Sundhedsstyrelsen
Danish Health and Medicines Authority

Data-driven assessment of the association of polymorphisms in 5-Fluorouracil metabolism genes with outcome in adjuvant treatment of colorectal cancer

Sinan B. Sarac, Senior Medical Officer, Danish Health and Medicines Authority

Christian H. Rasmussen, Industrial PhD student, DTU & Novo Nordisk A/S

Acknowledgements

Shoaib Afzal, Søren Astrup Jensen, Henrik Enghusen Poulsen, Steffen Thirstrup, Morten Colding-Jørgensen, and Erik Mosekilde.

Disclaimer

The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to the Danish Health and Medicines Authority, Technical University of Denmark, Copenhagen University Hospital (Rigshospitalet), or Novo Nordisk A/S.

Sundhedsstyrelsen
Danish Health and Medicines Authority

The benefit-risk balance……

Sundhedsstyrelsen
Danish Health and Medicines Authority

Introduction

Patient group

HTA

New fantastic drug!

EMA

FDA

Contents

- Background
- Aim
- Material
- Methods
- Results
- Conclusions

Background

- Afzal and co-workers demonstrated that specific combinations of functional polymorphisms in dihydropyrimidine dehydrogenase (DPYD) and thymidylate synthase (TYMS) polymorphisms were associated with increased DFS in colorectal cancer patients recieving adjuvant 5-FU based treatment, HR 0.69 [0.49 – 0.98].*

*Afzal S, Gusella M, Jensen SA, Vainer B, Vogel U, Andersen JT, et al.
The association of polymorphisms in 5-fluorouracil metabolism genes with outcome in adjuvant treatment of colorectal cancer. Pharmacogenomics 2011 Sep;12(9):1257-67.

Aim

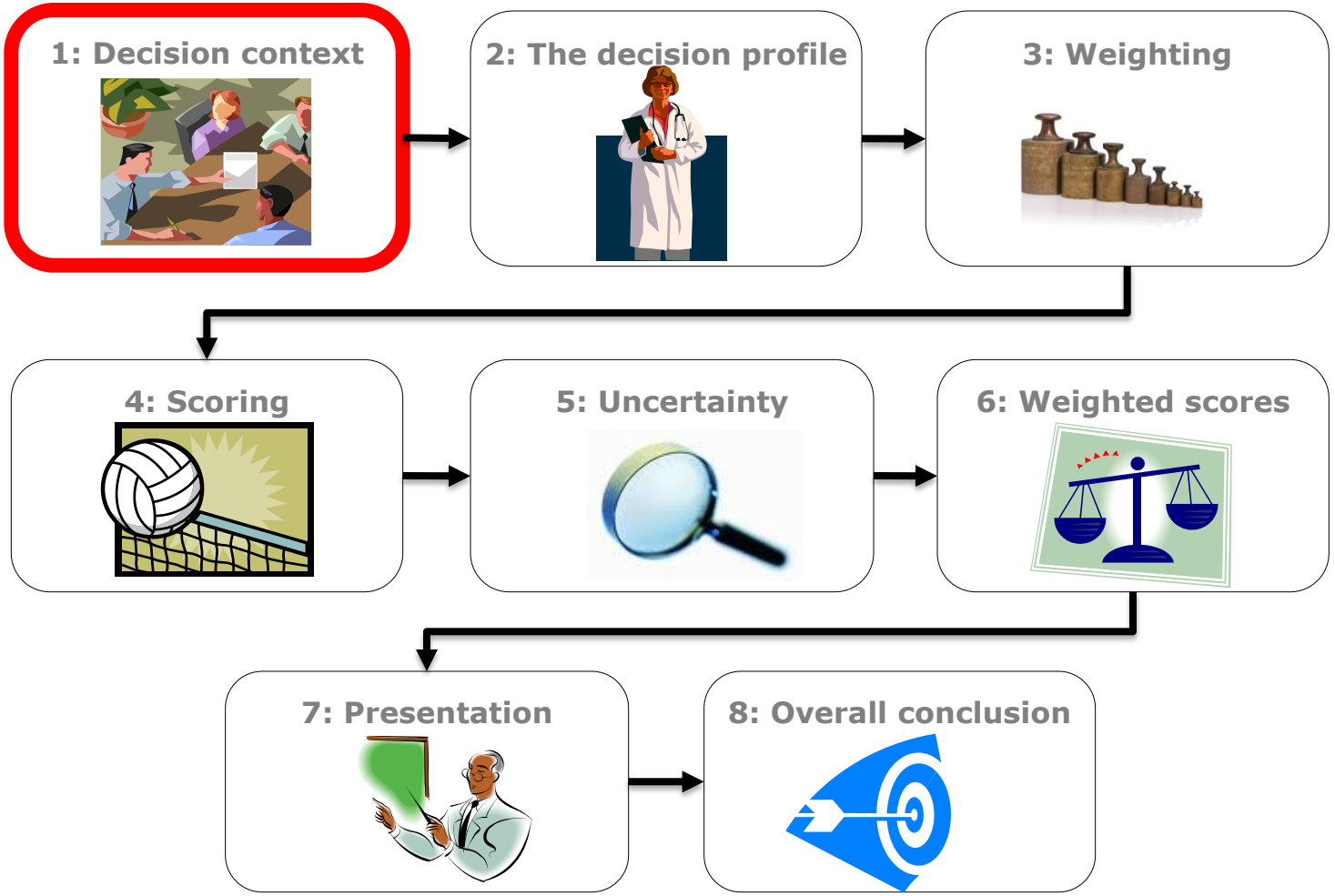
- A data-driven assessment with focus on:
  - transparency
  - clinical significance
  - visualisation
  - communication

Material

	Number of patients (N= 302)
MDR-1	111
MDR-0	158
Missing	33

The MDR-1 group consists of patients with the combination of variant alleles in the DPYD gene and the TYMS VNTR polymorphism, selected by the Multifactor Dimentionality Reduction algorithm as being associated with improved DFS.

Method: A Data-driven Assessment

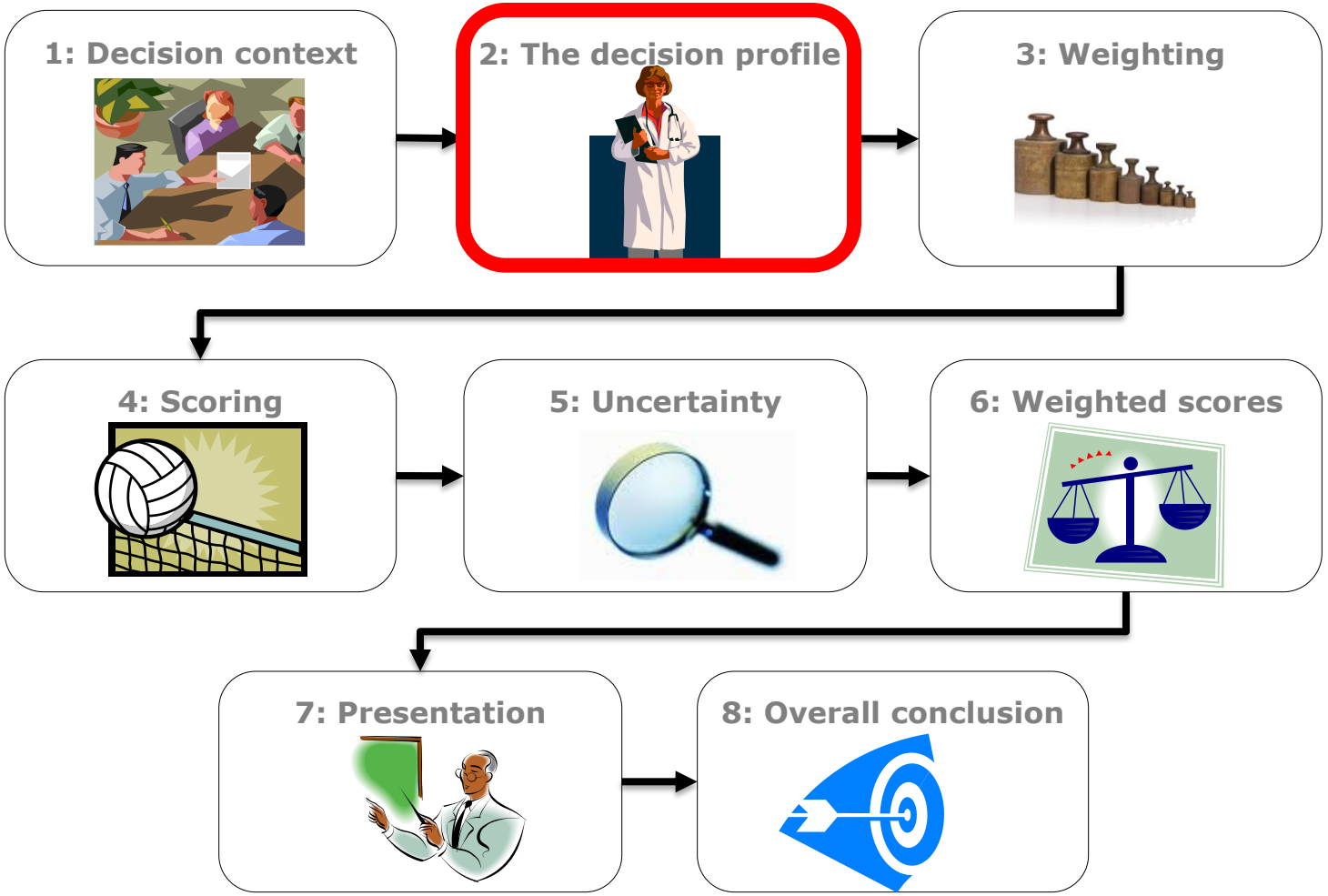


Sundhedsstyrelsen
Danish Health and Medicines Authority

1: Decision context –
Which question do you want answered?

- The question: How well do two groups (MDR-1 and MDR-0) of patients with the same disease, but different genetics respond to the same treatment?
- Disease: Colorectal cancer.
- Treatment: Chemotherapeutic agent (5-FU).
- The aim: A head to head comparison on
  - Cure rate, survival rate, time-to-death (TTD),time-to-relapse (TTR), and main adverse events.
- Expectations: Based on former knowledge, we expect that the specific combination of genetic polymorphisms in the MDR-1 group will have an advantage with reference to DFS.

Method: A Data-driven Assessment

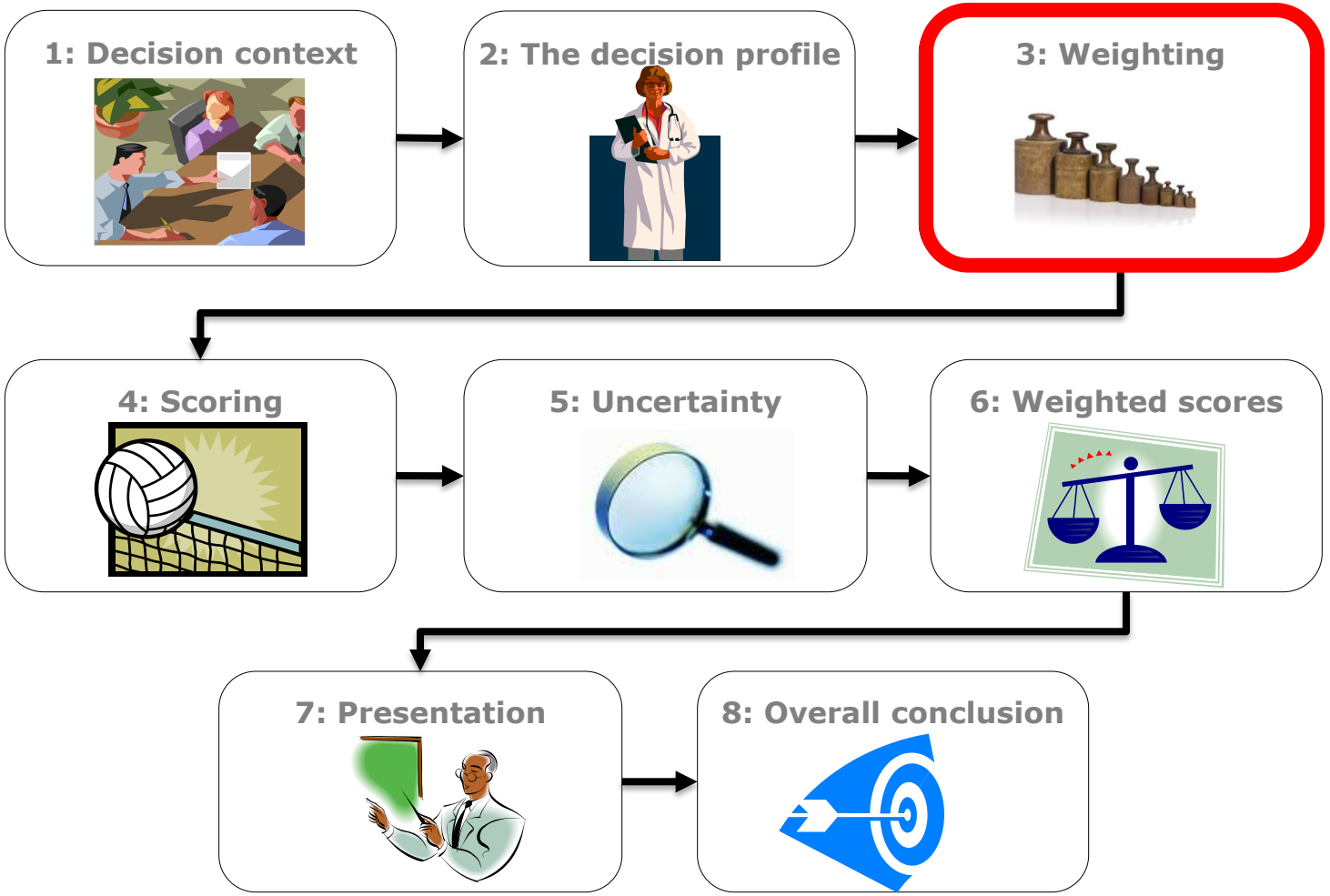


Sundhedsstyrelsen
Danish Health and Medicines Authority

2: Decision profile

Criterion	Weight	Score	Weighted Score
Survival rate			
Cure rate			
TTD			
TTR			
Infection			
Myocardial ischemia			
Bleeding			
Mucositis/Stomatitis			
Hand-foot skin syndrome			
Diarrhea			
Arthralgia/Myalgia			
Fatigue			
Nausea/Vomiting			

Method: A Data-driven Assessment

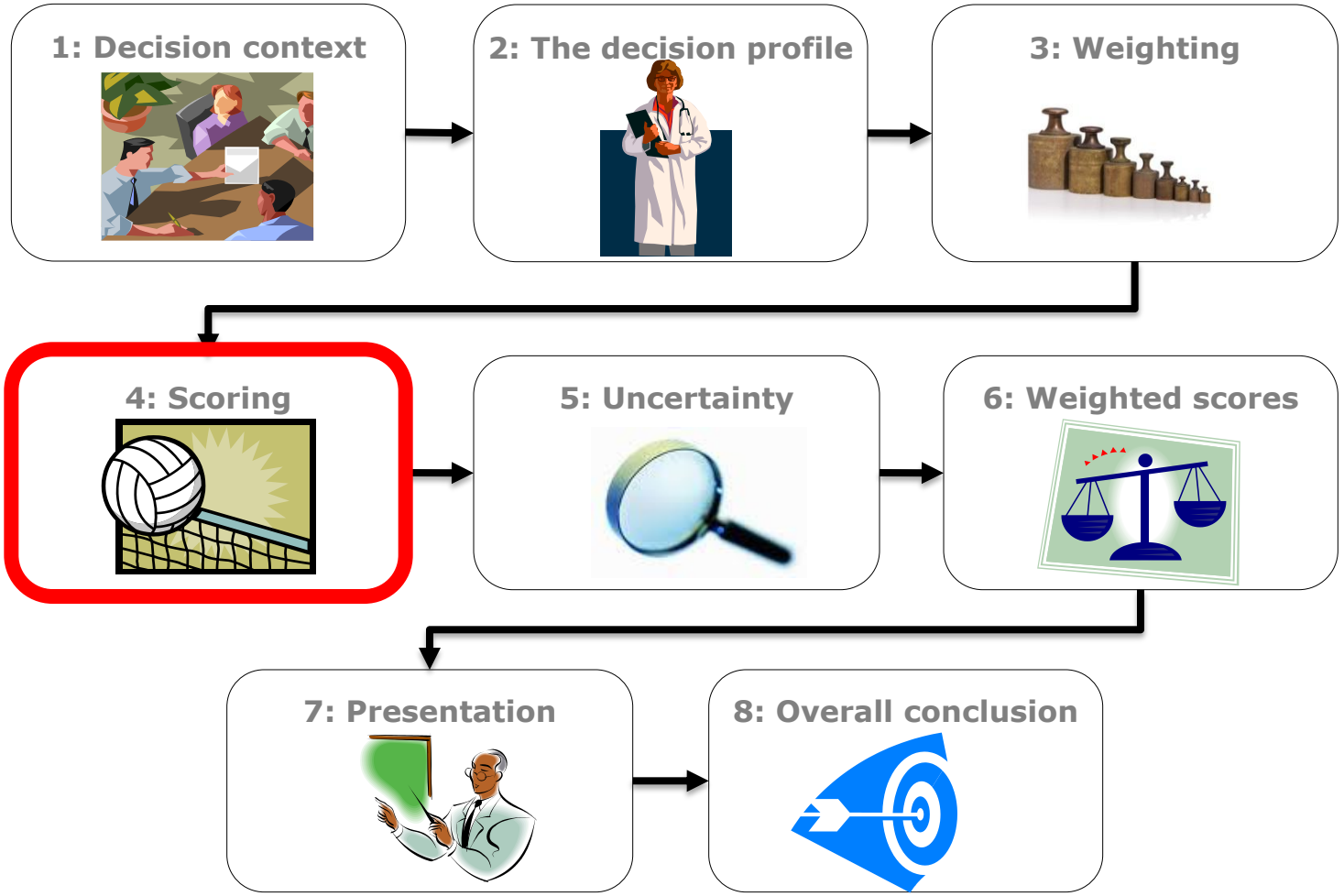


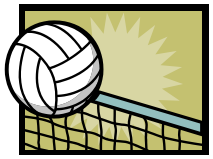
Sundhedsstyrelsen
Danish Health and Medicines Authority

3: Weighting

Criterion	Weight	Score	Weighted Score
Survival rate	3		
Cure rate	3		
TTD	3		
TTR	3		
Infection	2		
Myocardial ischemia	2		
Bleeding	2		
Mucositis/Stomatitis	2		
Hand-foot skin syndrome	2		
Diarrhea	2		
Arthralgia/Myalgia	1		
Fatigue	1		
Nausea/Vomiting	1		

Method: A Data-driven Assessment





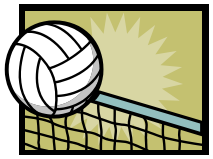
4: Scoring

Relative scoring

For each criterion, MDR-1 is scored relative to MDR-0

Criterion	Score
MDR-1 is **superior**	+1
MDR-1 is **non-inferior**	0
MDR-1 is **inferior**	-1

Sundhedsstyrelsen
Danish Health and Medicines Authority

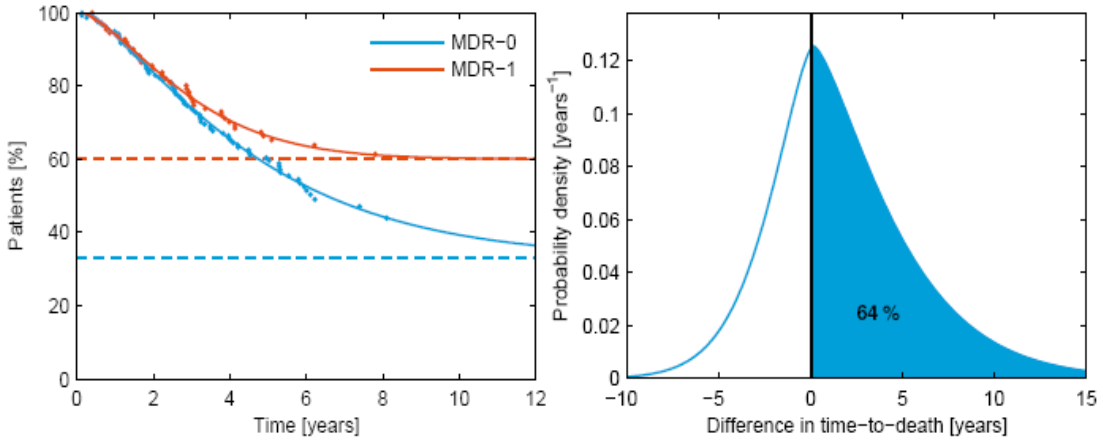


4.1: Difference Distribution Scoring

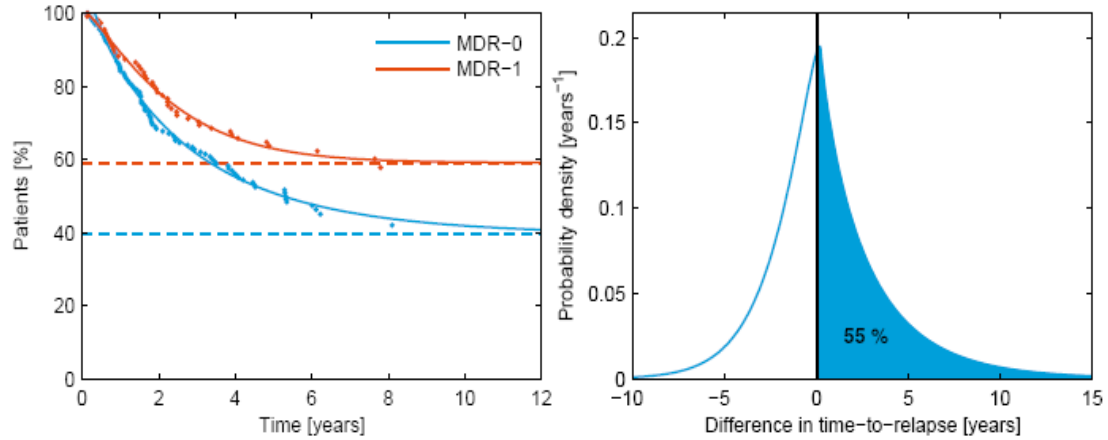
- Clinical relevance:
  - a difference is considered relevant if a substantial part of the subjects experience better performance with either drug or comparator.
  - the extent of the substantial part depends on disease area and decision context.
  - In the current setting 12 out of 20 (=60%) patients experiencing an effect, is defined as clinically relevant.

4.1: Difference Distribution Scoring

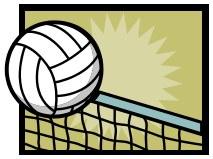
TTD



TTR



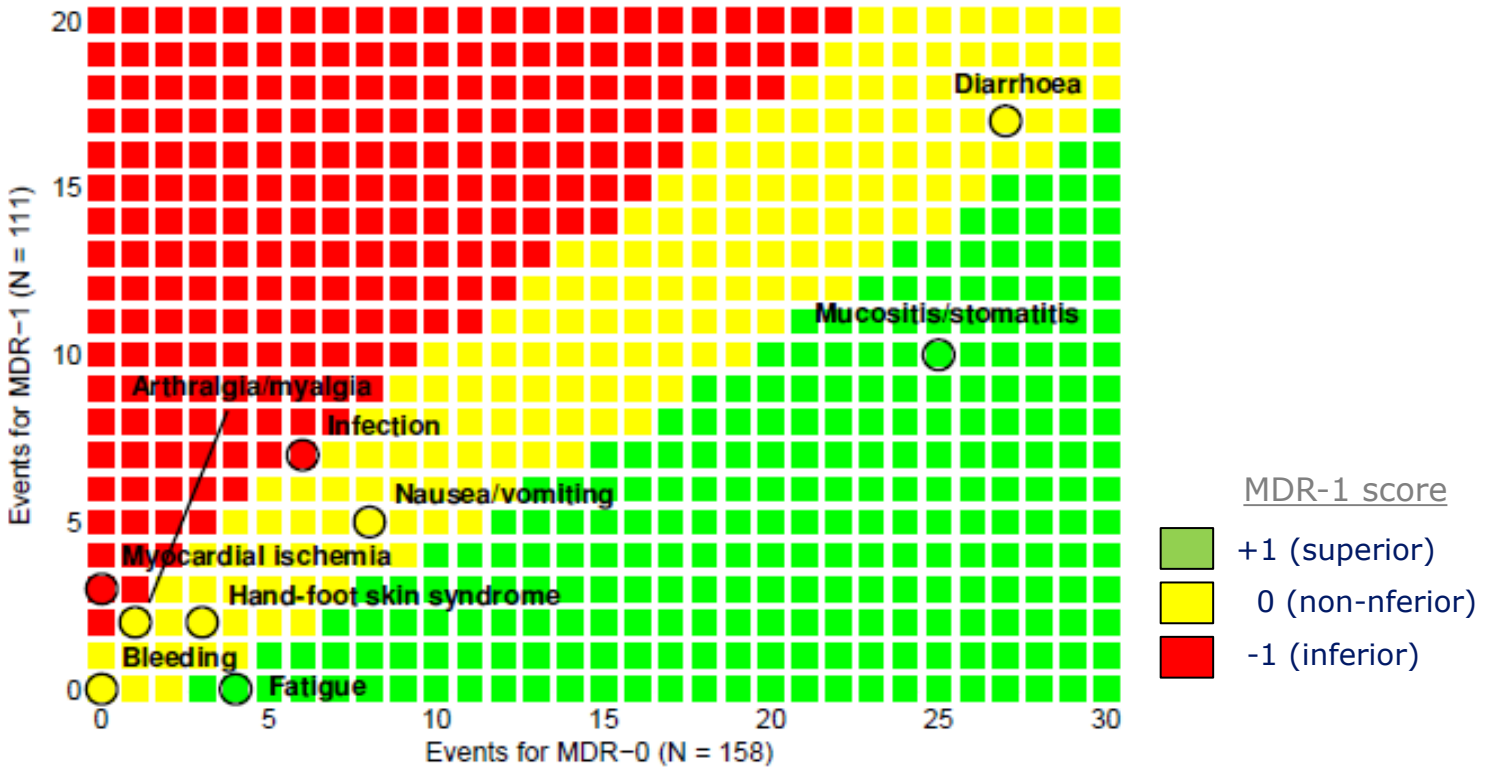
Sundhedsstyrelsen
Danish Health and Medicines Authority



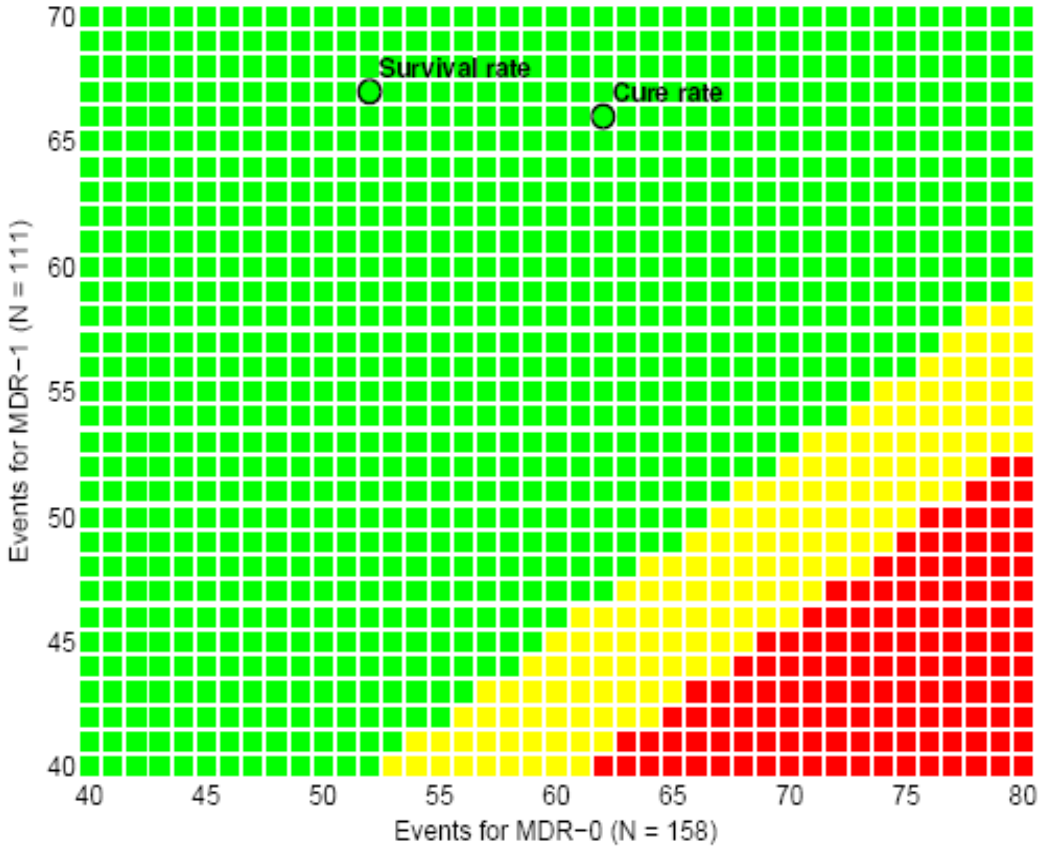
4.1: Confidence Interval Scoring

- For events the question is:
  - is the probability, p, of one event/subject different between MDR-1 and MDR-0?

4.1: Confidence Interval Scoring



4.1: Confidence Interval Scoring



MDR-1 score

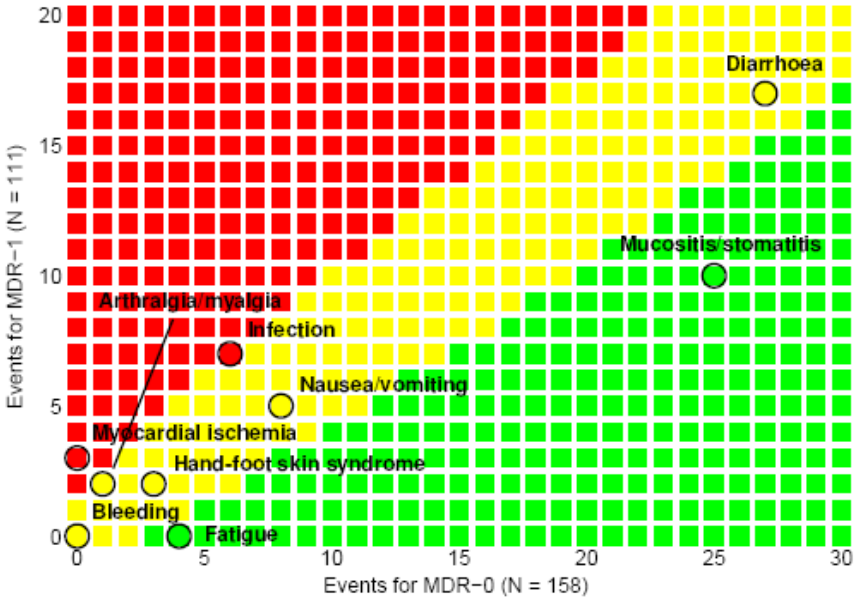
+1 (superior)

0 (non-nferior)

-1 (inferior)

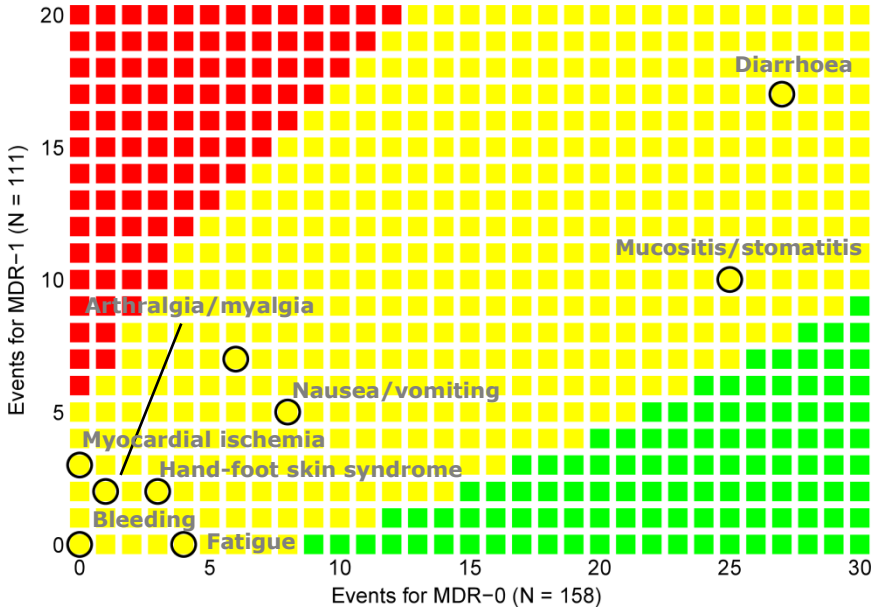
Sundhedsstyrelsen
Danish Health and Medicines Authority

4.1: Confidence Interval Scoring



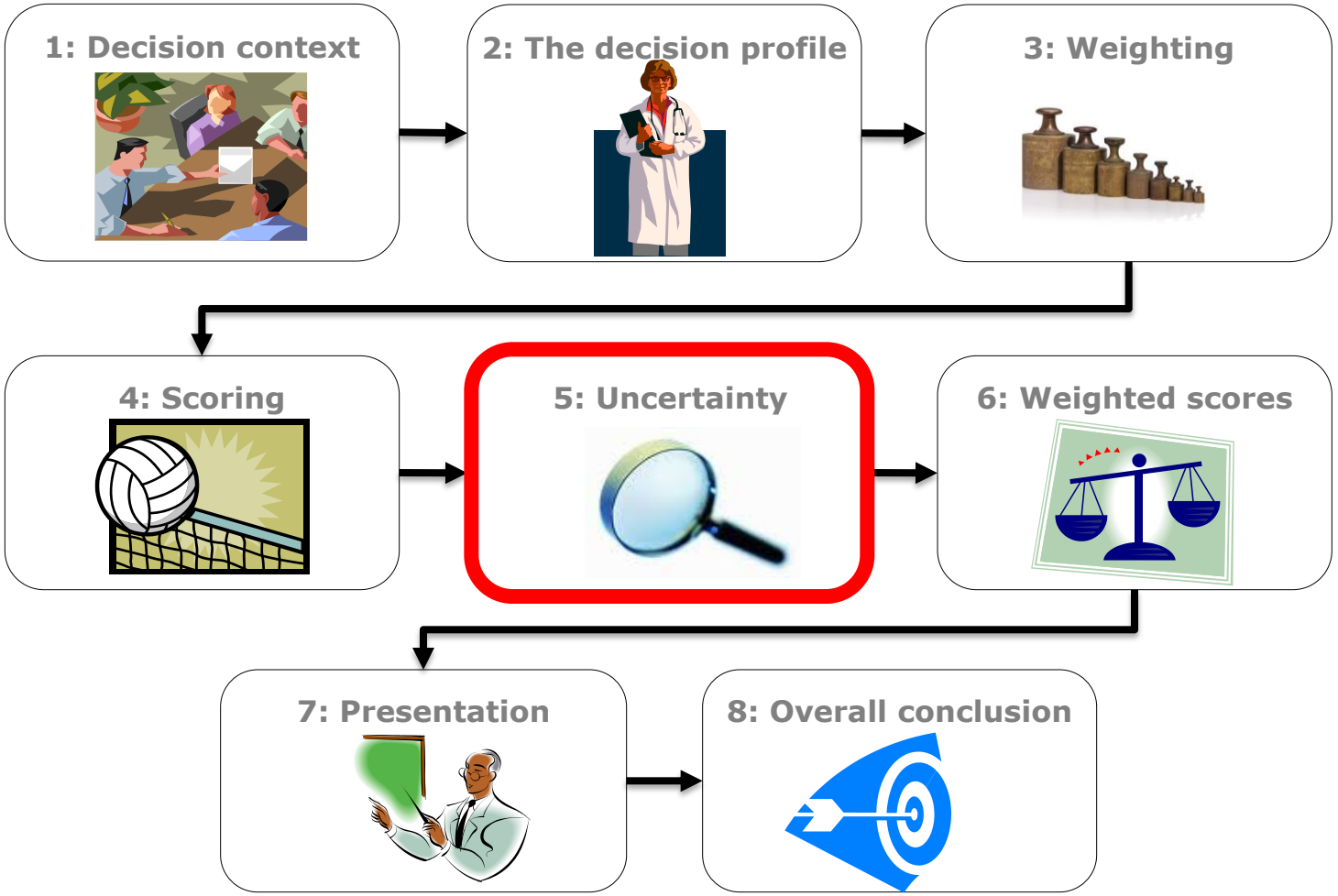
66,7 % confidence level

95 % confidence level



MDR-1 score
- +1 (superior)
- 0 (non-inferior)
- -1 (inferior)

Method: A Data-driven Assessment



Sundhedsstyrelsen
Danish Health and Medicines Authority

5: Evaluation of uncertainty

- In case of any uncertainty the score may be given as an interval (-1 → 0, 0 → 1 or -1 → 1).

1. Qualitative evaluation*:
   - Evaluate methodological flaws/deficiencies and their impact.
   - Describe any negative studies, studies showing no difference.
2. Quantitative evaluation:
   - Quantitative evaluations can be performed by the use of resampling.

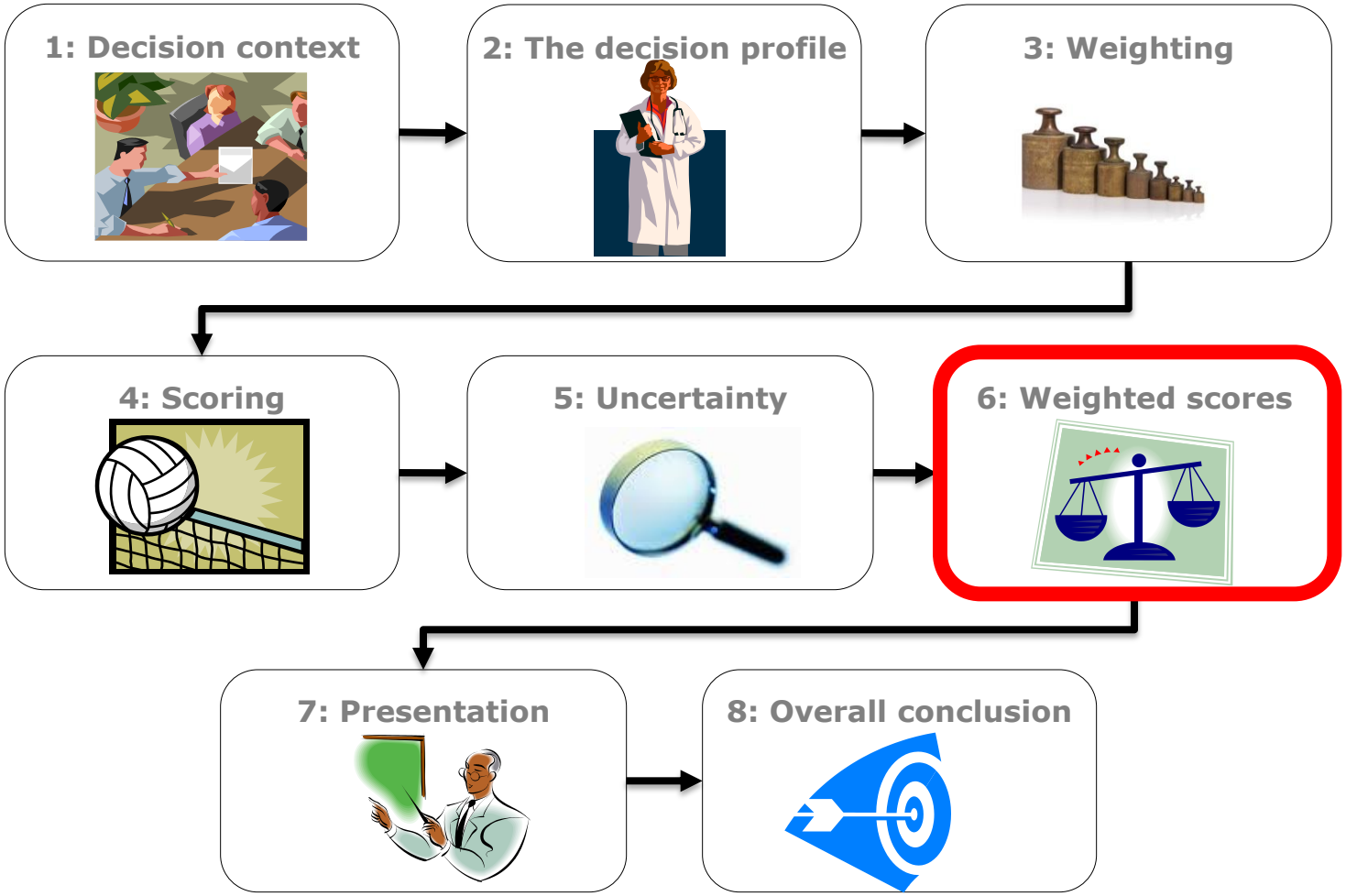
*CHMP working group on benefit-risk assessment models and methods. 2007.

Sundhedsstyrelsen
Danish Health and Medicines Authority

5: Evaluation of uncertainty

- Interval-scores are assigned to following borderline criteria:
  - Infections
  - Arthralgia/Myalgia
  - Fatigue

Method: A Data-driven Assessment



Sundhedsstyrelsen
Danish Health and Medicines Authority

6: Weighted Scores

Criterion	Weight	Score	Weighted Score
Survival rate			
Cure rate			
TTD			
TTR			
Infection			
Myocardial ischemia			
Bleeding			
Mucositis/Stomatitis			
Hand-foot skin syndrome			
Diarrhea			
Arthralgia/Myalgia			
Fatigue			
Nausea/Vomiting			

Sundhedsstyrelsen
Danish Health and Medicines Authority

6: Weighted Scores

Criterion	Weight	Score	Weighted Score
Survival rate	3		
Cure rate	3		
TTD	3		
TTR	3		
Infection	2		
Myocardial ischemia	2		
Bleeding	2		
Mucositis/Stomatitis	2		
Hand-foot skin syndrome	2		
Diarrhea	2		
Arthralgia/Myalgia	1		
Fatigue	1		
Nausea/Vomiting	1		

Sundhedsstyrelsen
Danish Health and Medicines Authority

6: Weighted Scores

Criterion	Weight	Score	Weighted Score
Survival rate	3	1	
Cure rate	3	1	
TTD	3	1	
TTR	3	0	
Infection	2	-1	
Myocardial ischemia	2	-1	
Bleeding	2	0	
Mucositis/Stomatitis	2	1	
Hand-foot skin syndrome	2	0	
Diarrhea	2	0	
Arthralgia/Myalgia	1	0	
Fatigue	1	1	
Nausea/Vomiting	1	0	

Sundhedsstyrelsen
Danish Health and Medicines Authority

6: Weighted Scores

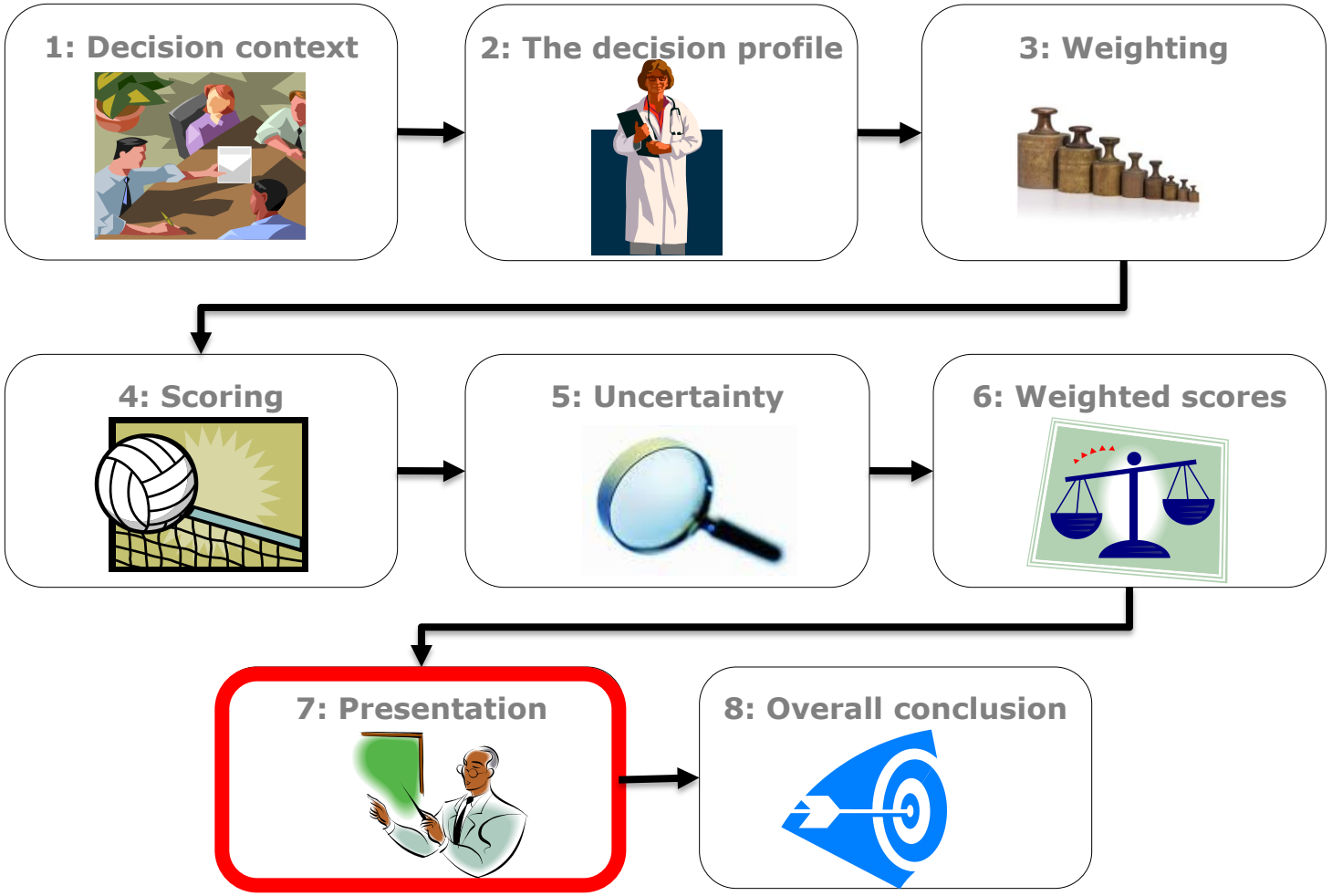
Criterion	Weight	Score	Weighted Score
Survival rate	3	1	
Cure rate	3	1	
TTD	3	1	
TTR	3	0	
Infection	2	-1 → 0	
Myocardial ischemia	2	-1	
Bleeding	2	0	
Mucositis/Stomatitis	2	1	
Hand-foot skin syndrome	2	0	
Diarrhea	2	0	
Arthralgia/Myalgia	1	0 → -1	
Fatigue	1	1 → 0	
Nausea/Vomiting	1	0	

Sundhedsstyrelsen
Danish Health and Medicines Authority

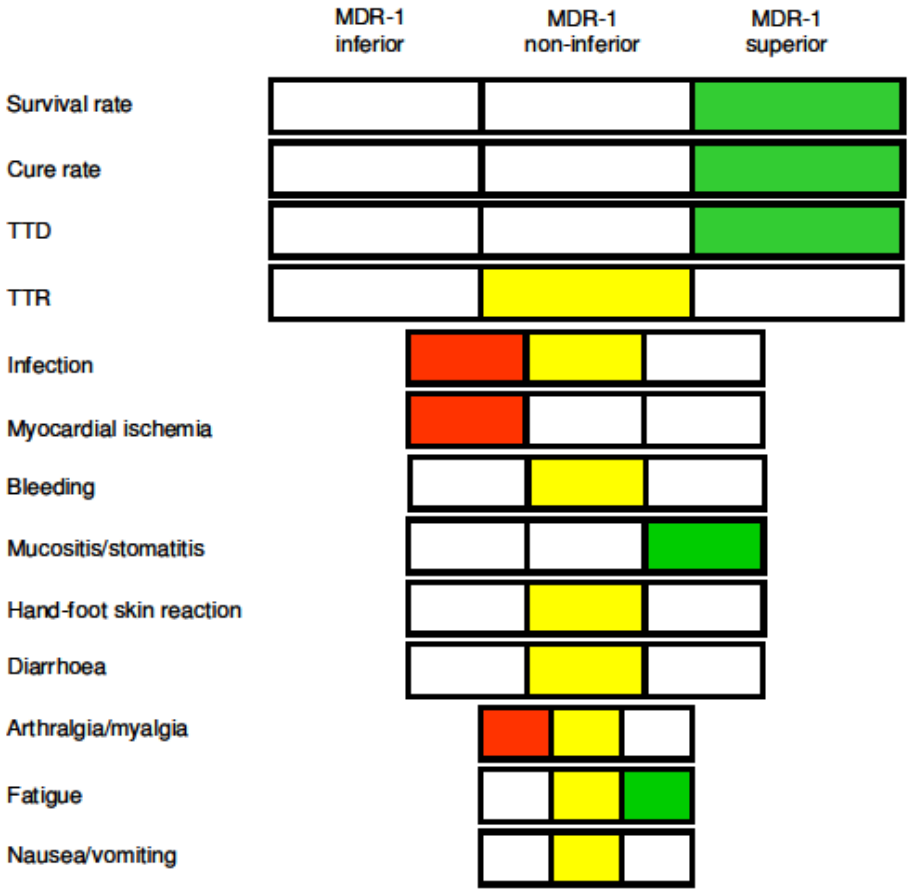
6: Weighted Scores

Criterion	Weight	Score	Weighted Score
Survival rate	3	1	3
Cure rate	3	1	3
TTD	3	1	3
TTR	3	0	0
Infection	2	-1 → 0	-2→ 0
Myocardial ischemia	2	-1	-2
Bleeding	2	0	0
Mucositis/Stomatitis	2	1	2
Hand-foot skin syndrome	2	0	0
Diarrhea	2	0	0
Arthralgia/Myalgia	1	0 → -1	0 → -1
Fatigue	1	1 → 0	1 → 0
Nausea/Vomiting	1	0	0

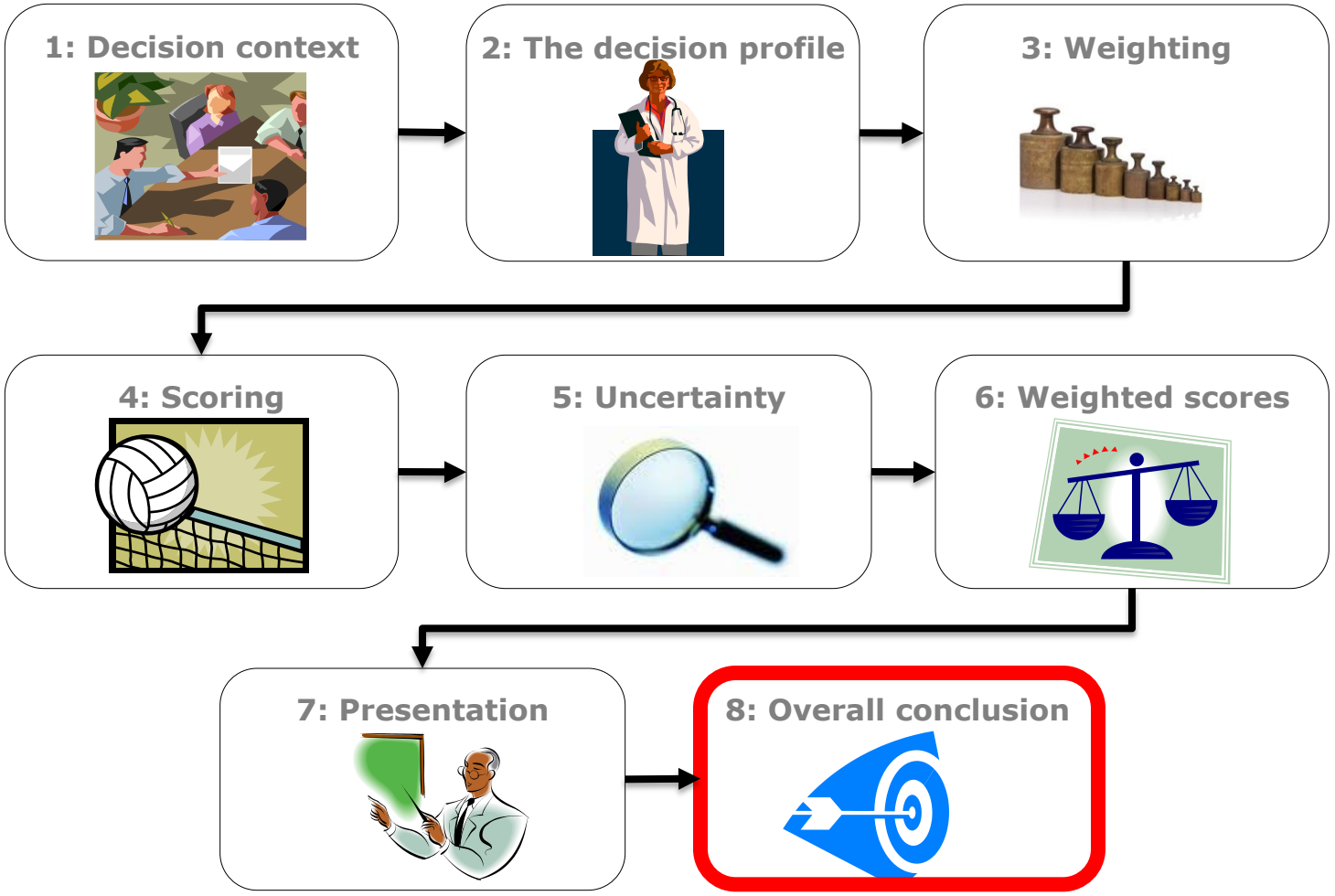
Method: A Data-driven Assessment



7: Presentation



Method: A Data-driven Assessment



8: Overall conclusion

The assessment is concluded by:

- A clinically significant and relevant difference for the high importance criteria cure rate, survival rate, and TTD was found in favour of the MDR-1 group.
- A higher risk of severe cases of the medium importance criterion myocardial ischemia and a slightly higher risk for the medium importance criterion infection were seen in MDR-1.
- The clinical implications of this study are that genetic profiling is advisable in patients with colorectal cancer, to enable individualised treatment and follow-up.

Conclusions

- We have demonstrated a comprehensive approach to data-driven benefit-risk assessments and how it can be used in a clinical setting.
- The method can handle a variety of different types of clinical data and can be used in a single study as well as on multiple studies.

Conclusions

- **Transparency** in decision making increase credability of the assessment and can be secured by:
  - Following a structured framework
  - Justification of choices at critical steps in the assessment
  - Being consistent with previuos decisions

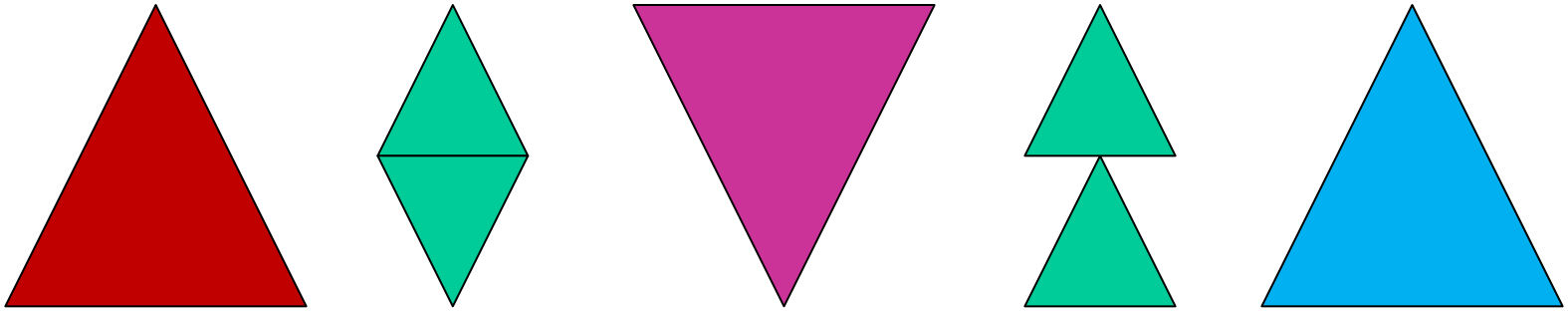
Conclusions

- Discussion of **clinical significance** of data support decision making in greater perspective and can be incorporated by:
  - Considering proportion of patients experiencing an effect
  - Being proactive and looking for tendencies in sparse data, instead of rejecting any signal due to high confidence level

- **Visualisation** tools help comprehend more data at the same time.

Sundhedsstyrelsen
Danish Health and Medicines Authority

Take home message



Experts tend to focus on the greater picture
There is a need to see the individual...

Thank for your attention!