Educational Seminar: Introduction to HTA

Finn Børlum Kristensen, MD, PhD
University of Southern Denmark
Copenhagen, Denmark

Panos Kanavos, PhD
London School of Economics and Political Science
LSE Health and Medical Technology Research Group (MTRG)
London, United Kingdom

Zoltan Kalo, PhD
Institute of Economics, Faculty of Social Sciences, Eötvös Loránd University (ELTE)
Budapest, Hungary
Educational Seminar: Introduction to HTA

Finn Børlum Kristensen, MD, PhD
University of Southern Denmark
Copenhagen, Denmark
Health Technology Assessment and international collaboration

ISPOR Dubai 2018

Finn Børlum Kristensen, MD, PhD

Professor of Health Services Research and HTA, Faculty of Health Sciences, University of Southern Denmark
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

Decision-making steps
- Request for HTA Support
- Health care technology decision problem
- Policy analysis
- Recommendation
- Decision

Questions
- What level of support does the decision maker need?
- What is the problem and what research is needed?
- How should research be conducted?
- What does the research say? What do we know? What can we infer? What don’t we know?
- How should the results of the research be put into context?
- What should the decision be?

HTA Process
- 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)
  - 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
- 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 expert panels or grading systems
    - Reporting
- Contextualization
  - What considerations should be made explicit?
    - 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?
- 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)
“Identifying the need for good practices in HTA:
Summary of the ISPOR HTA Council Working Group Report”
Request for HTA

Decision-making steps

- Request for HTA Support
- Health care

Questions

What level of support does the decision maker need?

HTA Process

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)
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“Identifying the need for good practices in HTA: Summary of the ISPOR HTA Council Working Group Report”
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- Structure and governance / organizational aspects (e.g., government/health insurance based)
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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”
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”

Finn Børlum Kristensen | Science & Policy | www.scienceandpolicy.dk
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
Policy analysis and assessment

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”
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)

“Identifying the need for good practices in HTA: Summary of the ISPOR HTA Council Working Group Report”
Informing recommendations and decisions

Recommendation

How should the results of the research be put into context?

What should the decision be?

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?

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)

“Identifying the need for good practices in HTA: Summary of the ISPOR HTA Council Working Group Report”
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
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“Identifying the need for good practices in HTA:
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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
Scientific and technical cooperation in HTA – with a view to EUnetHTA, European network for HTA
“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)

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”
Globalize the evidence, localize the decision

Locate the decision, globalize the evidence, localize the reporting

J.M. Eisenberg

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

<table>
<thead>
<tr>
<th>HTA Core Model DOMAINS</th>
<th>SCOPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Health problem and current use of technology</td>
<td>Rapid REA</td>
</tr>
<tr>
<td>2. Description and technical characteristics</td>
<td></td>
</tr>
<tr>
<td>3. Safety</td>
<td></td>
</tr>
<tr>
<td>4. Clinical effectiveness</td>
<td></td>
</tr>
<tr>
<td>5. Costs and economic evaluation</td>
<td></td>
</tr>
<tr>
<td>6. Ethical analysis</td>
<td></td>
</tr>
<tr>
<td>7. Organisational aspects</td>
<td></td>
</tr>
<tr>
<td>8. Patient and social aspects</td>
<td></td>
</tr>
<tr>
<td>9. Legal aspects</td>
<td></td>
</tr>
</tbody>
</table>

Source: EUnetHTA
www.eunethta.eu
LEGO® the obvious analogue of the HTA Core Model®
EUnetHTA → → → → → → → → → →
Project  JA1  JA2  JA3

Establishment  Putting into practice  Strengthening practical application  Joint production and national uptake

Source: EUnetHTA
www.eunethta.eu
HTA along the Health Technology Life-cycle – the HTA Core Model provides framework
Educational Seminar: Introduction to HTA

Panos Kanavos, PhD
London School of Economics and Political Science
LSE Health and Medical Technology Research Group (MTRG)
London, United Kingdom
Approaches to HTA Implementation

Panos Kanavos, PhD
London School of Economics
ISPOR Dubai, September 2018
A Taxonomy of HTA Systems

Arm’s Length HTA
- Advisory
  - NICE (ENGLAND)
- Regulatory
  - TLV (SWEDEN)
- Coordination
  - TNO (NETHERLANDS)

HTA Function
Incorporated/Integrated
- (Quasi-) Independent HTA function w/in insurance body
- Use HTA to inform pricing and/or coverage decisions
  - Advisory
    - INAMI (BELGIUM)
  - Regulatory
    - AIFA (ITALY)

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 Benefit Assessment (Comparative)
  - France
  - Germany

- Clinical & Cost Effectiveness (Comparative)
  - Sweden, Canada
  - The Netherlands, Australia

- Value-Based Pricing Model (Comparative)
  - United Kingdom
  - Sweden, Italy
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?

**Question 2**

2) Does the cost of the particular technology provide:
   - No value-for-money?
   - Poor value-for-money?
   - Good value-for-money?
Incremental cost-effectiveness ratio (ICER)

Cost-effectiveness plane

- Difference in effect between the intervention of interest and the alternative
- Difference in costs

New treatment dominates

Existing treatment dominates

New treatment more effective and more costly

New treatment cheaper but less effective

New treatment more costly

New treatment less effective

New treatment less costly
Incremental cost-effectiveness ratio (ICER)

\[
ICER = \frac{\Delta \text{costs}}{\Delta \text{effectiveness}} = \frac{\text{Cost}_{\text{int}} - \text{Cost}_{\text{comp}}}{\text{Eff}_{\text{int}} - \text{Eff}_{\text{comp}}}
\]

- 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 \textbf{external value} system is needed - something to compare the ICER to:

- ‘Cut-off point’, ‘ceiling value’, threshold \((\lambda)\) for the ICER
- \(\lambda\) 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)

\[
ICER = \frac{\text{Cost}_{\text{int}} - \text{Cost}_{\text{comp}}}{\text{Eff}_{\text{int}} - \text{Eff}_{\text{comp}}} < \lambda
\]
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
<table>
<thead>
<tr>
<th>Added value</th>
<th>ASMR</th>
<th>Pricing consequences</th>
</tr>
</thead>
</table>
| 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

Prevalence of Social Value Judgements by HTA Agency, cancer drugs

<table>
<thead>
<tr>
<th>Social Value Judgements</th>
<th>NICE (n=15)</th>
<th>SMC (n=14)</th>
<th>PBAC (n=12)</th>
<th>pCODR (n=14)</th>
<th>HAS (n=15)</th>
<th>TLV (n=9)</th>
<th>Total (n=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better Adverse Reactions</td>
<td>10</td>
<td>6</td>
<td>8</td>
<td>9</td>
<td>2</td>
<td>1</td>
<td>33</td>
</tr>
<tr>
<td>Cost Impact of Treatments on the Family</td>
<td>3</td>
<td>10</td>
<td>7</td>
<td>1</td>
<td>7</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>New Mechanism of Action</td>
<td>10</td>
<td>10</td>
<td>1</td>
<td>3</td>
<td>9</td>
<td>2</td>
<td>33</td>
</tr>
<tr>
<td>Innovative Treatment</td>
<td>7</td>
<td>8</td>
<td>5</td>
<td>6</td>
<td>22</td>
<td>33</td>
<td>36</td>
</tr>
<tr>
<td>Administration Advantage</td>
<td>8</td>
<td>7</td>
<td>6</td>
<td>4</td>
<td>10</td>
<td>9</td>
<td>30</td>
</tr>
<tr>
<td>Improvement of Quality of Life</td>
<td>12</td>
<td>11</td>
<td>4</td>
<td>9</td>
<td>5</td>
<td>9</td>
<td>37</td>
</tr>
<tr>
<td>Innovative Treatment</td>
<td>5</td>
<td>10</td>
<td>8</td>
<td>7</td>
<td>10</td>
<td>13</td>
<td>51</td>
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<tr>
<td>Extension of Life</td>
<td>2</td>
<td>9</td>
<td>1</td>
<td>8</td>
<td>7</td>
<td>13</td>
<td>43</td>
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<tr>
<td>Impact on Society / Budget Impact</td>
<td>10</td>
<td>11</td>
<td>1</td>
<td>1</td>
<td>10</td>
<td>1</td>
<td>22</td>
</tr>
<tr>
<td>Impact on Work and Activities</td>
<td>5</td>
<td>9</td>
<td>8</td>
<td>7</td>
<td>10</td>
<td>1</td>
<td>21</td>
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<tr>
<td>Burden on Family and Carers</td>
<td>12</td>
<td>13</td>
<td>9</td>
<td>10</td>
<td>13</td>
<td>1</td>
<td>51</td>
</tr>
<tr>
<td>End-of-Life / Orphan Status</td>
<td>5</td>
<td>7</td>
<td>1</td>
<td>8</td>
<td>1</td>
<td>1</td>
<td>43</td>
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<tr>
<td>Unmet Need</td>
<td>7</td>
<td>11</td>
<td>1</td>
<td>10</td>
<td>13</td>
<td>1</td>
<td>51</td>
</tr>
<tr>
<td>Severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
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)

Variations in HTA Recommendations by Country

<table>
<thead>
<tr>
<th>Country</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia (CADTH/pCODR)</td>
<td>L: 14%</td>
</tr>
<tr>
<td>Canada (Quebec)</td>
<td>LWC: 6%</td>
</tr>
<tr>
<td>England</td>
<td>L: 6%</td>
</tr>
<tr>
<td>Scotland</td>
<td>L: 14%</td>
</tr>
<tr>
<td>Sweden</td>
<td>L: 33%</td>
</tr>
</tbody>
</table>

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; pCODR, pan-Canadian Oncology Drug Review.


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.

Note: ASMR I, Major; ASMR II, Important; ASMR III, Moderate; ASMR IV, Minor; ASMR V, Non-Existent.


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

- Drugs with clinical restrictions: 44%
- Drugs with economic restrictions: 24%
- Drugs with both clinical and economic restrictions: 15%
- Drugs with unspecified restrictions: 16%

Abbreviation: LWC, List with criteria.


Source: LSE, September 2017.
Restricted Recommendations on Product Utilization Emphasize HTA Agency Focus on Quality Clinical Evidence

Variations in Restricted Recommendations

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.
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.

Choice of Endpoint

<table>
<thead>
<tr>
<th>Endpoint Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surrogate endpoint</td>
<td>71%</td>
</tr>
<tr>
<td>Clinical endpoint</td>
<td>29%</td>
</tr>
</tbody>
</table>

HTA Recommendation

<table>
<thead>
<tr>
<th>Recommendation Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>LW C</td>
<td>15%</td>
</tr>
<tr>
<td>L</td>
<td>60%</td>
</tr>
<tr>
<td>LW C</td>
<td>15%</td>
</tr>
</tbody>
</table>

Abbreviations: DNL, do not list; L, list; LWC, list with criteria.

*Clinical endpoint, overall survival; surrogate endpoint, progression-free survival.

Source: LSE Database, September 2017.

[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
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

<table>
<thead>
<tr>
<th>Country</th>
<th>Limited/poor clinical benefit</th>
<th>Study design</th>
<th>Lack of clinical evidence</th>
<th>Economic model and modelling</th>
<th>Lack of cost-effectiveness</th>
<th>Other*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada (CADTH/pCODR)</td>
<td>![Symbol]</td>
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<td>![Symbol]</td>
<td>![Symbol]</td>
<td>![Symbol]</td>
</tr>
<tr>
<td>Canada (Quebec)</td>
<td>![Symbol]</td>
<td>![Symbol]</td>
<td>![Symbol]</td>
<td>![Symbol]</td>
<td>![Symbol]</td>
<td>![Symbol]</td>
</tr>
</tbody>
</table>

*Other includes computation and submission errors, and country-specific statutory criteria.

Note: There are no DNL decisions in Germany.


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

<table>
<thead>
<tr>
<th>Contributing clinical uncertainties</th>
<th>Economic reasons for DNL recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor study design</td>
<td>Lack of cost-effectiveness 36%</td>
</tr>
<tr>
<td>Limited clinical benefit</td>
<td>Poor modelling 32%</td>
</tr>
<tr>
<td>Lack of clinical evidence</td>
<td>Misrepresentation of utility values 13%</td>
</tr>
<tr>
<td>Non-representative of clinical practice</td>
<td>Choice of economic comparator 13%</td>
</tr>
<tr>
<td>Choice of comparators</td>
<td>Othera 6%</td>
</tr>
<tr>
<td>Non-generalizable population</td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
</tr>
<tr>
<td>No clinical outcomes</td>
<td></td>
</tr>
</tbody>
</table>

*Contributing economic uncertainties* | 70% |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of cost-effectiveness 36%</td>
<td>30%</td>
</tr>
<tr>
<td>Poor modelling 32%</td>
<td></td>
</tr>
<tr>
<td>Misrepresentation of utility values 13%</td>
<td></td>
</tr>
<tr>
<td>Choice of economic comparator 13%</td>
<td></td>
</tr>
<tr>
<td>Othera 6%</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: ICER: incremental cost-effectiveness ratio.


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!

Contact: p.g.kanavos@lse.ac.uk
Visit us on:
http://www.lse.ac.uk/health-policy/people/dr-panos-kanavos
www.advance-hta.eu
www.impact-hta.eu
Q&A Session
Introduction to HTA: Q&A Session

Finn Børlum Kristensen, MD, PhD
University of Southern Denmark
Copenhagen, Denmark

Panos Kanavos, PhD
London School of Economics and Political Science
LSE Health and Medical Technology Research Group (MTRG)
London, United Kingdom
Educational Seminar: Introduction to HTA

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

Zoltán Kaló
Professor of Health Economics

ISPOR Dubai 2018
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:


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.

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.

### Determinants influencing the transferability of economic evaluations

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

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-Bahi 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

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

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%).
• 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

Today’s research for tomorrow’s health
Educational Seminar: Introduction to HTA

Panos Kanavos, PhD
London School of Economics and Political Science
LSE Health and Medical Technology Research Group (MTRG)
London, United Kingdom
Value Frameworks

Panos Kanavos, PhD
London School of Economics
ISPOR Dubai, September 2018
Whose ‘Value’ are we talking about? Value is in the eyes of the beholder

**Private payers**
- Reduction in total cost of care
- Budgetary certainty
- Improved disease outcomes
- Improved health of the population
- Satisfied patients and providers

**Manufacturers**
- First-in-class or best-in-class
- High unmet medical need
- Lower development, regulatory and reimbursement hurdles
- Better patient experience
- Ability to create shareholder value

**Patients/caregivers**
- Affordable co-pays
- Individualized medicines
- Improved disease outcomes
- Better quality of life
- Easy to understand drug coverage

**Government/-regulators**
- Improved health of the population
- Budgetary certainty
- Comparative effectiveness
- Limiting fraud, off-label promotion
- Ability to use reference pricing (Europe)

**Physicians/health systems**
- Lower treatment costs
- Improved disease outcomes
- Increased care coordination
- Better patient experience

**Employers**
- Wellness and disease prevention
- Disease management
- Drug adherence
- Worker productivity
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

<table>
<thead>
<tr>
<th>Added value</th>
<th>ASMR</th>
<th>Pricing consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>I</td>
<td>Possibility of a higher price as compared to comparators. Faster access (price notification instead of negotiation) and price consistency with European ones.</td>
</tr>
<tr>
<td>Important</td>
<td>II</td>
<td>Possibility of a higher price as compared to comparators. Faster access (price notification instead of negotiation) and price consistency with European ones.</td>
</tr>
<tr>
<td>Moderate</td>
<td>III</td>
<td>Possibility of a higher price as compared to comparators. Faster access (price notification instead of negotiation) and price consistency with European ones.</td>
</tr>
<tr>
<td>Minor</td>
<td>IV</td>
<td>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</td>
</tr>
<tr>
<td>No clinical improvement</td>
<td>V</td>
<td>The drug can be listed only if the costs are less than the comparators: • Lower price • Or induces cost saving</td>
</tr>
</tbody>
</table>

Reimbursement rate

<table>
<thead>
<tr>
<th>Importance</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important</td>
<td>65%</td>
</tr>
<tr>
<td>Moderate</td>
<td>30%</td>
</tr>
<tr>
<td>Mild</td>
<td>15%</td>
</tr>
<tr>
<td>Insufficient</td>
<td>not reimbursed/included in the positive list</td>
</tr>
</tbody>
</table>

Source: LSE Database, 2018.
## Value Assessment - The case of Germany

### Germany (IQWiG)

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

<table>
<thead>
<tr>
<th>SCORE</th>
<th>“ADDED BENEFIT” CLASSIFICATION CRITERIA</th>
<th>PRICE IMPLICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>Major/considerable</td>
<td>Price negotiation</td>
</tr>
<tr>
<td>Level 2</td>
<td>Significant</td>
<td></td>
</tr>
<tr>
<td>Level 3</td>
<td>Small/Minor</td>
<td></td>
</tr>
<tr>
<td>Level 4</td>
<td>Unquantifiable</td>
<td></td>
</tr>
<tr>
<td>Level 5</td>
<td>None</td>
<td>Reference pricing</td>
</tr>
<tr>
<td>Level 6</td>
<td>Below</td>
<td></td>
</tr>
</tbody>
</table>

### Added benefit not proven

- Added benefit not proven
- Indication of considerable added benefit

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.
## HTA - The case of Germany (IV)

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Indication</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>Treatment of adult patients with advanced (unresectable or metastatic) melanoma. (Pretreated patients for whom ipilimumab is appropriate)</td>
<td><strong>Level 2</strong>: Indication of major added benefit</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>Patients with rapidly evolving severe RRMS</td>
<td><strong>Level 3</strong>: Hint of a minor added benefit</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>Treatment of Genotype 1 chronic HCV infection. Treatment-naive patients without cirrhosis with a high baseline viral load</td>
<td><strong>Level 1</strong>: Proof of an added benefit of telaprevir (extent “non-quantifiable”)</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>In combination with other antiretroviral Medicinal products for the treatment of Infections with HIV-1 at antiretroviral</td>
<td><strong>Level 4</strong>: Added benefit not proven</td>
</tr>
<tr>
<td></td>
<td>Not pretreated children and Between 12 and 18 years of age With a viral load of ≤ 100,000 HIV-1-RNA copies / mlb</td>
<td></td>
</tr>
</tbody>
</table>
Value Scores in France and Germany for Use in Price Negotiation for Drugs

<table>
<thead>
<tr>
<th>Innovative</th>
<th>ASMR</th>
<th>G-BA/ IQWiG Level of Added Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>I – Major innovation (&quot;majeure&quot;)</td>
<td>Major (&quot;erheblich&quot;)</td>
<td></td>
</tr>
<tr>
<td>II – Important improvement (&quot;importante&quot;)</td>
<td>Considerable (&quot;beträchtlich&quot;)</td>
<td></td>
</tr>
<tr>
<td>III – Moderate improvement (&quot;modérée&quot;)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Innovative</td>
<td>IV – Minor improvement (&quot;mineure&quot;)</td>
<td>Minor (&quot;gering&quot;)</td>
</tr>
<tr>
<td></td>
<td>V – No improvement (&quot;inexistante&quot;)</td>
<td>Non-quantifiable (&quot;nicht quantifizierbar&quot;)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No added benefit (&quot;kein Zusatznutzen&quot;)</td>
</tr>
</tbody>
</table>
## Approaches to Value-Based Pricing: The Italian Innovation Algorithm

<table>
<thead>
<tr>
<th>Dimention</th>
<th>Status / Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UNMET THERAPEUTIC NEEDS</strong></td>
<td></td>
</tr>
<tr>
<td>Maximum: Absence of Therapeutic Options</td>
<td>• Funded via ‘innovative drugs fund’</td>
</tr>
<tr>
<td>Maximum: Greater efficacy / curative relative to alternatives</td>
<td>• No payback mechanism</td>
</tr>
<tr>
<td><strong>ADDED THERAPEUTIC VALUE</strong></td>
<td></td>
</tr>
<tr>
<td>Maximum: Greater efficacy</td>
<td>• Immediate regional formulary inclusion</td>
</tr>
<tr>
<td>Maximum: Better benefit / risk ratio</td>
<td>• Benefit duration period of 36 months</td>
</tr>
<tr>
<td><strong>QUALITY OF EVIDENCE</strong></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>• Immediate regional formulary inclusion</td>
</tr>
<tr>
<td><strong>DESIGNATION</strong></td>
<td></td>
</tr>
<tr>
<td>Innovative</td>
<td>• Benefit duration period of 18 months</td>
</tr>
<tr>
<td>Conditionally Innovative</td>
<td></td>
</tr>
<tr>
<td>Not Innovative</td>
<td>• No benefits</td>
</tr>
</tbody>
</table>

- **RATINGS**
  - **Maximum**: Alternatives lack relevant clinical impact
  - **Moderate**: Alternatives have uncertain safety / clinical impact
  - **Poor**: Alternatives with high impact on outcomes are available
  - **Absent**: Alternatives that modify history of disease are available
New generation value frameworks and MCDA
## Dimensions of “value” and attribution by country, based on primary and secondary evidence

<table>
<thead>
<tr>
<th>Burden of disease</th>
<th>France</th>
<th>Germany</th>
<th>Sweden</th>
<th>England</th>
<th>Italy</th>
<th>Netherlands</th>
<th>Poland</th>
<th>Spain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity</td>
<td>***</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>***</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Availability</td>
<td>***</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Prevalence</td>
<td>*</td>
<td>**</td>
<td>*</td>
<td>**</td>
<td>*</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
</tbody>
</table>

| Therapeutic       |        |         |        |         |       |             |        |       |
| Direct endpoints  | ***    | ***     | ***    | ***     | ***   | ***         | ***    | ***   |
| Surrogate endpoints|  **   |   **    |   **   |   **    |   **  |   **        |   **   |   **  |

| Safety            |        |         |        |         |       |             |        |       |
| Adverse events    | ***    | ***     | ***    | ***     | ***   | ***         | ***    | ***   |
| Tolerability      |   **   |   **    |   **   |   **    |   **  |   **        |   **   |   **  |
| Contraindications |   **   |   **    |   **   |   **    |   **  |   **        |   **   |   **  |

| Innovation        |        |         |        |         |       |             |        |       |
| Clinical novelty  | ***    |   *     |   *    |   **    |   **  |   **        | ***    | **    |
| Nature of treatment|   *   |   *     |   **   |   x     |   x   |   **        |   ***  | **    |
| Ease of use & comfort |   * |   *     |   **   |   x     |   x   |   *         |   **   |   **  |

| Socioeconomic     |        |         |        |         |       |             |        |       |
| Public health     |   **   |   **    |   **   |   **    |   **  |   **        | ***    | **    |
| Budget impact     |   *    |   *     |   **   |   **    |   **  |   **        | ***    | **    |
| Social productivity|   *    |   **    |   **   |   **    |   **  |   **        | ***    | **    |

### Notes
- *******: 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

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”

<table>
<thead>
<tr>
<th>Framework</th>
<th>ACC/AHA</th>
<th>ASCO</th>
<th>ESMO</th>
<th>ICER</th>
<th>MSKCC</th>
<th>NCCN</th>
<th>MoCA</th>
<th>Advance Value Framework</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decision context</td>
<td>Clinical practice</td>
<td>Shared decision making</td>
<td>Clinical practice</td>
<td>Coverage/reimbursement</td>
<td>Pricing</td>
<td>Shared decision making</td>
<td>Pricing and reimbursement</td>
<td>Health Technology Assessment</td>
</tr>
<tr>
<td>Key actor(s)</td>
<td>Physicians</td>
<td>Patients - Physicians</td>
<td>Physicians</td>
<td>Payer</td>
<td>Payer-Provider</td>
<td>Patients - Physicians</td>
<td>Payers - Manufacturers</td>
<td>All stakeholders</td>
</tr>
<tr>
<td>Value parameters or dimensions</td>
<td>• Clinical benefit vs. risks</td>
<td>• Clinical benefit (efficacy) &quot;Value&quot; (CEA)</td>
<td>• Variability of estimated Hazard Ratio</td>
<td>• Clinical care value Health system value</td>
<td>• Dollars per life year Toxicity</td>
<td>• Efficacy of regimen Safety of regimen</td>
<td>• Alternatives available/unmet need</td>
<td>• Burden of disease Therapeutic impact Safety profile Innovation level Socio-economic impact</td>
</tr>
</tbody>
</table>

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**

<table>
<thead>
<tr>
<th>Step 1: Determine the regimen’s CLINICAL BENEFIT</th>
<th>OS Score</th>
<th>PFS Score</th>
<th>RR Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival (OS) reported?</td>
<td>Improvement in median OS (% change in median OS)</td>
<td>&gt; 0%-24%</td>
<td>25%-49%</td>
</tr>
<tr>
<td>NO. Proceed to 1.B.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If OS is not reported, is Progression-Free Survival (PFS) reported?</td>
<td>Improvement in median PFS (% change in median PFS)</td>
<td>&gt; 0%-24%</td>
<td>25%-49%</td>
</tr>
<tr>
<td>NO. Proceed to 1.C.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If neither OS nor PFS reported, is Response Rate (RR) reported?</td>
<td>What was the reported response rate (CR + PR)?</td>
<td>&gt; 0%-20%</td>
<td>21%-40%</td>
</tr>
</tbody>
</table>

**Step 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.

**Step 2: Determine the regimen’s TOXICITY**

<table>
<thead>
<tr>
<th>Step 2: Determine the regimen’s TOXICITY</th>
<th>Toxicity Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the new regimen represent an improvement in toxicity over the standard of care/ comparator?</td>
<td>Substantially less well tolerated (75%-100% increase in the number of grade 3-5 toxicities reported for the new regimen.)</td>
</tr>
<tr>
<td></td>
<td>Less well tolerated (50%-74% increase in the number of grade 3-5 toxicities reported for the new regimen.)</td>
</tr>
<tr>
<td></td>
<td>Toxicity is the same (less than 49% increase and up to 49% fewer toxicities are reported for the new regimen.)</td>
</tr>
<tr>
<td></td>
<td>Better tolerated (50%-74% decrease in the number of grade 3-5 toxicities reported for the new regimen.)</td>
</tr>
<tr>
<td></td>
<td>Substantially better tolerated (75%-100% decrease in the number of grade 3-5 toxicities reported for the new regimen.)</td>
</tr>
</tbody>
</table>

**Notes:**

- OS Score:
  - 1: 0%-24%
  - 2: 25%-49%
  - 3: 50%-75%
  - 4: 76%-100%

- PFS Score:
  - 1: 0%-24%
  - 2: 25%-49%
  - 3: 50%-75%
  - 4: 76%-100%

- RR Score:
  - 1: > 0%-20%
  - 2: 21%-40%
  - 3: 41%-60%
  - 4: 61%-80%
  - 5: 81%-100%

*Schnipper et al, Journal of Clinical Oncology 2015*
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.
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: Decision-making is not facilitated

Assessment

Costs
Health Gains

Trade-offs

ICER

Decision

Explicitly
Explicitly

Other Gains
Stakeholder Views

Implicitly
Implicitly

Appraisal

Costs
Health Gains

Value
Trade-offs

Explicitly
Explicitly

WP

Decision

Multiple Criteria Decision Analysis: Process facilitates decision-making

Source: Angelis, Kanavos, Montibeller, Global Policy, 2016
MCDA methodological process in the context of HTA

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

Value dimensions considered as HTA criteria in EU study countries

Top-level criteria clusters and decomposition into lower level criteria

Validation of top-level criteria clusters and decomposition into lower level criteria

Enhanced validation of bottom-level sub-criteria or attributes

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!

Contact: p.g.kanavos@lse.ac.uk
Visit us on:
http://www.lse.ac.uk/health-policy/people/dr-panos-kanavos
www.advance-HTA.eu
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
Today’s research for tomorrow’s health

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

Research & Development

Product launch & evaluation

Decision about patient access at macro or mezo level

Decision about utilization at individual level
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)
<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Defining the decision problem</td>
<td>Identify objectives, type of decision, alternatives, decision-makers, other stakeholders and output required.</td>
</tr>
<tr>
<td>2. Selecting and structuring the criteria</td>
<td>Specify appropriate criteria for the decision problem that are relevant to decision-makers and other stakeholders.</td>
</tr>
<tr>
<td>3. Scoring and weighting the criteria</td>
<td>Eliciting stakeholders’ priorities or preferences for changes within criteria (scoring functions) and between criteria (i.e. the weights placed on the criteria).</td>
</tr>
<tr>
<td>4. Evaluating alternatives’ performance</td>
<td>Gather data about the alternatives’ performance on the criteria and summarise this in a ‘performance matrix’.</td>
</tr>
<tr>
<td>5. Calculating aggregate scores</td>
<td>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.</td>
</tr>
<tr>
<td>6. Dealing with uncertainty</td>
<td>Perform uncertainty analysis to understand the robustness of the MCDA results.</td>
</tr>
<tr>
<td>7. Interpretation and reporting</td>
<td>Interpret the MCDA outputs, including sensitivity analysis, to support decision-making.</td>
</tr>
</tbody>
</table>

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

Today’s research for tomorrow’s health
## Case study: Which generic antihypertensive should be purchased by the National Procurement Agency in Indonesia?

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

## Proposal for National Procurement of Off-Patent Pharmaceuticals in Indonesia

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

MCDA scores for National Procurement of generic antihypertensives in Indonesia

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

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
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

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

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
- Full transparency of MCDA rules, regulation and evaluation criteria increases the justifiability of policy decisions
- Scientific publication of MCDA tool
- Trust & Consistency: Prevent misuse of MCDA (e.g. small vs. big companies; local vs. foreign; block market access vs. too easy market access)
- Periodic review of MCDA tool based on real world experience and to accommodate for evolving policy settings
Q&A Session
Educational Seminar: Introduction to HTA
Q&A Session

Finn Børlum Kristensen, MD, PhD
University of Southern Denmark
Copenhagen, Denmark

Panos Kanavos, PhD
London School of Economics and Political Science
LSE Health and Medical Technology Research Group (MTRG)
London, United Kingdom

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