25 September 2012

Benefit-Risk Assessment from a Clinical Point of View:

a structured approach with focus on transparency, clinical significance and visualization

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Disclaimer

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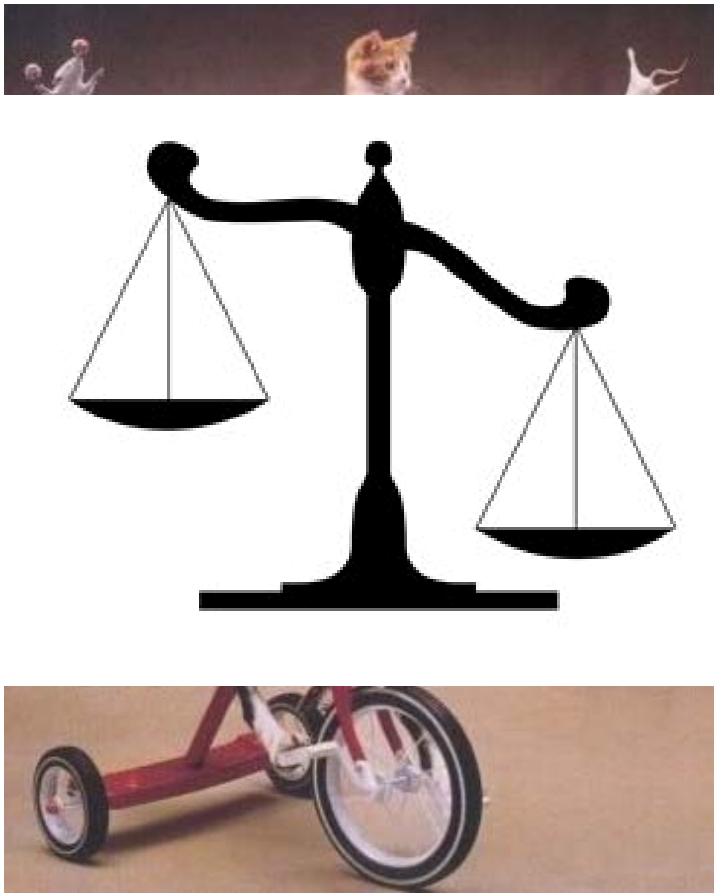
The benefit-risk balance



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 disease-free survival (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.

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Aim of talk

- Demonstrate a data-driven benefit-risk assessment method with focus on:
  - Transparency
  - Clinical significance
  - Visualisation
  - Communication
- Use 5-FU and the polymorphisms as a case.
- Same treatment, but different responses in subgroups.

Data material

- 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 Dimensionality Reduction algorithm as being associated with improved DFS.

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

Method overview

1: Decision context

2: Decision profile

3: Weighting

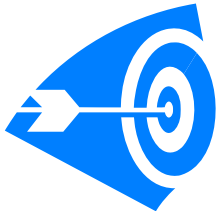
4: Scoring

5: Uncertainty

6: Weighted scores

7: Presentation

8: Overall conclusion



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1: Decision context

- 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)
  - 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.

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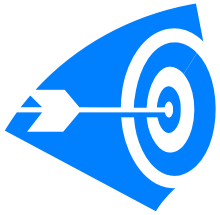

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2: Decision profile

- Identify benefit and risk criteria.
- Select the most important criteria in the given context.
- Justify the choice of criteria.

2: Decision profile

The 5-FU case

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			

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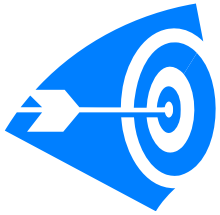

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3: Weighting

The 5-FU case

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		

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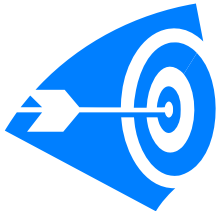

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4: Scoring

- Relative scoring is used.
- 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

- The specific scoring method depends on the data type.

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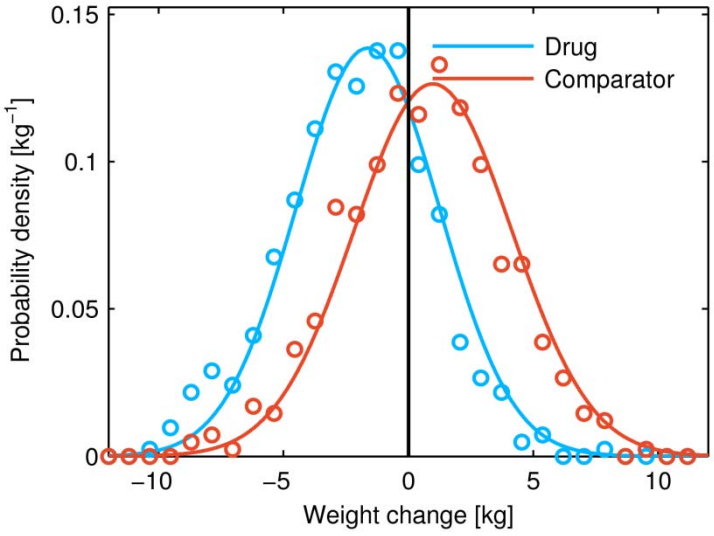
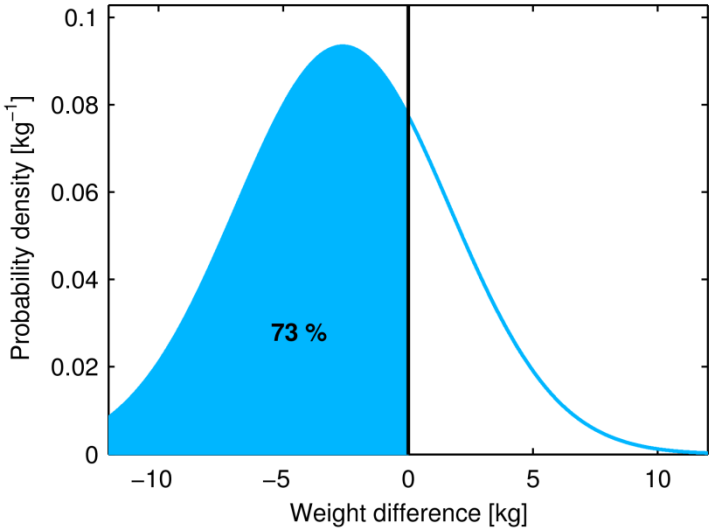
4.1: Endpoints with continuous values

Example with simulated data: a drug vs. a comparator

End-of-trial values

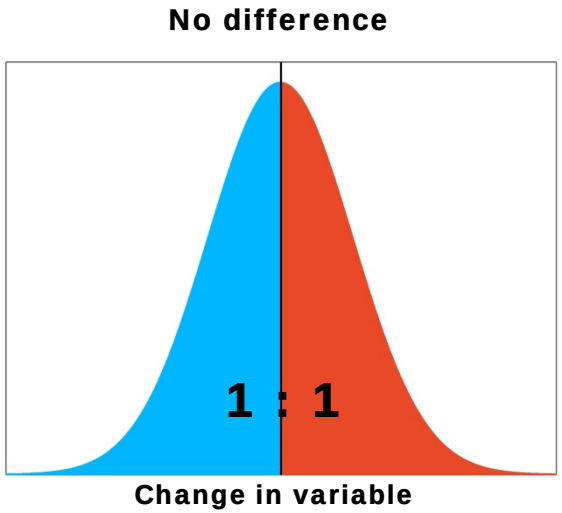


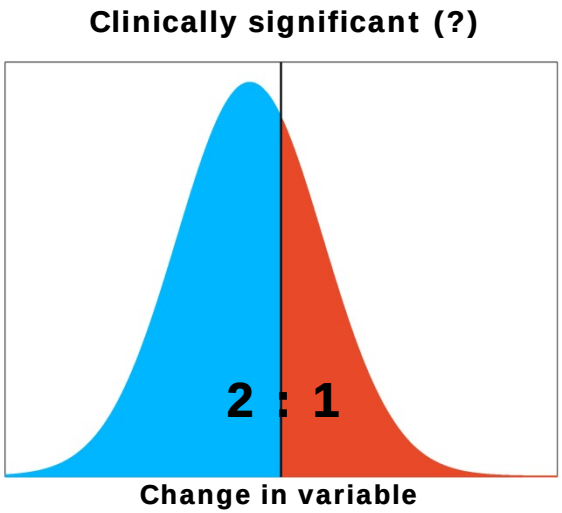
Difference distribution



4.1: Endpoints with continuous values

- If the areas are equal (1:1) the treatment is not different from the comparator.
- When one area is adequately larger than the other this difference is deemed **clinically significant**.
- If the number of subjects per trial arm is large enough (~ 15-18) the difference is usually **statistically significant**.



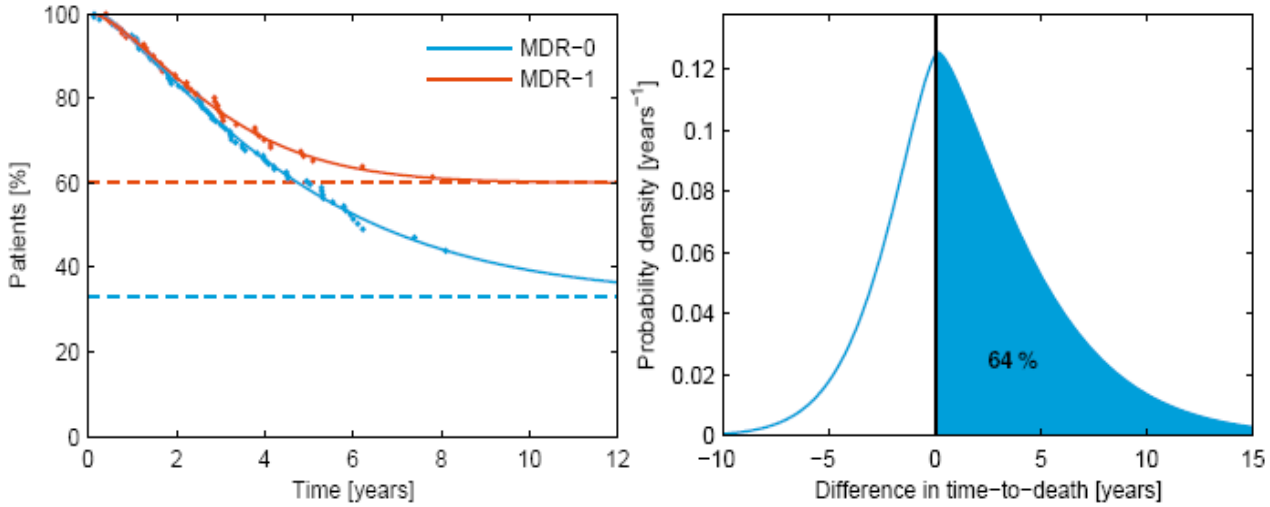


4.1: Endpoints with continuous values

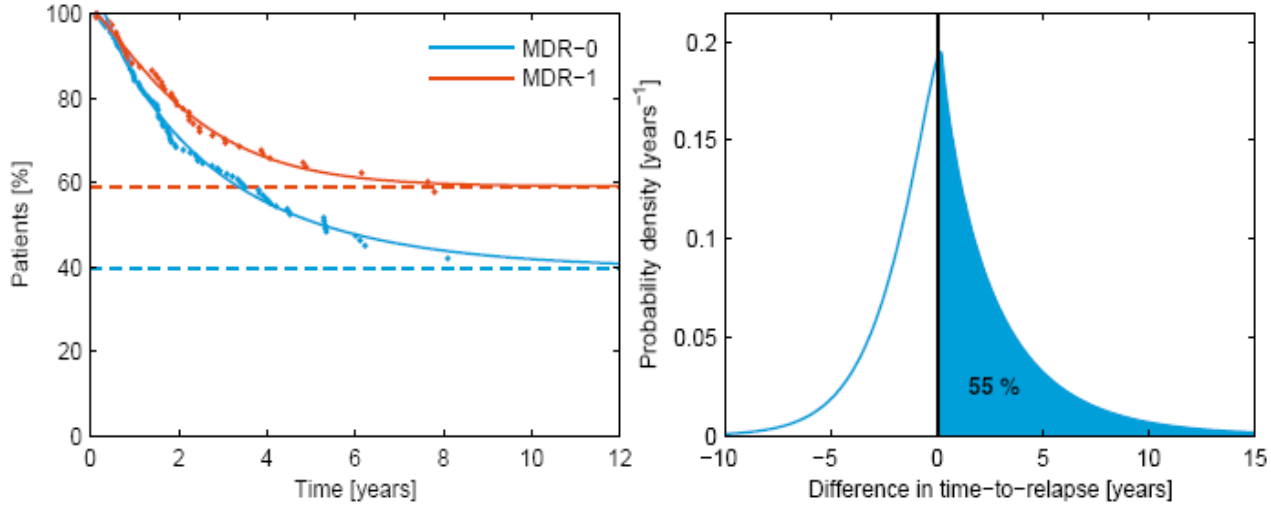
The 5-FU case

MDR1 – MDR0

TTD



TTR



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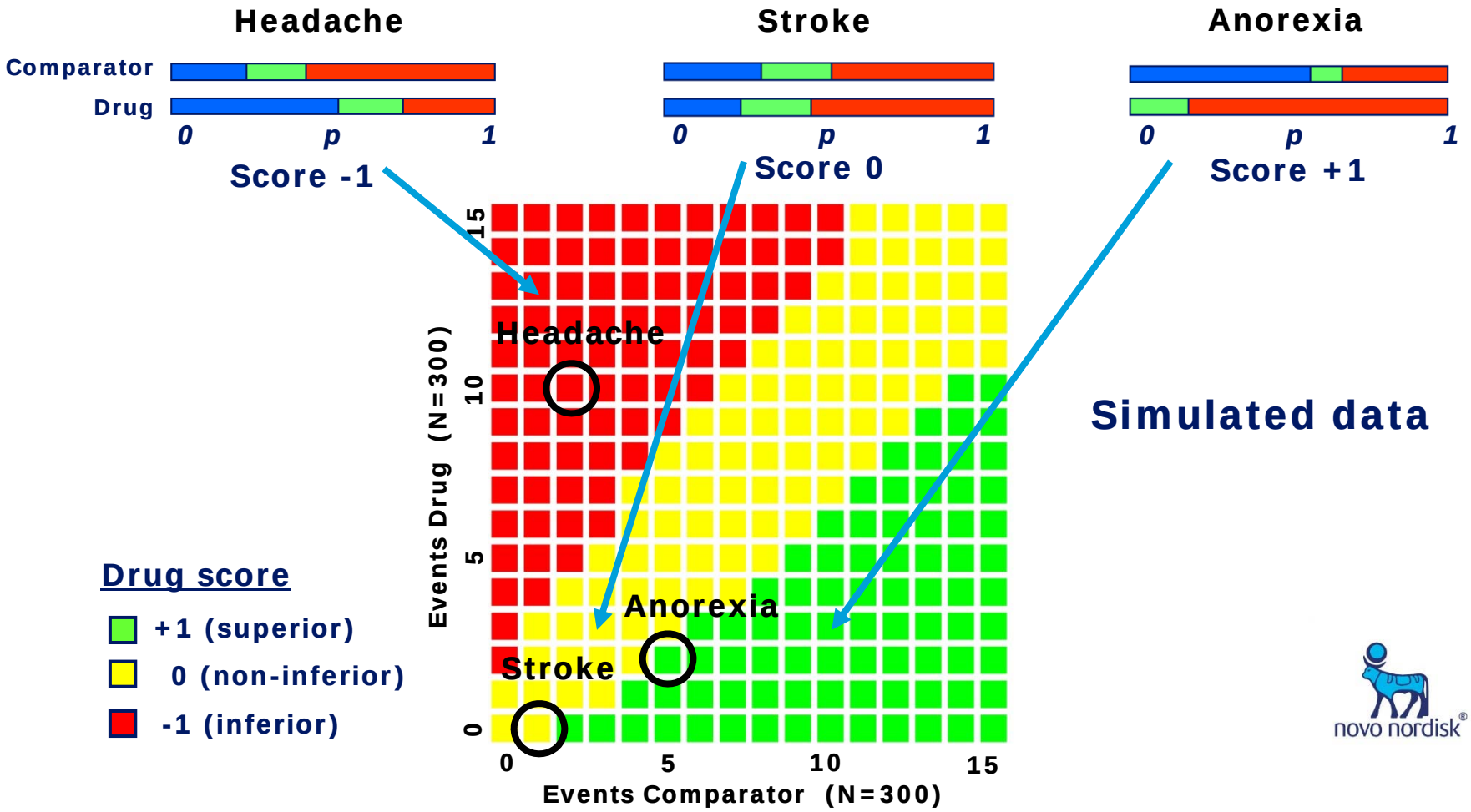
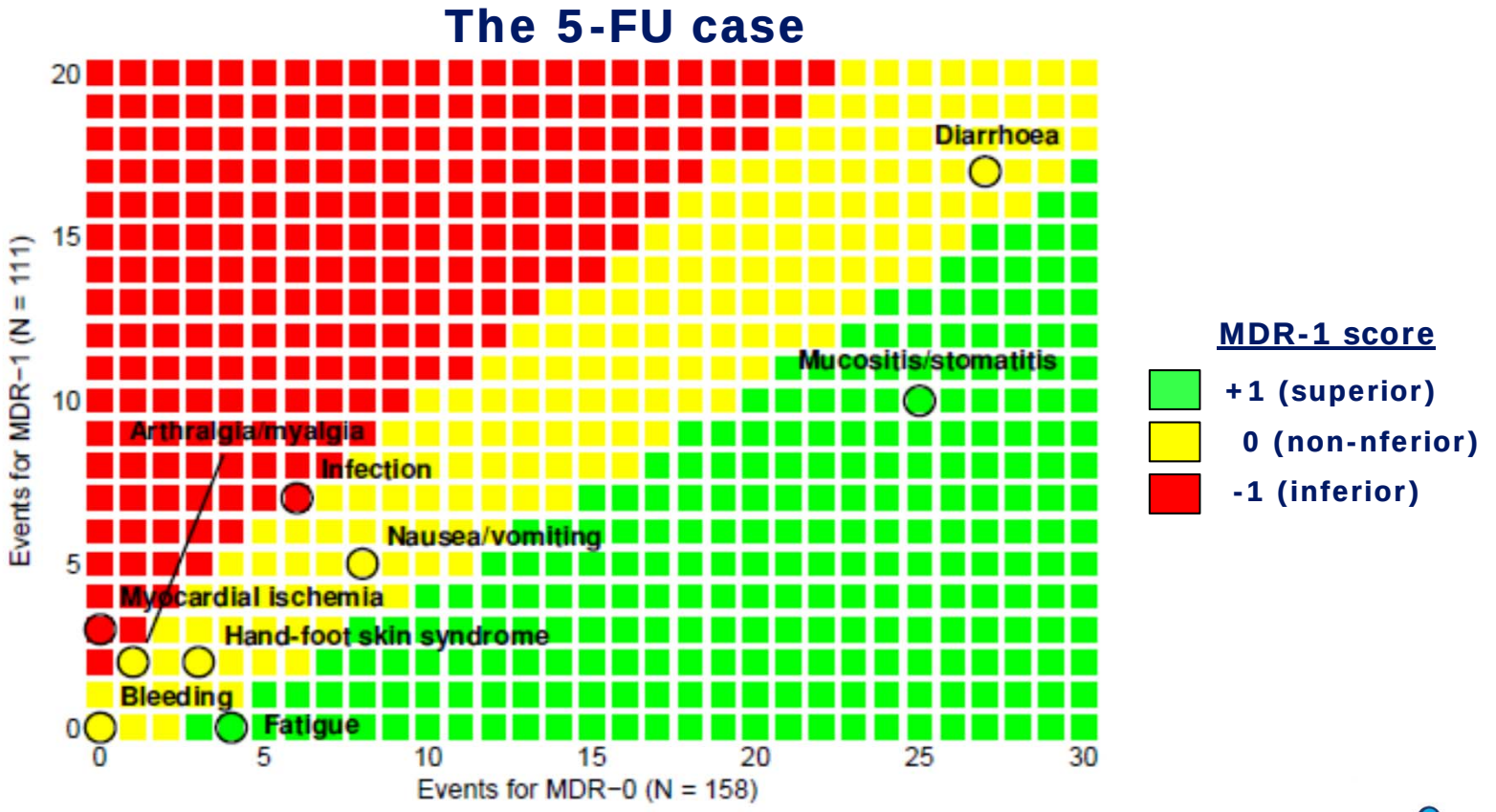
4.2: Binary endpoints (events)

- For discrete variables two one-sided confidence intervals (e.g. 67 %) for the probability of an event are combined to form a scoring interval.
- Non-overlapping scoring intervals indicate a trend towards a difference.

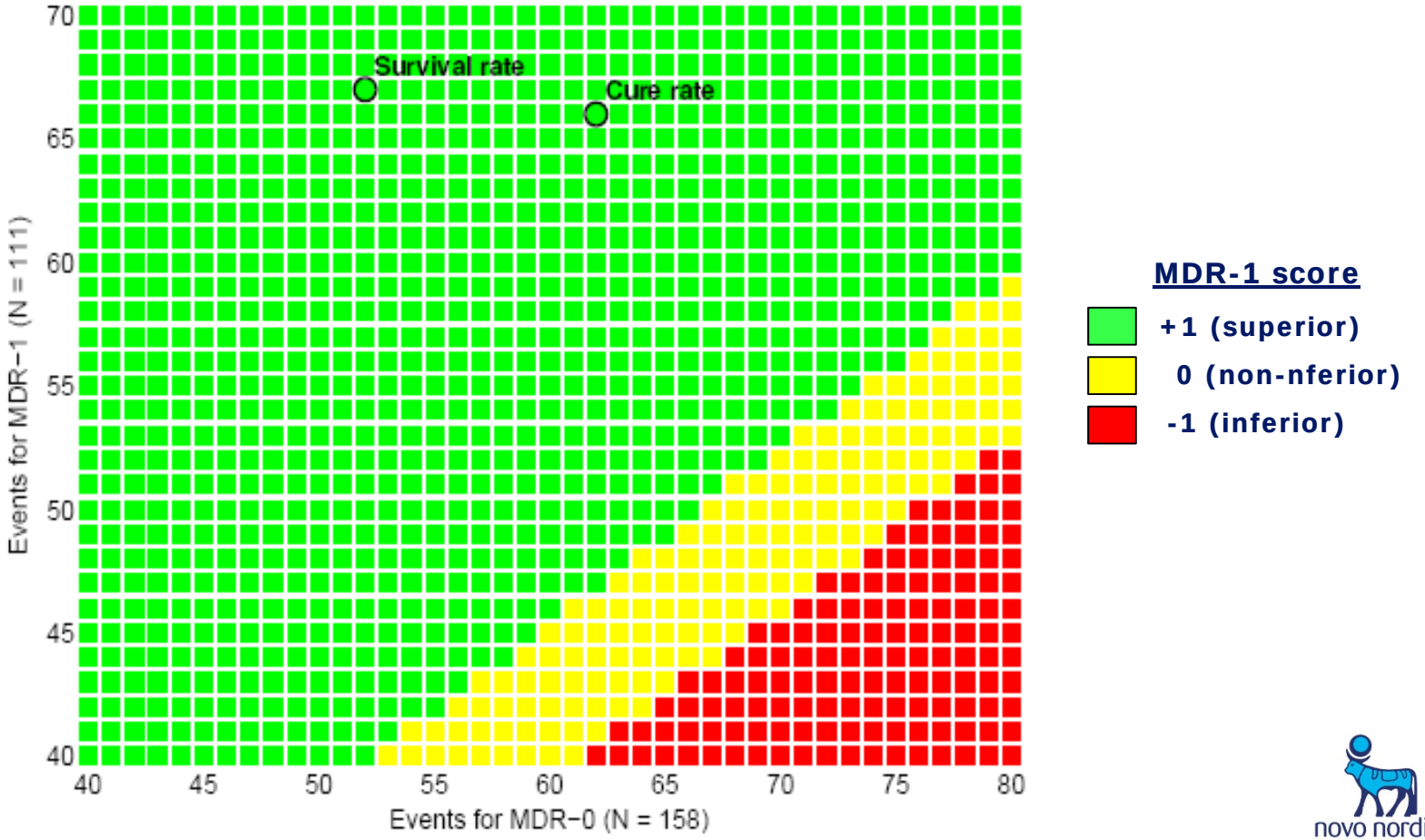


4.2: Binary endpoints (events)



4.2: Binary endpoints (events)

The 5-FU case



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4: Scoring

The 5-FU case

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	

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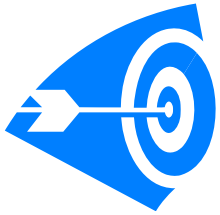

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5: Uncertainties

- In case of any uncertainty the score may be given as an interval (-1 → 0, 0 → 1 or -1 → 1).
- Justification can be qualitative:
  - Discussion of choice of dose, comparator and endpoints.
  - Evaluate methodological flaws/deficiencies and their impact.
  - Describe any negative studies, studies showing no difference.
- Justification can be quantitative:
  - Evaluations can be performed by the use of resampling, which this method is currently being developed to incorporate.

5: Uncertainties

The 5-FU case

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	

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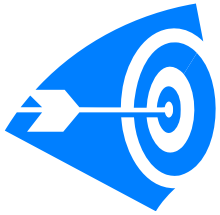

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6: Weighted scores

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

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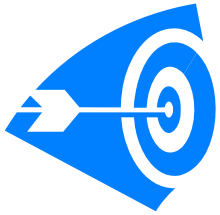

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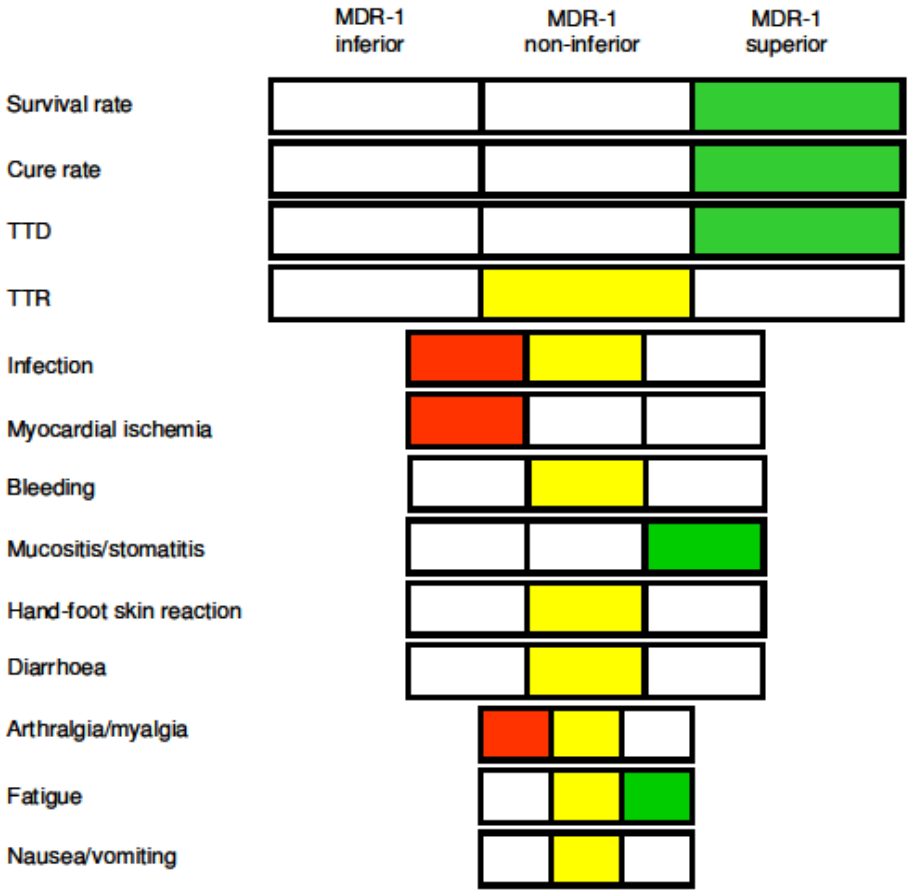
7.1: Presentation of results, single trial

The 5-FU case



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7.2: Real life example - many endpoints

- Another example* we have worked with is ordinal data from a questionnaire with 78 questions rated on a discrete scale 1 – 5.
- Same questions were given to schizophrenia patients before and after to types of treatment schemes (active and control).
- The differences in scores from baseline to end-of-trial were dichotomized into three groups: Responder, adverse responder, and no change.
- Number of responders and adverse responders for active group were scored against control group (comparator).
- Green indicates active group superiority.

* Jürgens et al., Bispebjerg Hospital, Denmark

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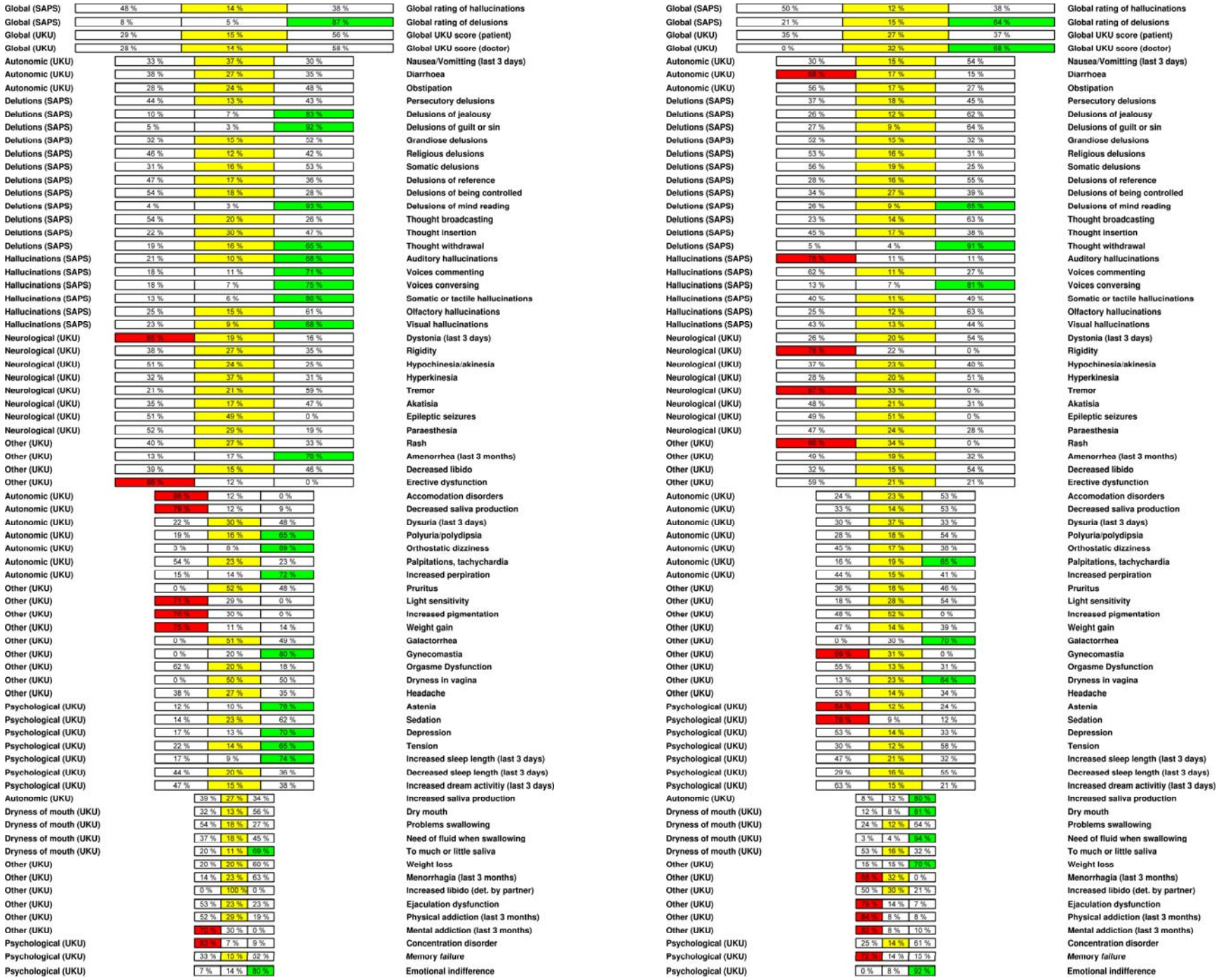
Responders
Global (SAPS) 48 % 14 % 38 % Global rating of hallucinations
Global (SAPS) 8 % 5 % 87 % Global rating of delusions
Global (UKU) 29 % 15 % 56 % Global UKU score (patient)
Global (UKU) 28 % 14 % 58 % Global UKU score (doctor)
Autonomic (UKU) 33 % 37 % 30 % Nausea/Vomitting (last 3 days)
Autonomic (UKU) 38 % 27 % 35 % Diarrhoea
Autonomic (UKU) 28 % 24 % 48 % Obstipation
Delutions (SAPS) 44 % 13 % 43 % Persecutory delusions
Delutions (SAPS) 10 % 7 % 83 % Delusions of jealousy
Delutions (SAPS) 5 % 3 % 92 % Delusions of guilt or sin
Delutions (SAPS) 32 % 15 % 52 % Grandiose delusions
Delutions (SAPS) 46 % 12 % 42 % Religious delusions
Delutions (SAPS) 31 % 16 % 53 % Somatic delusions
Delutions (SAPS) 47 % 17 % 36 % Delusions of reference
Delutions (SAPS) 54 % 18 % 28 % Delusions of being controlled
Delutions (SAPS) 4 % 3 % 93 % Delusions of mind reading
Delutions (SAPS) 54 % 20 % 26 % Thought broadcasting
Delutions (SAPS) 22 % 30 % 47 % Thought insertion
Delutions (SAPS) 19 % 16 % 65 % Thought withdrawal
Hallucinations (SAPS) 21 % 10 % 68 % Auditory hallucinations
Hallucinations (SAPS) 18 % 11 % 71 % Voices commenting
Hallucinations (SAPS) 18 % 7 % 75 % Voices conversing
Hallucinations (SAPS) 13 % 6 % 80 % Somatic or tactile hallucinations
Hallucinations (SAPS) 25 % 15 % 61 % Olfactory hallucinations
Hallucinations (SAPS) 23 % 9 % 68 % Visual hallucinations
Neurological (UKU) 65 % 19 % 16 % Dystonia (last 3 days)
Neurological (UKU) 38 % 27 % 35 % Rigidity
Neurological (UKU) 51 % 24 % 25 % Hypochinesia/akinesia
Neurological (UKU) 32 % 37 % 31 % Hyperkinesia
Neurological (UKU) 21 % 21 % 59 % Tremor
Neurological (UKU) 35 % 17 % 47 % Akatisia
Neurological (UKU) 51 % 49 % 0 % Epileptic seizures
Neurological (UKU) 52 % 29 % 19 % Paraesthesia
Other (UKU) 40 % 27 % 33 % Rash
Other (UKU) 13 % 17 % 70 % Amenorrhea (last 3 months)
Other (UKU) 39 % 15 % 46 % Decreased libido
Other (UKU) 88 % 12 % 0 % Erective dysfunction
Autonomic (UKU) 88 % 12 % 0 % Accomodation disorders
Autonomic (UKU) 78 % 12 % 9 % Decreased saliva production
Autonomic (UKU) 22 % 30 % 48 % Dysuria (last 3 days)
Autonomic (UKU) 19 % 16 % 65 % Polyuria/polydipsia
Autonomic (UKU) 3 % 8 % 89 % Orthostatic dizziness
Autonomic (UKU) 54 % 23 % 23 % Palpitations, tachychardia
Autonomic (UKU) 15 % 14 % 72 % Increased perpiration
Other (UKU) 0 % 52 % 48 % Pruritus
Other (UKU) 71 % 29 % 0 % Light sensitivity
Other (UKU) 70 % 30 % 0 % Increased pigmentation
Other (UKU) 75 % 11 % 14 % Weight gain
Other (UKU) 0 % 51 % 49 % Galactorrhea
Other (UKU) 0 % 20 % 80 % Gynecomastia
Other (UKU) 62 % 20 % 18 % Orgasme Dysfunction
Other (UKU) 0 % 50 % 50 % Dryness in vagina
Other (UKU) 38 % 27 % 35 % Headache
Psychological (UKU) 12 % 10 % 78 % Astenia
Psychological (UKU) 14 % 23 % 62 % Sedation
Psychological (UKU) 17 % 13 % 70 % Depression
Psychological (UKU) 22 % 14 % 65 % Tension
Psychological (UKU) 17 % 9 % 74 % Increased sleep length (last 3 days)
Psychological (UKU) 44 % 20 % 36 % Decreased sleep length (last 3 days)
Psychological (UKU) 47 % 15 % 38 % Increased dream activitiy (last 3 days)
Autonomic (UKU) 39 % 27 % 34 % Increased saliva production
Dryness of mouth (UKU) 32 % 13 % 56 % Dry mouth
Dryness of mouth (UKU) 54 % 18 % 27 % Problems swallowing
Dryness of mouth (UKU) 37 % 18 % 45 % Need of fluid when swallowing
Dryness of mouth (UKU) 20 % 11 % 69 % To much or little saliva
Other (UKU) 20 % 20 % 60 % Weight loss
Other (UKU) 14 % 23 % 63 % Menorrhagia (last 3 months)
Other (UKU) 0 % 100 % 0 % Increased libido (det. by partner)
Other (UKU) 53 % 23 % 23 % Ejaculation dysfunction
Other (UKU) 52 % 29 % 19 % Physical addiction (last 3 months)
Other (UKU) 70 % 30 % 0 % Mental addiction (last 3 months)
Psychological (UKU) 83 % 7 % 9 % Concentration disorder
Psychological (UKU) 33 % 15 % 52 % Memory failure
Psychological (UKU) 7 % 14 % 80 % Emotional indifference
Adverse responders
Global (SAPS) 50 % 12 % 38 % Global rating of hallucinations
Global (SAPS) 21 % 15 % 64 % Global rating of delusions
Global (UKU) 35 % 27 % 37 % Global UKU score (patient)
Global (UKU) 0 % 32 % 68 % Global UKU score (doctor)
Autonomic (UKU) 30 % 15 % 54 % Nausea/Vomitting (last 3 days)
Autonomic (UKU) 68 % 17 % 15 % Diarrhoea
Autonomic (UKU) 56 % 17 % 27 % Obstipation
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Delutions (SAPS) 26 % 12 % 62 % Delusions of jealousy
Delutions (SAPS) 27 % 9 % 64 % Delusions of guilt or sin
Delutions (SAPS) 52 % 15 % 32 % Grandiose delusions
Delutions (SAPS) 53 % 16 % 31 % Religious delusions
Delutions (SAPS) 56 % 19 % 25 % Somatic delusions
Delutions (SAPS) 28 % 16 % 55 % Delusions of reference
Delutions (SAPS) 34 % 27 % 39 % Delusions of being controlled
Delutions (SAPS) 26 % 9 % 65 % Delusions of mind reading
Delutions (SAPS) 23 % 14 % 63 % Thought broadcasting
Delutions (SAPS) 45 % 17 % 38 % Thought insertion
Delutions (SAPS) 5 % 4 % 91 % Thought withdrawal
Hallucinations (SAPS) 78 % 11 % 11 % Auditory hallucinations
Hallucinations (SAPS) 62 % 11 % 27 % Voices commenting
Hallucinations (SAPS) 13 % 7 % 81 % Voices conversing
Hallucinations (SAPS) 40 % 11 % 49 % Somatic or tactile hallucinations
Hallucinations (SAPS) 25 % 12 % 63 % Olfactory hallucinations
Hallucinations (SAPS) 43 % 13 % 44 % Visual hallucinations
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Other (UKU) 55 % 13 % 31 % Orgasme Dysfunction
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Other (UKU) 53 % 14 % 34 % Headache
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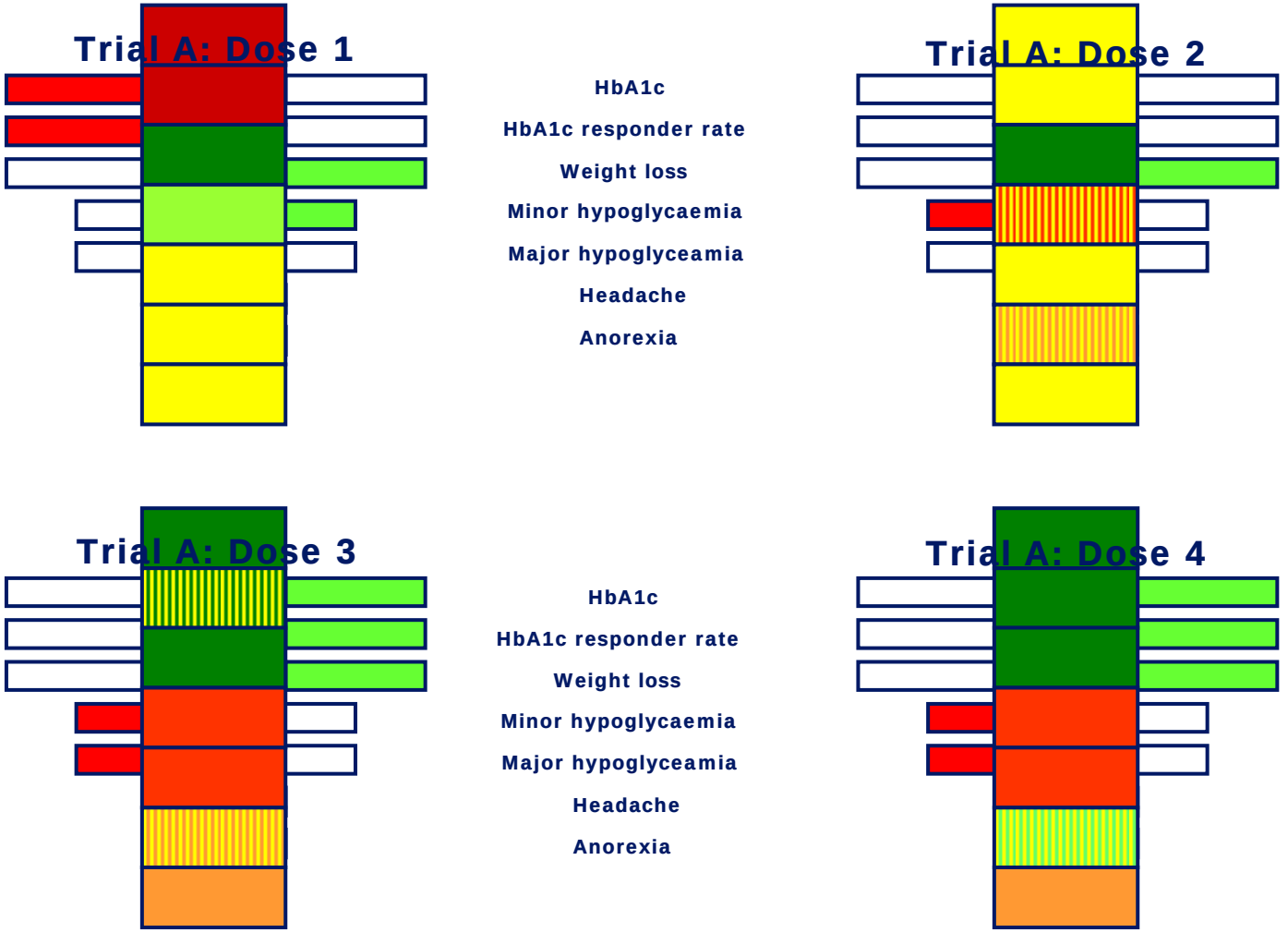
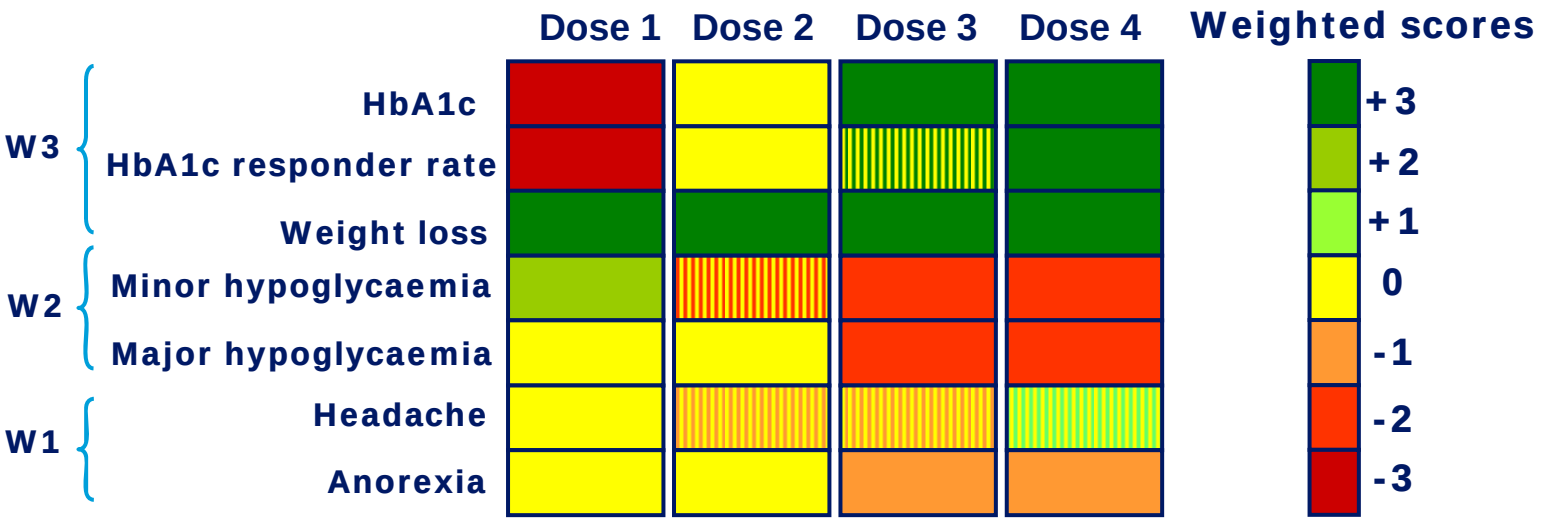
Autonomic (UKU) 8 % 12 % 80 % Increased saliva production
Dryness of mouth (UKU) 12 % 8 % 81 % Dry mouth
Dryness of mouth (UKU) 24 % 12 % 64 % Problems swallowing
Dryness of mouth (UKU) 3 % 4 % 94 % Need of fluid when swallowing
Dryness of mouth (UKU) 53 % 16 % 32 % To much or little saliva
Other (UKU) 15 % 15 % 70 % Weight loss
Other (UKU) 68 % 32 % 0 % Menorrhagia (last 3 months)
Other (UKU) 50 % 30 % 21 % Increased libido (det. by partner)
Other (UKU) 79 % 14 % 7 % Ejaculation dysfunction
Other (UKU) 84 % 8 % 8 % Physical addiction (last 3 months)
Other (UKU) 82 % 8 % 10 % Mental addiction (last 3 months)
Psychological (UKU) 25 % 14 % 61 % Concentration disorder
Psychological (UKU) 77 % 14 % 10 % Memory failure
Psychological (UKU) 0 % 8 % 92 % Emotional indifference

7.3: Dose-finding trials



7.3: Dose-finding trials



What is the optimal dose....?

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Method overview

1: Decision context

2: Decision profile

3: Weighting

4: Scoring

5: Uncertainty

6: Weighted scores

7: Presentation

8: Overall conclusion

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8: Overall conclusion

- 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 the MDR-1 group.
- The clinical implications of this study are that genetic profiling is advisable in patients with colorectal cancer, to enable individualised treatment and follow-up.

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Conclusions of talk

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

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Conclusions of talk

- 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.

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Further reading

- *A comprehensive approach to benefit-risk assessment in drug development*. Sarac et al. (2012). http://dx.doi.org/10.1111/j.1742-7843.2012.00871.x
- *Data-Driven assessment of the association of polymorphisms in 5-fluorouracil metabolism genes with outcome in adjuvant treatment of colorectal cancer*. Sarac et al. (2012). http://dx.doi.org/10.1111/j.1742-7843.2012.00885.x

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Thank you for your attention.

Questions?