ISPOR 14th ANNUAL EUROPEAN CONGRESS
5 - 8 November, 2011
Hotel Auditórium 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 fro MCDA
Dr Mireille Goetghebeur	An open source MCDA-based framework adaptable to the continuum of healthcare decisionmaking

Introduction for ISPOR Issue Panel

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

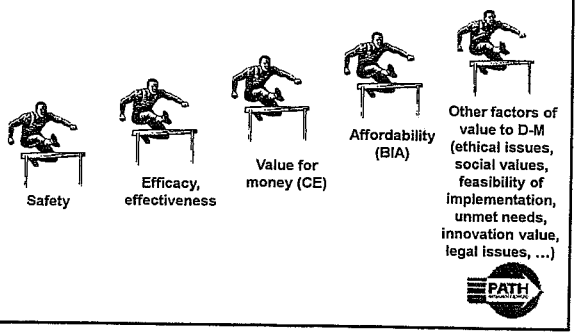
Ron Goeree
Director PATH Research Institute
Associate Professor, McMaster University

St. Joseph's Healthcare Hamilton
McMaster University

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 – Σ (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

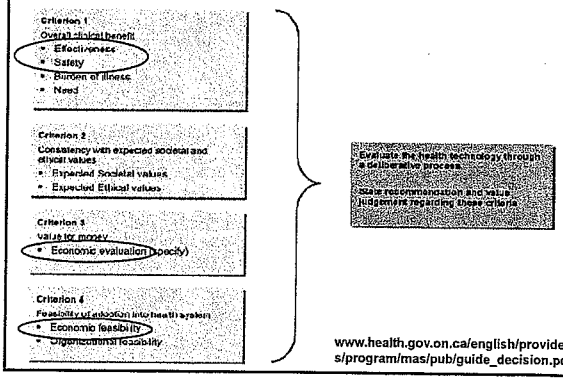
Revised September 2010

Ontario

Medical Advisory Secretariat
Ministry of Health and Long-Term Care

www.health.gov.on.ca/english/providers/program/mas/pub/guide_decision.pdf

9 Criteria Holistic Deliberative Process



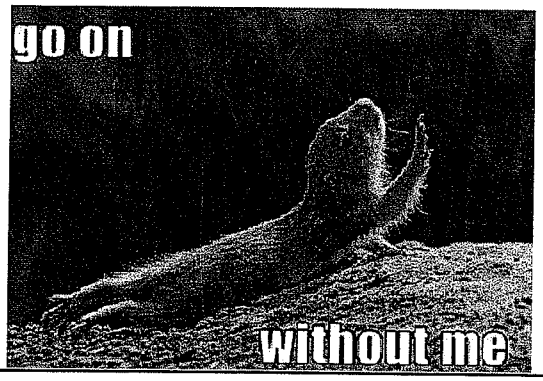
www.health.gov.on.ca/english/providers/program/mas/pub/guide_decision.pdf

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

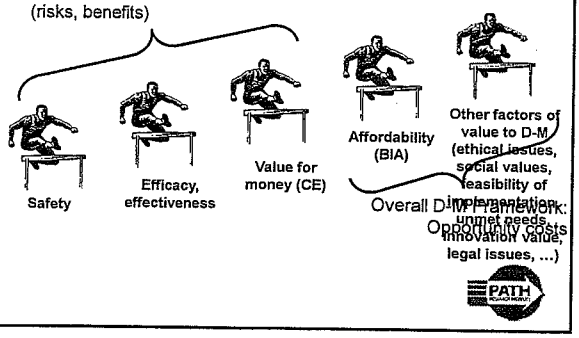
www.health.gov.on.ca/english/providers/program/mas/pub/guide_decision.pdf

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

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

INAMI RIZIV

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.

Preamble – the regulators' task

10 Gb

Benefits *Harms & risks*

YES ? **NO**

The 2008 CHMP Reflection

European Medicines Agency

2008

London, 19 March 2008
Doc. Ref. EMEA/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/213487/2010
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

The EMA report on Work Package 2 (1)

August 2010

WP 2

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 August 2010
EMA/549662/2010 - 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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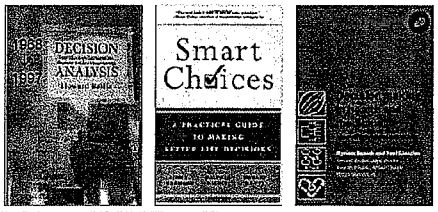
The EMA report on Work Package 2 (2)

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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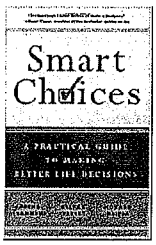
The PrOACT-URL framework



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 BRF (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

WP 3

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 August 2011
EMA/754124/2011
Human Medicines Development and Evaluation

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

Is quantitative benefit-risk modelling of drugs desirable or possible?[☆]

- 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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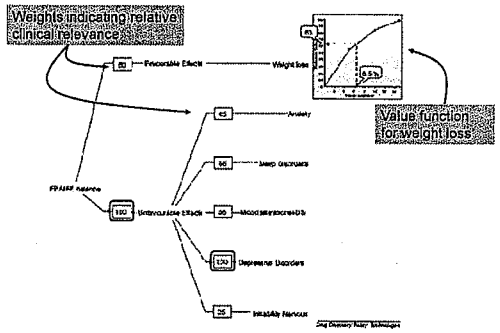
The EMA report on Work Package 3 (2)



A value tree for rimonabant (Acomplia®)

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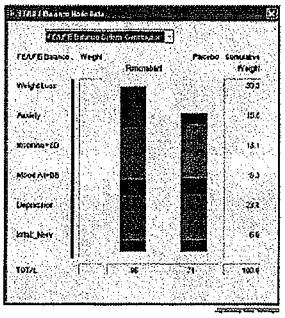
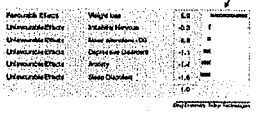
The EMA report on Work Package 3 (3)



Added Value bar graph based on the original clinical trial data

Difference Display if weight reducing effect of rimonabant was halved



Graphical representations of the B/R balance for rimonabant (Acomplia®)

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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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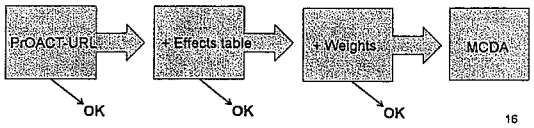
The future of MCDA at EMA/CHMP

1. The ongoing B/R Methodology Project shows that quantitative B/R modelling of (new) drugs for the purpose of Marketing Authorisation is possible
2. 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
3. A flexible framework allowing increasingly complex approaches may be an efficient way forward



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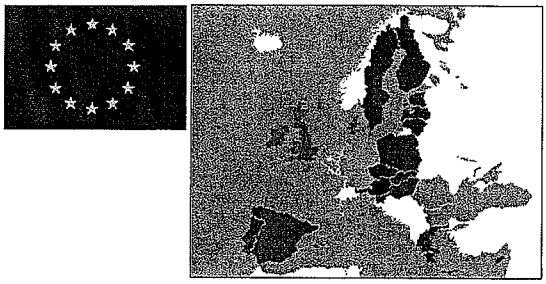
Thank you !!



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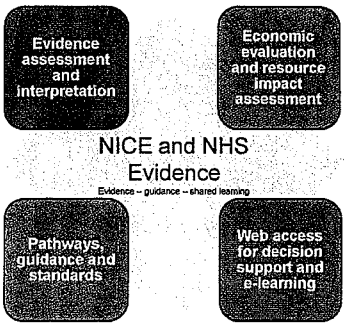
Structured decision making at NICE; is there a role for 'MCDA'?

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

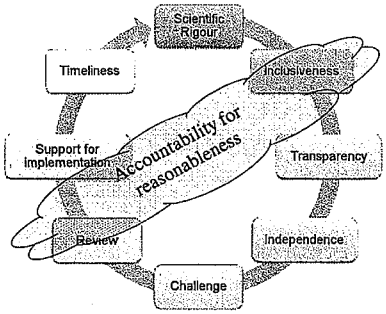
Meindert Boysen
Programme Director Technology Appraisals

This is what we do



CURRENT APPROACH TO DECISION MAKING

Procedural Principles



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'

Application of 'special circumstances'

Table 1
Application of 'special circumstances' in the appraisal of some products with incremental cost-effectiveness above £30000 per quality adjusted life year

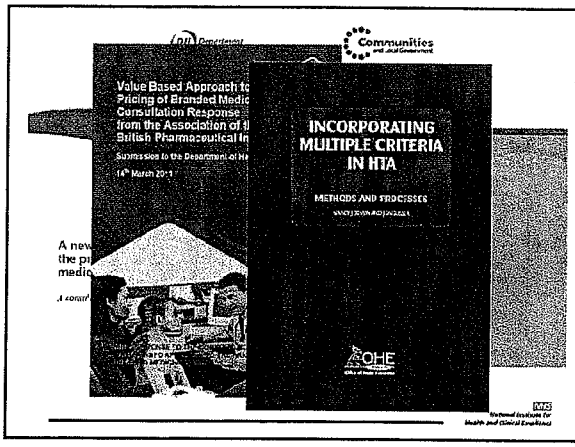
Topic	ICER (000s)	Severity	End of life*	Stakeholder persuasion	Significant innovation	Disadvantaged population	Children
Rituximab (second relapsing illness)	29-41						
Trastuzumab (advanced breast cancer)	375	✓					
Imatinib (chronic myeloid leukaemia)	30-45	✓					
Imatinib (gastrointestinal stromal tumour)		✓					
Docetaxel (malignant neoplasms)	145	✓					
Ranibizumab (age-related macular degeneration)	34-50	✓					
Oxaliplatin (second relapse)	100	✓					
Gemcitabine (advanced renal cancer)	50	✓	✓	✓			
Imatinib (multiple myeloma)	33	✓	✓	✓			
Somatropin (growth hormone deficiency)	70	✓					✓
Chronic intravenous insulin infusion	70	✓		✓			
(Additional Type 1 diabetes)							

*End-of-life considerations have only been explicitly taken into account since January 2009 on the basis of supplementary advice from the Institute to the Appraisals Committee
ICER: incremental cost-effectiveness ratio (£ per quality-adjusted life year)

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)

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



Methods 2008-11 ... 2012-15

Table 5.1 Summary of the reference case

Element of health technology assessment	Reference case	Section providing details
Defining the decision problem	The scope developed by the institute	5.2.5 & 5.2.6
Comparator	Therapies routinely used in the NHS including technologies regarded as current best practice	5.2.6 & 5.2.4
Perspective on costs	NHS and PSS	5.2.7 to 5.2.10
Perspective on outcomes	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.0.11 & 5.2.11
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and/or 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
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individual receiving the health benefit	5.12

HRQL=health-related quality of life; NHS=National Health Service; PSS=personal social services; QALY=quality-adjusted life year

Patient Access Schemes

Innovation (Kennedy)

End of life & life extension

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 ACs
- 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 eg. 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)

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?

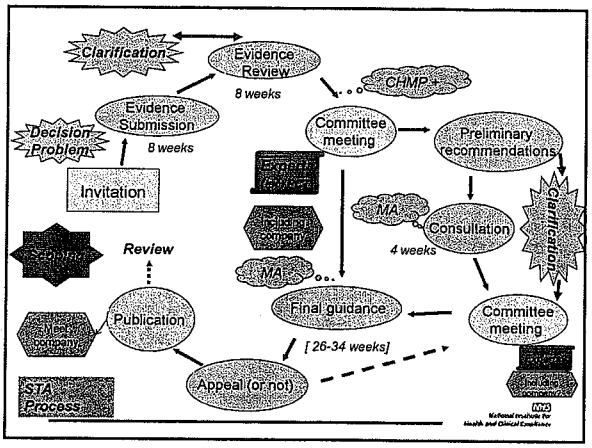
(BUT) WILL 'IT' MAKE A DIFFERENCE?

Most new technologies are worth using

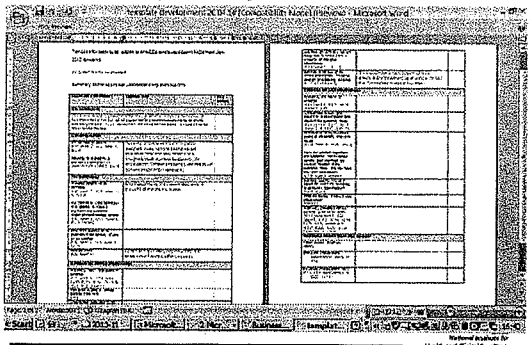
Decision	Recommendations	
Yes	276	(63%)
Optimised	83	(19%)
Only in research	24	(5%)
No	56	(13%)

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

82% of NICE recommendations are positive



Transparency & 'innovation'



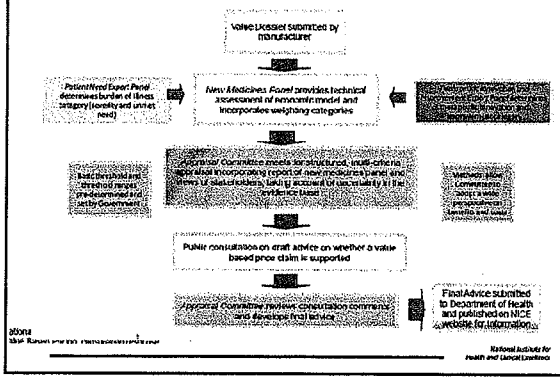
NICE Methods Guide review Workshop (III)

3.4 Options for improving the transparency of the deliberative process

- Arguably, some element of judgement will always be required/desirable
- Multiple criteria *already* used in HTA decision making; VBP 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 conferencing); potentially maintaining the current threshold "range"; but more explicit reporting of the influence of other criteria within and above that range
  - 'Fully algorithmic' 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'. Redefine opportunity cost and the threshold in terms of that benefit score

K. Claxton at NICE Workshop (31 Oct 2011)

Proposed New Value Based Pricing Appraisal Process



EVIDEM

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
Mireille M Goetghebeur PhD, BioMedCom Consultants inc, CHU Ste Justine, Canada
Paul Kind PhD, University of York, UK
Sharon Kletchko MD, Nelson Marlborough District Health Board, New Zealand
Mark Legault MA, Pfizer Canada
Jacqui Miot PhD, University of Pretoria, South Africa
Donna Rindress PhD, BioMedCom Consultants inc, Canada

1

Healthcare decisionmaking continuum

Develop intervention and data	Authorize use	Prioritize/ Reimburse/ Implement	Prescribe intervention	Receive/take intervention
•Clinicians •Industry •Researchers	•Regulatory bodies	•Health systems & institutions	•Clinicians	•Patients

Addressing health needs

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

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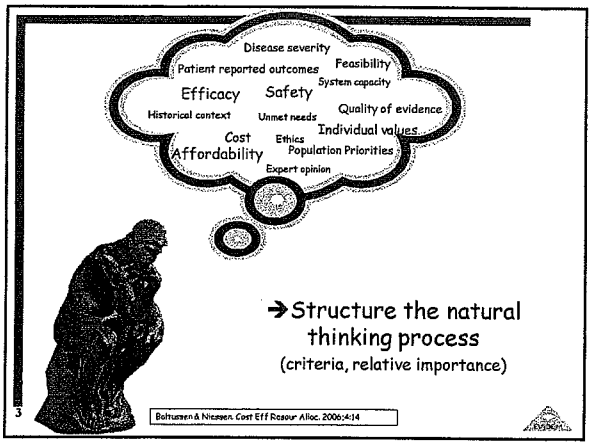
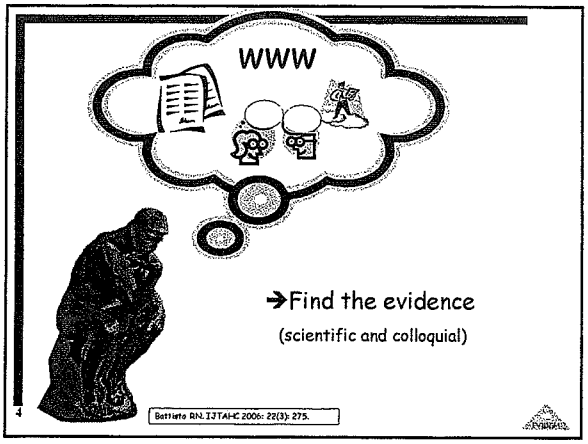


→Structure the natural thinking process
(criteria, relative importance)

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

3



→Find the evidence
(scientific and colloquial)

Battista RN. IJTAHC 2006; 22(3): 275.

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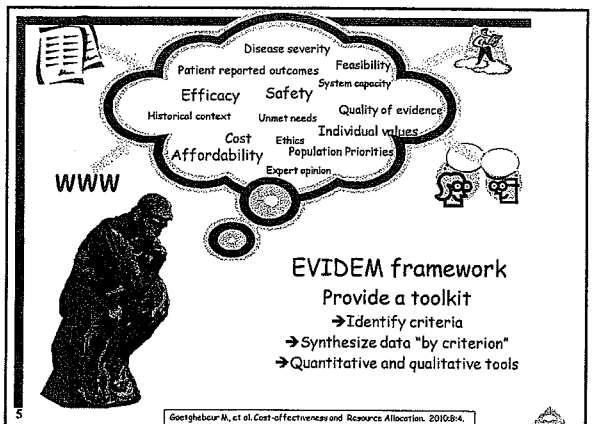

EVIDEM framework
Provide a toolkit
→Identify criteria
→Synthesize data "by criterion"
→Quantitative and qualitative tools

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

5

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, Hanane Khoury PhD
Initial developers at BioMedCom
Staff (part-time)
Michele Tony MSc, Danielle Badgley BSc

Membership
- 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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