Benefit – Risk Assessment,
Corner stone of the evaluation of (new) products

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CLINICAL RESEARCH TRAINING

Disclaimer

- Although I have been a member of the CHMP, my presentation might not be the view of the CHMP, the European Medicines Agency (EMA), the Belgian Medicines Commission, neither of the Vaccine Working Party.

- My presentation is a personal viewpoint and binds in no way the organisations mentioned before.

Declaration of interest

I have signed consultancy contracts with more than 100 organisations and companies under which

- WHO
- B&MGF
- Universities of Antwerp, Ghent, Leuven, Namur, Brussels, Paris, Lausanne, Köln, …
- Big pharma
- Medium pharma
- Small pharma

Preamble – the regulators' task

Confronted with the complexity of registration dossiers, regulators have been "realistic" and have relied on "value" judgments

→ The basis and process of the regulatory decisions are mostly implicit

There is/was no agreed approach on methodology
for B/R assessment
Much was based on "gut feeling"

Preamble – the regulators' task

A part of this "objectivation of value judgement" (**but not all**) is linked to the increased concern about risk
(cf. highly publicised drug withdrawals)

Risk aversion or risk awareness?
(pointless debate)

And our society has shifted towards the individual concern:

- My child should be vaccinated with a vaccine without any AE.
- What is my benefit, if I get a vaccine, and not what is the benefit for the population…

The regulatory paradox

- Protection of the user/patient
  - Incidents from the past
  - Need for rules for public health for criteria for
    - Quality
    - Efficacy
    - Safety
    - Risk Management
  - Declaration of Helsinki: regulation of Clinical Trials
- Promotion of the availability of indispensable medicines

The regulatory paradox

Elixir Sulfanilamide case

- Diethyleen Glycol (DEG), organic solvent
- Used in a solution of sulfanilamide → Elixir Sulfanilamide, cause of 107 deaths in US in 1938
- Reason to implement the FDA Federal Food, Drug and Cosmetic Act (1938)

The regulatory paradox

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Thalidomide

- Between 1957 en 1961 in ± 50 countries sold under at least 40 different names
- Indication: nausea and insomnia for pregnancy
- Between 1956 en 1962: ± 10.000 children with focomelia
- Impact in US limited, FDA did not approve the use due to limited safety data

IABS

Vaccine Advice

History (1)

1992: CIOMS working group II in :

- "regular, systematic review of global safety data available to the MAH"

1993: Implementation in the EU (Council Directive 93/39/EEC)

1995: From now required!

1996: ICH Guideline E2C, Clinical Safety Data Management: periodic Safety Update Reports for Marketed Drugs

- intended to harmonise the periodic reporting requirements to regulatory authorities and to provide, in a common format, the worldwide interval safety experience of a medicinal product at defined times post-approval

But all this seemed not to be efficacious enough to obtain the data on safety of medicinal products

History (2)

This led to new initiatives after several “cases”

- E.g.: Fen-Phen: obesitas treatment led to valvulopathy with a significant mortality

2012: Implementation of B/R of PSUR: request for
PBRER: Psur Benefit Risk Evaluation Report

Indeed the only way forward:

- Medicines are evaluated on their benefits and their risks at registration
- Thus it seems obvious to put the PSUR in the same context:
  - First, what is the relevance of an ADE?
  - What is the Observed versus Expected equation?
    - Do we know the incidence of a given disease (e.g. intussusception…)
  - If there is an increase of incidence, what is the causality?
  - Weighting the benefits against the observed risk...

History (3)

However....

- **What is the benefit of a vaccination against a disease that has disappeared or almost disappeared (polio, HiB, tetanus, HepB in US/EU and other countries, ...)**
  - **If there is an increase of incidence of AE, causality?**
  - **Weightening the benefits against the observed risk...**

Sources

ICH

- **PERIODIC BENEFIT-RISK EVALUATION REPORT (PBRER) E2C(R2)**
  - http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2C/E2C_R2_Step4.pdf

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

PERIODIC BENEFIT-RISK EVALUATION REPORT (PBRER)

E2C(R2)

1. INTRODUCTION

The Periodic Benefit-Risk Evaluation Report (PBRER) described in this Guideline is intended to be a common standard for periodic benefit-risk evaluation reporting on marketed products (including approved drugs that are under further study) among the ICH regions.

This Guideline defines the recommended format and content of a PBRER and provides an outline of points to be considered in its preparation and submission.

Definitions of many technical terms used in the Guideline are included in a glossary (Appendix A); the first mention of a term in the Guideline is identified with an asterisk (*).

Sources

ICH

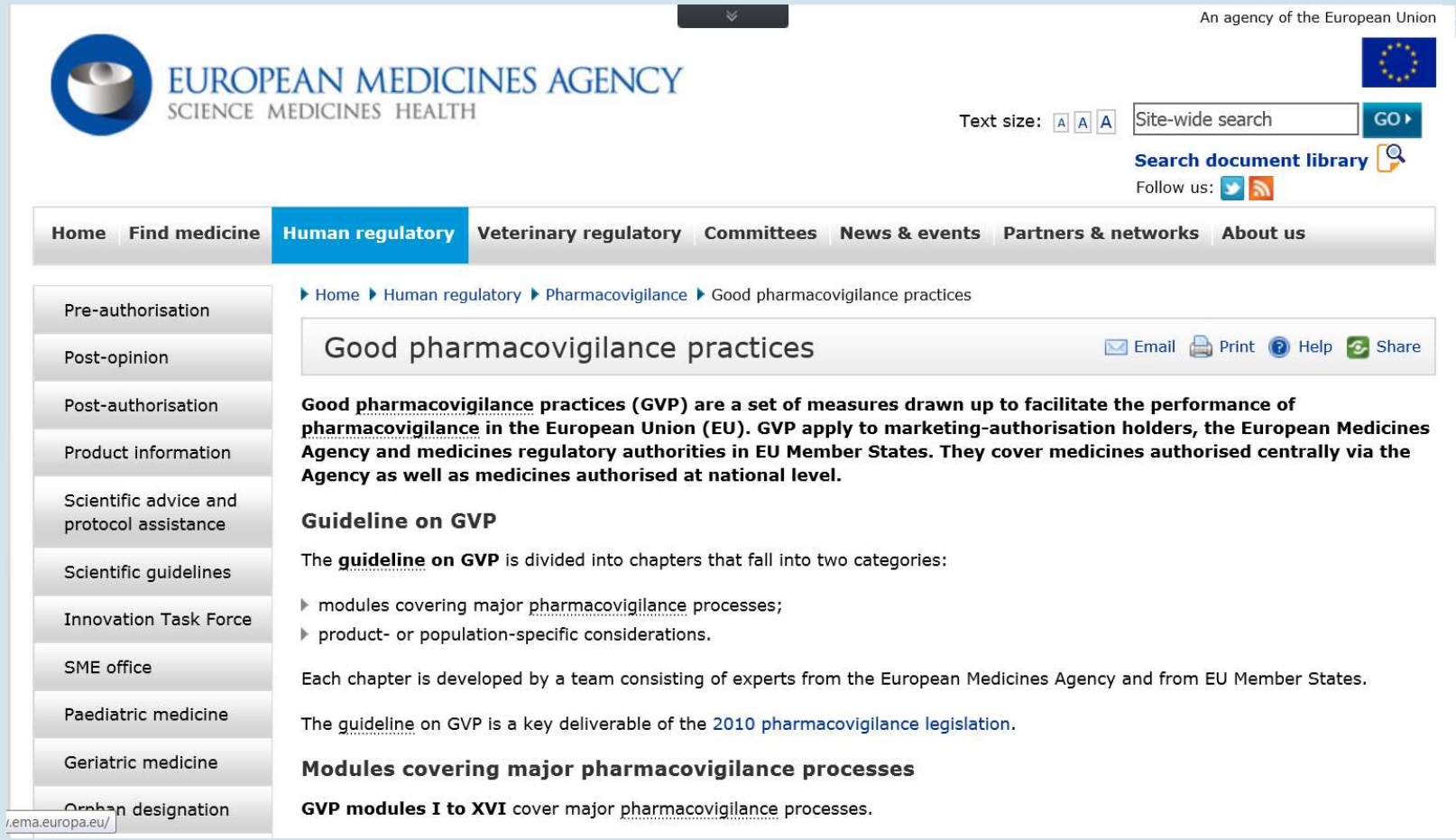
- PERIODIC BENEFIT-RISK EVALUATION REPORT (PBRER) E2C(R2)
  - http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2C/E2C_R2_Step4.pdf

EMA

- Guideline on good pharmacovigilance practices (GVP)

  Module VII – Periodic safety update report
  - http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c



Sources

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- PERIODIC BENEFIT-RISK EVALUATION REPORT (PBRER) E2C(R2)
  - http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2C/E2C_R2_Step4.pdf

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- Guideline on good pharmacovigilance practices (GVP)

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  - http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c
- Guidance document on the content of the <Co-> Rapporteur day 80 critical assessment report
  - http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004800.pdf

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Guidance document on the content of the <Co-> Rapporteur day 80 critical assessment report

Overview and list of questions

<Invented name>

<(Active substance)>

EMEA/H/C/<xxx>

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004800.pdf

Definition of Benefit/Risk (B/R)

Benefit: proven therapeutic good
Risk: probability of harm being caused

Benefit & risk are evaluative terms
(contain value judgments)

⇒B/R ***balance*** is more accurate than ratio

B/R assessment is complex

Definition of Benefit/Risk (B/R)

How to define a Benefit for vaccines?

- **Ideally:**
  - ❑ Infection prevention: once vaccinated you don't spread the disease
- **But real world**
  - ❑ Disease prevention: once vaccinated you don't get the disease
  - ❑ Complication prevention: a percentage of vaccinnees get ill, but:
    - No hospitalisation, intensive care, deaths,…
- **E.g. Polio:**
  - ❑ OPV (oral polio vaccine): gives local mucosal immunity: prevents infections
  - ❑ IPV (IM polio vaccine): disease prevention (no myelitis), but shedding, poor mucosal immunity, and the possibility to spread the virus…

Definition of Benefit/Risk (B/R)

How to define a Benefit for vaccines?

- **How to measure the effect, or how to translate disease prevention in primary parameter:**

In clinical trials, a surrogate endpoint (or surrogate marker) is a measure of effect of a specific treatment that may correlate with a real clinical endpoint but does not necessarily have a guaranteed relationship. The National Institutes of Health (USA) defines surrogate endpoint as "a biomarker intended to substitute for a clinical endpoint"

Correlates of immunity/protection to a virus or other infectious pathogen are measurable signs that a person (or other potential host) is immune, in the sense of being protected against becoming infected and/or developing disease.

For many viruses, antibodies and especially neutralizing antibodies serve as a correlate of immunity. So for example, pregnant women are routinely screened in the UK for rubella antibodies to confirm their immunity to this infection which can cause serious congenital abnormalities. In contrast for HIV, the simple presence of antibodies is clearly not a correlate of immunity/protection since infected individuals develop antibodies without being protected against disease.

Definition of Benefit/Risk (B/R)

How to define a Benefit for vaccines?

- How to measure the effect, or how to translate disease prevention in primary parameter:
  - Hepatitis B, due to vaccination: endemicity is gone down: disease prevention is not an option as outcome for a clinical trial, thus
    - Surrogate of protection: Ab concentration, (strange: no CMI parameter)
    - For Hep B it is written in stone: a concentration above 10 IU/L = long live protection
  - Influenza: Influenza like Illness (ILI PCR proven) is the standard: no Ab standard is available for the time being
  - Haemophilus Influenza:
    - 2 cut-off 1,0 and 0,1

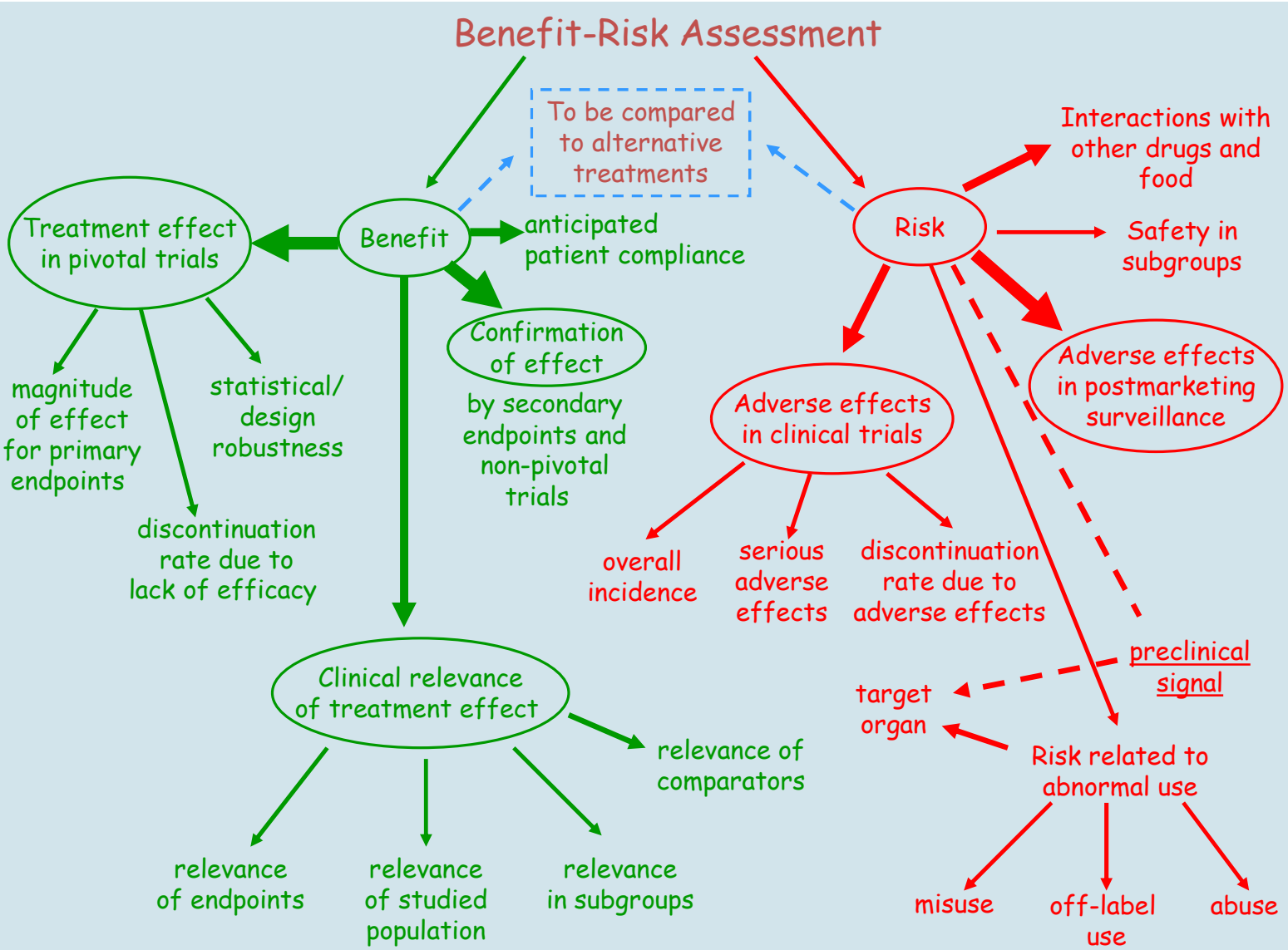
Preamble – the regulators' task

The new CHMP assessment report template for B/R

1. Describe B&R **in the specific therapeutic context**
2. Describe amount, reliability and **accuracy** of available evidence
3. Be explicit about the **perspectives of the various stakeholders**, in particular patients and treating physicians
4. State the benefits in a way that is comparable to the risks – **avoid relative expressions of B&R**. Define the **level of risk acceptability** corresponding to the perceived degree of clinical benefit (in the specific context).
5. Describe how the B/R balance may vary across different factors (**ex. patient characteristics**)
6. Discuss the sensitivity of the B/R balance assessment to different assumptions (ex. "**worst case scenario**")

https://www.ema.europa.eu/en/about-us/support-research/benefit-risk-methodology

https://www.ema.europa.eu/documents/template-form/day-80-assessment-report-overview-d120-loq-template-guidance-rev-1019_en.docx


Benefit-Risk Assessment
To be compared to alternative treatments
Benefit
Treatment effect in pivotal trials
magnitude of effect for primary endpoints
statistical/ design robustness
discontinuation rate due to lack of efficacy
anticipated patient compliance
Confirmation of effect
by secondary endpoints and non-pivotal trials
Clinical relevance of treatment effect
relevance of endpoints
relevance of studied population
relevance in subgroups
relevance of comparators
Risk
Interactions with other drugs and food
Safety in subgroups
Adverse effects in clinical trials
overall incidence
serious adverse effects
discontinuation rate due to adverse effects
Adverse effects in postmarketing surveillance
preclinical signal
target organ
Risk related to abnormal use
misuse
off-label use
abuse

Preamble – the regulators' task

This task is extremely difficult. It involves:

1. Uncertainty (re: probability of desirable and undesirable effects, effect size…)
2. Heterogeneity of effects across patient populations
3. Multiple objectives (maximising benefits & minimising risks)
4. Trading off effects of differential importance
5. Differences in **perspectives** (patient, societal, regulatory), ill-defined preferences and utilities of outcomes
6. Lack of agreement on what criteria to use

Preamble – the regulators' task

Excerpts from the CHMP B/R Assessment Template (BRA) (1)

Definition of a benefit = favourable effect

- **Any beneficial effect** for the target population (often referred to as "benefit" or "clinical benefit") that is associated with the product. These commonly include improvements in clinical efficacy but are not limited to efficacy (for example, a reduction in toxicity could also be a favourable effect).

- Describe the beneficial effects themselves **and the uncertainty in the knowledge** about these beneficial effects

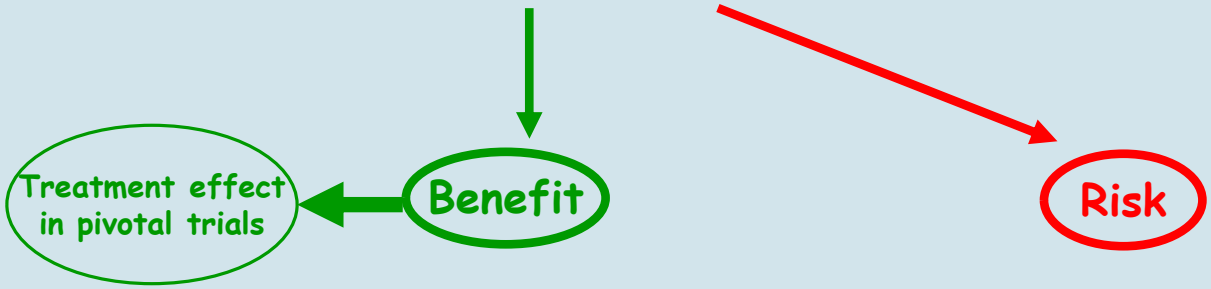
Preamble – the regulators' task

Excerpts from the CHMP BRA Template (2)

Definition of a risk = unfavourable effect

- This would include **any detrimental effects** (often referred to as "risks", "harms", "hazards" both known **and unknown**) that can be attributed to the product or that are otherwise of concern for their undesirable effect on patients' health, public health, or the environment.
- Unfavourable effects are not necessarily limited to safety endpoints. For example, unfavourable effects may also be loss of efficacy on some important efficacy endpoints or other undesirable effect.
- Describe the unfavourable effects themselves **and the uncertainty in the knowledge** about these unfavourable effects

Benefit-Risk Assessment

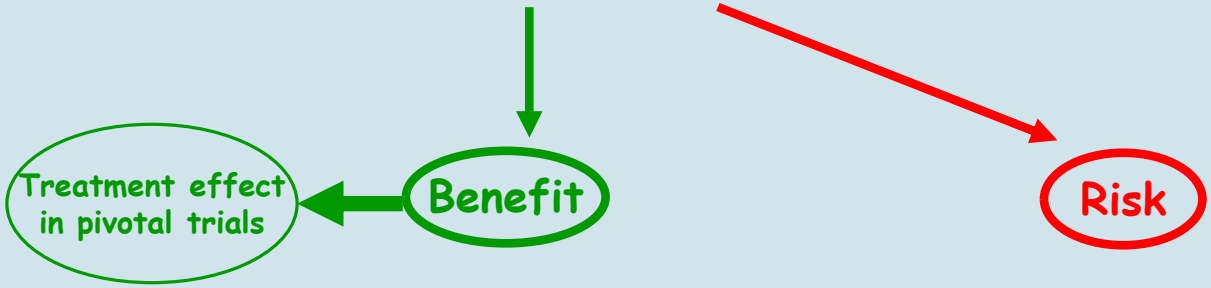


For HPV vaccines:

- Effect ✗ Cancer?

- **Not Ethical**
- **Too expensive**
- **Too long**

Benefit-Risk Assessment

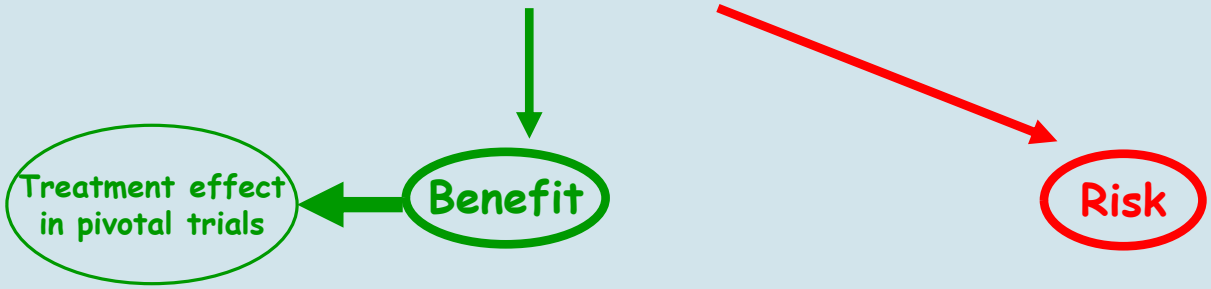


For HPV vaccines:

- Effect ~~=~~ Cancer?
- CIN2+?

- **Not Easy: interpretation bias**
- **Several readers necessary**
- **Frequency rather low**

Benefit-Risk Assessment

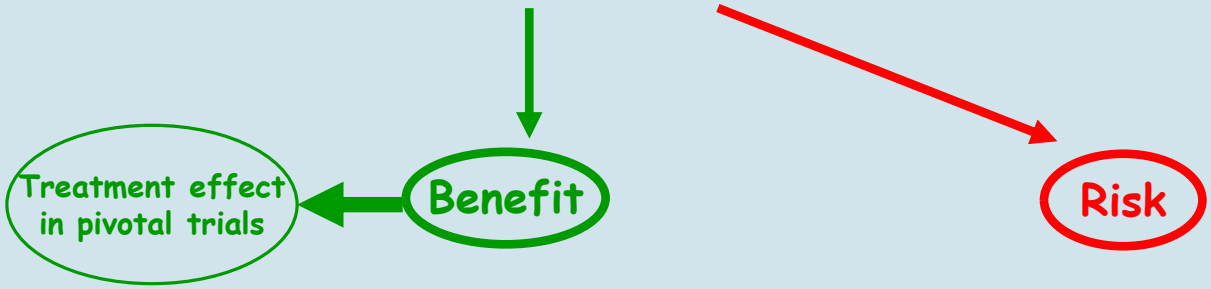


For HPV vaccines:

- Effect ~~s~~ Cancer?
- CIN2+?
- ~~C~~N1

- **Difficult to accept: clearance too high**

Benefit-Risk Assessment

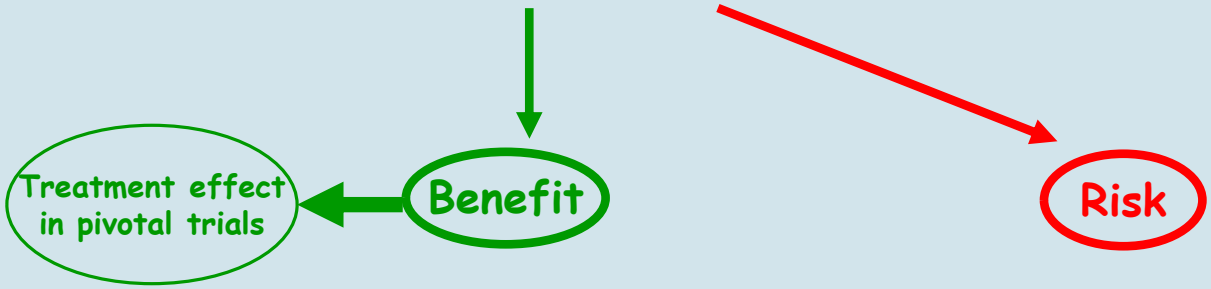


For HPV vaccines:

- Effect on Cancer?
- CIN2+?
- CIN1
- Persistent infection 12 months definition
- Persistent infection 6 months definition

- **Also not very easy to accept**
- **High clearance**
- **Far away from cancer development**
- **But: no infection, no CIN, no cancer**
- **Regulatory paradox: how to accept this**

Benefit-Risk Assessment

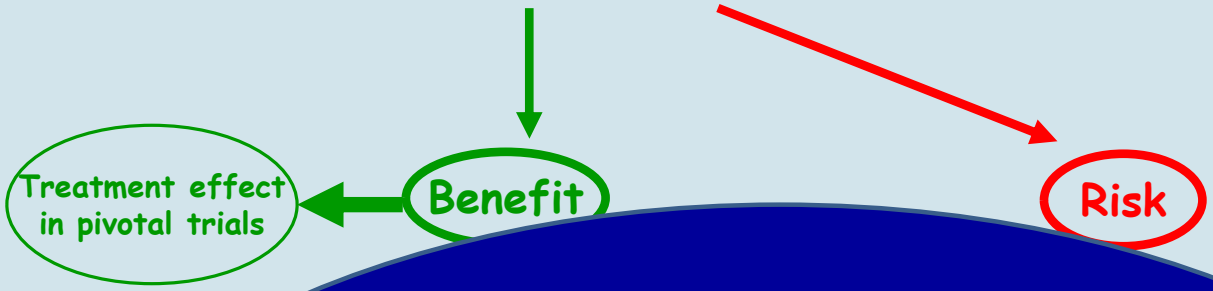


For HPV vaccines:

- Effect on Cancer?
- CIN2+?
- CIN1
- Persistent infection 12 months definition
- Persistent infection 6 months definition
- Immunogenicity, serum Ab levels ?

- **No protective threshold defined**
- **Will serum Ab translate in mucosal protection in utero?**
- **Mechanism of action?**

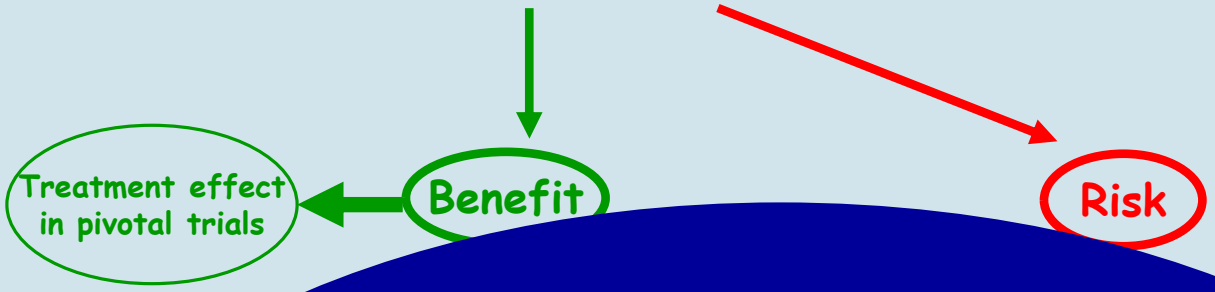
Benefit-Risk Assessment



<u>Uncertainty</u> in the knowledge about the beneficial effects

- **Pooling of data?**
- **Persistence of protection?**
- **Need for a booster?**
- **Comparability of study population and real world**
- **Extrapolation from 18-25 to 9-15**
  - **Higher immunity, and sufficient to be protective 10 years later?**
- **Extrapolation from clinical trial to real life**

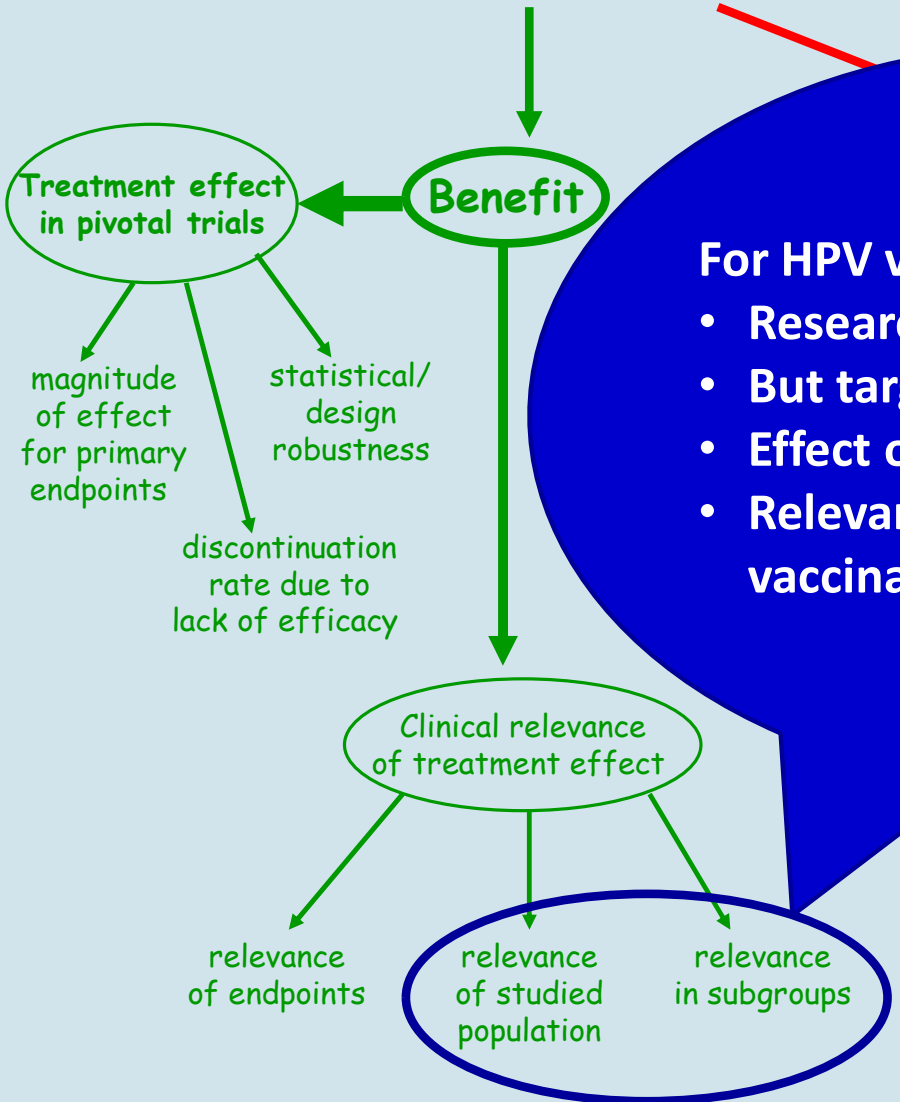
Benefit-Risk Assessment



<u>Uncertainty</u> in the knowledge about the beneficial effects

- Today an additional question (for Cervarix) could be put forward:
  - What is the role of the adjuvant
  - Why is it used?
  - Can the vaccine be used without
  - Why has the licensed competitor no (novel) adjuvant (only Alu)

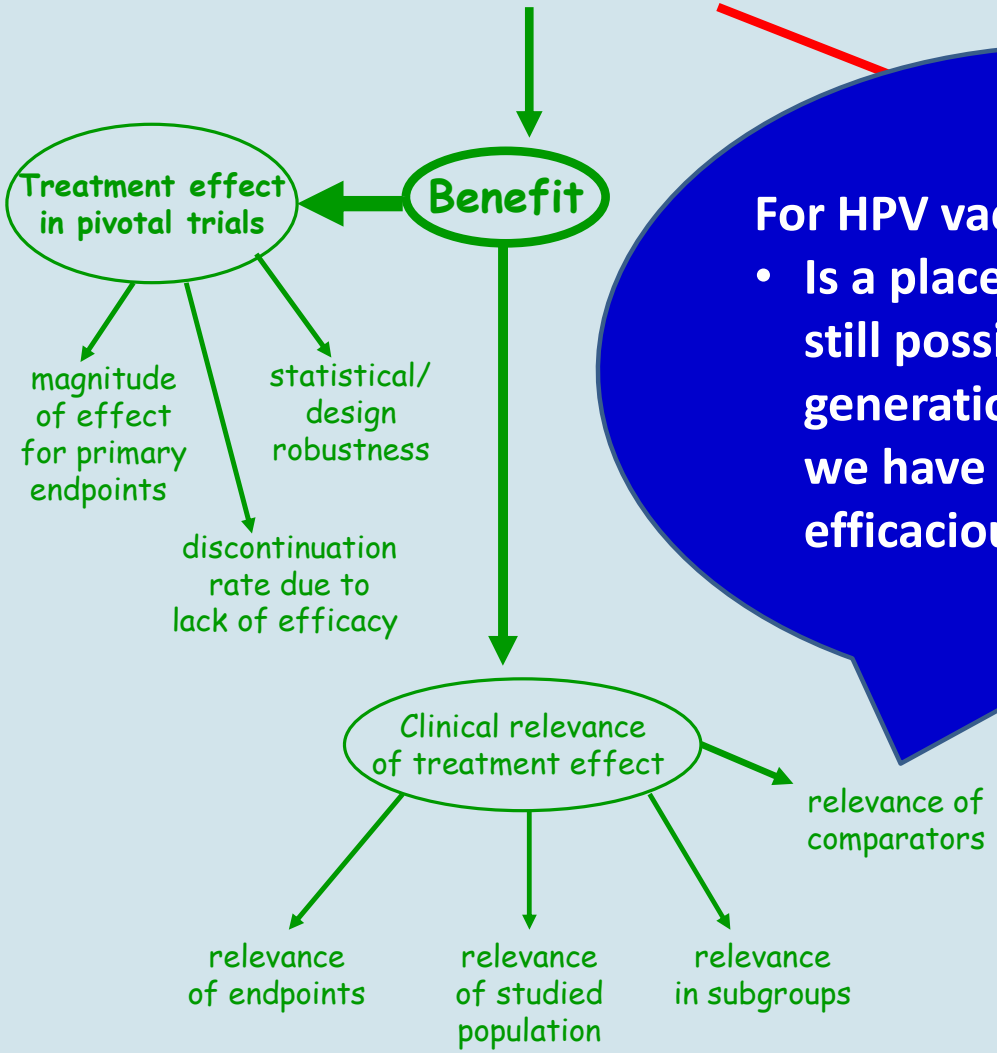
Benefit-Risk Assessment



For HPV vaccines:

- **Research was done on 18-25y**
- **But target is <13 y**
- **Effect on older populations?**
- **Relevance of vaccination of > 45**

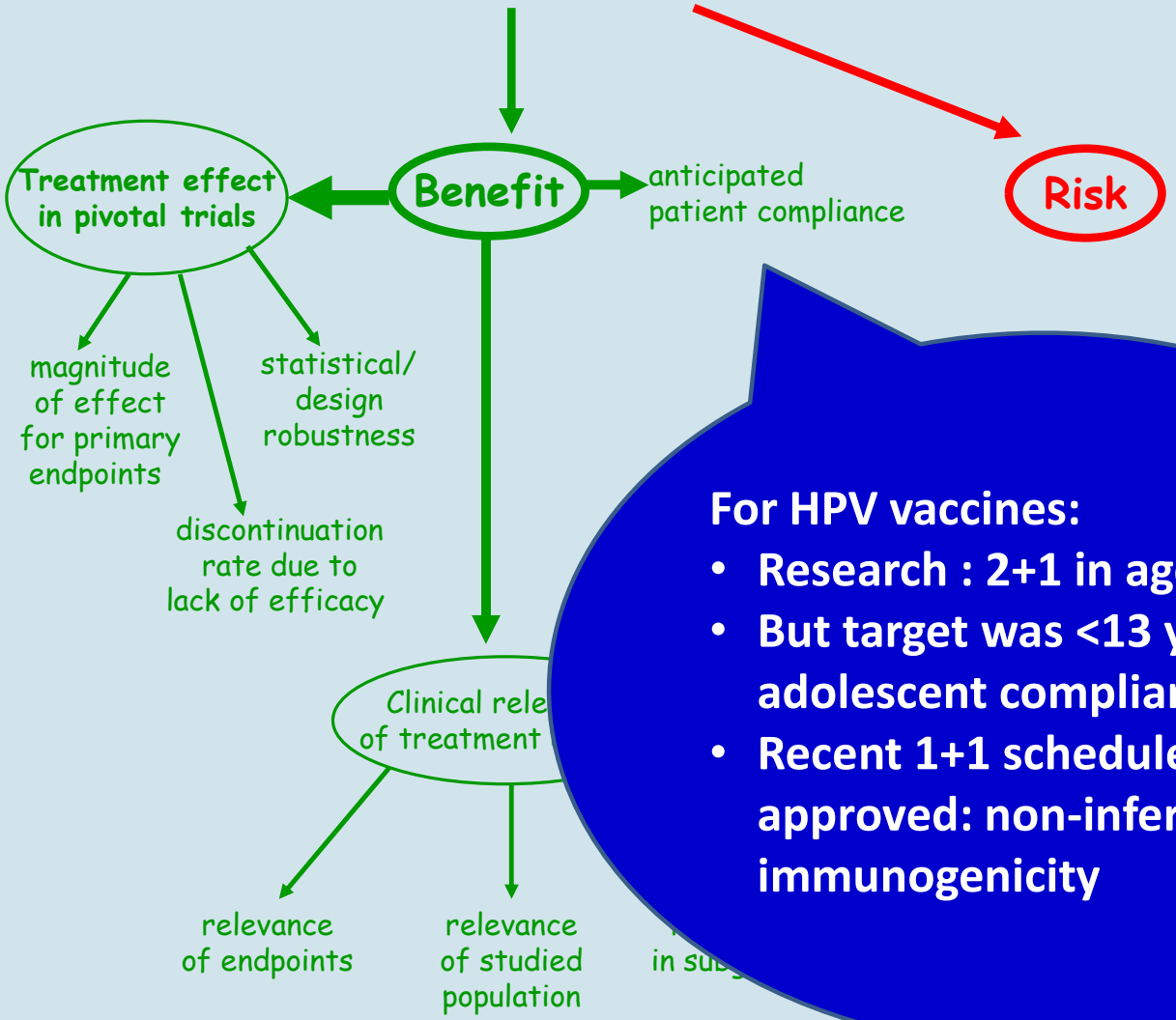
Benefit-Risk Assessment



For HPV vaccines:

- **Is a placebo controlled RCT still possible for the next generation HPV trials given we have 2 highly efficacious vaccines?**

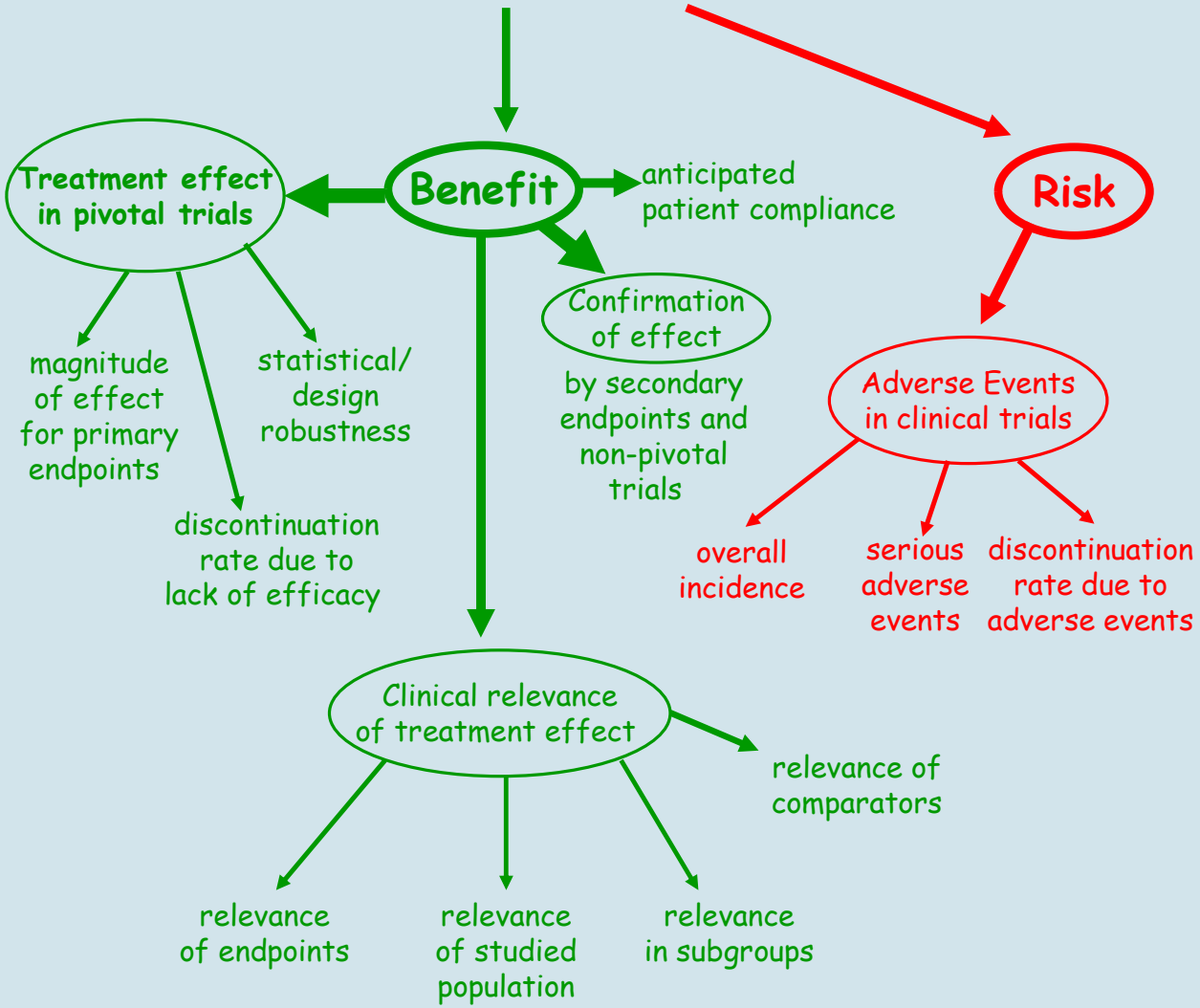
Benefit-Risk Assessment



For HPV vaccines:

- **Research : 2+1 in age 18-25**
- **But target was <13 y adolescent compliance?**
- **Recent 1+1 schedule approved: non-inferiority on immunogenicity**

Benefit-Risk Assessment



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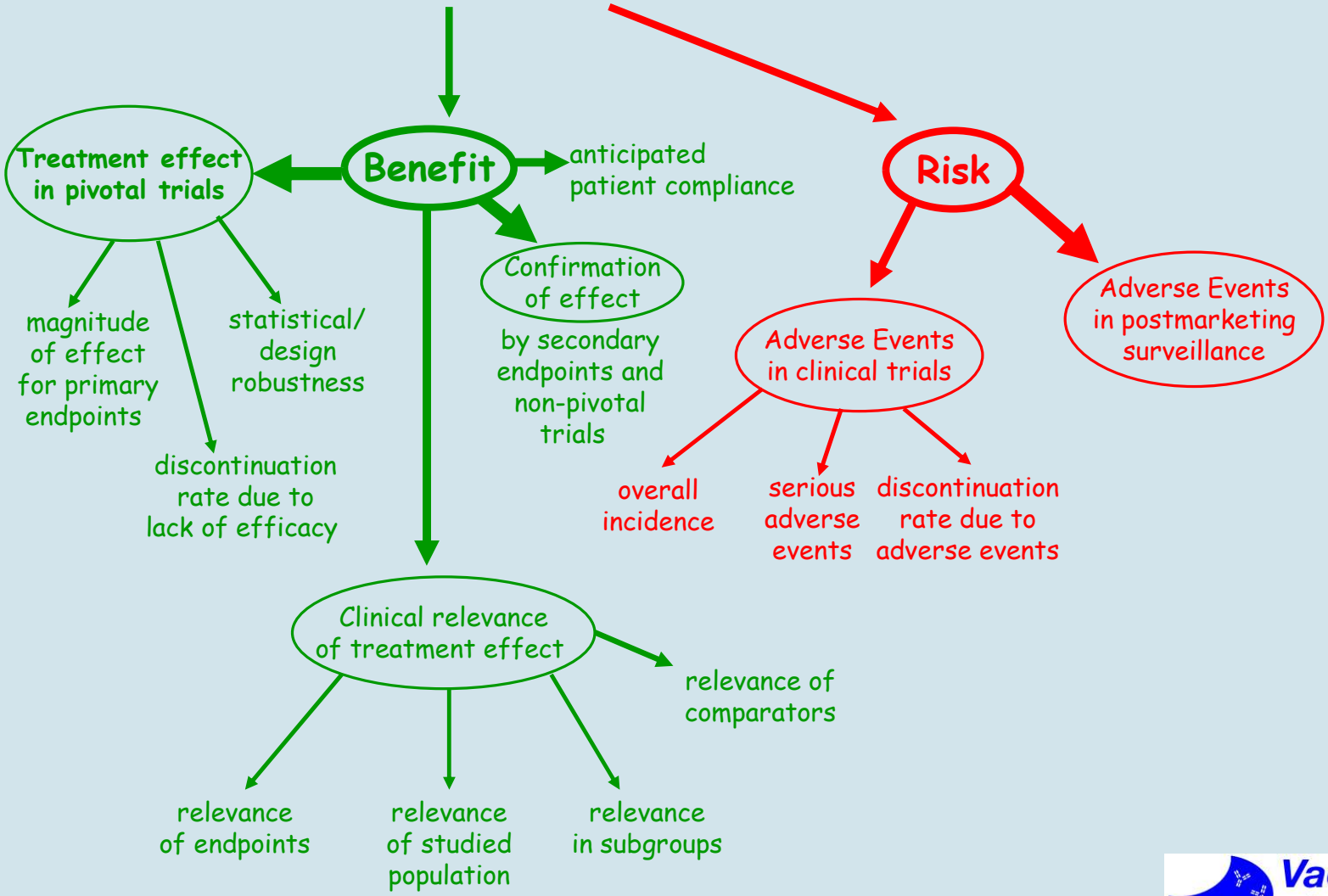


Assessment

For HPV vaccines:
All of a sudden:

THE Sun

Tragic Natalie 'not killed by cancer jab'

By ANDREW PARKER

Published: 30 Sep 2009

Add a comment (48)

TRAGIC schoolgirl Natalie Morton did NOT die as a result of a cancer jab, it was thought last night.

Early tests on the 14-year-old showed she had "a serious underlying medical condition".

Natalie died hours after being given a Cervarix injection as part of a school inoculation programme.

There was chaos last night as some health and schools chiefs suspended vaccinations while the batch used at her school in Coventry was tested.

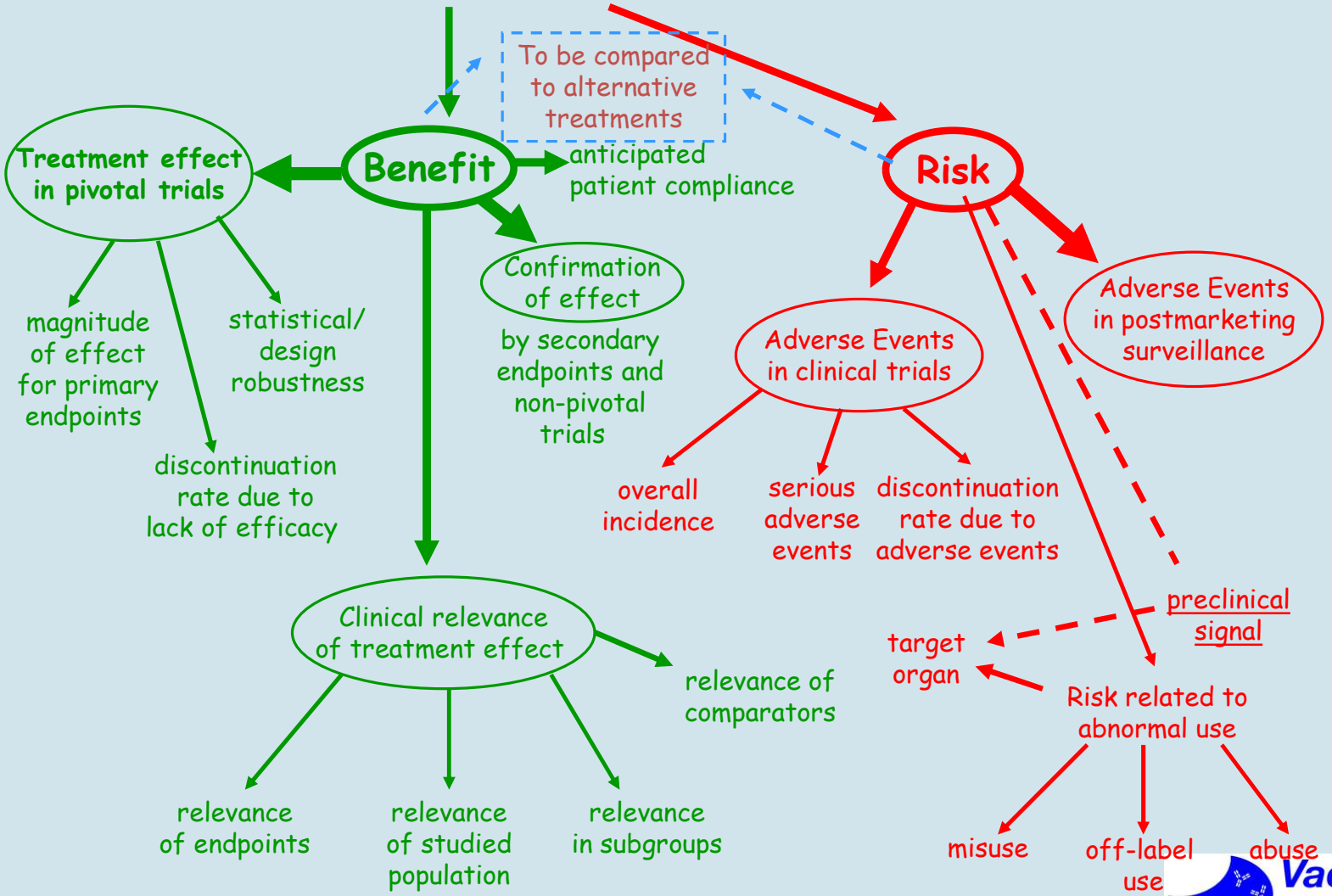
There ARE side-effects that we're NOT being told about

Published: 06 Oct 2009

Add a comment (6)

MUMS are fighting back over the controversial cervical cancer jab being dished out to young Scots schoolgirls.

Benefit-Risk Assessment



B/R: an example, HPV vaccine

Balance

- Importance of favourable
  - +Prevention of an aggressive cancer
  - +Even with high screening program activity: some patients will die
  - +Reduction of secondary burden: early cervical conisation due to CIN lesions may lead to complications in pregnancy
  - +Ongoing screening, decrease of CIN2 &CIN3 lesions
  - +Reduction of psychological burden of being diagnosed with a lesion

B/R: an example, HPV vaccine

Balance

- Importance unfavourable effects
  - Local tolerance: not a big issue
  - SAE from the CT database: not a big issue
  - Effect on auto-immunity: might be of importance, but no data yet
  - Effect on pregnancy: no clear signal from the CT data set

B/R: an example, HPV vaccine

Balance

- Importance of favourable and unfavourable effects
- Benefit-risk balance
  - ✓ In the absence of clear SAE
  - ✓ With a high potential of efficacy
    - Prevention of infection
    - Prevention of CIN lesions
  - ✓ Knowing the uncertainties
    - Will efficacy be translated in effectiveness: prevention of cancer
    - Large scale use: what will be the occurrence of SAE

➔ Balance is felt to be positive

Conclusions

Benefit / Risk Balance

- Is a continue process
- Needs to be repeated when new data become available
  - ✓ New data on benefit
  - ✓ New data on risks
  - ⇒ B/R evaluation is important even if the benefit is forgotten due to disappearance of the disease
- Stays a very difficult exercise knowing that for many AE the causal relationship is not known…

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Thank you for your attention!

Questions?

IABS

Vaccine Advice