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Bridging the efficacy/effectiveness gap (part 2)

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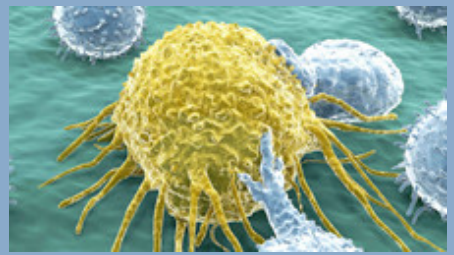

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Disclosure

Conflict of Interest: nothing to disclose

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Self-assessment questions

Answer yes or no

- A bias can NOT effect the estimation of the true intervention effect
- Applicability of study results is also dependent on the geographic and clinical setting of studies
- The ESMO-MCBS can only be used to evaluate the benefit of therapies for solid tumours

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Overview

Early identification of new, relevant drugs

- Horizon Scanning

Quality of evidence

- GRADE
- Risk of bias
- Applicability

Clinical benefit of drugs

- MCDAs
- ESMO-MCBS
- ASCO framework

Data availability at the time of approval (2011-2016)

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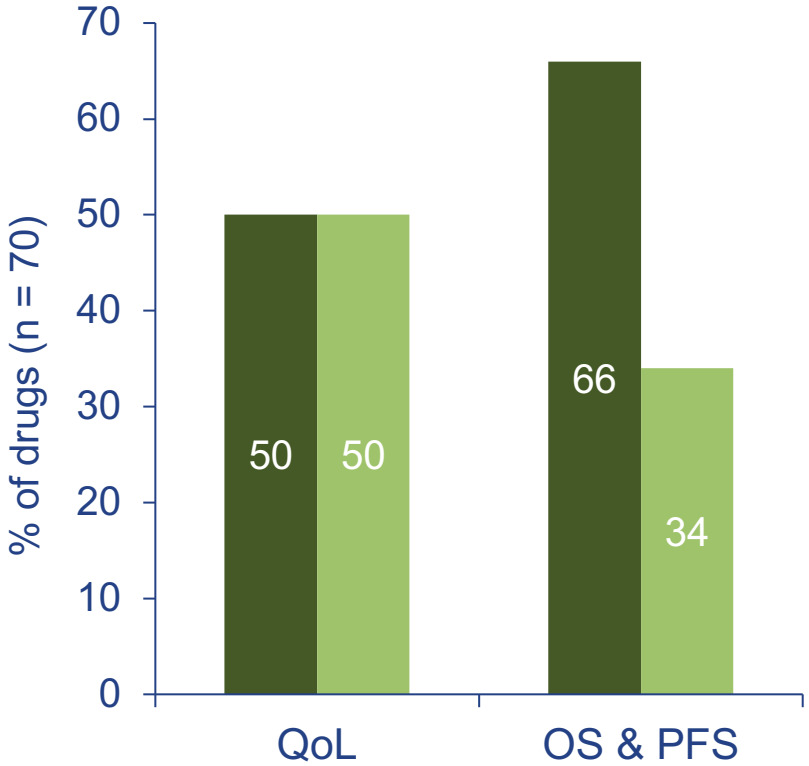

oncology drugs for solid tumours (n=70)

available
not available/negative

QoL…quality of life, OS…overall survival, PFS…progression-free survival

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Horizon Scanning (HS)

HS

Aims

- To identify **new** drugs/licensed drugs with extension of indication with **relevant therapeutic and financial impact**
- To provide information to decision makers (hospital administrators, drug commissions, social insurance organisations)
  - contribute to rational decision making
  - facilitate estimation of budget implication

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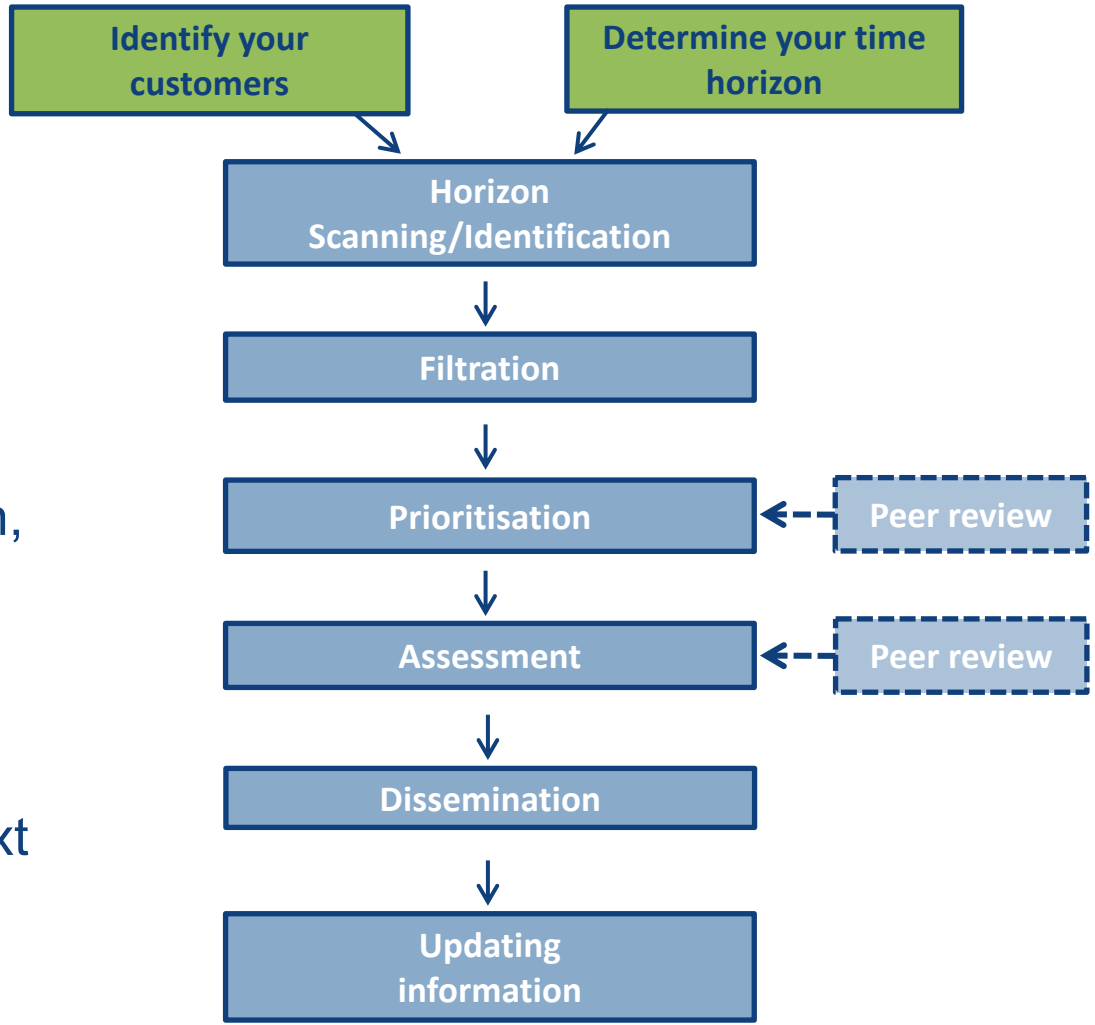
HS process:

basic processes are similar (UK, Canada, Sweden, Australia)

individual adaptions to the respective context



BeNeLuxA collaboration

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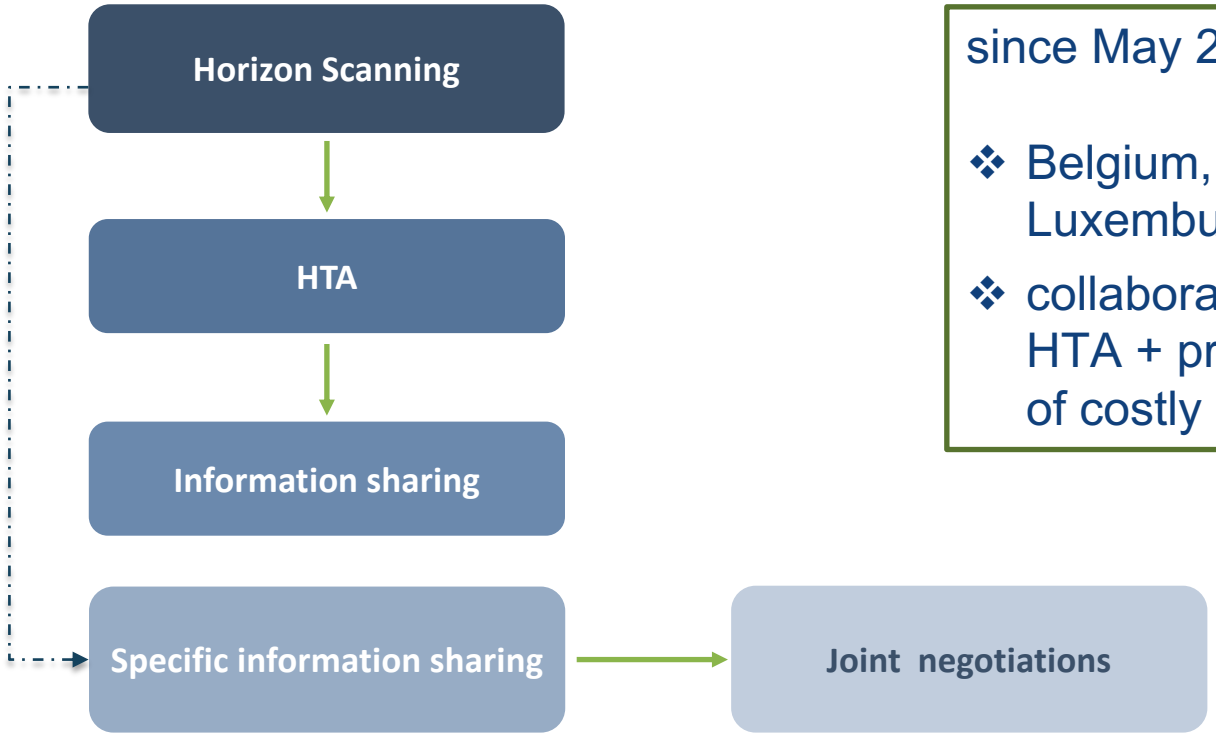

since May 2016 BeNeLuxA:

- Belgium, Netherlands, Luxemburg and Austria
- collaboration on HSS, HTA + price negotiation of costly drugs

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Quality of evidence

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Risk of bias

- systematic error → underestimation or overestimation of the true intervention effect
- different tools for randomised controlled trials (RCTs; e.g. EUnetHTA) and observational studies (e.g. Cochrane: ROBINS-I)
- bias: selection, performance, detection, attrition, reporting etc.

Types of bias

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- Selection bias: relevantly different patient characteristics between the treatment groups → true randomisation (random allocation sequence & concealment)
- Performance bias: difference in care levels between treatment groups → blinding
- Detection bias: different assessment of outcomes between treatment groups → blinding
- Attrition bias: important portion of patients are lost for the statistical analysis, e.g. lost to follow-up, withdrawals…→ intention-to-treat principle, sensitivity analyses
- Reporting bias: selective reporting of study results

Risk of bias - for RCTs based on EUnetHTA

Criteria for judging risk of bias		Risk of bias
Adequate generation of randomisation sequence		yes/unclear
Adequate allocation concealment		yes/unclear
Blinding	Patients	yes/no/unclear
	Treating physicians	yes/no/unclear
	Outcome assessment	yes/no/unclear
Selective outcome reporting unlikely		yes/no/unclear
No other aspects which increase the risk of bias		yes/no
Risk of bias – study level		low/high

Applicability of study results – based on EUnetHTA

Domain	Description of applicability of evidence
Population	General characteristics of enrolled populations, how this might differ from target population, and effects on baseline risk for benefits or harms.
Intervention	General characteristics and range of interventions and how they compare to those in routine use and how this might affect benefits or harms from the intervention.
Comparators	Do the comparators reflect best alternative treatment and how this may influence treatment effect size.
Outcomes	What outcomes are most frequently reported and over what time period? Do the measured outcomes and timing reflect the most important clinical benefits and harms?
Setting	Geographic and clinical setting of studies. Describe whether or not they reflect the settings in which the intervention will be typically used and how this may influence the assessment of intervention effect.

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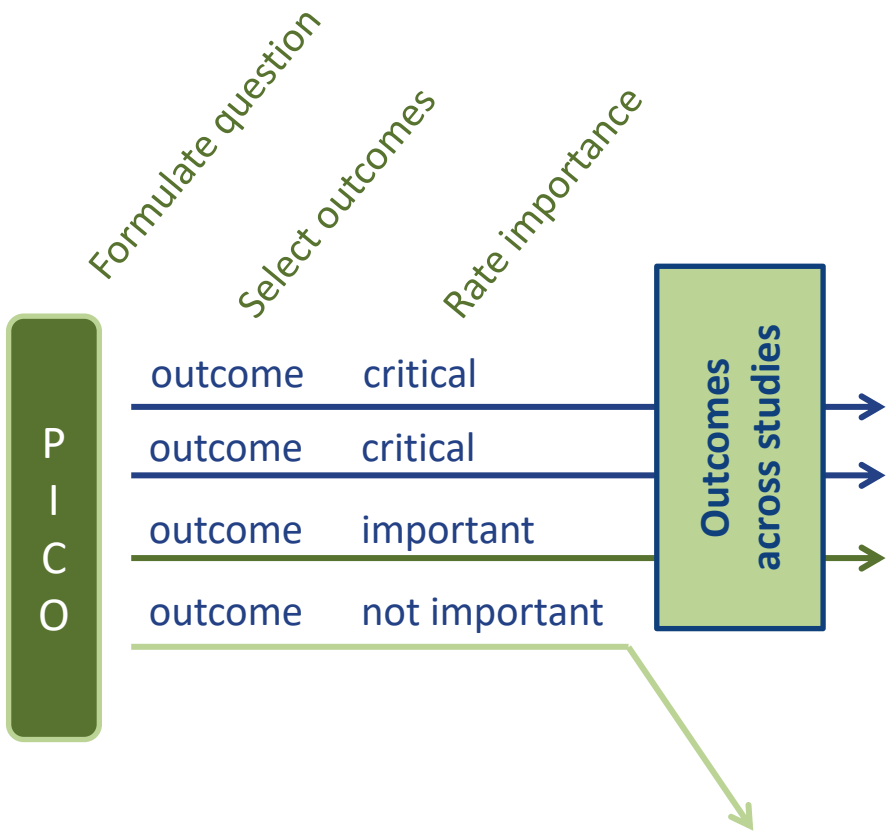
GRADE

Grading of Recommendations Assessment, Development and Evaluation

- sensible and transparent approach to grade the quality (or certainty) of evidence and strength of recommendations
- greater benefit than harm?
- estimate of effect for each outcome

GRADE – evidence synthesis



Adapted from: „GRADE Handbook“

Formulate question

Select outcomes

Rate importance

P
I
C
O

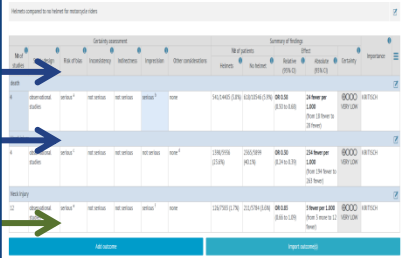
outcome critical

outcome critical

outcome important

outcome not important

Outcomes across studies



Summary of findings & estimate of effect for each outcome

Grade down

1. Risk of bias
2. Inconsistency
3. Indirectness
4. Imprecision
5. Publication bias

Grade up

1. Large effect
2. Dose response
3. Confounders

High ⊕⊕⊕⊕

Moderate ⊕⊕⊕◯

Low ⊕⊕◯◯

Very low ⊕◯◯◯

Randomisation raises initial quality
RCTs: high
Observational: low

Adapted from: „GRADE Handbook“

Formulate question

Select outcomes

Rate importance

P
I
C
O

outcome critical

outcome critical

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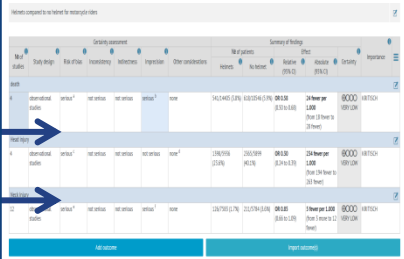
outcome not important

Outcomes across studies



Summary of findings & estimate of effect for each outcome

Grade down

1. Risk of bias
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5. Publication bias

Grade up

1. Large effect
2. Dose response
3. Confounders

Overall evidence across outcomes is based on lowest quality of critical outcomes

High ⊕⊕⊕⊕

Moderate ⊕⊕⊕◯

Low ⊕⊕◯◯

Very low ⊕◯◯◯

Adapted from: „GRADE Handbook“

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Tools to identify the clinical benefit of drugs

Multiple Criteria Decision Analysis (MCDA)

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a class of methods for analyzing decision-making or action options within the framework of decision theory

structured and explicit approach to make decisions based on multiple criteria

a method to evaluate alternatives to individual often contradictory criteria and to summarize them in an overall evaluation

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Procedure

- Defining the decision problem
- Selecting and structuring criteria
- Measuring the performance
- Scoring alternatives
- Weighting criteria
- Calculating aggregate scores
- Dealing with uncertainties
- Reporting and examination of findings

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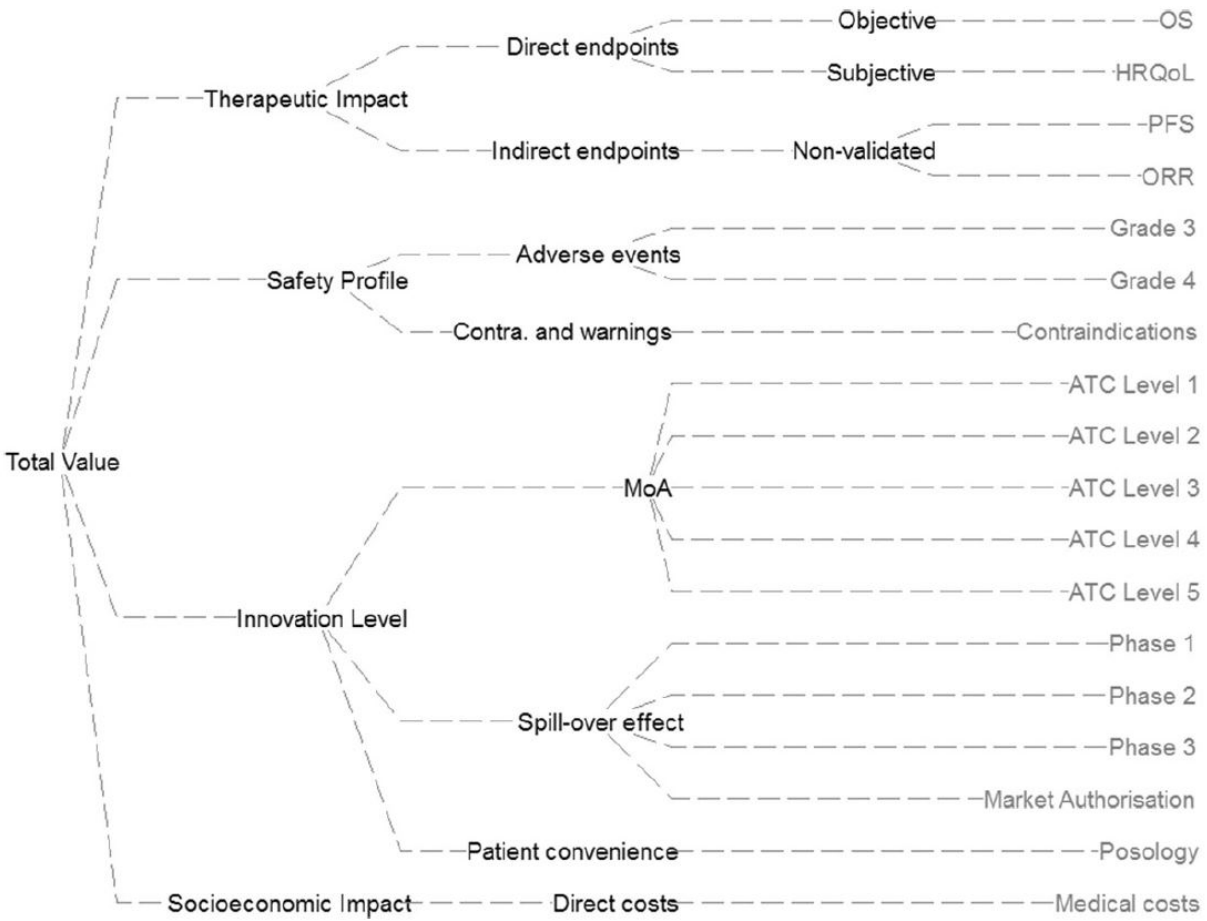
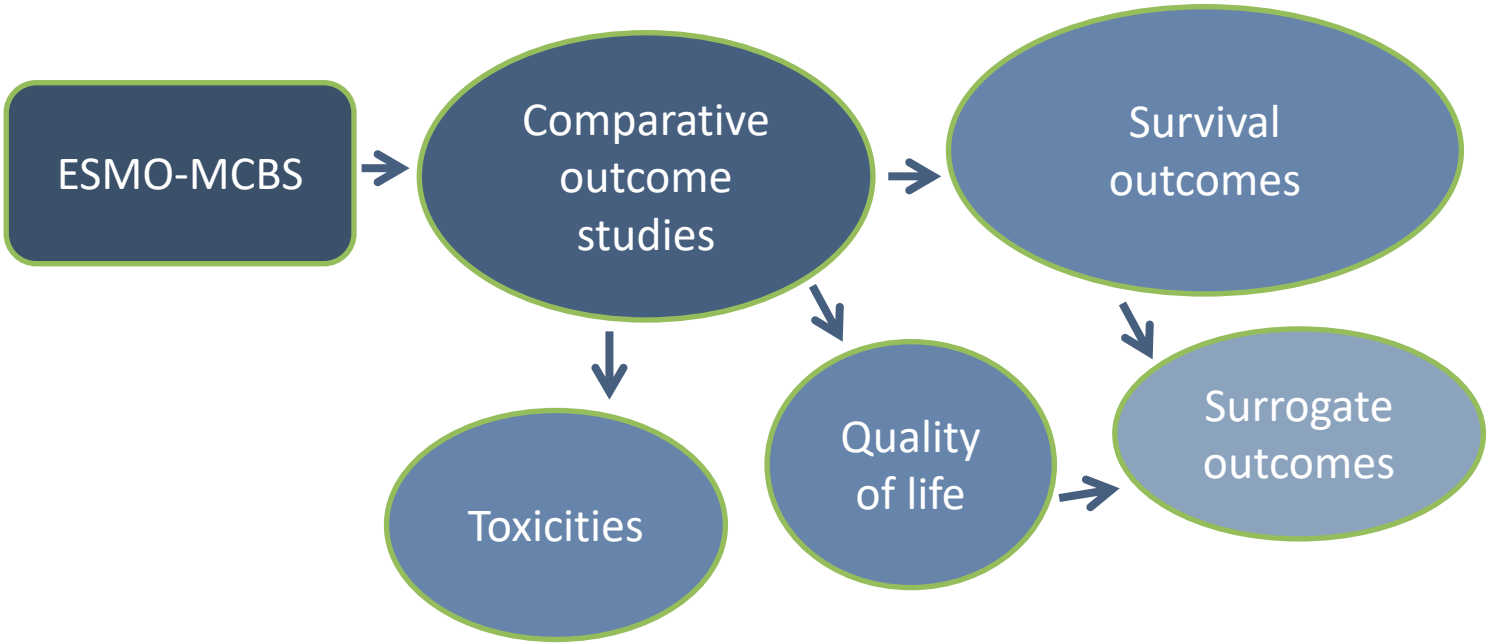


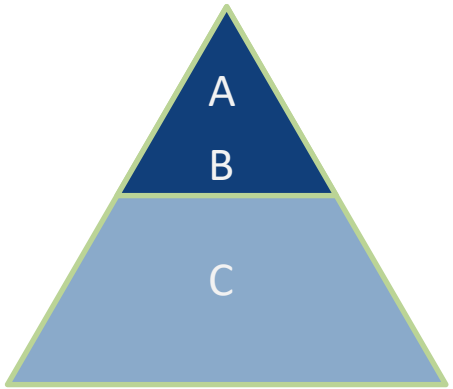
„Value Tree“

European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS)

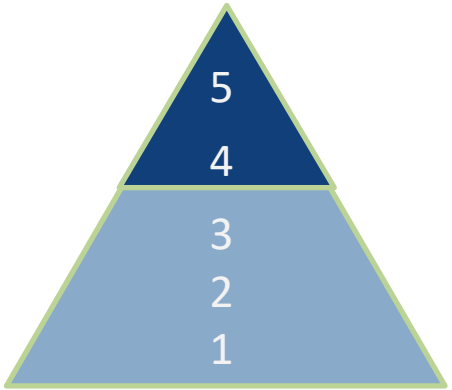


ESMO-MCBS

- Only applicable for solid tumours
- Costs are not taken into account, because of the high variability of prices across European countries
- New form for single arm studies in the ESMO-MCBS version 1.1
- One published real-life experience at the Medical University of Vienna



curative setting



non–curative setting

ESMO Magnitude of Clinical Benefit Scale v1.1

Form 2a: for therapies that are not likely to be curative with primary endpoint of OS

Name of study:		
Study drug:	Indication:	
First author:	Year:	Journal:
Name of evaluator:		

IF median OS with the standard treatment >12 months ≤24 months

	Mark with X if relevant
Grade 4	
HR ≤0.70 AND Gain ≥5 months	
Increase in 3 year survival alone ≥10%	
Grade 3	
HR ≤0.70 AND Gain ≥3-<5 months	
Grade 2	
HR ≤0.70 AND Gain ≥1.5-<3 months	
HR >0.70-0.75 AND Gain ≥1.5 months	
Grade 1	
HR > 0.75 OR Gain <1.5 months	

Preliminary magnitude of clinical benefit grade (highest grade scored)

4	3	2	1

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Quality of Life assessment /grade 3-4 toxicities assessment*

Does secondary endpoint quality of life show improvement	
Are there statistically significantly less grade 3-4 toxicities impacting on daily well-being*	

*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhoea, fatigue, etc.

Adjustments

1. Upgrade 1 level if improved quality of life and/or less grade 3-4 toxicities impacting daily well-being are shown
2. If there is a long term plateau in the survival curve, and OS advantage continues to be observed at 7 year, also score according to form 1 (treatments with curative potential) and present both scores i.e. A/4

Final adjusted magnitude of clinical benefit grade

5	4	3	2	1

American Society of Clinical Oncology (ASCO) Value Framework

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- Comparative trials
- Evaluation of treatments for solid tumours as well as for blood tissue cancer
- Two forms → advanced & adjuvant setting
- Intended use → clinical setting (not for policy discussions)
  - Planned to be used as a software for clinicians
  - Weighting of categories shall be dependent on the individual patient

Advanced disease setting

Step 1: Determine the regimen's CLINICAL BENEFIT		
1.A. Is hazard ratio (HR) for death reported?	**YES.** Assign an HR Score for death by subtracting the HR from 1, and then multiplying the result by 100. Write this number in the box labeled "HR Score (death)." **Proceed to 1.F.**	**HR Score (death)**
	No. Proceed to 1B.	
1.B. If HR for death is not reported, is median overall survival (OS) reported?	**YES.** Assign an OS Score by calculating the percentage (ie, fractional) difference in median overall survival between the two regimens and multiply the result by 100. Write this number in the box labeled "OS Score." **Proceed to 1.F.**	**OS Score**
	NO. Proceed to 1.C.	
1.C. If OS data are not reported, is hazard ratio (HR) for disease progression reported?	**YES.** Assign an HR Score for disease progression by subtracting the HR from 1, multiplying the result by 100, and then multiplying this number by 0.8. Write this number in the box labeled "HR Score (progression)." **Proceed to 1.F.**	**HR Score (progression)**
	NO. Proceed to 1.D.	
1.D. If HR for disease progression is not reported, is median progression-free survival (PFS) reported?	**YES.** Assign a PFS Score by calculating the percentage (ie, fractional) difference in median progression-free survival between the two regimens and multiply the result by 100. Multiply this number by 0.8. Write this number in the box labeled "PFS Score." **Proceed to 1.F.**	**PFS Score**
	NO. Proceed to 1.E.	
1.E. If median PFS is not reported, is response rate (RR) reported?	**YES.** Assign an RR Score by adding the complete response (CR) and partial response (PR) rates, multiply by 100, then multiply this number by 0.7. Write this number in the box labeled "RR Score." **Proceed to 1.F.**	**RR Score**
1.F. Calculate the Clinical Benefit Score	Insert the score for HR death, HR PFS, median OS, or median PFS. **Note: You should have a score for only 1 of the clinical benefit scales above.** Write the total in the box labeled "Clinical Benefit Score." **Proceed to Step 2.**	**Clinical Benefit Score**

Step 2: Determine the regimen's TOXICITY		
Does the new regimen represent an improvement in toxicity over the standard of care/ comparator?	For each of the regimens being assessed, compare the number and frequency of clinically relevant toxicities, and assign a Toxicity Score) as shown below. Each clinically meaningful toxicity (ie, exclude laboratory results only) is assigned a score between 0.5 and 2.0 based on grade and frequency: For every grade 1 or 2 toxicity with a frequency < 10%, record 0.5 points. For every grade 1 or 2 toxicity with a frequency ≥ 10%, record 1.0 points. For every grade 3 or 4 toxicity with a frequency < 5%, record 1.5 points. For every grade 3 or 4 toxicity with a frequency ≥ 5%, record 2.0 points. Calculate the total number of toxicity points for each regimen. Calculate the percentage difference in total toxicity points between the two regimens, then multiply by 20 to obtain a toxicity score. If the regimen being evaluated is more toxic than the comparator, subtract the toxicity score of the regimen from the clinical benefit score. If the regimen is less toxic than the comparator, add the toxicity score of the regimen to the clinical benefit score. **If there are unresolved symptomatic treatment-related toxicities at 1 year after completion of treatment, subtract 5 additional points from the clinical benefit score.** The maximum points that can be awarded is 20. **Proceed to Step 3.**	**Toxicity Score**

Value framework

- Net Health Benefit:
  - Clinical benefit (highest weight on overall survival)
  - Toxicity (scores are dependent on the grade and frequency)
  - Bonus points (e.g. quality of life)
- Costs:
  - Drug acquisition costs
  - Co-payment of patients (based on total costs of a treatment regimen)

Summary

- Early identification of drugs with relevant therapeutic and financial impact → Horizon Scanning
- Quality of evidence
  - GRADE → estimate of effect for each outcome
  - Risk of bias for RCTs (EUnetHTA) → bias assessment based on the whole study (different factors e.g. blinding)
  - Applicability of study results (EUnetHTA) → descriptive evaluation based on factors
- Clinical benefit of drugs
  - MCDAs → applicable in different areas (not only for drugs), based on multiple criteria
  - ESMO-MCBS → only for solid tumours, different forms (curative & non-curative setting), no costs included
  - ASCO value framework → also for blood tissue cancer, inclusion of costs, shall be available as a software for clinicians

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Self-assessment questions

Answer yes or no

- A bias can NOT effect the estimation of the true intervention effect
  - **NO**
- Applicability of study results is also dependent on the geographic and clinical setting of studies
  - **YES**
- The ESMO-MCBS can only be used to evaluate the benefit of therapies for solid tumours
  - **YES**

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Take home messages

- Various tools are available to evaluate the quality of evidence
  - Risk of bias → on a study level
  - Applicability → based on the setting and the PICO
  - GRADE → estimate of effect for each outcome
- Two recently published tools to investigate the clinical benefit of oncology drugs (ESMO-MCBS, ASCO value framework) → further research is needed evaluating the applicability of these tools in a real world setting
- MCDA → decisions based on multiple criteria