

**ISPOR 14th ANNUAL EUROPEAN CONGRESS**  
5 - 8 November, 2011  
Hotel Auditorium Madrid, Madrid, Spain



# **Issue Panels – Session I**

Sunday, 6 November 2011

14:45 – 15:45



**IP4: MULTICRITERIA  
DECISION ANALYSIS (MCDA):  
A COMMON ROAD MAP FROM  
DRUG DEVELOPMENT TO  
REGULATORY AND  
REIMBURSEMENT DECISIONS?**

# **ISPOR Annual European Congress Madrid, Spain 6 November 2011**

## **ISSUE PANEL**

### **Multi-Criteria Decision Analysis (MCDA): a common road map from drug development, regulatory and reimbursement decisions?**

Dr Ron Goeree

Overview

Dr Bruno Flamion

MCDA at the EMA: the benefit-risk assessment

Dr Meindert Boysen

Structured decision at NICE: is there a role for MCDA

Dr Mireille Goetghebeur

An open source MCDA-based framework, adaptable to the continuum of healthcare decisionmaking





## Introduction for ISPOR Issue Panel

### MCDM: A Common Road Map From Drug Development to Regulatory & Reimbursement Decisions?

Ron Goeree  
Director PATH Research Institute  
Associate Professor, McMaster University

St. Joseph's  
Healthcare of Hamilton

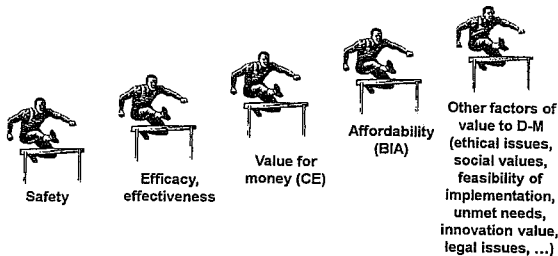


## Traditional Decision Making Criteria

- Often talk about 'traditional' D-M criteria
- Reality, hard to define 'traditional' D-M criteria
- Varies across jurisdictions, across technologies (e.g. drugs, devices, procedures), D-M level (national, provincial, local authority, hospital), time
- For the most part, D-M for both drug & non-drug technologies have been based largely on 4 criteria:
  - Safety
  - Efficacy, effectiveness
  - Cost-effectiveness
  - Budgetary impact/affordability



## Handling of Other Important Criteria?



## Multi-Criteria Decision Making Methods

- Broad set of methods which help make decisions on alternative approaches/treatments using multiple D-M criteria and levels of information
- Some argue 'traditional' D-M processes are already based on multiple criteria (safety, effectiveness, length of life, quality of life, cost)
  - MCDM methods is just an expansion of the risks and benefits explicitly considered as important criteria
- MCDM is a different D-M framework
  - More formal, transparent and explicit approach
  - More comprehensive, structured, predictable



## Classification of MCDM Methods

- Value function or measurement methods
  - Criteria weighting, level scores, ranking (e.g. MCDA)
- Goal programming or reference point methods
  - Closest to pre-defined levels (e.g. <\$/QALY)
- Dominance or Outranking methods
  - Overall superiority, pair-wise comparisons
- Holistic deliberative methods
  - No formal weighting of criteria, consider all together
- Other methods (fuzzy sets, soft system methodology,...)



## Multi-Criteria Decision Analysis (MCDA)

- Calculate an overall numerical score
  - Identify all criteria relevant (valued) by D-Mers
  - Define levels (scoring) for evidence around each criteria
  - Collect evidence (scientific, colloquial, surveys, opinions)
  - Obtain weights for each criteria
  - Calculate total score –  $\sum$  (criteria weights x level scores)
  - Prioritize for D-M based on score
- Advantages: Already discussed, panel to elaborate
- Challenges: Will briefly mention 2



## Is MCDA Too Prescriptive for D-Mers?

### Decision Determinants Guidance Document

The Ontario Health Technology Advisory Committee (OHTAC)  
Decision-Making Process for the Development of Evidence-Based  
Recommendations

Revised September 2010



Medical Advisory Secretariat  
Ministry of Health and Long-Term Care

[www.health.gov.on.ca/english/providers/program/mas/pub/guide\\_decision.pdf](http://www.health.gov.on.ca/english/providers/program/mas/pub/guide_decision.pdf)

## 9 Criteria Holistic Deliberative Process

Criterion 1  
Overall clinical benefit  
• Effectiveness  
• Safety  
• Burden of illness  
• Need

Criterion 2  
Consistency with expected societal and  
ethical values  
• Expected Societal values  
• Expected Ethical values

Criterion 3  
Value for money  
• Economic evaluation (costs)

Criterion 4  
Feasibility of adoption into health system  
• Economic feasibility  
• Organizational feasibility

• Evaluate the health technology through  
a deliberative process  
• Make recommendation and value  
judgements on basis of these criteria

[www.health.gov.on.ca/english/provider/sprogram/mas/pub/guide\\_decision.pdf](http://www.health.gov.on.ca/english/provider/sprogram/mas/pub/guide_decision.pdf)

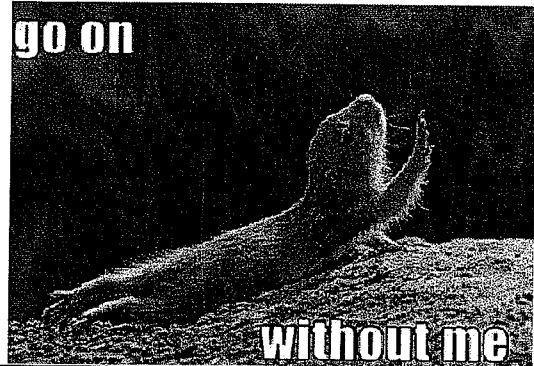
## OHTAC's DD Scoring System

Symbol	Meaning
●	High/Large
◐	Moderate/Medium
○	Low/Small
⊖	Uncertainty in the evidence as reflected by quality of evidence or assessment of quality of evidence
?	Unknown

[www.health.gov.on.ca/english/providers/program/mas/pub/guide\\_decision.pdf](http://www.health.gov.on.ca/english/providers/program/mas/pub/guide_decision.pdf)

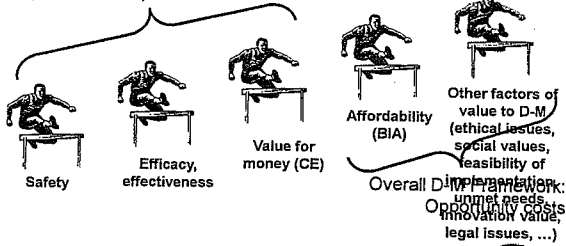


## What About Value-for-Money (CE)?



## Criteria vs Overall D-M Framework?

Criteria: broader definition of value  
(risks, benefits)




## Panel Speakers

- > Dr. Bruno Flamion
  - Pharmacological and Medical Expert
  - Federal Agency for Medicines and Health Products
  - Brussels, Belgium
- > Dr. Meindert Boysen
  - Program Director, Technology Appraisals
  - Centre for Health Technology Evaluation
  - National Institute for Health & Clinical Excellence (NICE)
  - Manchester, United Kingdom
- > Dr. Mireille Goetghebeur
  - Vice President, Operations
  - BioMedCom Consultants Inc.
  - Dorval, Quebec, Canada




**Issue Panel 4**  
**MCDA: A COMMON ROAD MAP FROM DRUG DEVELOPMENT TO REGULATORY AND REIMBURSEMENT DECISIONS?**

**MCDA at the EMA:**  
**the benefit-risk (B/R) assessment**



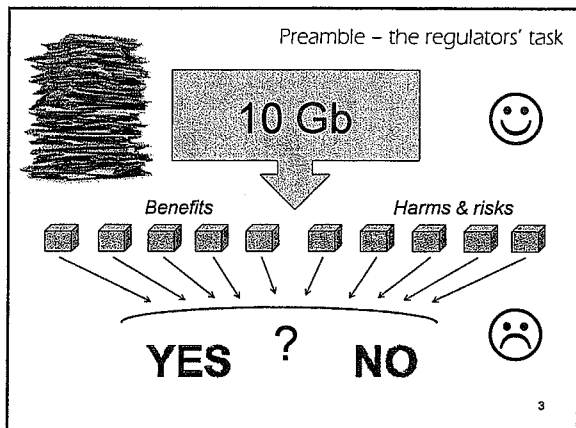
**Bruno FLAMION, MD, PhD**  
 2005-2010 Chair, Scientific Advice Working Party (SAWP) of the CHMP (EMA)  
 Member of the Benefit-Risk Methodology Project Steering Group (EMA)  
 Expert, Federal Agency for Medicines and Health Products (FAMHP), Belgium  
 Chair, Belgian Committee for Reimbursement of Medicines (CTG-CRM, INAMI-RIZIV)  
 Professor of Physiology & Pharmacology, University of Namur, Belgium



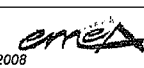
**Disclaimer**

My presentation might not be the view of the organisations I am working for.  
 My presentation is a personal viewpoint and binds in no way the organisations mentioned above.  
 I have no financial interest to disclose.

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The 2008 CHMP Reflection



2008 London, 19 March 2008  
 Doc. Ref. EMA/CHMP/15404/2007

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)


REFLECTION PAPER ON BENEFIT-RISK ASSESSMENT METHODS IN THE CONTEXT OF THE EVALUATION OF MARKETING AUTHORISATION APPLICATIONS OF MEDICINAL PRODUCTS FOR HUMAN USE

2009

- Start of the BR Methodology Project (EMA sponsor: Xavier Luria):
  - London School of Economics (Prof. Larry Phillips) & University of Groningen (Prof. Andrea Beyer)
  - CHMP/EMA Steering Group

The EMA report on Work Package 1 (1)

March 2010



Work Package 1

EUROPEAN MEDICINES AGENCY  
 SCIENCE MEDICINES HEALTH

30 March 2010  
 EMA/213482/2010  
 Human Medicines Development and Evaluation

European Medicines Agency Benefit-Risk methodology project  
 Description of the current practice of benefit-risk assessment for centralised procedure products in the EU regulatory network

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The EMA report on Work Package 1 (2)

6 participating agencies:

- FR
- NL
- SE
- ES
- UK
- DE (PEI)


Figure 1. The EMA's four-fold model of 'benefits' and 'risks'

Favourable effects (or beneficial)	Uncertainty of favourable effects
Unfavourable effects	Uncertainty of unfavourable effects

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The EMA report on Work Package 2 (1)

August 2010



WP2

EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

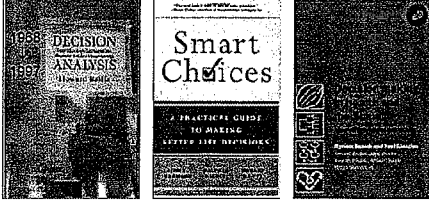
31 August 2010  
EMA/54962/2010 - Revision 1  
Human Medicines Development and Evaluation

**Benefit-risk methodology project**  
Work package 2 report: Applicability of current tools and processes for regulatory benefit-risk assessment

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The EMA report on Work Package 2 (2)

1. Any quantitative method requires a qualitative framework within which the model can be effectively developed. The qualitative approach may be sufficient for simpler B/R decisions.
2. The EMA favours the 8-step ProACT-URL framework (Hammond et al., 1999; Hunink et al., 2001)



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The ProACT-URL framework



1. PROBLEM formulation
2. OBJECTIVES (establish criteria)
3. ALTERNATIVES (options to be evaluated)
4. CONSEQUENCES (of all effects)
5. TRADE-OFFS (= balance)
6. UNCERTAINTY (of all effects)
7. RISK ATTITUDE (of the participants or the decision makers)
8. LINKED DECISIONS

→ Similar frameworks presented by, e.g., Felli et al. (Eli Lilly, 2009), Prof. Stuart Walker (CMR/CIRS CASS study, 2010), FDA BRP (2010), PhRMA's BRAT group (2011)...

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The EMA report on Work Package 2 (3)

3. 18 quantitative approaches were analysed. Only 3 are sufficiently comprehensive for a numerical representation of the B/R (as a difference or as a ratio) along with its uncertainties:
  - Bayesian statistics
  - Decision trees and influence/relevance diagrams
  - Multi-criteria decision analysis (MCDA)

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The EMA report on Work Package 2 (4)

4. Five other approaches, while more restricted in scope, may well prove useful for particular cases:
  - Probabilistic simulation
  - Markov processes
  - Kaplan-Meier estimates (both for estimating changes in health states over time)
  - QALYs (for modelling multiple health outcomes)
  - Conjoint analysis (to explicate trade-offs among effects, especially for eliciting patient preferences)
5. Combination of approaches will prove useful in some situations

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The EMA report on Work Package 3 (1)

August 2011



WP3

EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

31 August 2011  
EMA/54962/2011 - Revision 1  
Human Medicines Development and Evaluation

Benefit-risk methodology project  
Work package 3 report: Field tests

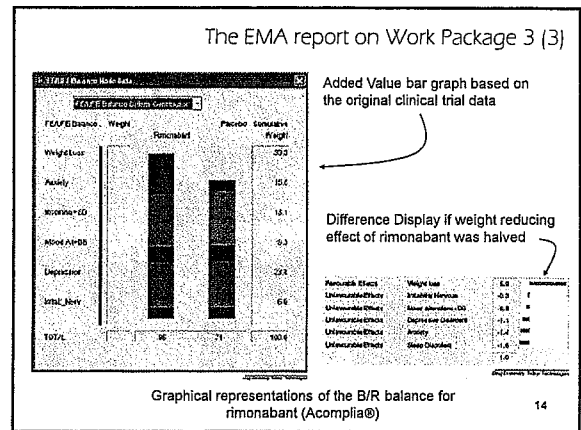
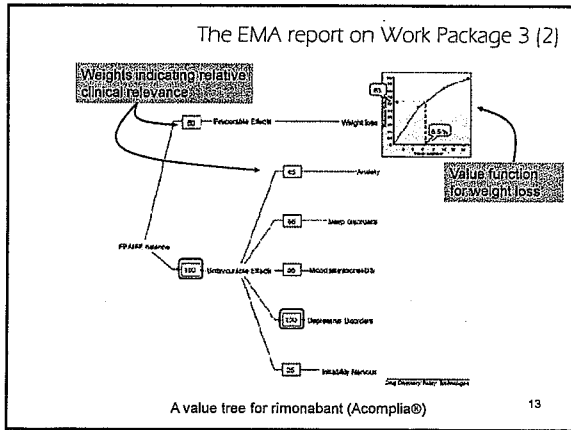
Drug Discovery Today: Technology  
Spring 2011; 8(1): 62-10

**Is quantitative benefit-risk modelling of drugs desirable or possible?**<sup>1,2</sup>

Laura van den Broek<sup>1,2,3</sup>, Annette Faust<sup>1,2</sup>, Nikolaos Zafropoulos<sup>1</sup>, Andrea Bayer<sup>3,4</sup>

- 5 agencies → each chose a drug under review by the CHMP, at different stages
- Sessions were conducted as a 1-day « decision conference » (facilitated workshop)

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### The ongoing Work Package 4

WP 4 deliverables:

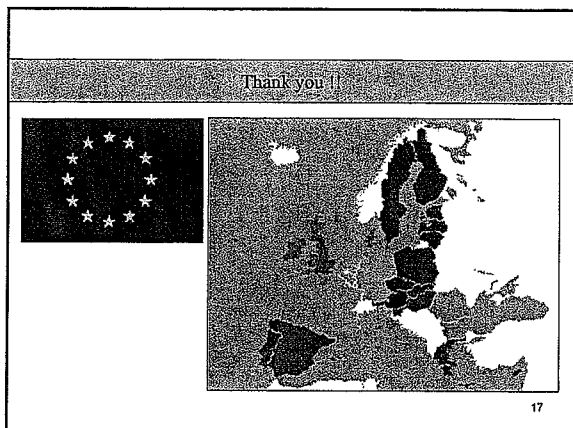
- Operational decision aid / framework approved by the CHMP (end 2011 or later). This framework should be flexible to accommodate increasing degrees of B/R modelling
- Draft CHMP reflection paper
- Public consultation and workshop (early 2012)

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### The future of MCDA at EMA/CHMP

- The ongoing B/R Methodology Project shows that quantitative B/R modelling of (new) drugs for the purpose of Marketing Authorisation is possible
- Is it desirable?  
The added value of this exercise (especially MCDA) for the national assessors and for the CHMP decision makers remains to be demonstrated
- A flexible framework allowing increasingly complex approaches may be an efficient way forward

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## Structured decision making at NICE; is there a role for 'MCDA'?

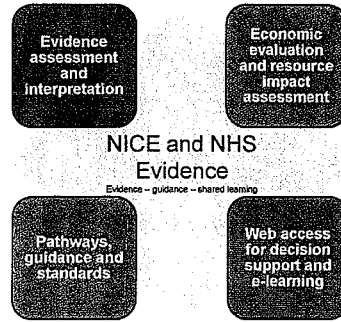
ISPOR 2011  
Issue Panel 4  
Sunday 6 November 2011 (14:45-15:45)

Meindert Boysen  
Programme Director Technology Appraisals

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National Institute for  
Health and Clinical Excellence

## This is what we do

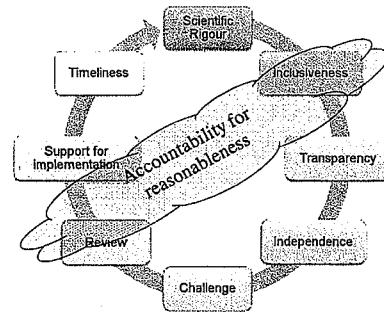


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## CURRENT APPROACH TO DECISION MAKING

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## Procedural Principles



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## Appraising Cost-Effectiveness

- Below £20,000/QALY - CE
- Above £20,000/QALY - CE and other factors
  - The degree of certainty surrounding the calculation of ICERs
  - Change in HRQoL inadequately captured
  - The innovative nature of the technology
- Above £30,000/QALY as above but much stronger (!)
- Always give reasons
- ADDENDUM 2009: 'Appraising life-extending, end of life treatments'

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## Application of 'special circumstances'

Table 1  
Application of special circumstances in the appraisal of some products with incremental cost-effectiveness above £30,000 per quality adjusted life year

Case	ICER (QALY)	Severity	End of life*	Strategic importance	Novelty/innovation	Disadvantaged population	Children
1. Rituximab (non-relapsing disease)	£31						
2. Atorvastatin (advanced breast cancer)	£75						
3. Sorafenib (hepatocellular carcinoma)	£36						
4. Erlotinib (adenocarcinoma of the lung)	£55						
5. Gemtuzumab (acute myeloid leukaemia)	£40						
6. Docetaxel (breast cancer)	£20						
7. Sorafenib (hepatocellular carcinoma)	£36						
8. Sorafenib (hepatocellular carcinoma)	£36						
9. Sorafenib (hepatocellular carcinoma)	£36						
10. Sorafenib (hepatocellular carcinoma)	£36						
11. Sorafenib (hepatocellular carcinoma)	£36						
12. Sorafenib (hepatocellular carcinoma)	£36						
13. Sorafenib (hepatocellular carcinoma)	£36						
14. Sorafenib (hepatocellular carcinoma)	£36						
15. Sorafenib (hepatocellular carcinoma)	£36						
16. Sorafenib (hepatocellular carcinoma)	£36						
17. Sorafenib (hepatocellular carcinoma)	£36						
18. Sorafenib (hepatocellular carcinoma)	£36						
19. Sorafenib (hepatocellular carcinoma)	£36						
20. Sorafenib (hepatocellular carcinoma)	£36						

\* End of life conditions: have only been used by NICE since January 2009 on the basis of advice from the structure to the Appraisal Committee. NICE reserves the right to change this definition in the future.

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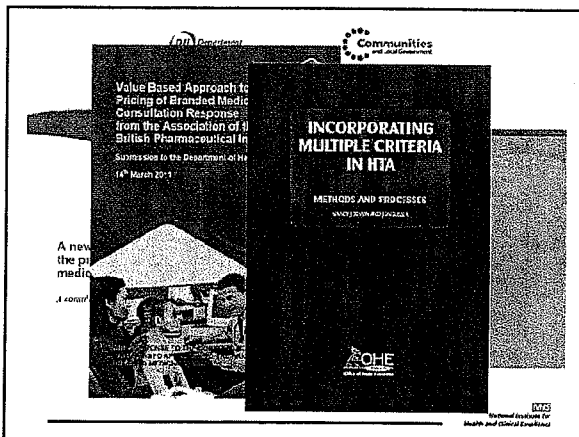
## Targeted approach depending on guidance product ...

- Clinical guidelines
  - Consensus (+/- formal)
  - Strength of recommendation (~GRADE / LETR)
- Diagnostics
  - ... (scope & evidence)
- Medical devices
  - 'Cost minimisation' & cost effectiveness
  - Research recommendations
- Interventional procedures
  - ... (efficacy & safety)
  - Special arrangements consent/audit/research
- Public Health
  - Methodological protocols for committees on how to interpret expert testimony to develop guidance
  - Cost utility analysis (ref case) & cost consequences analysis (ref case) & cost benefit analysis (> NHS)

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## A(N) (EVEN) MORE STRUCTURED APPROACH TO DECISION MAKING?

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## Methods 2008-11 ... 2012-15

Table 5.4 Summary of the reference case

Element of health technology assessment	Reference case	Options (preference weights)
Defining the decision problem	The scope developed by the committee	5.2.3 & 5.2.4
Comparator	Therapies routinely used in the NHS including best practice regarded as current best practice	5.2.6 & 5.2.6
Perspective on costs	NHS and PSI	5.2.7 to 5.2.10
Perspective on outcomes	All health effects on QALYs	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.0.11 to 5.2.13
Synthesis of evidence	Based on a systematic review	5.3
Structure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients or proxy carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Quality weighting	An additional QALY has the same weight regardless of the other characteristics of the individual receiving the health benefit	5.12

NICE, Health-related quality of life (HRQL), National Health Service, PSI, personal social services, QALY, quality-adjusted life years.

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## NICE Methods Guide review Workshop (I)

2. Potential benefits of a more structured approach
- Improve the transparency of the decision making process and the accountability of NICE to taxpayers
  - Improve consistency of decision making eg. across the 4 ACGs
  - Facilitate greater consistency between the way NICE decides on new technologies and the way the NHS decides to allocate its budgets
  - Provide an opportunity for NICE to engage the public on the criteria and weights—leading to more 'buy in' to the difficult decisions NICE must make
  - Sharpen signals to industry about what aspects of innovation NICE (acting as an agent for the NHS) values and where R&D should be directed.

N. Devlin at NICE Workshop (31 Oct 2011)


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## NICE Methods Guide review Workshop (II)

1. Which criteria might be included and how could performance be measured and scored?
2. How can weights be assigned to performance on each of the criteria?
3. How should the costs and opportunity costs of achieving an improvement in a composite measure of benefit be considered?
4. How could the transparency of the deliberative process be improved?

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**(BUT) WILL 'IT' MAKE A DIFFERENCE?**



  
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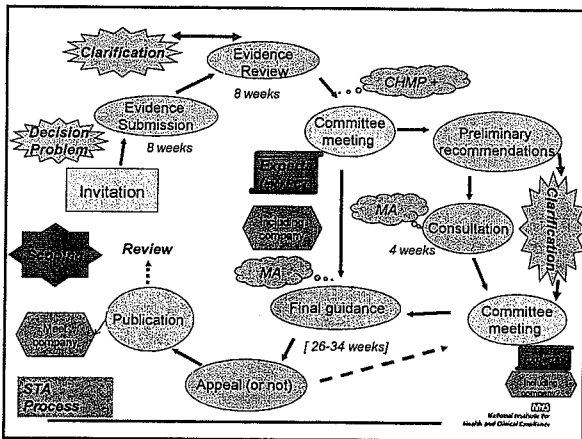
### Most new technologies are worth using

Decision	Recommendations	
Yes	276	(63%)
Optimised	83	(19%)
Only in research	24	(5%)
No	55	(13%)


*82% of NICE recommendations are positive*

Breakdown of all decisions contained in published NICE Technology Appraisals 1-236 (January 2000 to October 2011)  
 Note: 6 withdrawn recommendations and 10 non-submissions are not included


  
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### Transparency & 'innovation'



  
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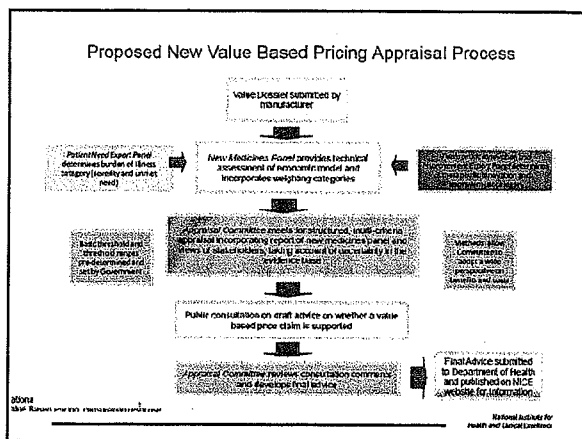
### NICE Methods Guide review Workshop (III)


#### 3.4 Options for improving the transparency of the deliberative process

- Arguably, some element of judgment will always be required/desirable
- Multiple criteria already used in ITA decision making; VDP adds to the pressure to be more explicit about what those other criteria are and the weight attached to them.
- Given that decision making is not based solely on the ICER, where on the spectrum of quantification w.r.t other criteria should NICE decision making processes be?
- Options include:
  - The status quo
  - MCDA as a supplement to existing deliberative processes (eg. decision conference); potentially maintaining the current threshold 'range', but more explicit reporting of the influence of other criteria within and above that range
  - 'Tully algorithm': MCDA to score/weight agreed criteria; with both criteria and weights (eg based on stated preference studies with the general public); to achieve a 'benefit score'. Re-define opportunity cost and the threshold in terms of that benefit score

K. Claxton at NICE Workshop (31 Oct 2011)


  
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**An open source MCDA-based framework adaptable to the continuum of healthcare decisionmaking**

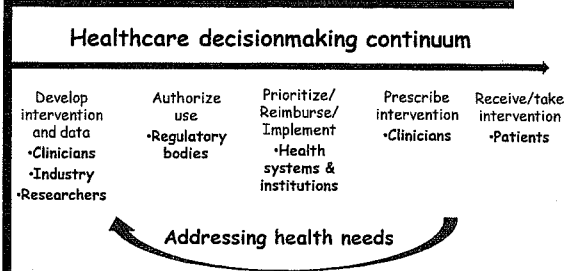
6 November 2011  
Madrid, Spain

**EVIDEM Collaboration - Board of Directors**

Rob Baltussen PhD, Radboud University, Netherlands (formerly WHO)  
Renaldo Battista MD, University of Montreal, Hospital University Center (CHU) Ste Justine, Canada  
Alirelle M. Goetghebuer PhD, BioMedCom Consultants Inc, CHU Ste Justine, Canada  
Paul Kind PhD, University of York, UK  
Sharon Kletzko MD, Nelson Marlborough District Health Board, New Zealand  
Mark Legault MA, Pfizer Canada  
Jacqui Alot PhD, University of Pretoria, South Africa  
Donna Rindress PhD, BioMedCom Consultants Inc, Canada

1

**Healthcare decisionmaking continuum**



Develop intervention and data  
•Clinicians  
•Industry  
•Researchers

Authorize use  
•Regulatory bodies

Prioritize/Reimburse/Implement  
•Health systems & institutions

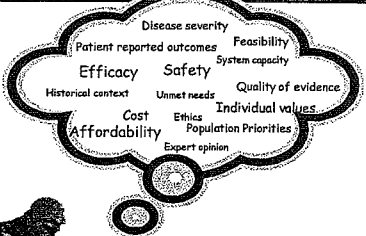
Prescribe intervention  
•Clinicians

Receive/take intervention  
•Patients

Addressing health needs

→ Common road map: Which interventions contribute the most to patient health and to an equitable, efficient and sustainable healthcare system?

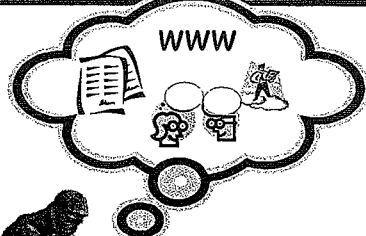
2



→ Structure the natural thinking process (criteria, relative importance)

Baltussen & Nissen. *Cost Eff Resour Alloc*. 2006;4:14


3



→ Find the evidence (scientific and colloquial)

Battista RM. *JTAHC*. 2006; 22(3): 275.

4



**EVIDEM framework**

Provide a toolkit

- Identify criteria
- Synthesize data "by criterion"
- Quantitative and qualitative tools

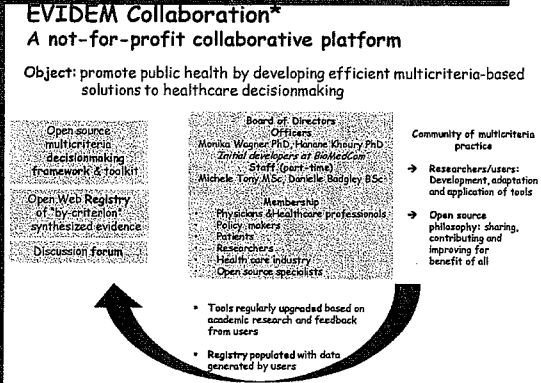
Goetghebuer M, et al. *Cost of Effectiveness and Resource Allocation*. 2010;8:4.  
Goetghebuer et al. *Medical Decision Making* 2011, Oct 10 - On-line first.

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**EVIDEM Collaboration\***

**A not-for-profit collaborative platform**

Object: promote public health by developing efficient multicriteria-based solutions to healthcare decisionmaking



**Open source multicriteria decisionmaking framework & toolkit**

**Open Web Registry of "by-criterion" synthesized evidence**

**Discussion forum**

**Board of Directors Officers**  
Monika Wagner PhD, Monique Khoury PhD  
\*Initial developers of BioMedCom Staff (part-time)  
Michelle Tony MSc, Danielle Badgley BSc

**Memberships**  
Physicians & healthcare professionals  
Policy makers  
Patients  
Researchers  
Health care industry  
Open source specialists

**Community of multicriteria practice**

- Researchers/users: Development, adaptation and application of tools
- Open source philosophy: sharing, contributing and improving for benefit of all

- Tools regularly upgraded based on academic research and feedback from users
- Registry populated with data generated by users

\*International collaboration registered under and structured according to the Canadian laws in January 2009  
Latest funding received for EVIDEM operations: Canadian Institutes of Health Research (CIHR)

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