

Benefit-risk decisions in the licensing of medicines

Current EU practice and challenges

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Agenda

- **Split responsibilities in the EU**
- **Present licensing of medicines in the EU**
 - Principles
 - Limitations
- **Future development of benefit risk decisions in the licensing of medicines**



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Responsibilities in the EU - Licensing



44 national authorities

24 official languages

501 mio inhabitants

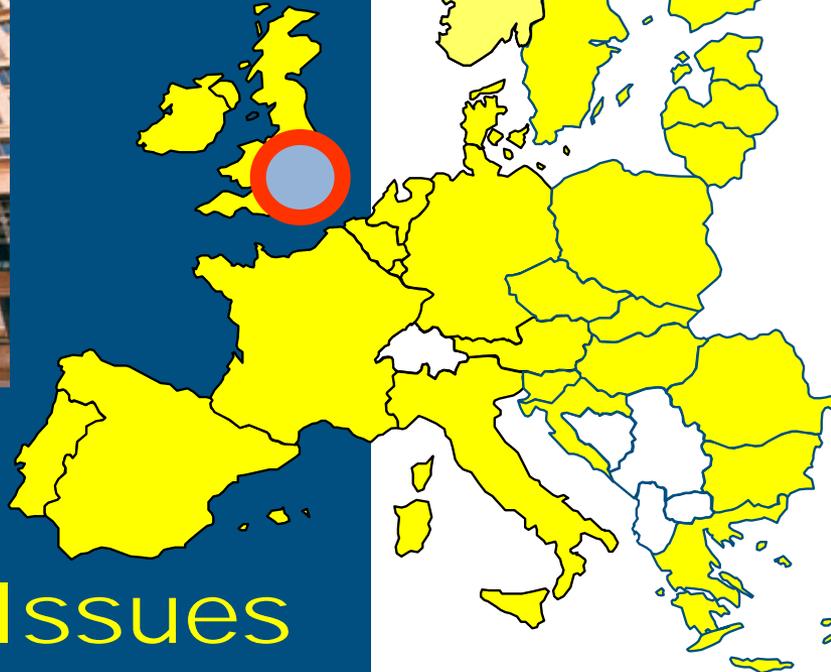
28 member states

National authorisations, MRP, DCP

Generic

Innovative

Responsibilities in the EU – Post Licensing



Safety Issues

National or regional
decision makers

24 official
languages

501 mio inhabitants

28 member states

HTA
and payers

Reimbursement &
Price Decisions

Agenda

- Split responsibilities in the EU
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Benefit-Risk Decisions in Licensing

Scientific Content in Marketing Authorization Application

- **Efficacy: (two pivotal studies)**
 - Superior to placebo or active comparator
 - Non-inferior to active comparator
- **Safety: (preclinical and clinical)**
 - Safety risk must be outweighed by expected benefits
 - Comparison with active comparator important
- **NO economics**
 - prize of product, costs of treatment are **NOT** part of the dossier



Benefit-Risk Decisions in Licensing

Assessment of Marketing Authorization Applications

1. Description of Benefits and Risks

- Benefits

- Beneficial effects
 - Beneficial effects, focussed on but not limited to clinical efficacy
- Uncertainty
 - Impact of supportive data, subgroup differences, assumptions

- Risks

- Unfavourable effects
 - Adverse drug reactions, drug-drug interactions, toxicity profile, potential for misuse, environmental impact
- Uncertainty
 - Trial specifics, e.g. limited no. of patients, above average supervision in trials, non-clinical safety findings



Benefit-Risk Decisions in Licensing

Assessment of Marketing Authorization Applications

2. Value Judgments of Benefits and Risks

- **Assign values**
 - Compare the favourable effects among each other
 - Compare the unfavourable effects among each other
- **Assess the benefit-risk balance**
 - “Evaluation of the positive effects in relation to the risks”
 - Compare and trade-off favourable and unfavourable effects
- **Discuss the benefit-risk balance critically**
 - Impact of uncertainties
 - Values according to perspectives of different stakeholders
 - Need for further studies



Objective Description of Benefits

Example: Efficacy Endpoints in Oncology

- Cure
- Overall survival
- Progression / disease free survival
- These endpoints include both efficacy and safety aspects
- **Not dependent on patients' perception**
- CHMP/205/95 Evaluation of anticancer medicinal products in man Rev.4/ Effective June 2013
- Acceptable primary endpoints include cure rate, OS and PFS/DFS. Convincingly demonstrated favourable effects on survival are, from both a clinical and methodological perspective, the most persuasive outcome of a clinical trial. Prolonged PFS/DFS as such, however, is considered to be of benefit to the patient. ... If PFS/DFS is the selected primary endpoint, OS should be reported as a secondary and vice versa.

Standardized Grading of Risks

- What are the AEs – as reported by patients or doctors
- How frequent are the AEs - as reported by patients or doctors
- How severe* are the AEs – may not reflect patients' perception
 - Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
 - Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL**.
 - Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL***.
 - Grade 4 Life-threatening consequences; urgent intervention indicated.
 - Grade 5 Death related to AE.

* Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

** Instrumental Activities of Daily Living ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

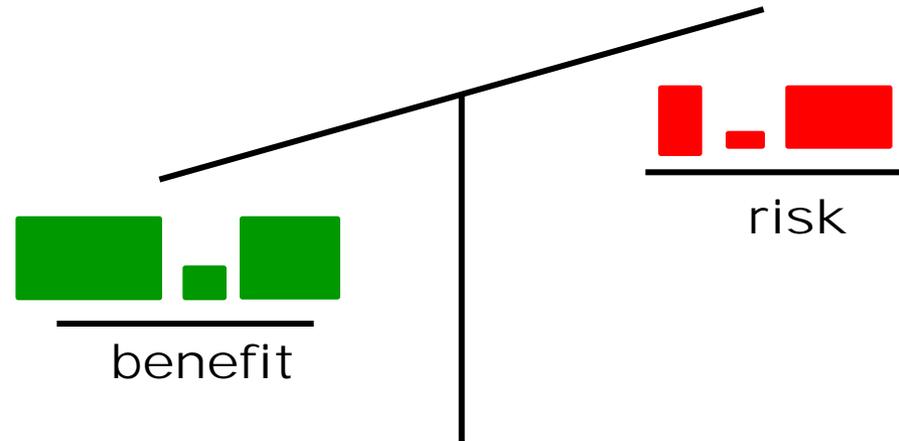
*** Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.



Regulators' Decision versus Treatment Decision

Regulatory decision
for a clearly defined
group of patients or
target population

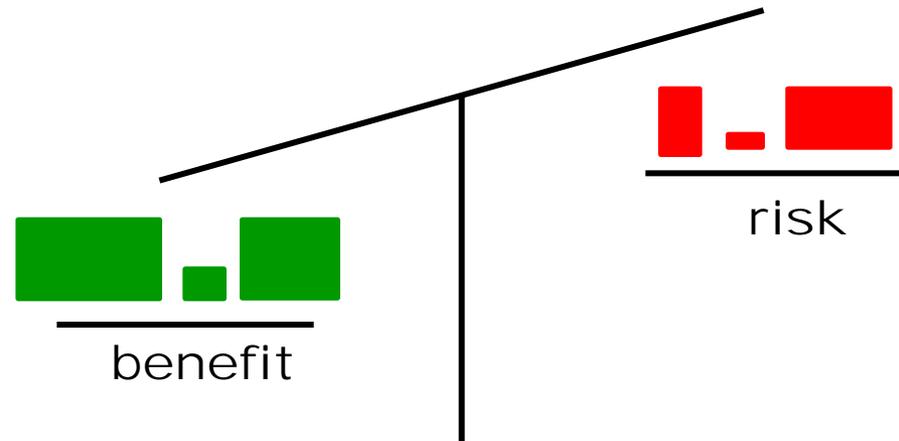
positive



Regulators' Decision versus Treatment Decision

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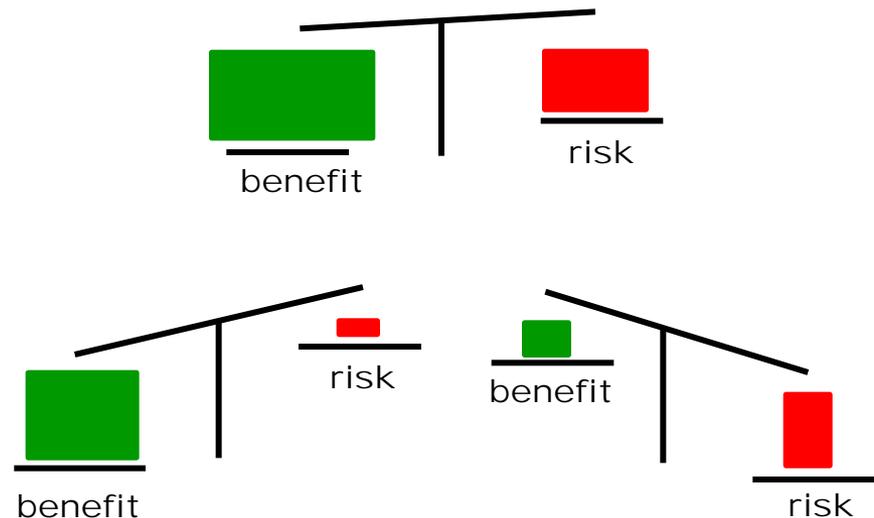
positive



but benefit risk may be negative for individual patients

Treatment decision

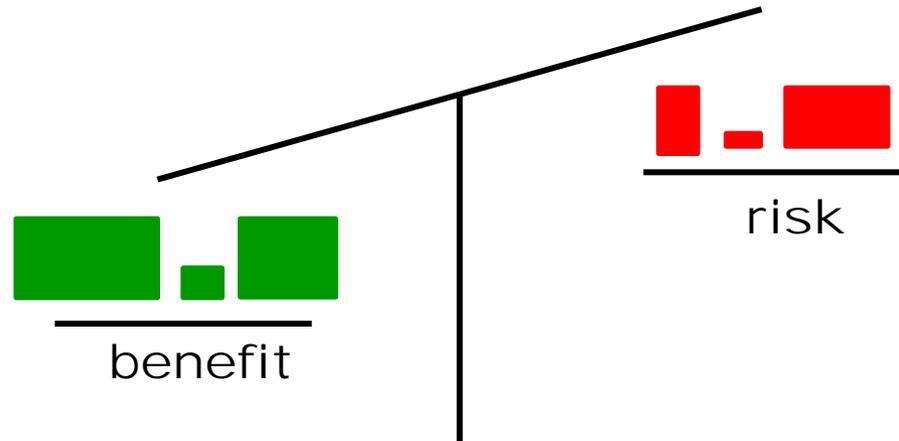
individual patients
depend on **objective findings**
depend on **subjective perception**
or judgment



Decision Based on Objective Findings

Regulatory decision
for a clearly defined
group of patients or
target population

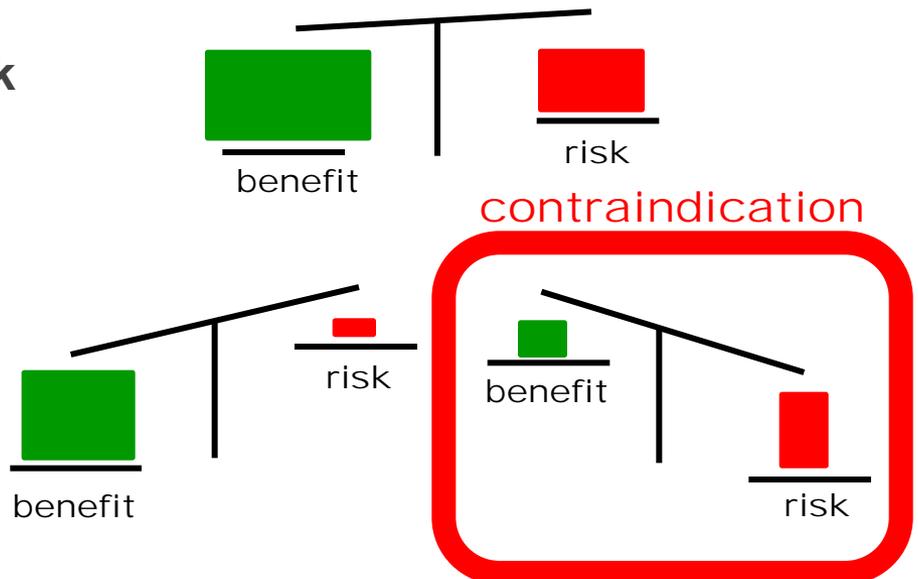
positive



Treatment decision

Objective findings make benefit risk
negative in individual patients

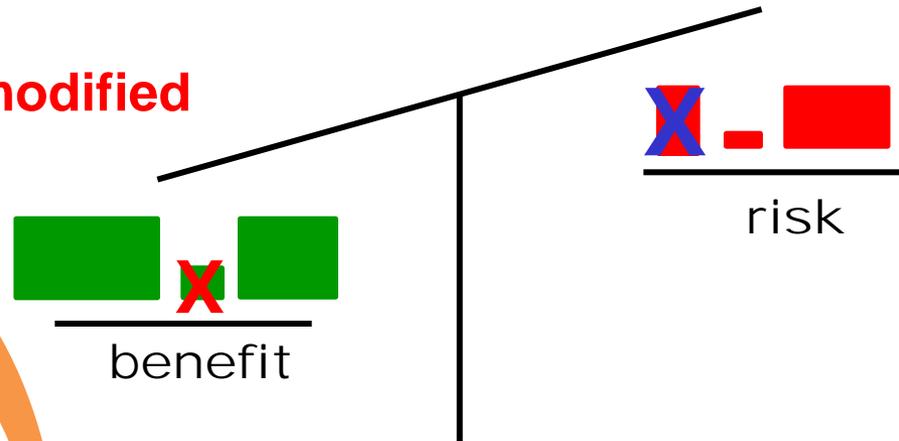
- *If predictable*
treatment must not be started
- modified indication or
contraindication



Decision Based on Objective Findings

Regulatory decision is **modified**
for a **more** clearly defined
group of patients or
target population

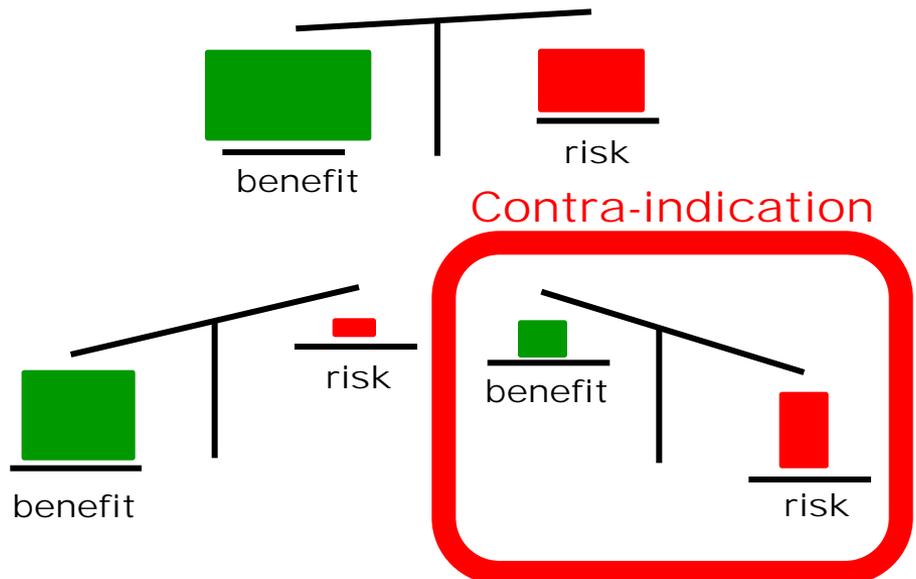
positive



Treatment decision
Objective findings make
benefit risk **negative**
in individual patients

If predictable

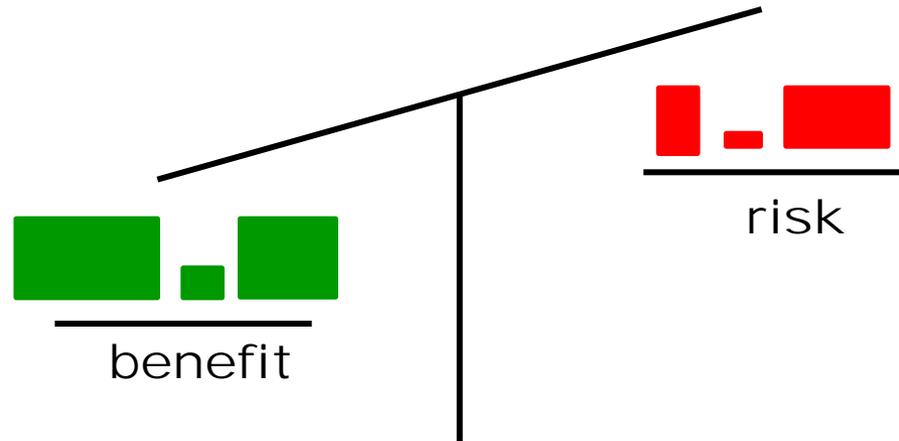
- Do not use product
- modified indication
- or contraindication



Decision Based on Objective Findings

Regulatory decision
for a clearly defined
group of patients or
target population

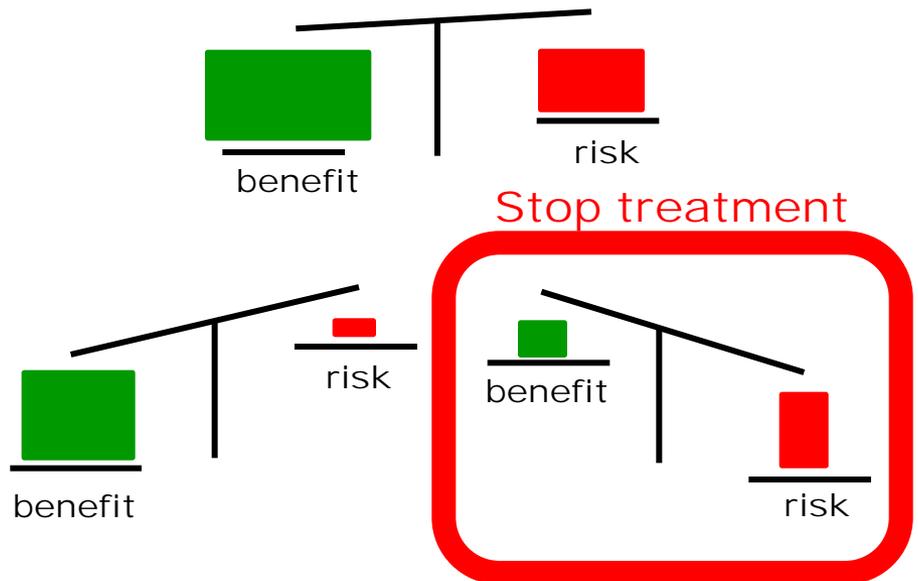
positive



Treatment decision
Objective findings make
benefit risk **negative**
in individual patients

If **NOT** predictable

- Stop treatment when necessary
- Define stopping criteria



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Decision Based on Perception and Personal Judgment

Treatment decision

Individual patients may perceive or weigh benefits and/or risk differently depending on their personal preference



- Treatment decisions may differ from regulatory decisions
- Final decision by individual patients and their physicians (Opt in, Opt out)

Importance of Patients' Perception for Treatment Decisions

Regulators' view :

An increased cure rate in cancer, a potentially life-saving treatment will always outweigh a grade 1 or 2 AE (e.g. (permanent hair loss) - positive regulatory decision

Some patients' view:

This permanent hair loss is important, severe enough for me to decline the potentially curative and life-saving adjuvant therapy – negative treatment decision

“The mastectomy and loss of breast are NOTHING compared to the loss of my hair.”

“Not a day goes by that I don't regret doing the NN (therapy). Oh, if we could only turn back the hands of time!”

“I never, never, never would have agreed to take NN if I was informed of this 6.3% risk; even a 3% risk...or any risk...”

Decision Based on Perception and Personal Judgment

Treatment decision:

Individual patients may perceive or weigh benefits and/or risk differently depending on their personal preference

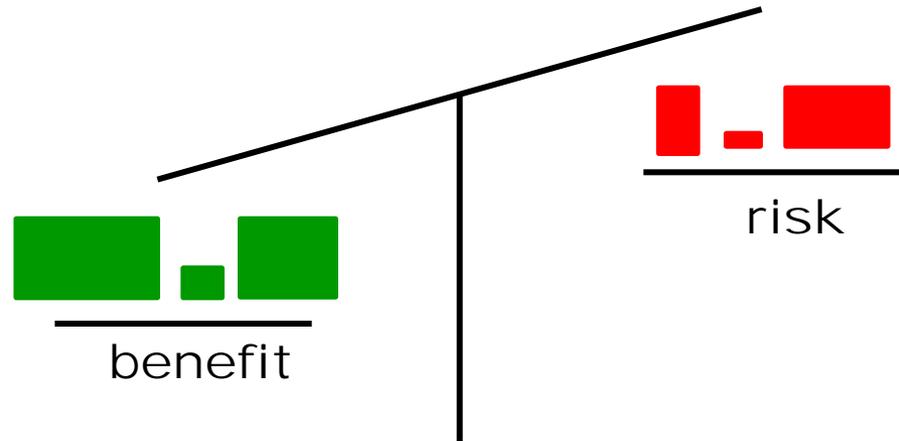


- Treatment decisions may differ from regulatory decisions
- **Final decision by individual patients** supported by their physician (Opt in, Opt out)

Patients' "Opt out" (based on personal judgment)

Regulatory decision
a clearly defined
group of patients
target population

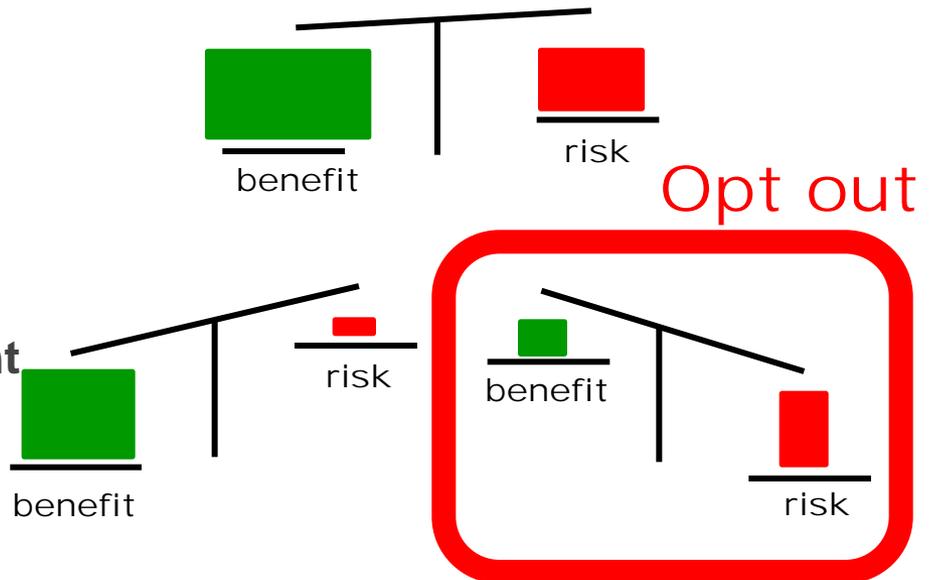
positive



Treatment decision

negative

- Individual patients perceive or weigh benefits and/or risk differently
- Individual preference, judgment and final decision

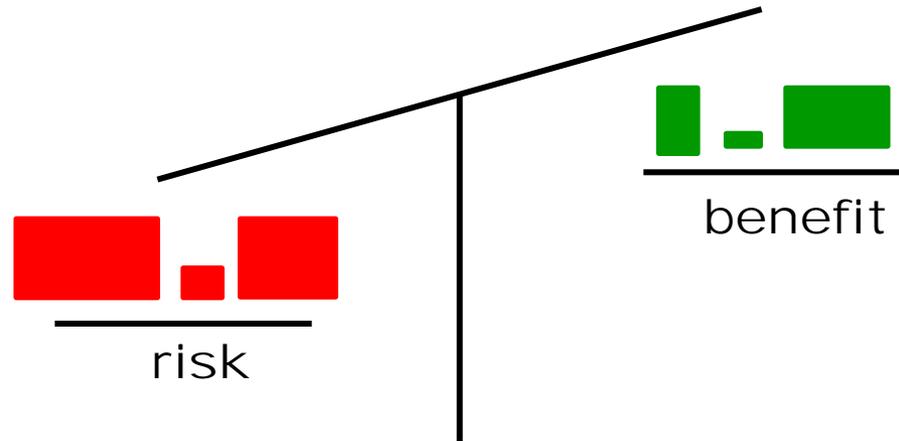


Patients' "Opt in" (based on personal judgment)

Regulatory decision

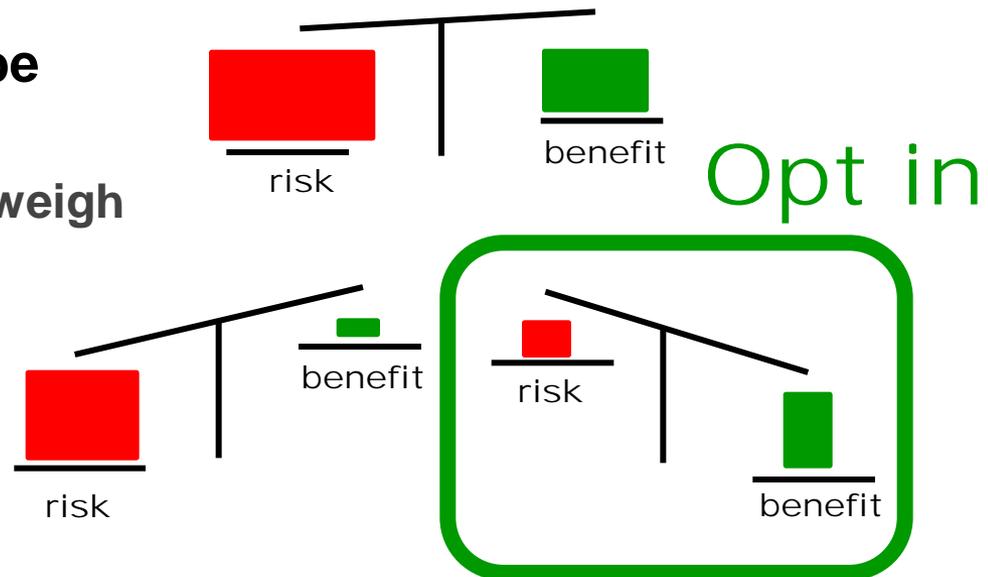
group of patients
target population

negative



Treatment decision would be
positive

- Individual patients perceive or weigh benefits and/or risk differently
- Individual preference and judgment for final decision

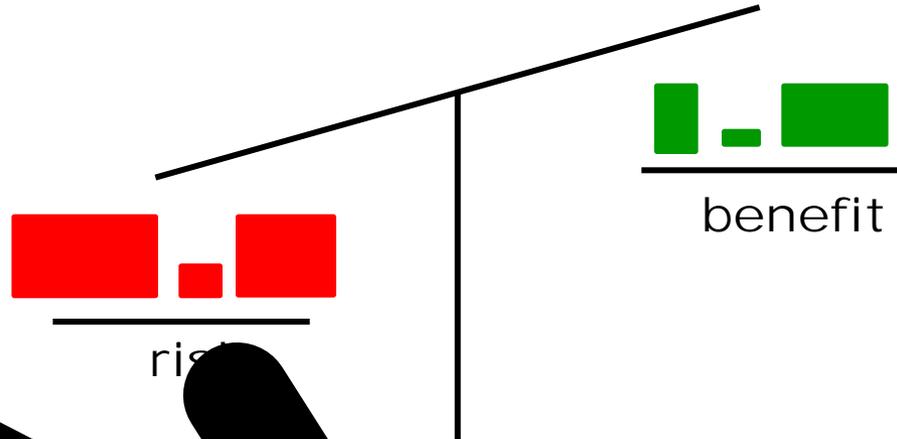


Patients' "Opt in" won't work !

Regulatory decision

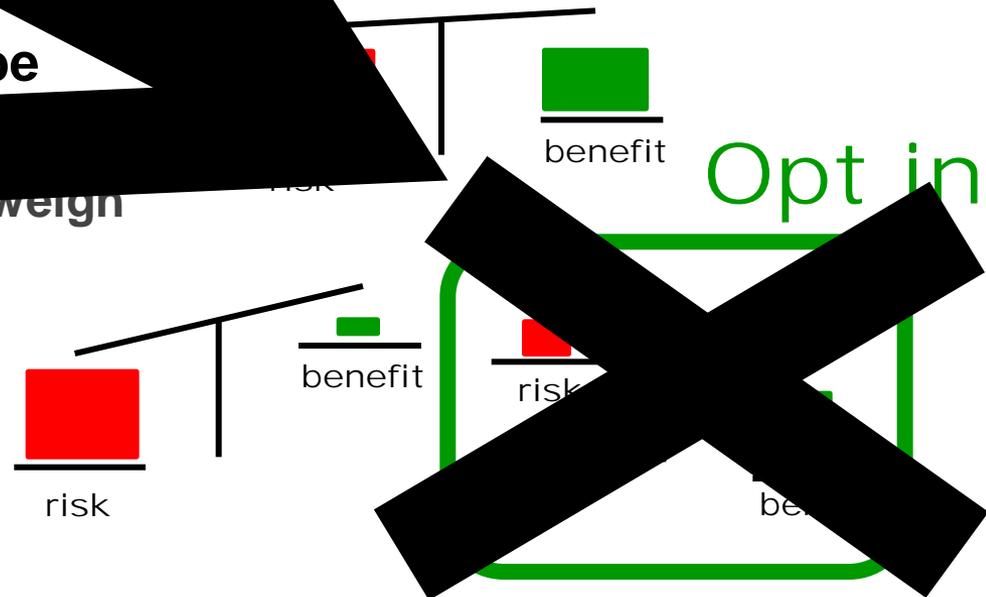
group of patients
target population

negative



Treatment decision would be positive

- Individual patients perceive or weigh benefits and/or risk differently
- Individual preference and judgment for final decision



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Important Steps for New Medicines

milestone	clinical development	marketing authorization	price and reimbursement	treatment decision
decision maker	industry investors	regulators (EUC, NCA)	HTA bodies payers	physicians patients
rationale for decision	economic success expected	evidence of positive benefit-risk	evidence of acceptable cost-effectiveness	individual benefit expected



Important Steps for New Medicines

milestone	clinical development	marketing authorization	price and reimbursement	treatment decision
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rationale for decision	economic success expected	evidence of positive benefit-risk	evidence of acceptable cost-effectiveness	individual benefit expected

- **Marketing Authorization is but one stepping stone from bench to bedside**
- **Sequential decisions: usually positive decision for earlier milestone necessary for decision on next milestone**



Developing Role of Regulators (PURR)

- **P**rovide the first impartial assessment of benefit-risk
 - Description of benefits and risks (strengths and weakness)
 - Judgment on benefit risk balance
- **U**nderstand their assessment as a stepping stone for subsequent decisions
 - Give rationale for judgment / decision
 - Comprehensible and useful for non-regulators
- **R**espect (and give room for) divergent value judgments
 - From social communities (HTA bodies, payers)
 - From individuals (patients and physicians)
- **R**emember the common ultimate goal
 - Benefit the (individual) patient



Thank you for your attention!

