Establishing the value of innovative medicines While dealing with uncertainty using multicriteria decision analysis (MCDA)

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EVIDEM Collaboration - Board of Directors

Rob Baltussen PhD, Radboud University, Netherlands (formerly WHO)
Renaldo Battista MD, University of Montreal, 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

Outline

- Overview
- Defining value - MCDA
  - Decision criteria
  - Weighting techniques
  - Scoring scales
  - Mathematical model & qualitative considerations
- Exploring uncertainty – HTA
  - By-criterion evidence synthesis
  - Interactive open web registry
- Users & applications
- Advantages & challenges
- Future developments

Overview - EVIDEM Collaboration

- **Not-for profit** independent legal entity

- **Object:** promote health and efficient decisionmaking via systematic assessment of evidence and value of healthcare interventions
  - **MCDA based decision making framework tools*** freely available under Creative Commons license
  - **Collaborative development**
    - Open tools **regularly upgraded** based on academic research and feedback from users
    - **Open web** registry

- **On-going collaborations**
- Canada, Italy, Netherlands, New Zealand, South Africa, UK, USA
- Tools used and tested by **government agencies** and **academic centers**

- **Funding & support:** Canadian Institutes of health Research (CIHR), Pfizer Canada (start up), BioMedCom (in kind)

*Goetghebeur M, et al. BMC Health Services 2008; 8:270.
Goetghebeur M, et al. Cost-effectiveness and Resource Allocation. 2010:8:4.

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Structuring the natural thinking process to define value

→ **MCDA**

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

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Defining value of interventions
Criteria?

Which criteria define the most valuable healthcare interventions?

- ➔ Elicit from evaluators
- ➔ Use an existing set of criteria & adapt
  - ➔ MCDA-based EVIDEM framework

Defining value of interventions
Criteria?

Apply MCDA principles

- criteria should be complete,
- with minimum overlap
- mutually independent
- operationalizable*

*National Economic Research Associated. Multi-criteria analysis manual 2005. www.communities.gov.uk/pub/252/MulticriteriaanalysismanualPDF1380Kb_id1142252.pdf

Defining value of interventions
EVIDEM conceptual approach

➔ Develop a universal generic tool and a contextualization tool

- ❖ MCDA Core Model
- ❖ Contextual Tool

**Criteria identified from extensive analysis of literature and decisionmaking processes, feedback from users and selected to fulfill MCDA principles

MCDA Core Model
What should we do for sustainable healthcare systems?

15 universally normative criteria

➔ **Highest rank/value or priority should be given to interventions**

- For severe disease (D1)
- For common disease (D2)
- For disease with many unmet needs (C2)
- Recommended in consensus guidelines by experts (C1)
- Conferring major improvement in efficacy/effectiveness over standard of care (I1)
- Conferring major improvement in safety & tolerability over standard of care (I2)
- Conferring major improvement of patient perceived health over standard of care (I3)
- Either conferring major risk reduction (T1) or major alleviation of suffering (T2)
- That results in savings in treatment expenditures (E1) as well as other medical and non medical expenditures (E3); *cost-effective (E2)**
- For which there is sufficient data (Q1), that is fully reported (Q2) and valid and relevant (Q3)

*Cost-effectiveness is a composite of some elements of other criteria and does not comply with the non-redundancy design requirement of MCDA. It may be included in the framework since many decisionmaking processes currently rely on this composite measure.

Contextual Tool
What is our context and what can be done?

6 criteria

➔ **Define objectives & priorities – 2 contextual normative criteria**

- Alignment with scope and mission of health care system/plan (Et1)
- Defining country/institutional priorities for populations & access (Et2)

➔ **4 Feasibility criteria**

- Exploring opportunity costs (forgone interventions) and affordability (Et3)
- Verifying system capacity (e.g., infrastructure, skills) and appropriate use of intervention (O1)
- Assessing political/historical context (e.g. cultural acceptability, precedence) (O2)
  - *Impact of intervention on innovation and research?*
- Realizing pressures/barriers from healthcare stakeholders (O3)

Overall EVIDEM framework structure
Clustering criteria

MCDA core model

Universally normative criteria (quantitative)

Disease impact
- Disease severity (D1)
- Size of population affected by disease (D2)

Context of intervention
- Clinical guidelines (C1)
- Comparative intervention limitations (C2)

Intervention outcomes
- Improvement of efficacy/effectiveness (I1)
- Improvement of safety and tolerability (I2)
- Improvement of patient reported outcomes (I3)

Type of benefit
- Public health interest (e.g., prevention, risk reduction) (T1)
- Type of medical service (e.g., symptom relief, cure) (T2)

Economics
- Budget impact on health plan (cost of intervention only) (E1)
- Impact on other spending (e.g., hospitalization, disability) (E2)
- Cost-effectiveness of intervention (E3)

Quality/uncertainty of evidence
- Adherence to requirements of decisionmaking body (Q1)
- Completeness and consistency of reporting (Q2)
- Relevance and validity of evidence (Q3)

Contextual tool

Context & feasibility criteria (qualitative)

Ethical framework*
- **Utility** - Goals of healthcare (Et1)
- **Fairness** - Population priority & access (Et2)
- **Efficiency** - Opportunity costs & affordability (Et3)

Other system-related criteria
- System capacity and appropriate use (e.g., infrastructure, skills) (O1)
- Stakeholder pressures (O2)
- Political/historical context (e.g. precedence) (O3)

*Based on three principles; since often conflicting, clearly identify trade-offs and legitimize decision by engaging a broad range of stakeholders & explaining decision; legitimizing decision is key to provide accountability for reasonableness (A4R)

Adaptation
Define value in your context

- **Include priorities** defined using the contextual tool as additional criteria of the MCDA Core Model (e.g., rare diseases)

- **Transfer** other contextual criteria in the MCDA core model

- **Expand** criteria into subcriteria*

Criteria	Possible sub criteria
E3 Impact on other spending	•Impact on primary care expenditures •Impact on hospital care expenditures •Impact on long-term care expenditures •Impact on productivity •Financial impact on patients •Financial impact on caregivers

- **Remove** criteria

*A number subcriteria are available in tools to expand model - apply MCDA principles

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Not all criterion are equal

?

=

Disease severity

Improvement of efficacy

Measuring value
Weight elicitation techniques*

- **Capture individual perspective** on relative importance of criteria independently of healthcare interventions
- No gold standard

  → Simple techniques
  - EVIDEM

Criteria	Weights Low ⟷ High
Example **Disease severity**	❑1 ❑2 ❑3 ❑4 ❑5

  - Kepner -Tregoe Analysis (KTA)
  - Direct point allocation

  → More complex
  - Analytical hierarchy process (AHP)
  - Best/worst scaling
  - Conjoint analysis

→ Adapt to user preference/context

*Dolan J. Patient 2010; 3(4): 229-248. Clemen and Reilly. Making Hard Decision. 2001

Measuring value
Scoring scale?

- **Measure performance** of intervention
- Need to define:
  - Type of scale/number of options
  - Scale anchors for each criteria

➔ Simple approach

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Criteria	Scoring scale
Example **Disease severity**	❑0 – not severe ❑1 ❑2 ❑3 – very severe

➔ More complex (e.g., more scale options, boolean operators for each option)

➔ Adapt to user preference/context

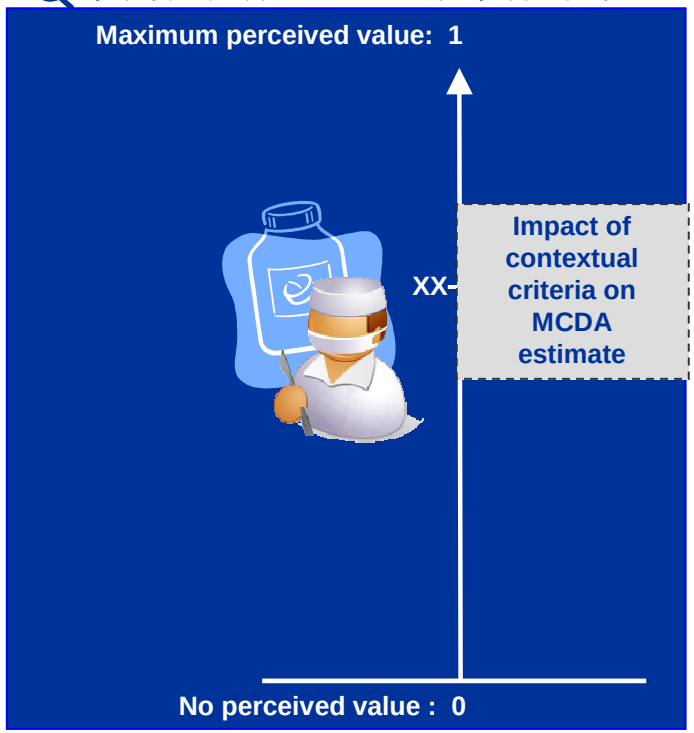
Appraising interventions
Mathematics & qualitative considerations

Type of mathematical model

- Simple linear model (combine normalized weights and scores) to calculate perceived value of intervention

Ranking of healthcare interventions

- Quantitative evaluation



- Combined with qualitative impact of context

Contextual criteria	Qualitative impact on appraisal/ranking
Example **Political/ historical context**	❑Negative ❑Neutral ❑Positive

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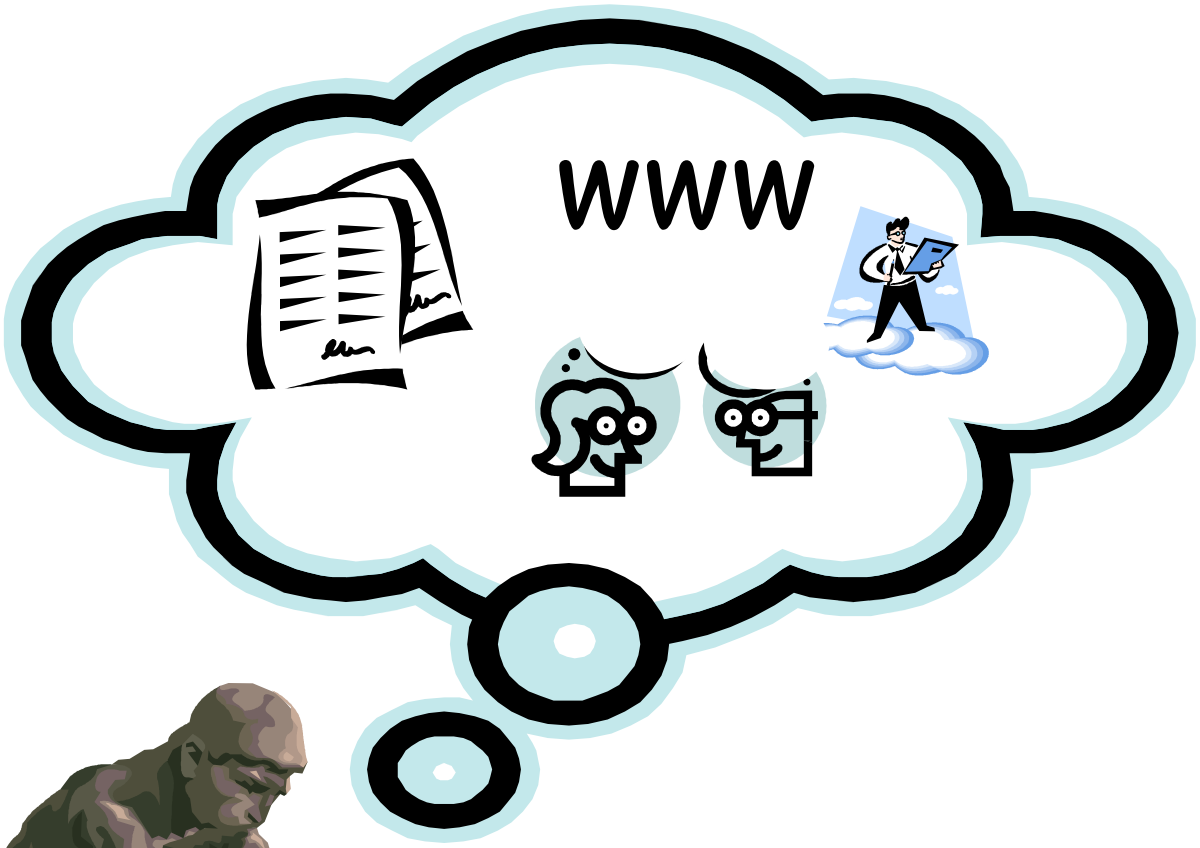

Finding the evidence
(scientific and colloquial)
& assess uncertainty

→ HTA

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HTA objectives

- Inform healthcare decisionmaking/priority setting
- Systematic reviews & synthesis of evidence
- Multidisciplinary and pragmatic
- Dissemination and reaching out

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

By-criterion HTA report

- **Detailed methodology in agreement with good HTA practices***
  - Comprehensive literature review
  - Analyses & synthesis of evidence (scientific and colloquial)
  - Assessment of the quality of studies (clinical, economic, epidemiologic)
  - Validation by experts

- **Data synthesized for each criterion (multidisciplinary)**
  - Highly synthesized (quick grasp)
  - Details with evidence tables
  - Full text source documentation (hyperlinks)

- **Web based (dissemination)**
  - Open source software (Tikiwiki)

*Busse et al. IJTAHC 2002; 18(2): 361-422.

Web registry

http://www.evidem.org/evidem-collaborative.php

Demo: Interactive prototype

https://www.evidem.org/tiki/?page=DEMO-main

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Overview of intervention

Last Update: April 2009
Disease: Turner syndrome (TS)
Intervention: Growth Hormone (GH)
Setting: Canada

Drug class: Polypeptide hormone
Indication: treatment of short stature in girls with Turner Syndrome
Administration: subcutaneous injection 3 to 7 days a week
Intervention duration: Needs to be established. Initiate as soon as growth failure demonstrated until satisfactory height reached (6 years of treatment startin at 10 years)
Comparator(s): No treatment
Economic burden of illness: No data available

Interactive by-criterion HTA report – high level synthesis - excerpt

	Intrinsic criteria	Highly synthesized information	Score	Comments
	Disease impact			
D1	Disease severity	**Female-specific genetic disorder** characterized by short stature, cardiovascular defects, absence of puberty, infertility, increased risk of diabetes, defects in visuo-spatial organization and nonverbal problem-solving, and decreased life expectancy. (see details)	○ 0 Not severe (minor inconvenience) ○ 1 ○ 2 ○ 3 Very Severe	☐ Low Score due to da - specify
D2	Size of population	**Prevalence:** 40/100,000 female adults.	○ 0 Very rare disease ○ 1 ○ 2 ○ 3 Common disease	☐ Low Score due to da - specify
	Context of intervention			
C1	Clinical guidelines	**International guidelines** (no Canadian Guidelines): Consider GH treatment as soon	○ 0 No recommendation	

Interactive by-criterion HTA report
Details on evidence - example

D1 - Disease severity

Turner syndrome is a female-specific genetic disorder (complete or partial loss of one of the X chromosome) characterized by short stature and presenting a wide spectrum of abnormalities, including cardiovascular defects (17-45%), lymphedema, gonadal dysgenesis (90% requiring hormone replacement therapy to induce puberty), infertility, miscarriage, hypothyroidism (15-30%), risk of obesity, ophthalmic defects, hearing problems and ear malformations, gastrointestinal and renal manifestations (Bondy 2007, Sybert et al. 2004). Patients are at increased risk of impaired glucose tolerance and diabetes (Hjerrild 2008, Holl 1994). Overall, cancer risk appeared not to be significantly increased; increased risks were reported in some studies for brain and nervous system tumors, and for colon and rectal cancer (Stochholm 2006, Schoemaker 2008, Hjerrild 2008). Defects in visuo-spatial organization and nonverbal problem-solving affect most patients with TS; in addition, impaired psychomotor and social functioning have been reported (Bondy 2007, Sybert et al. 2004).

In young patients, psychosocial issues arise: impaired peer relationship, teasing, social isolation, anxiety, shyness, and poor self-esteem (Bondy 2007, Sybert et al. 2004, Schmidt et al, Busschbach et al. 1998). In audiotaped interviews, Turner Syndrome patients reported infertility as their biggest concern (range: 36% of girls aged 7–13 yrs to 74% of adults aged 20–39 yrs; Sutton et al. 2007). However, many Turner Syndrome patients of all ages reported to be bothered by short stature (36% girls, 44% adolescents and adults, 55% mature adults 40–59 yrs; Sutton et al. 2007); 44% of 25 adult Turner Syndrome patie
stature (Busschbach et al. 1998). Short stature is

Life expectancy is decreased in women with Turne
anomalies (Stochholm et al. 2006; Sybert et al. 20
(number of deaths / expected number of deaths =

Return to DEMO Scoring intervention (MCDA Ma
Return to DEMO Menu

Content of the Collaborative

Interactive by-criterion HTA report
Links to quality assessments – example clinical data

	interventions limitations	syndrome.	limitations ○ 1 ○ 2 ○ 3 Major	☐ Low - specif
	Intervention outcomes			
I1	Improvement of efficacy/ effectiveness	**4 placebo controlled RCTs** (2-year (toddlers) to 11-year treatments; N=42 to 104, 1 in Canada, 3 in USA): Final height of treated patients = 147 cm to 150 cm; difference with untreated = 7 cm **Observational studies** (2-year to 8-year treatments, N=26 to 123, 1 in Germany, 1 in Greece, 1 in Israel, 3 in Italy): : Final height of treated patients = 148 cm to 151 cm; difference with controls = 2.1 to 6.8 cm. Example of critical analysis	○ 0 Lower efficacy/effectiveness than comparators presented ○ 1 ○ 2 ○ 3 Major improvement in efficacy/effectiveness	☐ Low - specif
I2	Improvement of safety & tolerability	**Common AEs (from RCTs -frequency at least twice of placebo):** Surgeries (50%), ear problems (6 % to 47 %), joint (13.5%) and respiratory (11%) disorders, sinusitis (18.9%) **Serious AEs (from registries, no control data):** Intracranial hypertension (0.2%), slipped capital femoral epiphysis (0.2 - 0.3%), scoliosis (0.7%), pancreatitis (0.1%), diabetes mellitus (0.2 to 0.3%), cardiac/aortic events (0.3%), malignancies (0.2%) **Warnings**: Scoliosis, slipped capital femoral epiphysis, intracranial hypertension, ear disorders, cardiovascular disorders, autoimmune thyroid disease, insulin resistance.	○ 0 Lower safety / tolerability than comparators presented ○ 1 ○ 2 ○ 3 Major improvement in safety / tolerability	☐ Low - specif
I3	Improvement of patient reported outcomes	Inconclusive data: **1 RCT** (2-year treatment data, N=28, Canada): higher rating on questionnaire by GH treated patients versus untreated for some domains but not for others **2 observational studies:** no significant differences on SF-36 dimensions in one study (5-year treatment, N=568, France) and significant differences in another (7-year treatment, N=29, Holland); other questionnaires, non significant differences **Convenience:** Subcutaneous injection 3 days a week or daily.	○ 0 Worse patient reported outcomes than comparators ○ 1 ○ 2 ○ 3 Major improvement	☐ Low - specif
	Type of benefit			
T1	Public health interest	No data on **risk reduction** with GH treatment.	○ 0 No risk reduction	

Interactive by-criterion HTA report
Quality of evidence assessment – overall clinical data

Relevance and validity – clinical data			
Disease: Turner Syndrome (TS) **Intervention:** recombinant human growth hormone (GH) **Setting**: Canada	**Series of key studies** Stephure et al, 2005: Canada – See full assessment Rosenfeld et al 1998: US - See full assessment Quigley et al 2002: US - See full assessment Davenport et al 2007: US – See full assessment		
Type of evidence	**Question(s)**	**Rationale**	
Efficacy/safety data	How relevant is the research program with regard to efficacy and safety? Are conclusions valid over the range of studies (conclusions across studies consistent or conflicting)? Are individual trials relevant and valid? *See assessment of individual studies below*	Overall, randomized controlled trials consistently demonstrate that GH treatment promotes height gain in girls with Turner Syndrome. Some uncertainty remains on extent to which GH may affect final height. High attrition rates were noted in the Canadian clinical trial (Stephure 2005); 2 multiphase trials were missing a control arm (no GH treatment) and chose GH administration mode (frequency of injections) that did not correspond to current practice (Rosenfeld et al. 1998; Quigley et al. 2002). Safety data monitoring is generally limited, despite the numerous warnings and AEs associated with GH treatment in Turner Syndrome populations. (Humatrope PM. 2007; Saizen PM. 2007; Nutropin PM. 2006).	1 [ ] Low relevance/validity 2 [ ] 3 [X] 4 [ ] High relevance/validity

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Interactive by-criterion HTA report
Quality of evidence assessment – excerpt single study

Relevance and validity – clinical data - study 1	
Disease: Turner Syndrome (TS) **Intervention:** recombinant human growth hormone (GH) **Setting**: Canada	**Study:** Stephure et al Canada 2005

Type of evidence	**Question**	**Rationale**	**Score**
Efficacy/safety data	Is the study question relevant (choice of comparator, time horizon, patient population, and outcome? Is the design appropriate (setting & design, sample size, patient allocation, analyses, statistics)? *See dimensions below*	This is the only study reporting final height (standard measure of GH effect; (Baxter et al. 2007) as the primary outcome. Although differences between GH treatment and no treatment are meaningful, high attrition rates, especially in the control arm (45%) might bias the study conclusions (Baxter et al. 2007). Authors report that supportive intent-to-treat analysis with conservative assumptions on missing data confirmed significance but no details are provided.	1 [] Low relevance/validity 2 [] 3 [X] 4 [] High relevance/validity

Dimension	**Question**	**Comment**
1 Target population	Is the target population relevant (age, gender, disease stage, comorbidities, inclusion criteria/exclusion criteria, setting etc)? Does it correspond to the actual population in which the intervention is envisioned to be used?	Target population is relevant and corresponds to the actual population in which the intervention is indicated: prepubertal Turner Syndrome girls (mean age: 10.3 ± 1.8 yrs; range: 7–13 yrs) with evidence of growth failure (height < 10th percentile) (Bondy 2007). Canadian setting but there is no mention of number and location of centers involved.
2 Intervention & comparators	Is the intervention in agreement with expected use? Does the choice of comparators reflect standard of care?	GH dose and schedule are in agreement with indication to treat short stature in Turner Syndrome girls (Humatrope PM. 2007; Saizen PM. 2007; Nutropin PM. 2006). Comparator is no treatment (standard of care).
3 Outcome measures	Are the selected outcomes measures (efficacy, safety and PRO) relevant? Are rationales for outcomes selection valid? Are the instruments/methods/units used to measure outcomes (efficacy,	The primary outcome is final height (cm), which is the gold standard measure of GH effectiveness (Baxter et al. 2007). Other efficacy analyses are relevant to the assessment of short-term growth, and instruments/units used are valid: height age-specific Turner Syndrome standard deviation score (SDS; allows

Interactive by-criterion HTA report
Capture uncertainty

	Interventions limitations	syndrome.	limitations ○ 1 ○ 2 ○ 3 Major	☐ Low Score due to data limitation - specify
	Intervention outcomes			
I1	Improvement of efficacy/ effectiveness	**4 placebo controlled RCTs** (2-year (toddlers) to 11-year treatments; N=42 to 104, 1 in Canada, 3 in USA): Final height of treated patients = 147 cm to 150 cm; difference with untreated = 7 cm **Observational studies** (2-year to 8-year treatments, N=26 to 123, 1 in Germany, 1 in Greece, 1 in Israel, 3 in Italy): : Final height of treated patients = 148 cm to 151 cm; difference with controls = 2.1 to 6.8 cm. Example of critical analysis	○ 0 Lower efficacy/effectiveness than comparators presented ○ 1 ○ 2 ○ 3 Major improvement efficacy/effectiveness	☐ Low Score due to data limitation - specify
I2	Improvement of safety & tolerability	**Common** ear problems (18.9%) **Serious A** slipped capital femoral epiphysis (0.2 - 0.3%), scoliosis (0.7%), pancreatitis (0.1%), diabetes mellitus (0.2 to 0.3%), cardiac/aortic events (0.3%), malignancies (0.2%) **Warnings**: Scoliosis, slipped capital femoral epiphysis, intracranial hypertension, ear disorders, cardiovascular disorders, autoimmune thyroid disease, insulin resistance.	y / ompar ○ 2 ○ 3 Major improvement safety / tolerability	☐ Low Score due to data limitation - specify
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	Type of benefit			
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Specify evidence limitations

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Value of innovation and uncertainty

➔ Strike a balance using a framework

Advantages

- **Define & measure value**
- Identify criteria at play in healthcare decisionmaking
- Allow simultaneous consideration of a wide range of criteria
- Stimulate reflection on perspectives, values and priorities
- Systematize judgment

- Transparent multidisciplinary evidence in a by-criterion HTA report

- Interactive

Challenges

- Criteria selection
- Perception of complexity
- Integration in existing processes
- MCDA estimate may be used as a formula

- Perceived difficulty of breakdown of evidence by criteria

Users & applications

Users	Applications
❖**Decisionmakers**	
Policy (macro/meso)	➢Priority setting ➢Reimbursement (Advisory committees)
Physicians & healthcare professionals	➢Clinical practice guidelines (CPGs) ➢Seamless access to evidence
Patients	➢Access to digested & validated information
❖**HTA developers**	➢HTA report at criteria level ➢Web-based multilevel evidence
❖**Research**	➢Identify research questions/data needs ➢Research planning ➢Explore the decisionmaking process
❖**Developers of new healthcare interventions**	➢Gap analysis ➢Positioning
❖**All**	➢Communication (evidence and values) ➢Knowledge translation

Future developments

- **Collaborative studies/applications**
  - ⇨ Field testing & implementation
  - ⇨ Methodological development

- **Web registry**
  - Interactive open access web resources

➔ **Optimize resources, decisions, priority-setting and health**

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Thank you

www.evidem.org