Quantitative methods for the benefit-risk assessment - a hands-on exercise

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From Safety and Efficacy to Benefit-Risk Balance

Legal framework: An application is to be refused if…

65/65/EEC

Harmful or,

Therapeutic **efficacy is lacking**

75/318/EEC

Harmfulness and therapeutic efficacy can only be examined in relation to each other;

*Therapeutic **advantages must outweigh potential risks***

2004/27/EC

The **risk-benefit balance** is not considered to be favourable

Therapeutic efficacy is insufficiently substantiated

Assessment through lexicographic ordering

- Senior assessor:
- *«First start from the benefits: “Is there a clinically significant benefit?”*
- *If yes, look at adverse events. Are they acceptable for the patient?»*

Benefit-risk methodology project Work package 1 report (2009) (WC500109478.pdf); http://www.ema.europa.eu

A ‘typical’ BR assessment problem

Criterion	Description	Treatment A	Treatment B
Favourable criteria			
Disease progression	Median time until the disease progressed to the next stage (yrs)	5.7	4
Unfavourable criteria			
Moderate side effect	Percentage of patients with an ARIA edema event	35	3
Severe side effect	Percentage of patients with a brain microhemorrhage event	19	7

Which of these treatments is preferred?

A ‘typical’ BR assessment problem/balance

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$$\text{B/R balance} = w_1 \cdot \text{DP}(5.7\text{-}4) - (w_2 \cdot \text{MSE}(35\text{-}3) + w_3 \cdot \text{SSE}(19\text{-}7))$$

A ‘typical’ BR assessment problem/balance

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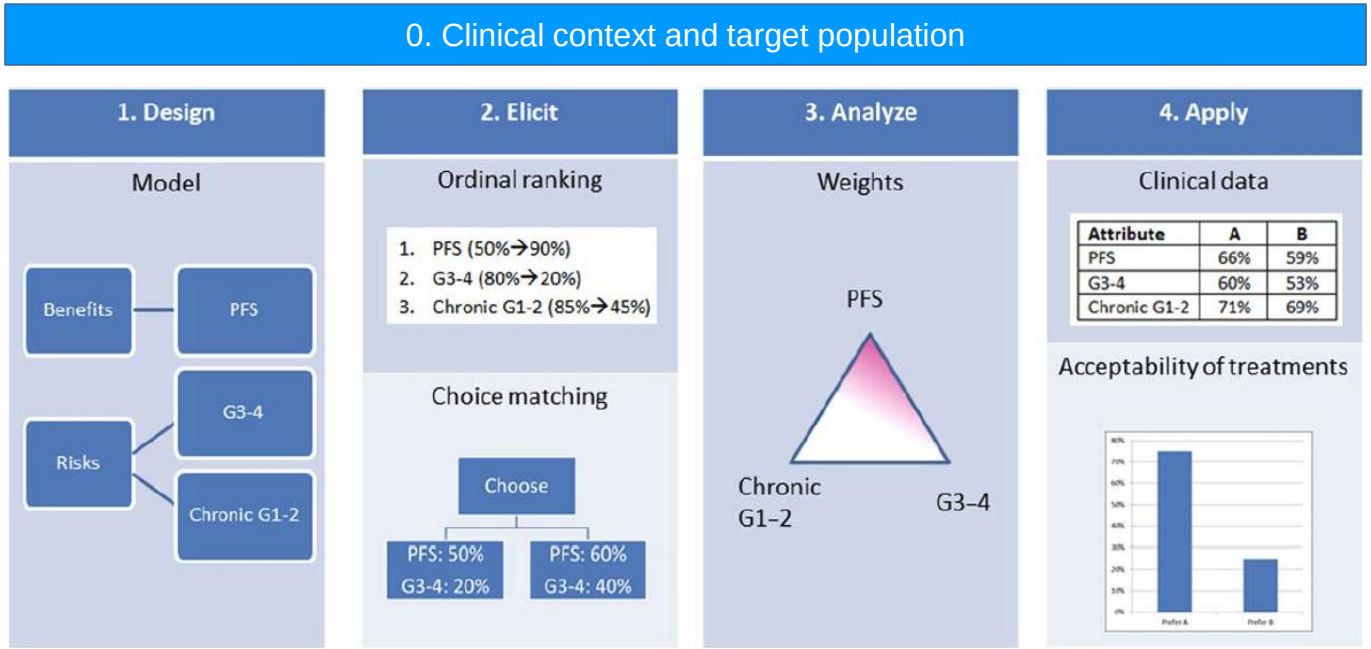
- $w_{2/}w_1$ What is your maximum acceptable increase in moderate adverse event risk for a decrease in the disease progression rate from 4 years to 5.7 years?
- $w_{3/}w_1$ What is your maximum acceptable increase in severe adverse event risk for a decrease in the disease progression rate from 4 years to 5.7 years?

Interactive case study in Alzheimer's disease

Content at a glance



0. Clinical context

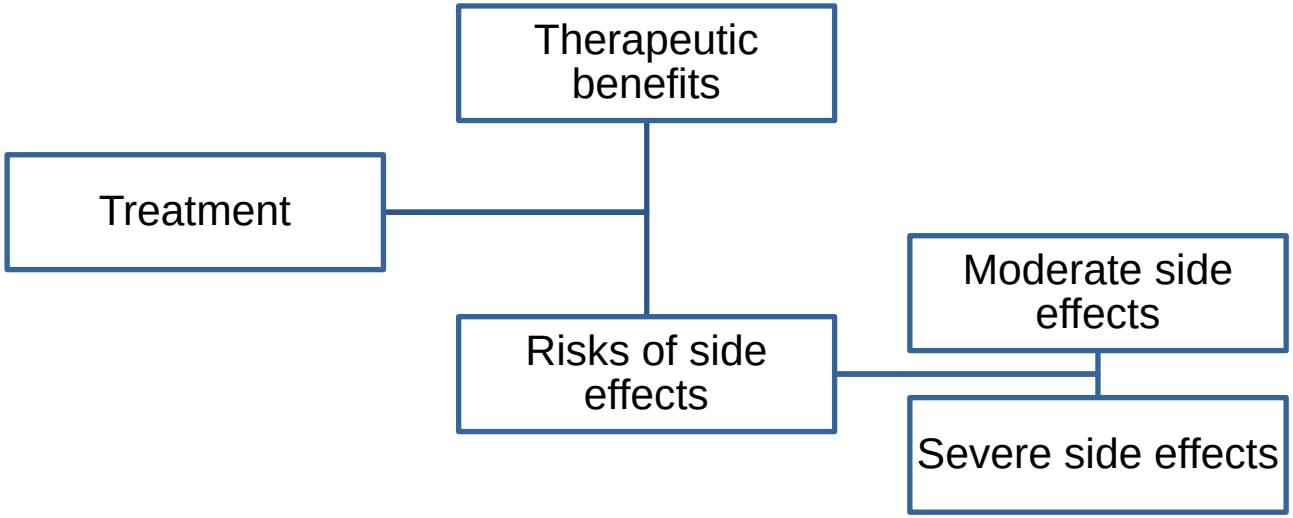
- Alzheimer's disease (AD) is the main cause of dementia, which affects more than 50 million people worldwide
- Traditional treatments -> combination of pharmaceutical and non-pharmaceutical treatments to mitigate cognition decline and alleviate symptoms
- New potential treatments -> second-generation anti-amyloid β monoclonal antibodies should reduce amyloid plaques in the brain, modifying the disease progression

0. Target population

People living with mild cognitive impairment

Initial forgetfulness	• Loss of memory for specific episodes, dates (e.g., birthdays) and names. • Challenges with learning new information • May need some help with complex tasks (e.g., taking care of their finances) • Self-awareness of the onset of symptoms, depression and irritability
Mild to moderate dementia	• Loss of spatial orientation, difficulty to find words, or misunderstanding of events and situations • Requires full assistance with complex tasks (e.g. taking care of their finances) • No longer safe to travel alone or being left alone at home • Mild depression or apathy, less often irritable/aggressive
Severe dementia	• No longer being able to converse or hold conversations. • Loss of ability to use simple tools, dress, take care of hygiene, and to recognise people • Progressively more apathetic with increasing irritability/aggression

1. Design


Therapeutic benefits
Treatment
Moderate side effects
Risks of side effects
Severe side effects

1. Design – therapeutic benefits

Number of years until more care and support is needed

- Description: how long it takes, on average, for people on the treatment to progress to the next stage of the disease
- Range: 4 to 6 years

1. Design – risk of side effects

Moderate side effects

Number of people who experience periods of discomfort

- Description: Percentage of people who have periods of discomfort that affect their ability to carry out daily activities. The discomfort is caused by side effects such as dizziness, nausea, diarrhoea, and headache. Urgent medical attention is not needed. However, a person may have the same side effects many times while receiving the treatment.

- Range: Risk of 30 to 85%

1. Design – risk of side effects

Severe side effects

Number of people who experience a side effect that could cause long-term or permanent disability

- Percentage of people who experience a severe side effect that stops them performing activities as usual. This type of side effect could cause a long-term or permanent disability. An example would be paralysis in half of the body or loss of speech, caused by a non-fatal stroke.

- Range: Risk of 10 to 65%

2. Elicit

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2. Elicit

What are the maximum risks you would be willing to accept to delay for 2 years the progression of the disease?

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	Treatment characteristics	Treatment A	Treatment B
Therapeutic benefits	Number of years until more care and support is needed	4 years	6 years
***Moderate** side effects*	Number of people who experience periods of discomfort	30% (30 out of 100 people)	**???**

	Treatment characteristics	Treatment A	Treatment B
Therapeutic benefits	Number of years until more care and support is needed	4 years	6 years
***Severe** side effects*	Number of people who experience a side effect that could cause long-term or permanent disability	10% (10 out of 100 people)	**???**

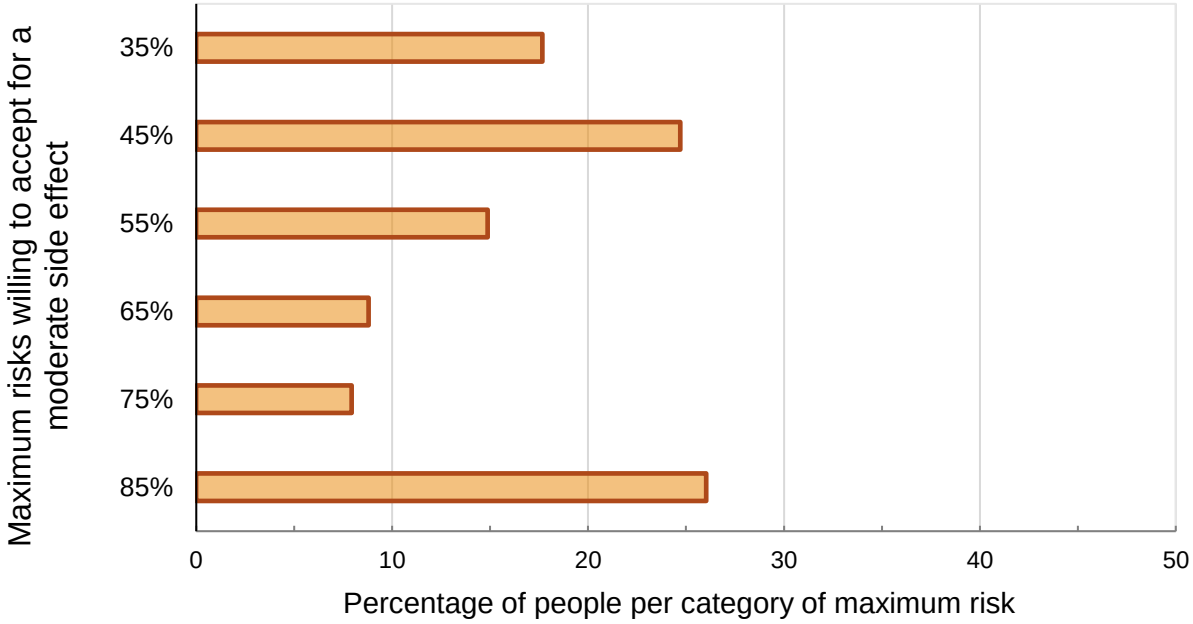
What are the maximum risks you would be willing to accept to delay for 2 years the progression of the disease?

PollEv.com/yourpreferences

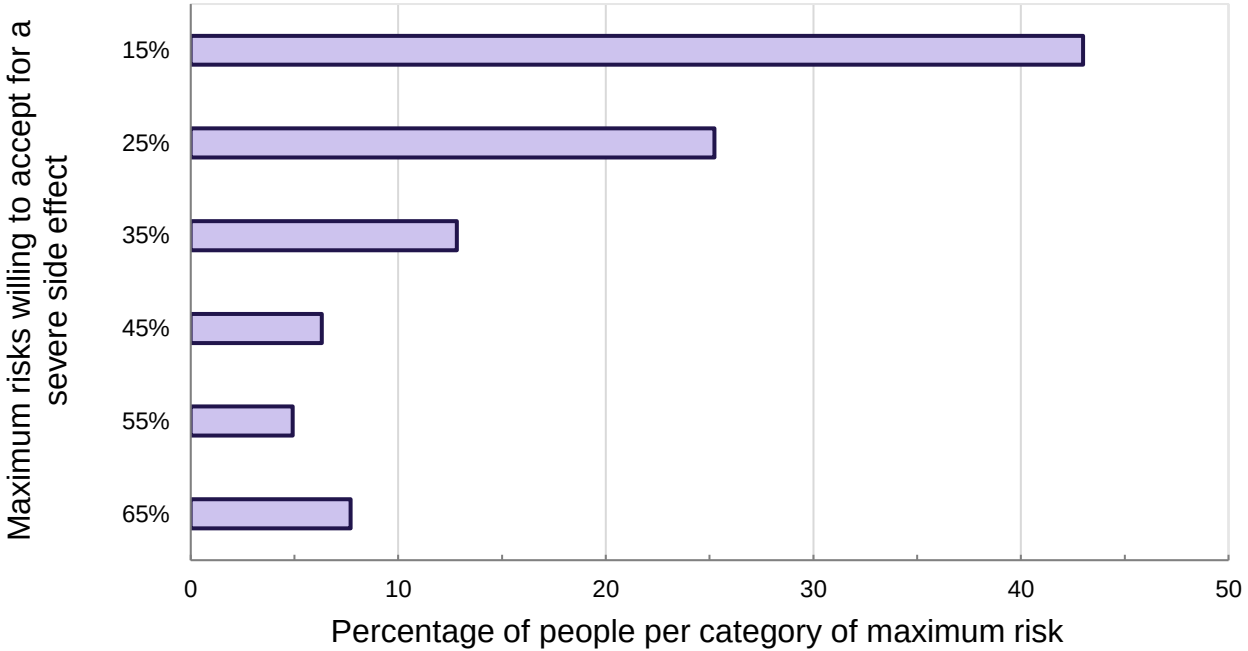
3. Analyze

What are the maximum risks you would be willing to accept to delay for 2 years the progression of the disease?

Results of a previous study
Moderate side effects



Results of a previous study
Severe side effects



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4. Apply

4. Apply - Aducanumab for the treatment of early Alzheimer's Disease

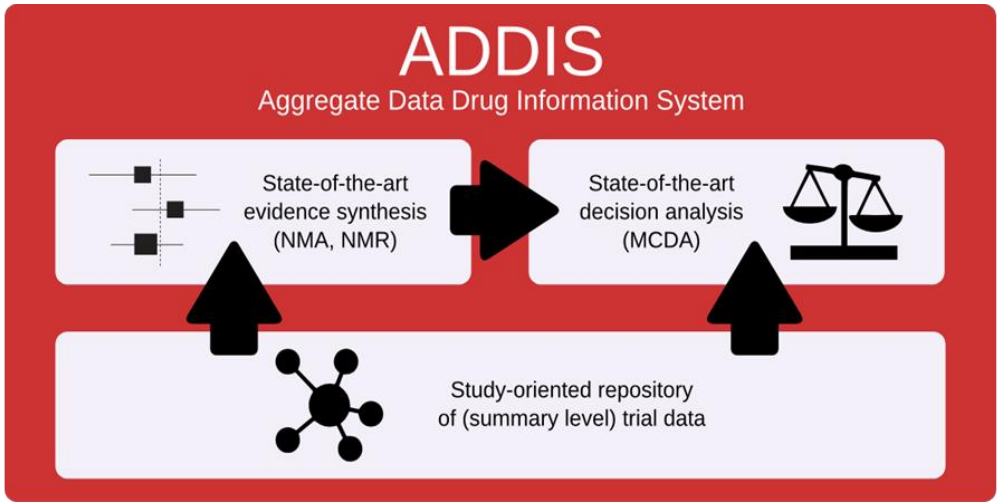
- Approved for marketing authorization by the FDA but not by EMA
- Presented evidence: EMERGE and ENGAGE trials
  - Randomised, double-blind, placebo-controlled trials
  - ~3000 individuals in the early stage of AD (MCI)
  - Outcomes:
    - Scores of cognition and ability to perform daily activities (e.g., CDR- sum of boxes, MMSE)
    - Change from baseline in amyloid PET and in plasma p-tau (subgroup of the population)
  - Halted based on futility analyses (50% of the patients)
  - The results of the full sample showed a (modest) effect for the primary and secondary endpoints for one of the studies
  - Side effects: ARIA-E and ARIA-H

Software implementation

umcg

TI PHARMA

project escher



imi Innovative Medicines Initiative

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Get Real

More info @ www.drugis.org

Conclusions

- Structured frameworks are important to govern B-R assessment process and to ensure transparency, consistency and quality of the decision
- BR analysis should take into account not only all clinical evidence, benefit-risk trade offs and thresholds but also the preferences and risk attitude of decision makers
- Understanding regulator and other stakeholder preferences regarding treatment outcomes improves the communication of regulatory decisions to health care policymakers, prescribers and patients
- What is the future going to bring us?

www.umcg.nl

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