



PROTECT



Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

**AGGREGATED DATA DRUG INFORMATION SYSTEM (ADDIS)
AN EVIDENCE-BASED DECISION SUPPORT SYSTEM FOR THE
BENEFIT-RISK ASSESSMENT OF MEDICAL PRODUCTS**

IMI-PROTECT Symposium

Benefit-Risk Integration and Representation Workshop

18th February 2015

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Disclaimer

“The processes described and conclusions drawn from the work presented herein relate solely to the testing of methodologies and representations for the evaluation of benefit and risk of medicines.

This report neither replaces nor is intended to replace or comment on any regulatory decisions made by national regulatory agencies, nor the European Medicines Agency.”

The 3 pillars of structured decision making

- Well-defined and transparent process
 - PrOACT-URL (EMA benefit-risk methodology project)
- Guidance on how to conduct the various steps in this process
 - IMI PROTECT benefit-risk group recommendations report
 - IMI PROTECT website and training materials
- Supporting software
 - ADDIS

ADDIS – a brief history

- The development of ADDIS started in 2009 as part of work package 3.2 of the Escher project
- This has resulted in the development of ADDIS 1
- ADDIS 2 is a web-based redevelopment of the previous prototype desktop application
- ADDIS 2 is currently still under heavy development but the software is now becoming useable as an analytical tool
- Both ADDIS 1 and 2 are open source and freely accessible from our website www.drugis.org

ADDIS 2: functional perspective

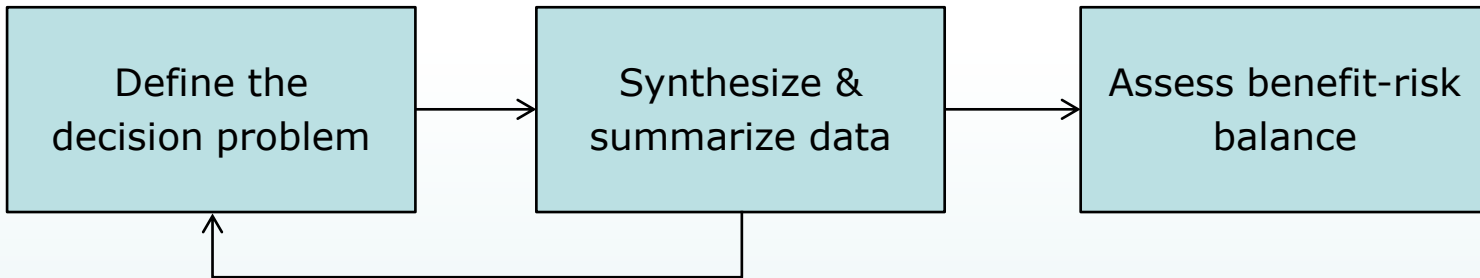
Quantitative methods

(network) meta-analysis

MCDA/SMAA

Disease progression modelling

Workflow



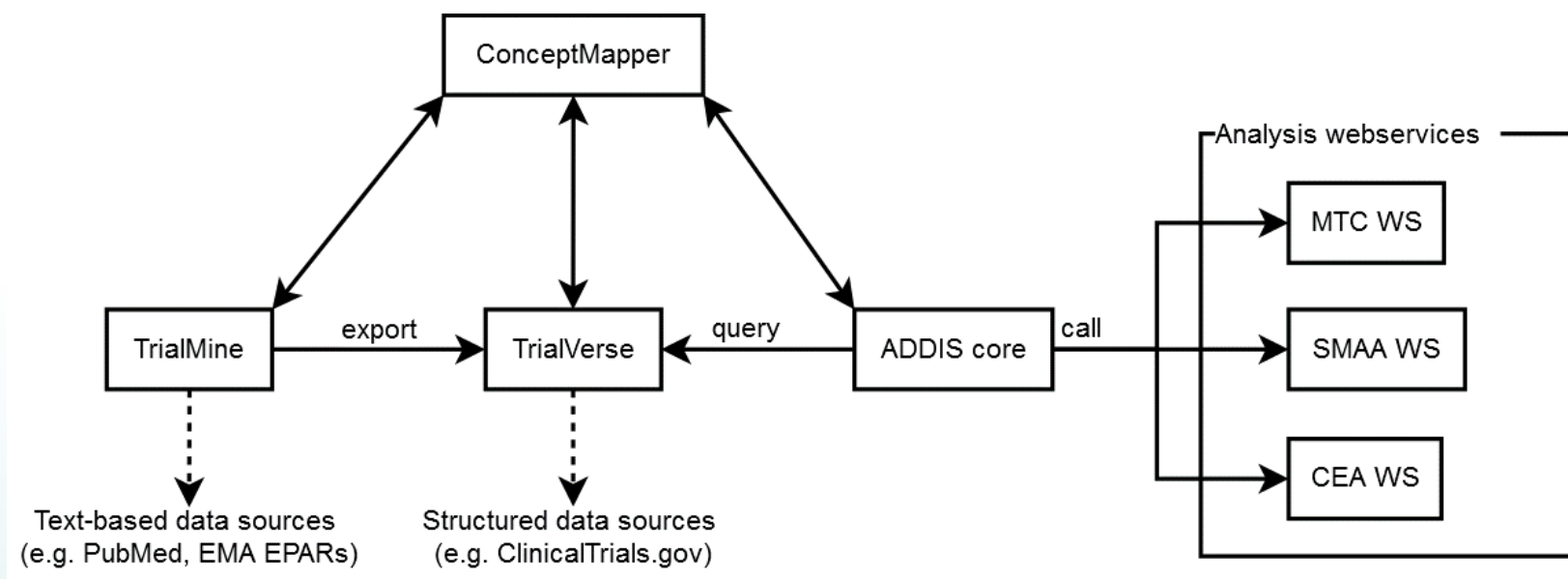
Visualisations

Value tree

Effects table

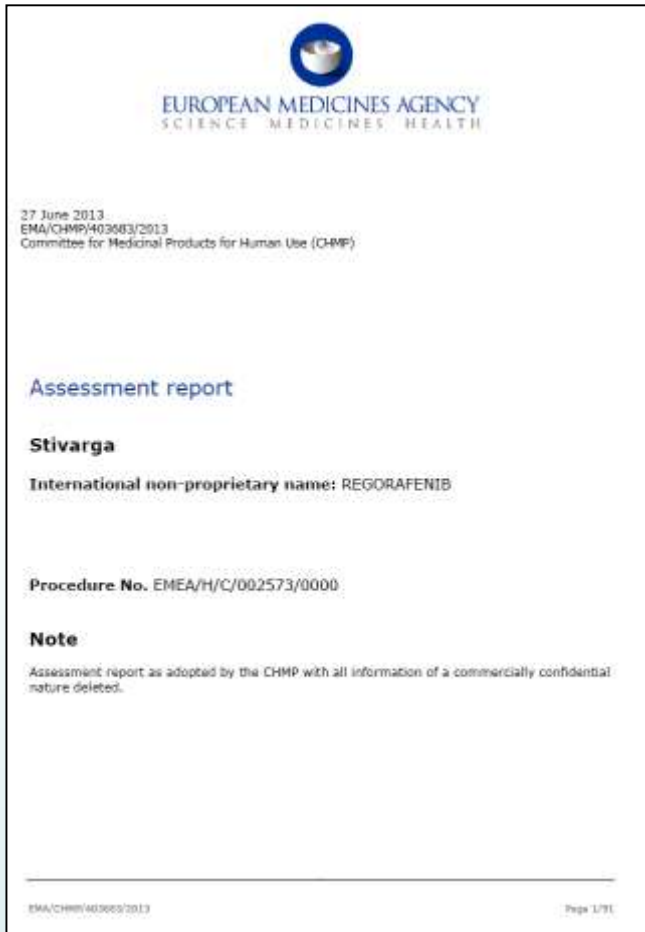
SMAA descriptive indices

ADDIS 2: technical perspective



MCDA WEB INTERFACE

Illustrative case study



The image shows a screenshot of a document header from the European Medicines Agency (EMA). At the top center is the EMA logo, which consists of a blue circle containing a white caduceus. Below the logo, the text reads "EUROPEAN MEDICINES AGENCY" in a bold, sans-serif font, with "SCIENCE MEDICINES HEALTH" in a smaller font underneath. To the left of the logo, the date "27 June 2013" is displayed, followed by the reference number "EMA/CHMP/403683/2013" and the name of the committee, "Committee for Medicinal Products for Human Use (CHMP)". Below this information, the text "Assessment report" is written in a blue font. The name of the drug, "Stivarga", is listed in bold. Underneath, the "International non-proprietary name: REGORAFENIB" is provided. The "Procedure No." is given as "EMA/H/C/002573/0000". A "Note" section follows, stating that the report is as adopted by the CHMP with all commercially confidential information deleted. At the bottom left, the reference number "EMA/CHMP/403683/2013" is repeated, and at the bottom right, it says "Page 1/31".

27 June 2013
EMA/CHMP/403683/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Stivarga
International non-proprietary name: REGORAFENIB

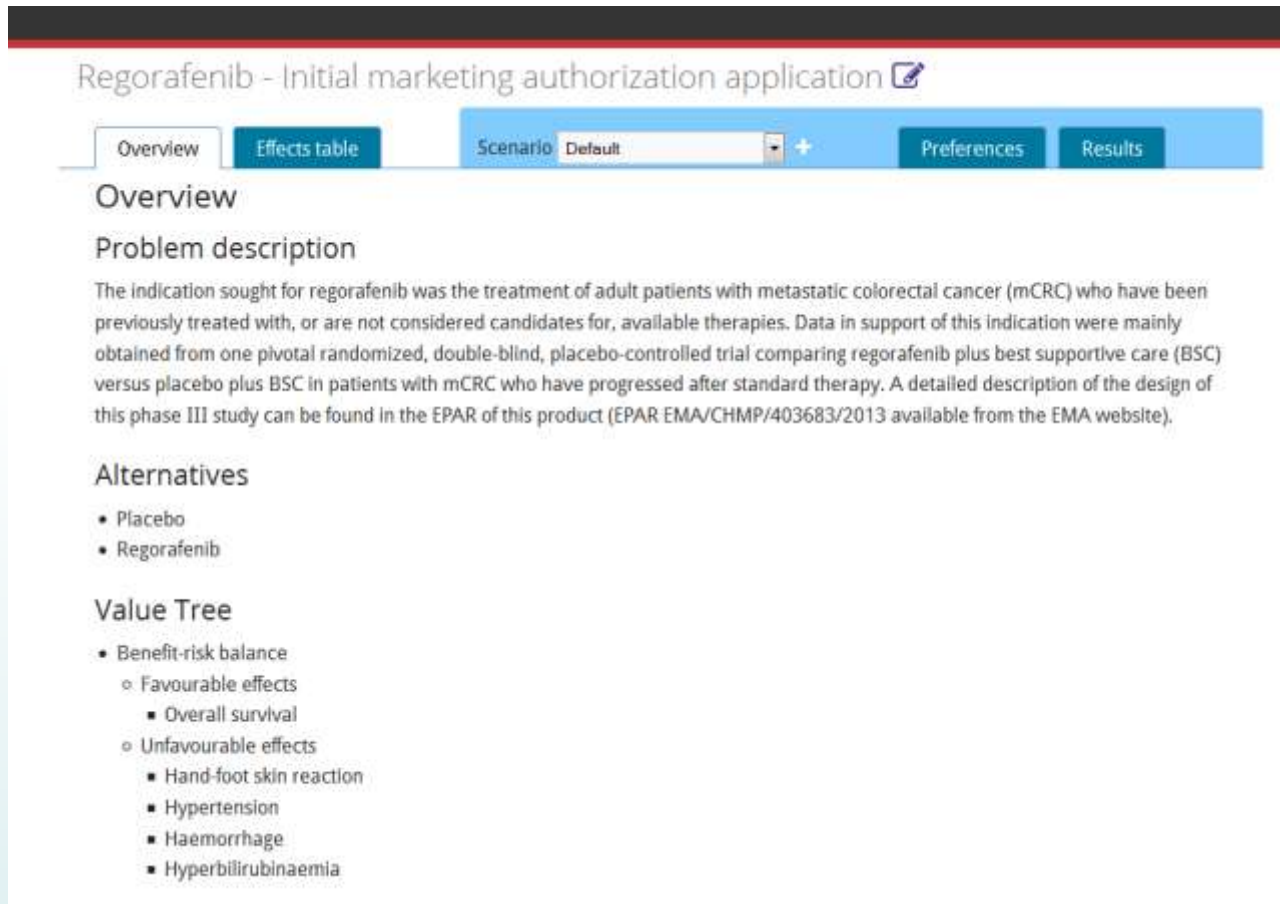
Procedure No. EMA/H/C/002573/0000


Note
Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

EMA/CHMP/403683/2013 Page 1/31

- We consider the problem of assessing the benefit-risk balance of regorafenib using the data available at the time of the initial marketing authorization application of this product
- All data used for this assessment were directly taken from the EPAR of this product (EPAR EMA/CHMP/403683/2013 available from the EMA website)
- The value judgments provided throughout this example are hypothetical and do not reflect the opinion of the CHMP

Overview of the decision problem



Regorafenib - Initial marketing authorization application 

Overview Effects table Scenario Default Preferences Results

Overview

Problem description

The indication sought for regorafenib was the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with, or are not considered candidates for, available therapies. Data in support of this indication were mainly obtained from one pivotal randomized, double-blind, placebo-controlled trial comparing regorafenib plus best supportive care (BSC) versus placebo plus BSC in patients with mCRC who have progressed after standard therapy. A detailed description of the design of this phase III study can be found in the EPAR of this product (EPAR EMA/CHMP/403683/2013 available from the EMA website).

Alternatives

- Placebo
- Regorafenib

Value Tree

- Benefit-risk balance
 - Favourable effects
 - Overall survival
 - Unfavourable effects
 - Hand-foot skin reaction
 - Hypertension
 - Haemorrhage
 - Hyperbilirubinaemia

Effects table

Regorafenib - Initial marketing authorization application

Overview

Effects table

Scenario Default

+













Preferences

Results


Effects table

Show alternatives

Placebo Regorafenib


Criterion	Description	Units	Placebo	Regorafenib
 Favourable effects				
  Overall survival	Median overall survival time	Months	4.96 4.96, 4.96	6.44 6.44, 6.44
 Unfavourable effects				
  Hand-foot skin reaction	Incidence of grade 3 events	%	0.4 0.4, 0.4	16.6 16.6, 16.6
  Hypertension	Incidence of grade 3 events	%	0.8 0.8, 0.8	7.6 7.6, 7.6
  Haemorrhage	Incidence of grade 3-5 events	%	0.8 0.8, 0.8	2 2, 2
  Hyperbilirubinaemia	Incidence	%	9.5 9.5, 9.5	20 20, 20


Preference elicitation: scale ranges

Regorafenib - Initial marketing authorization application 

Overview Effects table Scenario: Default - + Preferences Results

Preferences

Default 



Scale Ranges Partial Value Functions Trade-off Order Trade-off Ratios


Results

Scale Ranges

Criterion	Theoretical Range	Observed Range	Configured Range	Units
Overall survival	0, ∞	4.96, 6.44	4, 8	Months
Hand-foot skin reaction	0, 100	0.4, 16.6	0, 20	%
Hypertension	0, 100	0.8, 7.6	0, 10	%
Haemorrhage	0, 100	0.8, 2	0, 5	%
Hyperbillirubinaemia	0, 100	9.5, 20	5, 20	%

Define Scale Ranges

Preference elicitation: partial value functions

Regorafenib - Initial marketing authorization application 

Overview

Effects table

Scenario Default



Preferences

Results

Define Partial Value Function for: Overall survival

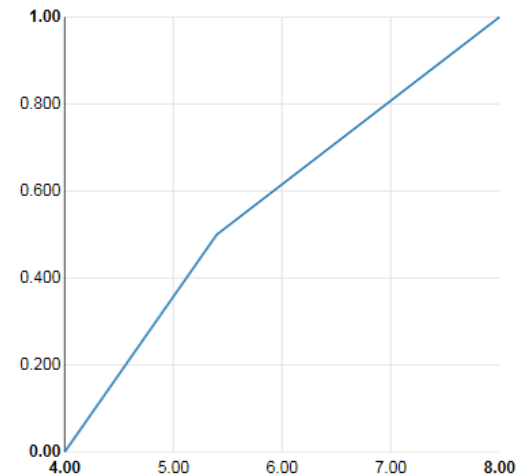
What is the value of x such that an improvement in Overall survival from 4 (Months) to x is equivalent to an improvement from x to 8 (Months)?

Adjust the slider:



So that the following statement is true:

The improvement from 4 to 5.4
is equivalent to the improvement from 5.4 to 8.



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Preference elicitation: ordinal trade-offs

Regorafenib - Initial marketing authorization application

Overview

Effects table

Scenario Default



Preferences

Results

Ordinal SWING weighting (1/4)

Given the following situation:

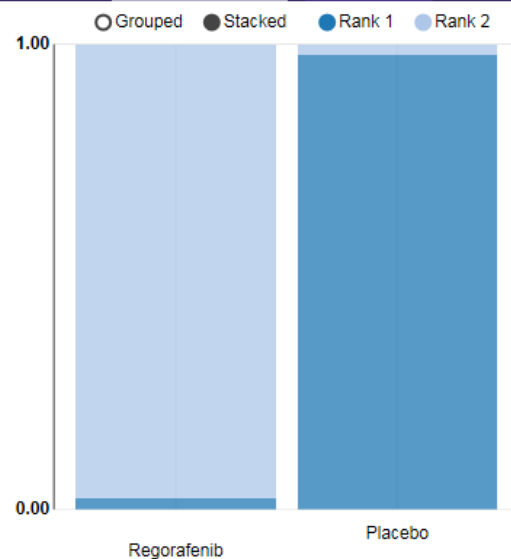
Hand-foot skin reaction = 20 Haemorrhage = 5 Hypertension = 10
 Hyperbilirubinaemia = 20 Overall survival = 4

Which of these improvements is most desired:

- Hand-foot skin reaction → 0
- Haemorrhage → 0
- Hypertension → 0
- Hyperbilirubinaemia → 5
- Overall survival → 8

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Preference elicitation: ordinal trade-offs

Regorafenib - Initial marketing authorization application

Overview

Effects table

Scenario Default

+

Preferences

Results

Ordinal SWING weighting (2/4)

Given the following situation:

Hand-foot skin reaction = 20 Haemorrhage = 5 Hypertension = 10

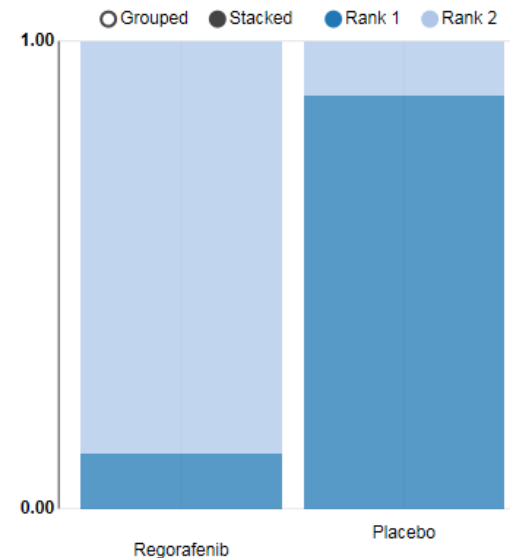
Hyperbilirubinaemia = 20 Overall survival = 8

Which of these improvements is most desired:

- Hand-foot skin reaction → 0
- Haemorrhage → 0
- Hypertension → 0
- Hyperbilirubinaemia → 5

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Preference elicitation: ordinal trade-offs

Regorafenib - Initial marketing authorization application

Overview

Effects table

Scenario Default



Preferences

Results

Ordinal SWING weighting (DONE)

You have given the following trade-offs:

w_1 : Overall survival (4 → 8)

w_2 : Hand-foot skin reaction (20 → 0)

w_3 : Hypertension (10 → 0)

w_4 : Haemorrhage (5 → 0)

w_5 : Hyperbilirubinaemia (20 → 5)

$$w_1 \geq w_4$$

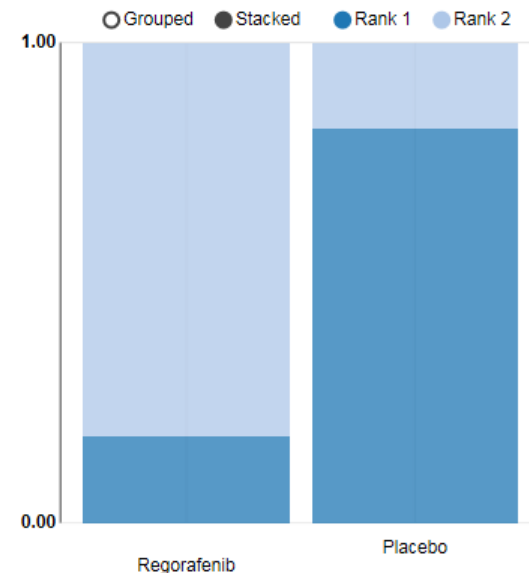
$$w_4 \geq w_2$$

$$w_2 \geq w_5$$

$$w_5 \geq w_3$$

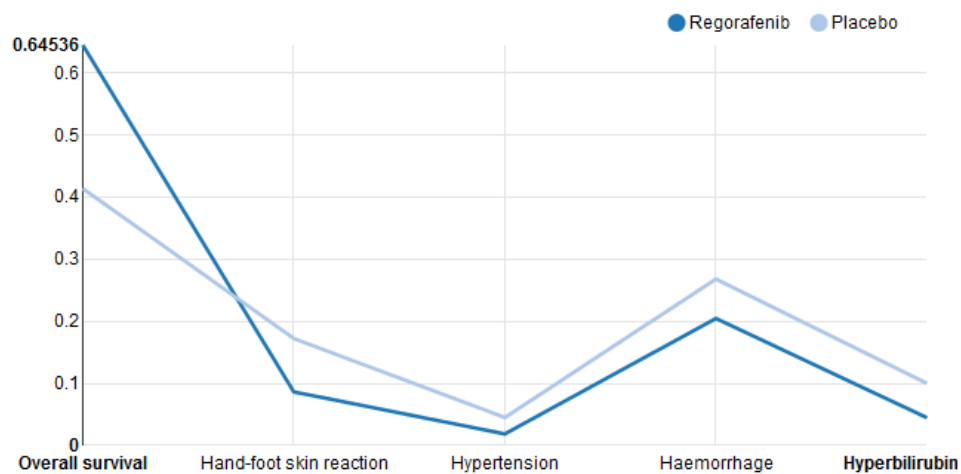
Previous

Save



Results based on ordinal trade-offs

Central Weights



Alternative	Confidence	Hand-foot skin reaction	Haemorrhage	Hypertension	Hyperbilirubinaemia	Overall survival
Placebo	1	0.17248	0.26829	0.045044	0.10019	0.414
Regorafenib	1	0.086353	0.20483	0.018686	0.04477	0.64536

Preference elicitation: exact trade-offs

Exact SWING weighting (1/4)

Determining the relative importance of:

Overall survival (4.000 → 8.000)

Haemorrhage (5.000 → 0.000)

Given the following situation:

Overall survival = 4.000, Haemorrhage = 0.000

Adjust the slider:



So that the following alternative is equally desirable:

Overall survival = 5 Haemorrhage = 5.000

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Preference elicitation: exact trade-offs

Exact SWING weighting (2/4)

Determining the relative importance of:

Haemorrhage (5.000 → 0.000)

Hand-foot skin reaction (20.000 → 0.000)

Given the following situation:

Haemorrhage = 5.000, Hand-foot skin reaction = 0.000

Adjust the slider:



So that the following alternative is equally desirable:

Haemorrhage = 3 Hand-foot skin reaction = 20.000

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Preference elicitation: exact trade-offs

Exact SWING weighting (3/4)

Determining the relative importance of:

Hand-foot skin reaction (20.000 → 0.000)

Hyperbilirubinaemia (20.000 → 5.000)

Given the following situation:

Hand-foot skin reaction = 20.000, Hyperbilirubinaemia = 5.000

Adjust the slider:



So that the following alternative is equally desirable:

Hand-foot skin reaction = 8 Hyperbilirubinaemia = 20.000

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Preference elicitation: exact trade-offs

Exact SWING weighting (4/4)

Determining the relative importance of:

Hyperbilirubinaemia (20.000 → 5.000)

Hypertension (10.000 → 0.000)

Given the following situation:

Hyperbilirubinaemia = 20.000, Hypertension = 0.000

Adjust the slider:



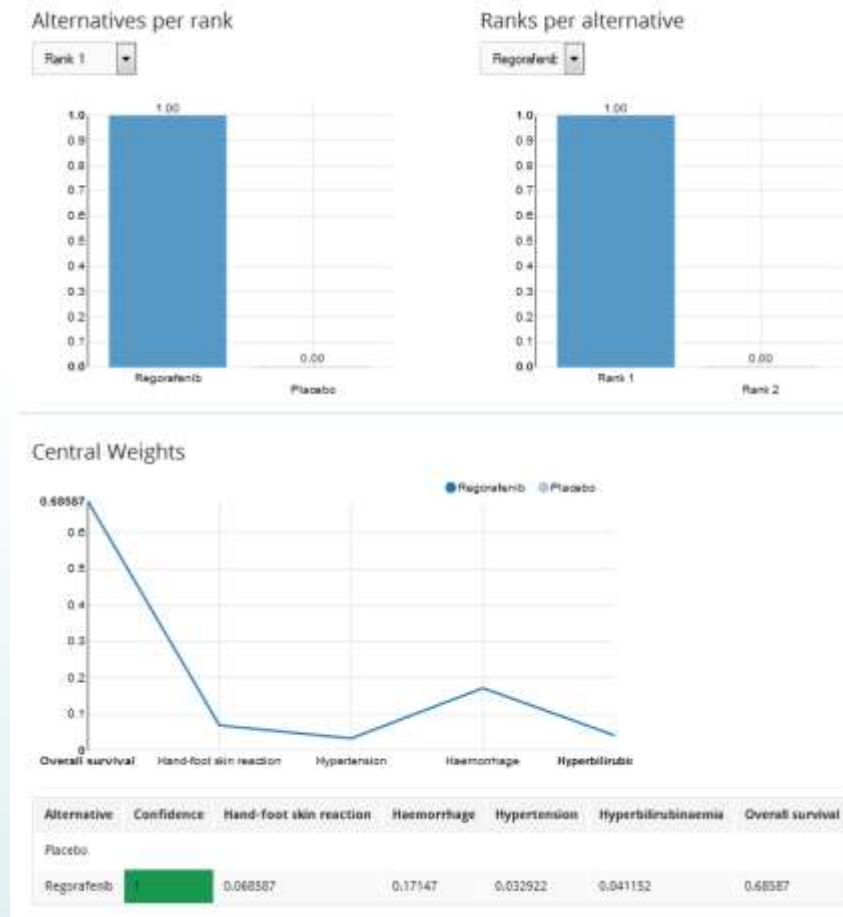
So that the following alternative is equally desirable:

Hyperbilirubinaemia = 8 Hypertension = 10.000

Previous

Save

Results based on exact trade-offs



Concluding remarks

- Developing quantitative methods that are both theoretically sound and easy to use by decision makers has proven to be far from straightforward
- Our ultimate aim will be to arrive at methodologies that allow decision makers to simultaneously explore
 - Imprecision in the preference statements (i.e. shape of the partial value functions, criteria weights)
 - Uncertainty in the effect size estimates
 - Uncertainty in the long-term clinical consequences
- We have started to develop a flexible set of tools to address all these aspects (www.drugis.org)

ACKNOWLEDGEMENT

Support



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ADDIS

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