higher than the number of drugs for 2 reasons: first, because there are a few drugs with more than one indication; second, and more important, a sub-indication in the IQWiG assessment system will count as a separate indication, e.g. a patient sub-group, or a disease stage would count as such.

SCORE	"ADDED BENEFIT" CLASSIFICATION CRITERIA	PRICE IMPLICATION
Level 1	Major/considerable	Price negotiation
Level 2	Significant	
Level 3	Small/Minor	
Level 4	Unquantifiable	
Level 5	None	Reference pricing
Level 6	Below	

LEVEL OF PROOF		Number of studies required	Certainty of results	Effect
Proof	Requires strong evidence as per IQWiG guidelines, esp. Phase III RCTs with preferred comparator	≥2	Mostly high	In the same direction
Indication of proof	Evidence provided is perceived satisfactory (although partial) as per IQWiG guidelines	≥2	Mostly moderate	In the same direction
		1	High	Statistically significant
Hint of proof	Evidence provided is perceived as weak as per IQWiG guidelines	≥2	Mostly low	In the same direction
		1	Moderate	Statistically significant

HTA - The case of Germany (IV)

Drug name	Indication	Outcome
Pembrolizumab	Treatment of adult patients with advanced (unresectable or metastatic) melanoma. (2nd Pretreated patients for whom ipilimumab is appropriate)	**Level 2**: Indication of major added benefit
Fingolimod	Patients with rapidly evolving severe RRMS	**Level 3**: Hint of a minor added benefit
Telaprevir	Treatment of Genotype 1 chronic HCV infection. Treatment-naïve patients without cirrhosis with a high baseline viral load	**Level 1**: Proof of an added benefit of telaprevir (extent "non-quantifiable")
Rilpivirine	In combination with other antiretroviral Medicinal products for the treatment of Infections with HIV-1 at antiretroviral Not pretreated children and Between 12 and 18 years of age With a viral load of ≤ 100,000 HIV-1-RNA copies/ml	**Level 4**: Added benefit not proven

Value Scores in France and Germany for Use in Price Negotiation for Drugs

	France	Germany
	ASMR	**G-BA/ IQWiG Level of Added Benefit**
Innovative	I – Major innovation (“majeure”)	Major (“erheblich”)
	II – Important improvement (“importante”)	Considerable (“beträchtlich”)
	III – Moderate improvement (“modérée”)	
Non-innovative	IV – Minor improvement (“mineure”)	Minor (“gering”)
	V – No improvement (“inexistante”)	Non-quantifiable (“nicht quantifizierbar”)
		No added benefit (“kein Zusatznutzen”)
		Lesser benefit (“geringerer Nutzen”)

Approaches to Value-Based Pricing: The Italian Innovation Algorithm

AIFA INNOVATION ALGORITHM: DIMENSIONS OF EVALUATION / IMPLICATIONS

	DIMENSION			STATUS / IMPLICATIONS	
RATINGS	UNMET THERAPEUTIC NEEDS	ADDED THERAPEUTIC VALUE	QUALITY OF EVIDENCE	DESIGNATION	COMMERCIAL IMPLICATIONS
	MAXIMUM *Absence of therapeutic options*	**MAXIMUM** *Greater efficacy / curative relative to alternatives*	**HIGH**	**INNOVATIVE**	• *Funded via 'innovative drugs fund'* • *No payback mechanism* • *Immediate regional formulary inclusion* • *Benefit duration period of 36 months*
	IMPORTANT *Alternatives lack relevant clinical impact*	**IMPORTANT** *Greater efficacy / better benefit / risk ratio*			
	MODERATE *Alternatives have uncertain safety / clinical impact*	**MODERATE** *Moderately greater efficacy in subpopulations relative to alternatives / surrogate outcomes used*	**MODERATE**	**CONDITIONALLY INNOVATIVE**	• *Immediate regional formulary inclusion* • *Benefit duration period of 18 months*
	POOR *Alternatives with high impact on outcomes are available*	**POOR** *Minimally greater efficacy than alternatives; irrelevant medical outcomes used*	**LOW**	**NOT INNOVATIVE**	• *No benefits*
	ABSENT *Alternatives that modify history of disease are available*	**ABSENT** *No greater efficacy relative to alternatives*	**VERY LOW**		

New generation value frameworks and MCDA

Dimensions of “value” and attribution by country, based on primary and secondary evidence

		France	Germany	Sweden	England	Italy	Netherlands	Poland	Spain
Burden of disease									
	Severity	***	**	**	**	*	**	**	**
	Availability	***	*	*	***	*	**	*	**
	Prevalence	*	**	*	*	**	**	**	**
Therapeutic									
	Direct endpoints	***	***	***	***	***	***	***	***
	Surrogate endpoints	**	**	**	**	**	**	**	**
Safety									
	Adverse events	***	***	***	***	***	***	***	***
	Tolerability	**	**	**	**	**	**	**	**
	Contraindications	**	**	**	**	**	**	**	**
Innovation									
	Clinical novelty	***	*	*	*	**	**	***	**
	Nature of treatment	***	*	*	**	x	*	***	**
	Ease of use & comfort	*	*	**	*	x	*	x	*
Socioeconomic									
	Public health	**	**	*	**	*	***	***	*
	Budget impact	*	***	**	***	**	**	***	**
	Social productivity	*	**	***	**	*	**	*	**

***	mandatory/ formal/explicit/ planned/ directly/ grading system
**	"considered", e.g. recommended, informal/implicit but planned, formal/explicit but ad-hoc/indirectly, etc.
*	optional/ informal/implicit/ad-hoc/ indirectly/ no grading system
x	not considered in any way

Angelis and Kanavos, *Social Science & Medicine* 2017; Angelis, Lange, Kanavos, *European J of Health Econs*, 2016

New generation of “Value Frameworks”

- Many initiatives have emerged through the development of value frameworks aiming to aid reimbursement agencies, health care professionals and patients **understand the value of new therapies and make better choices**.

  Examples: ACC/AHA, ASCO, ESMO, ICER, MSKCC, NCCN

- Adopt **multiple criteria approaches** in an attempt to decompose complex problems into simpler ones:
  - important step towards a more inclusive **Value Based Assessment (VBA)**
  - critical to satisfy decision theory principles

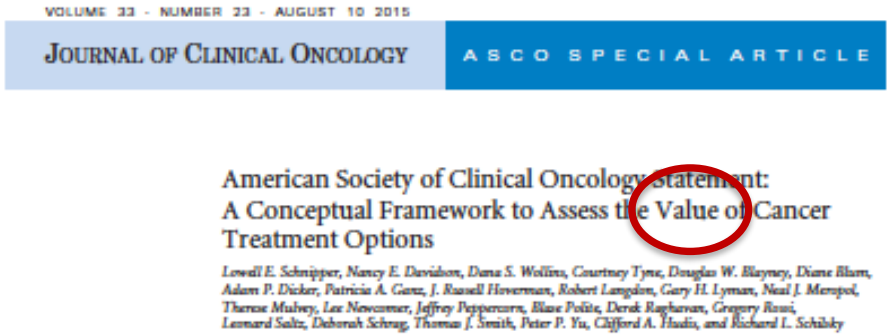
- ‘Value’ remains an elusive target and a wider consensus about **what dimensions of value** to include is still missing in HTA

Recent "Value Frameworks"

Framework	ACC/AHA	ASCO	ESMO	ICER	MSKCC	NCCN	MoCA	Advance Value Framework
Decision context	Clinical practice	Shared decision making	Clinical practice	Coverage/ reimburse-ment	Pricing	Shared decision making	Pricing and reimbursement	Health Technology Assessment
Key actor(s)	Physicians	Patients - Physicians	Physicians	Payer	Payer-Provider	Patients - Physicians	Payers - Manufacturers	All stakeholders
Value parameters or dimensions	• Clinical benefit vs. risks • "Value" (CEA)	• Clinical benefit (efficacy) • Toxicity (safety) • Palliation • Treatmen t-free interval • Cost (efficienc y)	• Variability of estimated Hazard Ratio • Observed absolute difference in treatment outcomes:	• Clinical care value • Health system value	• Dollars per life year • Toxicity • Novelty • Cost of developme nt • Rarity • Population burden of disease	• Efficacy of regimen • Safety of regimen • Quality of evidence • Consistenc y of evidence • Affordabili ty of regimen	• Alternatives available/ unmet need • Relative effectivenes s • Response rate • Degree of certainty	• Burden of disease • Therapeuti c impact • Safety profile • Innovation level • Socio-economic impact

Source: Angelis and Kanavos, *Social Science & Medicine* 2017.

An example: The ASCO Value Framework (1)



- Conceptual value framework based on treatment benefits, toxicities, and costs
- Accepts the need to account for dimensions that reflect economic impact and, therefore, stretch beyond the clinical benefit of drugs
- Incorporation of costs and the use of a transparent framework with explicit criteria and the attachment of weights to each criterion
- Produce a single, standardized net health benefit (NHB) score so that drugs for different cancer indications can be compared

Schnipper et al, *Journal of Clinical Oncology* 2015

An example: The ASCO Value Framework (2)

Step 1: Determine the regimen's CLINICAL BENEFIT

1.A. Is Overall Survival (OS) reported?	**YES.** Assign an OS Score (1 through 5 as shown below) and multiply by 16. Write this number in the box labeled, "OS Score." **Proceed to 1.D.**						**OS Score**
	OS Score	1	2	3	4	5	
	Improvement in median OS (% change in median OS)	> 0%-24%	25%-49%	50%-75%	76%-100%	At double the median OS of new regimen, there is a 50% improvement in the fraction of patients surviving	
	NO. Proceed to 1.B.						
1.B. If OS is not reported, is Progression-Free Survival (PFS) reported?	**YES.** Assign a PFS Score (1 through 5 as shown below) and multiply by 11. Write this number in the box labeled, "PFS Score." **Proceed to 1.D.**						**PFS Score**
	PFS Score	1	2	3	4	5	
	Improvement in median PFS (% change in median PFS)	> 0%-24%	25%-49%	50%-75%	76%-100%	At double the median PFS of new regimen, there is a 50% improvement in the fraction of patients without progression or death	
	NO. Proceed to 1.C.						
1.C. If neither OS nor PFS is reported, is Response Rate (RR) reported?	**YES.** Assign an RR Score (1 through 5 as shown below) and multiply by 8. RR should be calculated by adding the complete response (CR) and partial response (PR) rates. Write this number in the box labeled, "RR Score." Proceed to 1.D.						**RR Score**
	RR Score	1	2	3	4	5	
	What was the reported response rate (CR + PR)?	> 0%-20%	21%-40%	41%-60%	61%-80%	81%-100%	
1.D. Calculate the Clinical Benefit Score	Insert the OS, PFS, or RR Score. **Note: You should have EITHER an OS Score OR a PFS score OR an RR score, NOT MORE THAN ONE.** Write the total in the box labeled "Clinical Benefit Score." The maximum allowable points are 80. **Proceed to Step 2.**						**Clinical Benefit Score**

Step 2: Determine the regimen's TOXICITY

Calculate the Toxicity Score	For the regimens being assessed, compare the number of grade 3-5 toxicities (ie, calculate the sum of toxicities of grade 3-5 reported for each regimen) and assign a Toxicity Score (-20 through +20 as shown below). The score will be based on the difference in toxicity between the two regimens. Write this number in the box labeled, "Toxicity Score." The maximum allowable toxicity points are 20. **Proceed to Step 3.**						**Toxicity Score**
	Toxicity Score	-20	-10	0	+10	+20	
	Does the new regimen represent an improvement in toxicity over the standard of care/comparator?	Substantially less well tolerated (75%-100% increase in the number of grade 3-5 toxicities reported for the new regimen.)	Less well tolerated (50%-74% increase in the number of grade 3-5 toxicities reported for the new regimen.)	Toxicity is the same (less than 49% increase and up to 49% fewer toxicities are reported for the new regimen.)	Better tolerated (50%-74% decrease in the number of grade 3-5 toxicities reported for the new regimen.)	Substantially better tolerated (75%-100% decrease in the number of grade 3-5 toxicities reported for the new regimen.)	

Schnipper et al, *Journal of Clinical Oncology* 2015

ASCO Value Framework (3)

Step 3: Determine Bonus Points

3.A. PALLIATION BONUS. Are data related to the palliation of symptoms reported?	**YES.** If a statistically significant improvement in cancer-related symptoms is reported, award 10 points, and place this in the box labeled "Palliation Bonus Points." **Proceed to Step 3.B.** **NO.** No bonus points are awarded. **Proceed to Step 3.B.**	**Palliation Bonus Points**
3. B. TREATMENT-FREE INTERVAL BONUS. Are data related to treatment-free interval reported?	**YES.** If a statistically significant improvement in treatment-free interval is reported, award points based on the table below, and place this in the box labeled "Clinical Benefit Bonus Points." This is the interval from completion of study treatment to initiation of next treatment. **Proceed to 3.C.**	**Treatment-Free Interval Bonus**

Bonus Points	0	5	10	15	20
% Change	> 0%-19%	20%-35%	36%-49%	50%-74%	≥ 75%

NO. No bonus points are awarded. **Proceed to Step 3.C.**

3.C. Calculate Total Bonus Points	Add the Palliation Bonus Points (Step 3.A) and the Treatment-Free Interval Bonus Points (Step 3.B). Write this number in the box labeled "Total Bonus Points." The maximum points available for Bonus Points is 30. **Proceed to Step 4.**	**Total Bonus Points**

Step 4: Determine the regimen's NET HEALTH BENEFIT

Calculate the Net Health Benefit	Add the Clinical Benefit Score (Step 1), Toxicity Score (Step 2), and Bonus Points (Step 3). This yields a Net Health Benefit Score. Write this number in the box labeled "Net Health Benefit." The maximum points available for Net Health Benefit are 130 (100 + 30 bonus points). Proceed to **Step 5.**	Net Health Benefit

Step 5: Determine the regimen's COST

Insert the drug acquisition cost (DAC) and patient co-pay based on how much the treatment regimen costs per month.	**Cost Per Month:** **DAC:** _____ **Patient Co-Pay:** _____

Step 6: Summary Assessment – Advanced Disease Framework

Clinical Benefit	Toxicity	Bonus Points	Net Health Benefit	Cost (per month)
/80	/20	/30	/130	DAC: _____ Patient Payment: _____

Remarks on the ASCO Value Framework

- However, proposed methodological framework is incomplete and could lead to misleading treatment decisions
- Fluctuating weighting of the clinical endpoints is has been produced in an arbitrary manner, on the basis of the consensus of those who developed the framework
- Single generic clinical endpoint (even OS) would have as a tradeoff a decreased sensitivity (e.g. QoL?)
- Palliation bonus points assigned in a binary fashion (10 or 0, rather than allowing combinations), independently of the number of symptoms affected or the extent of symptom improvement, leaving no flexibility for differentiation

Angelis & Kanavos, JCO, 2016

Why Multiple Criteria Decision Analysis (MCDA)?

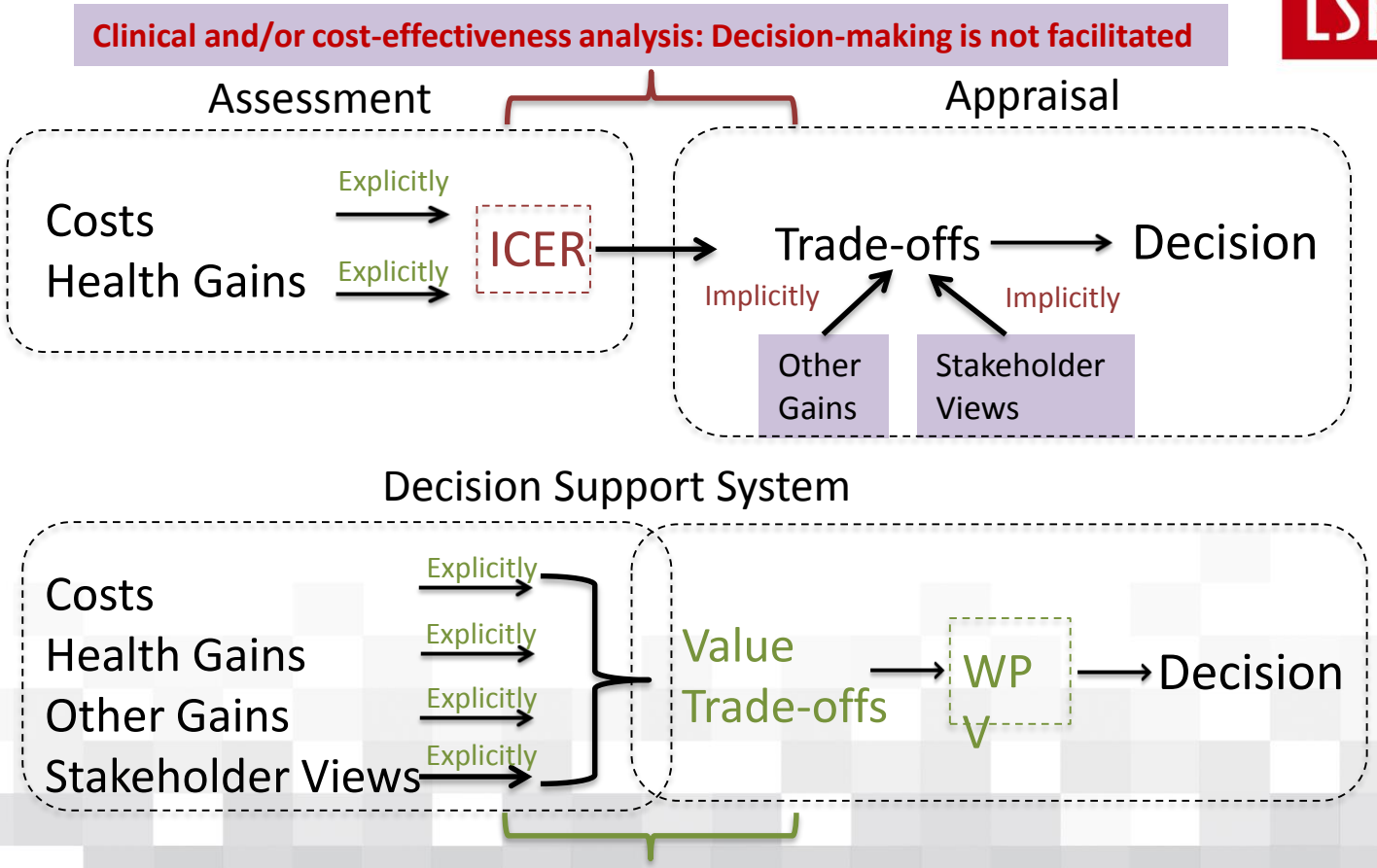
MCDA has emerged as a likely approach for HTA; there are several reasons for that:

- ***Comprehensive***: Incorporation of several dimensions of value in an explicit manner
- ***Constructive***: Facilitates expression of value judgements and construction of value preferences, including value trade-offs
- ***Encompassing***: Ability to include all relevant stakeholders across all stages
- ***Transparent***: Clear, structured, well-defined process

From Value Frameworks to MCDA

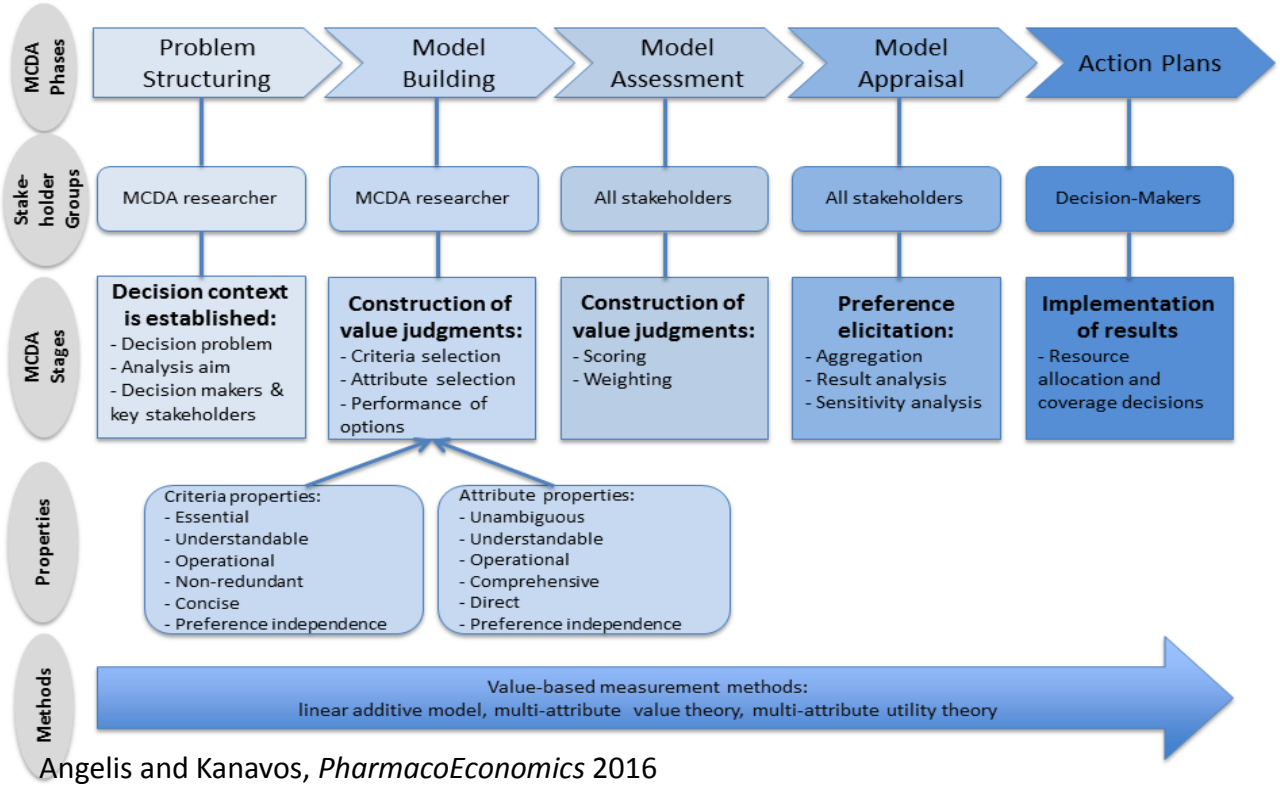
Clinical and/or Cost-effectiveness Analysis

Multiple Criteria Decision Analysis



Source: Angelis, Kanavos, Montibeller, Global Policy, 2016

MCDA methodological process in the context of HTA



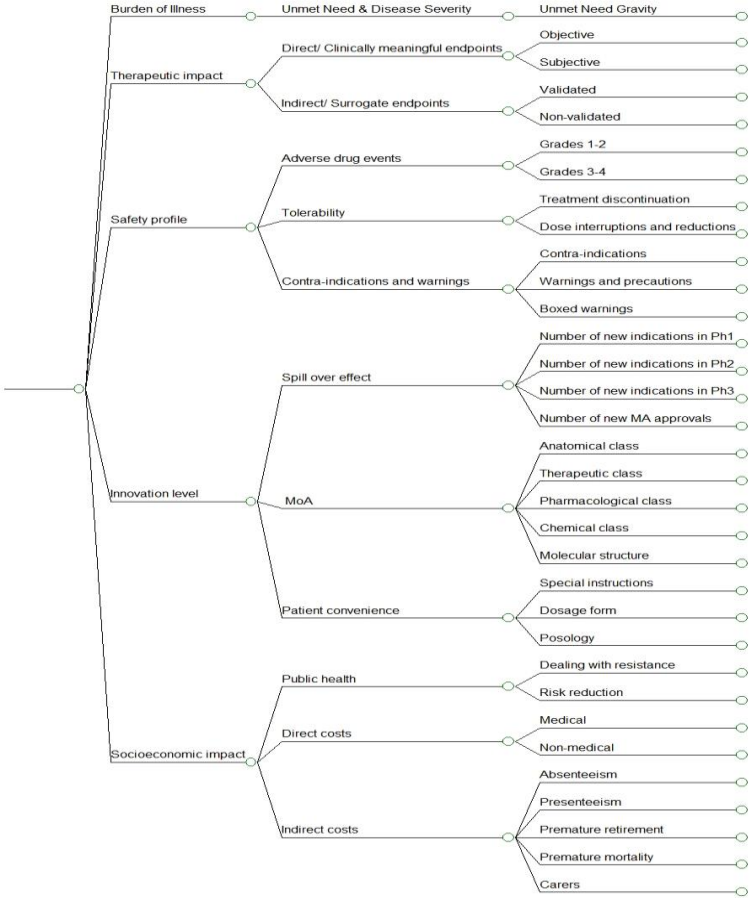
Angelis and Kanavos, *PharmacoEconomics* 2016

The Advance Value Framework

- A new value framework based on MCDA principles for the needs of HTA:
  - Encompassing societal perspective (views from wider stakeholder community, payer as the decision maker)
  - Value captured through the Advance Value Tree, incorporating scientific and social value concerns
  - Construction of preferences through MAVT* methods, using indirect techniques

* Multi-attribute value theory

The Advance Value Framework: Dimensions of Value & Criteria selection



Stage 1 - Systematic literature review in HTA

Value dimensions considered as HTA criteria in EU study countries	Top-level criteria clusters and decomposition into lower level criteria

Stage 2 - Expert consultation

Value dimensions considered as HTA criteria in EU study countries	Validation of top-level criteria clusters and decomposition into lower level criteria

Stage 3 - Targeted examination of methodological/ grey literature

Value concerns beyond current or formal HTA criteria	Lower level criteria and decomposition into bottom-level sub-criteria or attributes

Stage 4 - Consultation with Advance-HTA partners

Comprehensiveness and usefulness of the value tree	Revision of bottom-level sub-criteria or attributes

Stage 5 - Wider dissemination and consultation activities

Comprehensiveness and usefulness of the value tree	Enhanced validation of bottom-level sub-criteria or attributes

Source: Angelis and Kanavos, *Social Science & Medicine* 2017

THANK YOU!

شكرا

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www.impact-hta.eu

Educational Seminar: Introduction to HTA

Zoltan Kalo, PhD
Institute of Economics, Faculty of Social Sciences, Eötvös Loránd University (ELTE)
Budapest, Hungary

Multicriteria Decision Analysis (MCDA)

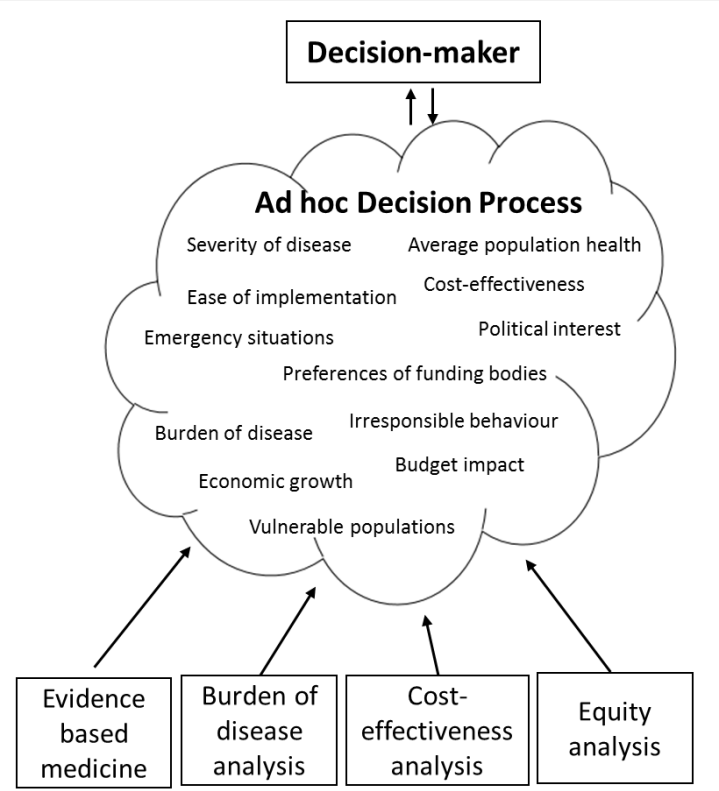
Zoltán Kaló
Professor of Health Economics

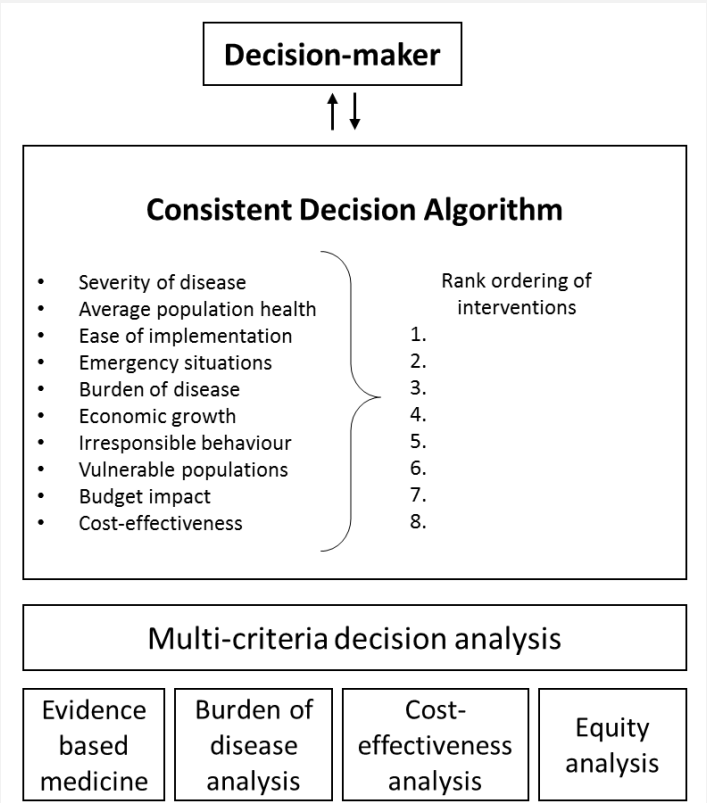
ISPOR Dubai 2018

syreon
Research Institute

Today's research for tomorrow's health

HTA / Value framework →
Consistent and Transparent Policy Decisions





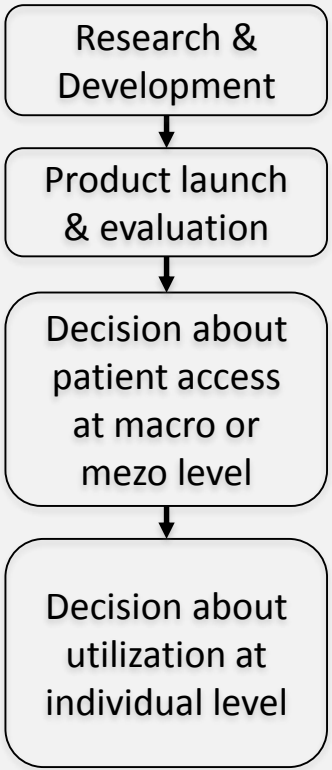
Adapted from: Baltussen R, Niessen L. Priority setting of health interventions: the need for multi-criteria decision analysis. Cost Eff Resour Alloc. 2006. 21;4:14.

Why is MCDA of Interest in Health Care?

- Transparency, consistency, rigor
- Facilitates a judgement of the value of multiple criteria
- Divide complex problem into smaller criteria for assessment
- Criteria can be expressed using any measure
- Formally incorporates stakeholder preferences

MCDA in Health Care

- Portfolio Decision Analysis in a Pharmaceutical Company
- “Go - no go” R&D decisions
- Market authorization / drug registration
- Health Technology Assessment
- Pricing decision
- Coverage / reimbursement decision
- Formulary listing
- National / Central Procurement
- Hospital tender
- Shared Decision Making (e.g. Oncoteam)
- Prioritizing Patients’ Access
  - Organs from deceased donors
  - Hepatitis C direct acting antivirals
  - Expensive cancer drugs



How MCDA implementation can help in Middle East and North Africa?

- Comprehensive approach to improve the evidence base of policy decisions related to health technologies
- It improves the transparency, consistency and accountability of policy decisions
- MCDA takes into and aggregate all attributes of policy decisions e.g.: health gain, cost-effectiveness, budget impact, equity

Development of MCDA: major questions

Questions regarding development of MCDA system

1. Selection of criteria
2. Scoring function of each criterion
3. Weighting of each criterion

How to apply MCDA?

1. Rule vs. Tool
2. One-off or reusable model

Foundation work for MCDA

1. "Non-scientific" MCDA
2. MCDA system developed by expert group with ongoing validation (revealed preferences)
3. Research based MCDA (stated preferences)

Steps in a MCDA process (for repeated use)

Step	Description
1. Defining the decision problem	Identify objectives, type of decision, alternatives, decision-makers, other stakeholders and output required.
2. Selecting and structuring the criteria	Specify appropriate criteria for the decision problem that are relevant to decision-makers and other stakeholders.
3. Scoring and weighting the criteria	Eliciting stakeholders' priorities or preferences for changes within criteria (scoring functions) and between criteria (i.e. the weights placed on the criteria).
4. Evaluating alternatives' performance	Gather data about the alternatives' performance on the criteria and summarise this in a 'performance matrix'.
5. Calculating aggregate scores	Multiply the alternatives' scores on the criteria by the weights for the criteria and sum to get 'total scores' – by which the alternatives are ranked.
6. Dealing with uncertainty	Perform uncertainty analysis to understand the robustness of the MCDA results.
7. Interpretation and reporting	Interpret the MCDA outputs, including sensitivity analysis, to support decision-making.

Adapted from: Thokala P, Devlin N, Marsh K, Baltussen R, Boysen M, Kalo Z, Longrenn T, Mussen F, Peacock S, Watkins J, Ijzerman M. Multiple Criteria Decision Analysis for Health Care Decision Making-An Introduction: Report 1 of the ISPOR MCDA Emerging Good Practices Task Force. Value Health. 2016. 19(1). 1-13.

Development and Application of an MCDA Tool for Repeated Use

Development of MCDA tool

Desk Research

- Defining the decision problem
- Initial selection and structure of criteria
- Initial scoring functions for criteria

Policy Workshop

- Final selection of criteria
- Scoring functions for criteria
- Weighting the criteria

Policy Application of MCDA tool

- Listing alternatives and collecting data (e.g. from pharmaceutical submission dossiers)
- Evaluating product performance by committee members
- Scoring the alternatives on the criteria
- Calculating aggregate scores
- Interpretation and reporting
- Policy decision

Case study: Which generic antihypertensive should be purchased by the National Procurement Agency in Indonesia?

Product A	Product B	Product C	Product D
2200 IDR	2900 IDR	3000 IDR	3800 IDR
Pharmacological equivalence based on local criteria	Bioequivalence proven based on local criteria	Bioequivalence proven based on local criteria	Bioequivalence proven based on European EMA or US FDA criteria
No real world data on equal outcomes	International real world data on equal outcomes	Local real world data on equal outcomes	Local real world data on equal outcomes
No data on product expiry or stability	Data on improved product stability	Data on improved product expiry	Data on improved product expiry
Local/non GMP quality assurance only for active product ingredient	Local/non GMP quality assurance for the entire manufacturing process	Local/non GMP quality assurance for the entire manufacturing process	WHO GMP certification
Minor but fairly frequent supply problems	Single precedence of supply problems	No precedence of supply problems	No precedence of supply problems
No pharmacovigilance system	Qualified person for pharmacovigilance	Qualified person and sophisticated pharmacovigilance system	Qualified person and sophisticated pharmacovigilance system

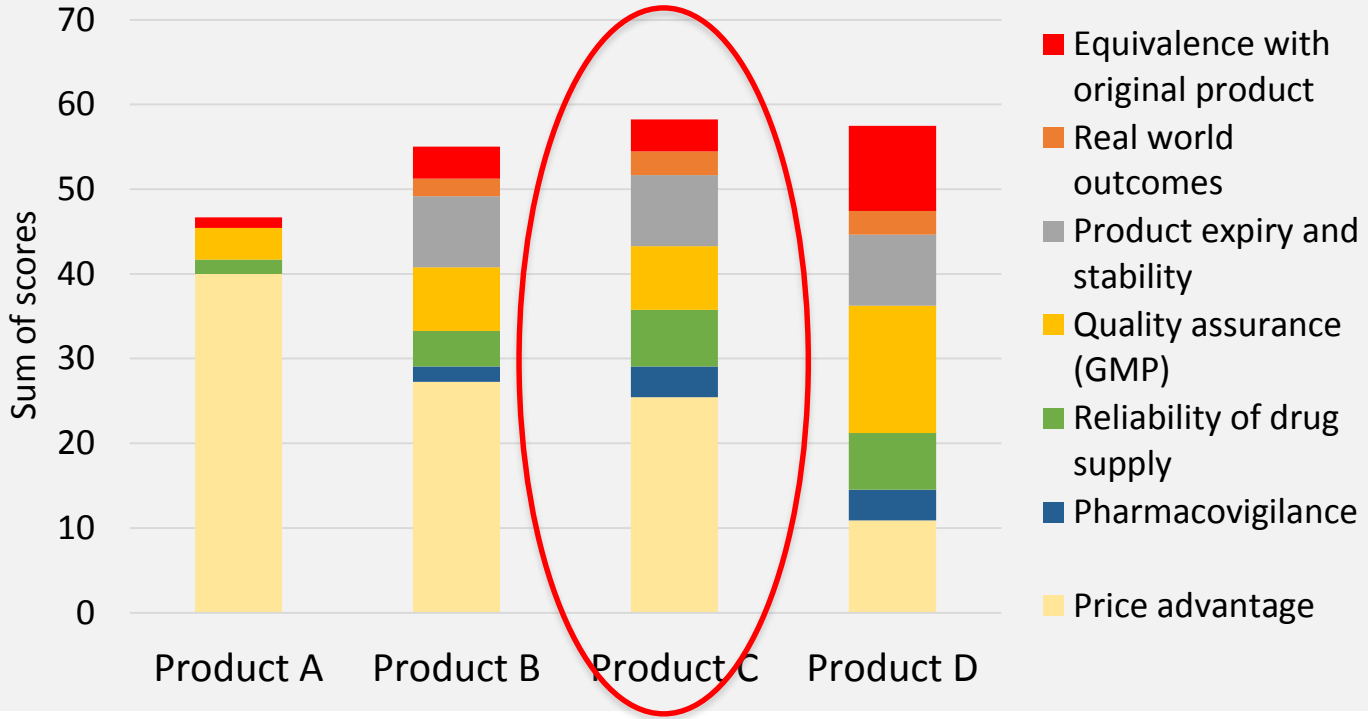
Ref: Inotai et al. Development and Implementation of Multi-Criteria Decision Analysis (MCDA) Framework for Off-Patent Pharmaceuticals – An Application on Improving Tender Decision Making in Indonesia. 2018. Manuscript in submission

Proposal for National Procurement of Off-Patent Pharmaceuticals in Indonesia

Criterion	SMART Ranking	Weights
Price advantage	N/A	**40.0%**
Quality assurance (GMP standards)	1	**18.8%**
Equivalence with the reference (original) product	2	**12.5%**
Product stability and drug formulation	2	**12.5%**
Reliability of drug supply	3	**8.4%**
Real world clinical or economic outcomes (adherence or non-drug costs)	4	**4.2%**
Pharmacovigilance	5	**3.6%**

Ref: Inotai et al. Development and Implementation of Multi-Criteria Decision Analysis (MCDA) Framework for Off-Patent Pharmaceuticals – An Application on Improving Tender Decision Making in Indonesia. 2018. Manuscript in submission

MCDA scores for National Procurement of generic antihypertensives in Indonesia



Ref: Inotai et al. Development and Implementation of Multi-Criteria Decision Analysis (MCDA) Framework for Off-Patent Pharmaceuticals – An Application on Improving Tender Decision Making in Indonesia. 2018. Manuscript in submission

Guidance toward the implementation of MCDA framework in developing countries:
A) *MCDA objectives*

1. MCDA should address a well-defined decision problem which is harmonized with the overall health system objectives
2. MCDA should be an unbiased and transparent exercise
3. MCDA should provide incentives to all stakeholders

Ref: Inotai A, Nguyen HT, Hidayat B, Nurgozhin T, Kiet PHT, Campbell JD, Németh B, Maniadakis N, Brixner D, Wijaya K, Kaló Z. Guidance towards the Implementation of Multi-Criteria Decision Analysis Framework in Developing Countries: Lessons Learned from Pilot Policy Research Projects to Apply MCDA for Off-Patent Pharmaceuticals in Indonesia, Kazakhstan and Vietnam. Expert Rev Pharm Outcome Res, 2018

Guidance toward the implementation of MCDA framework in developing countries:
B) *Methods - technical considerations of MCDA*

4. MCDA should be kept simple and easy to understand, while achieving the objectives
5. Criteria should be locally relevant, realistic, complete, preferential independent, with the lowest possible redundancy and overlap
6. Feasibility should be considered when proposing criteria, scoring and weighting methodology

Ref: Inotai A, Nguyen HT, Hidayat B, Nurgozhin T, Kiet PHT, Campbell JD, Németh B, Maniadakis N, Brixner D, Wijaya K, Kaló Z. Guidance towards the Implementation of Multi-Criteria Decision Analysis Framework in Developing Countries: Lessons Learned from Pilot Policy Research Projects to Apply MCDA for Off-Patent Pharmaceuticals in Indonesia, Kazakhstan and Vietnam. Expert Rev Pharm Outcome Res, 2018

Guidance toward the implementation of MCDA framework in developing countries:
C) *Processes - development of the MCDA based on methods*

7. MCDA development should be based upon the current decision-making criteria
8. Representatives from all key stakeholder groups should participate in the design of the MCDA
9. Local experts with in-depth knowledge on their own system should pre-validate initial criteria selection prior to implementing the most resource consuming phases (e.g. eliciting criteria weights)
10. Feasibility and reliability in eliciting weights should be considered
11. Knowledge transfer between project leaders and workshop participants should be ensured
12. Participants should have the opportunity for re-iteration during the workshop
13. An action plan for policy implementation should be agreed during the workshop

Ref: Inotai A, Nguyen HT, Hidayat B, Nurgozhin T, Kiet PHT, Campbell JD, Németh B, Maniadakis N, Brixner D, Wijaya K, Kaló Z. Guidance towards the Implementation of Multi-Criteria Decision Analysis Framework in Developing Countries: Lessons Learned from Pilot Policy Research Projects to Apply MCDA for Off-Patent Pharmaceuticals in Indonesia, Kazakhstan and Vietnam. Expert Rev Pharm Outcome Res, 2018

Guidance toward the implementation of MCDA framework in developing countries:
D) *Policy implementation - the use of MCDA in decision-making*

14. Policy implementation of MCDA should be stepwise and iterative
15. Feasibility and stability of policy implementation should be ensured
16. Standard procedure should be applied for policy implementation of MCDA
17. Transparency of decisions can be improved by scientific publications and non-scientific dissemination of the MCDA tool

Ref: Inotai A, Nguyen HT, Hidayat B, Nurgozhin T, Kiet PHT, Campbell JD, Németh B, Maniadakis N, Brixner D, Wijaya K, Kaló Z. Guidance towards the Implementation of Multi-Criteria Decision Analysis Framework in Developing Countries: Lessons Learned from Pilot Policy Research Projects to Apply MCDA for Off-Patent Pharmaceuticals in Indonesia, Kazakhstan and Vietnam. Expert Rev Pharm Outcome Res, 2018

Legislative process for the application of the MCDA Tool: *a potential example*

Evidence submission

- submission template for manufacturers to score and provide evidences
- easy to use cover page indicates initial scores by manufacturers (self-scoring)
- reference data / scientific evidence is submitted by manufacturers to substantiate scores of each criterion

Validation of submitted evidence

- MCDA Secretariat applies standard process for validation of manufacturers' scoring
- MCDA Secretariat archives submitted dossiers, initial and validated scores

Policy decision

- MCDA Committee compares validated cover pages and makes recommendation for decision-making body
- MCDA Committee publishes scores (aggregated or detailed)
- policy decision by relevant decision-makers

Conclusions

- Investment to health care and medical technologies should take into account societal ***value*** judgement
- The quantification of ***value*** depends on the context
- MCDA is an appropriate method for evaluation, because it takes into multiple dimensions in a highly transparent and inclusive manner
- For local implementation, it is of critical importance to
  1. define the objectives for improvement in decision making
  2. identify the key stakeholders with interest and power in these decisions
  3. plan how to work with key stakeholders to achieve improvement through adoption of the MCDA method

General recommendations for process to develop MCDA into real-world policy setting

- Gradual implementation throughout pilot phase, validation, improvement, expansion with consistent stakeholder consensus
- Scientific publication of MCDA tool
- Periodic review of MCDA tool based on real world experience and to accommodate for evolving policy settings
- Full transparency of MCDA rules, regulation and evaluation criteria increases the justifiability of policy decisions
- Trust & Consistency: Prevent misuse of MCDA (e.g. small vs. big companies; local vs. foreign; block market access vs. too easy market access)

SECTION

2

Q&A Session

Educational Seminar: Introduction to HTA Q&A Session

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