Vaccine Advice

Introduction to Clinical Benefit-Risk Assessment for the evaluation of (new) medicinal products

Pieter Neels, MD

Independent Regulatory Expert
Chair of the Human Vaccine Committee of IABS

Ex- CHMP member for Belgium

Ex- Vice-chair VWP (EMA)

Disclaimer

- Although I have been a member of the CHMP, my presentation might not represent the views 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.

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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

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Part 1: Context and Historical Background Information

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Context and Background Information (1)

- Regulation of medicinal products for human use has been developed in the past century.
- In the past, many regulatory decisions to license a new product have been based only on available clinical trials data.
- However, lessons learnt from public health incidents over the post-licensure period showed that clinical data is often limited at the time of licensure and therefore commitments to monitoring of rare serious adverse events in the post-marketing period, in large populations, became a requirement for licensure.
- Such monitoring programmes focused mostly on safety.

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Context and Background Information (1)

Example 1 Smallpox

- **Would the smallpox vaccine be licensed in 2022 knowing the AE data today:**

Historically, for every 1 million primary vaccine recipients, there would be approximately 5 to 10 persons with adverse reactions serious enough to require hospitalization and 1 or two deaths. In the absence of smallpox (or other poxvirus) exposure, these risks are unnecessary. However, they pale in comparison with those encountered during a smallpox epidemic. In fact, a smallpox outbreak with 1 million cases among an unvaccinated population would result in hundreds of thousands of deaths and long-term sequelae (blindness, limb deformities, facial scarring, and depigmentation) among the majority of the survivors.

Plotkin's Vaccines 7th edition 2015

⇒ **Thus in a scientific B/R analysis we look at the prevention of more than 100,000 deaths per million compared to 1-2 deaths due to vaccination.**

⇒ **B/R is still highly positive, however knowing the COVID-19 pandemic polemic on vaccine safety, which politician would take the decision today?**

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Context and Background Information (1)

Example 2 RotaShield

- **Rotashield was licensed in the US 08/1998, after commercialising a link with intussusception was found:**

> **Intussusception from all other causes is most common among infants in the first year of life; 1 child in 2,000 children to 1 child in 3,000 children is affected before one year of age. Based on the results of the investigations, CDC estimated that 1 or 2 additional cases of intussusception would be caused among each 10,000 infants vaccinated with RotaShield® vaccine.**
>
> ***https://www.cdc.gov/vaccines/vpd-vac/rotavirus/vac-rotashield-historical.htm***

⇒ **Thus in a scientific B/R analysis we look at the prevention of a treatable disease (diarrhea), while the vaccination could give a SAE, potentially life-threatening.**

⇒ **B/R in HIC's was evaluated as negative,… however in LMIC's where the disease might be related to a high mortality the B/R might be positive**

⇒ **Is it possible to license a vaccine in a LMIC, when the HIC's have refused the vaccine?**

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Context and Background Information (2)

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 was no agreed approach on the methodology for B/R assessment until the publication of ICH E2C*, in 1996
Prior to that, much was based on "gut feeling".

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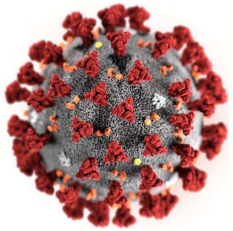
* https://www.ich.org/page/efficacy-guidelines

Context and Background Information (3)

Western societies have shifted towards a **risk-averse attitude**, based on the idea that vaccines should provide **a personal health benefit** to the vaccinee rather than **a benefit for the community or population** at risk of infectious diseases, conferred by heard immunity, which is the notion that vaccines may have global clinical benefits that are more valuable than individual adverse events.



Example of COVID-19 vaccination of all people:

while young age groups are less prone to complications of severe acute respiratory syndrome (COVID-19) caused by the SARS-Cov2 virus, creating an aversion to vaccination, vaccination of all age groups can help protection for vulnerable groups (e.g. elderly age groups) against disease/hospitalization ?

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Context and Background Information (4)

In part, this “objectivation of value judgement” (but not all) is linked to the increased concern about risk
(cf. highly media publicised drug withdrawals)

Does it reflects risk aversion or risk awareness?

The society has shifted towards the individual health 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…

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B/R Balance concept

The concept is dynamic:

- The first exercise is done at licensure, however every PSUR will have a new B/R analysis
- Whenever a new safety issue is discovered, a new B/R analysis has be to carried out

Example: Both vector vaccines of J&J and AZ, were re-analysed when thrombosis cases were linked to the vaccination.

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More implementations of the B/R Concept
The BRAVATI project (previously V3SWG)

Collaboration between WHO GACVS and Brighton Collaboration led to acceptance by GACVS of the B/R templates offered by Brighton:

New templates developed focusing on key questions related to the essential safety and benefit risk assessment of vaccine technologies for the main COVID 19 platforms (funded by CEPI)

- Nucleic Acid (RNA/ vaccines Kim D et al, https://doi.org/10.1016/j.vaccine.2020.06.017
- Inactivated viral vaccines Kochhar S et al, https://doi.org/10.1016/j.vaccine.2020.07.028
- Protein vaccines Kochhar S et al, https://doi.org/10.1016/j.vaccine.2020.06.044
- Viral vector vaccines Condit RS et al, https://doi.org/10.1016/j.vaccine.2020.08.009
- Live attenuated viral vaccines Gurwith M et al, https://doi.org/10.1016/j.vaccine.2020.09.042

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New paradigm for vaccine development and licensure

- The pandemic COVID-19 vaccine development in 2020 demonstrated that new, safe and efficacious vaccines can be developed and tested within less than 12 months. Cf. https://www.nature.com/articles/d41586-020-03626-1
- The question arises: is this fast enough for a potential future pandemic with higher pathogenicity and higher mortality rates than COVID-19?
- Therefore, the new approach for vaccine regulatory approval includes now also formal benefit-risk assessment, in addition to quality, safety, and efficacy evidence.
- CEPI has come with the “100 days” from development to license idea

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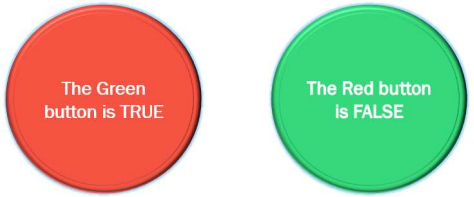
The regulatory paradox

- The above background and examples illustrate the regulatory paradox that, while regulatory authorities require thorough testing procedures, increasing amount of data and larger clinical studies, that may take a long time and high resources, and at the same time, health authorities need to have new efficacious medicinal products to be rapidly available to fight the spread of infectious diseases as soon as possible, to save lives in epidemic and pandemic situations.



- Protection of the user/patient are based on learnings from:
  - Incidents from the past
  - Guidance on public health criteria for
    - **Quality**
    - **Efficacy**
    - **Safety**
    - **Risk Management**
  - Declaration of Helsinki: ethical regulation of Clinical Trials

- Promotion of the availability of indispensable medicines

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Two major examples of the regulatory paradox

1) 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)

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The regulatory paradox: example

2) Thalidomide

- Between 1956 and 1961 thalidomide was used in ± 50 countries, sold under at least 40 different brand names
- Indication: nausea and insomnia in early pregnancy
- Between 1957 and 1962: ± 10.000 children were born with phocomelia, or limbs' malformation
- Impact in the US was limited, as the FDA did not approve the use of thalidomide due to limited safety data

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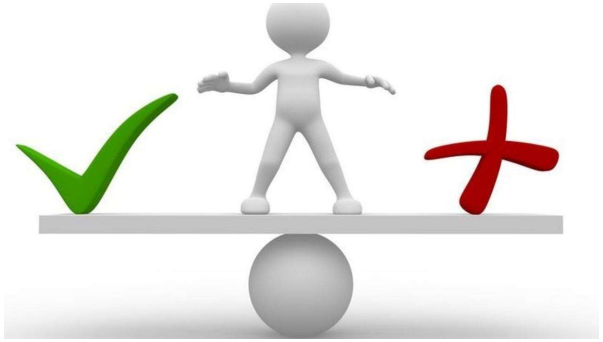
Part 2: Discussion on Benefit-Risk balance assessment and a few examples



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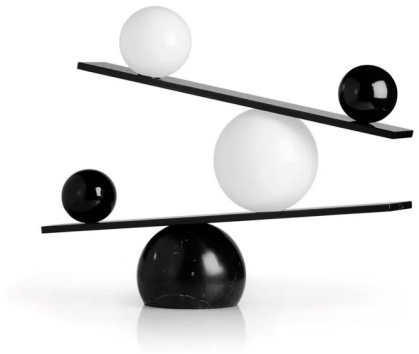
Definition of Benefit/Risk (B/R):

Benefit/Risk assessment for medicinal products is a complex area requiring solid scientific knowledge and expertise



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 a complex dynamic analysis rather than only a mathematical formula

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Definition of Benefit/Risk (B/R)

How to define a Benefit for vaccines?

Ideally:

- Infection prevention goal:

  is the most desired goal for public health, so that vaccinated people don't spread the disease. But infection prevention is a more difficult endpoint to achieve.

However, real world experience accepts clinical benefits of vaccination, such as:

- Disease prevention goal:

  vaccinated people don't get the disease, but still get infected and can carry and spread the disease agent.

- Complication prevention goal:

  a percentage of vaccinnees get clinical disease, but **mild** such as measured by no hospitalisation, no intensive care needs, no mortality from the disease.

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Definition of Benefit/Risk (B/R): Examples

1. Example Poliomyelitis vaccines:

- OPV (attenuated oral polio vaccines): elicits local mucosal immunity and prevents further spread of infections
- IPV (Inactivated Polio Vaccine): elicits disease prevention (no clinical myelitis), but elicits poor mucosal immunity, causing shedding of viruses in the environment, and the possibility to spread the virus.

2. Example COVID-19 vaccines:

All known COVID-19 vaccines elicit certain degree of disease prevention (e.g. no clinical or mild clinical disease), but still enables carriage and shedding of viruses in the environment, and the possibility to spread the virus to vulnerable individuals.

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Definition of Benefit/Risk (B/R): role of surrogates and correlates of protection

Because of the time lag period between infection and the manifestation of clinical disease for some pathogens, such as:

- Hepatitis B-virus, HPV, HIV,

it is extremely important to identify reliable surrogate endpoints for vaccine efficacy, as well as correlates of protection that allow to accelerate vaccine clinical development, licensure and availability to fight disease and save lives, without much delays.

Correlate of protection for Hepatitis B vaccines corresponds to sera antibody titters of 10 IU (International Units) per L? that confers life long protection. Demonstration that HepB vaccines elicit such level of titers in over 95% of naïve subjects allows licensure and protection to populations. (= Sero conversion rate)
However, for HIV candidate vaccines, the presence of antibodies is not correlated to any protection, unfortunately.

Definition of Benefit/Risk (B/R)

How to define a Benefit for vaccines?

- **How to measure the effect of vaccines on disease, or how to translate disease prevention in a measurable clinical 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.

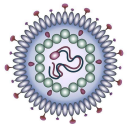
For many viruses, antibodies and especially neutralizing antibodies serve as a correlate of immunity. So for example, pregnant women are routinely screened in the UK for rubella antibodies to confirm their immunity to this infection which can cause serious congenital abnormalities. In contrast for HIV,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

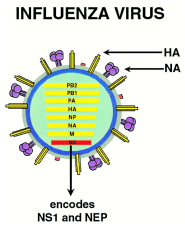
Definition of Benefit/Risk (B/R)

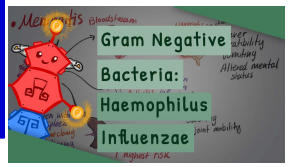
How to define a Benefit for vaccines?

- How to measure the effect of vaccines on disease, or how to translate disease prevention in a measurable clinical parameter?
  - Hepatitis B virus [(1)] can cause hepatocarcinoma, and due to vaccination the HepB endemicity has decreased: disease prevention is not an option as outcome for a clinical trial, hence
    - Surrogate of protection: Ab concentration (though no Cell Mediated Immune-parameter)
    - For Hep B it is established that a concentration above 10 IU/L confers lifelong protection
  - Influenza: Influenza like Illness (ILI PCR proven) is the standard: no Ab standard is available for the time being
  - Haemophilus Influenzae:
    - 2 cut-off 1,0 and 0,1

Hepatitis B virus







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(1) https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/vaccine-standardization/hep-b

How to define a Benefit for vaccines?

The European Committee for Human Medicinal Products(CHMP) has requested improvements for the B/R description in the assessment report for B/R (report template available at https://www.ema.europa.eu/en/about-us/support-research/benefit-risk-methodology).

Some specific queries include:

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 comparable with 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**")

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

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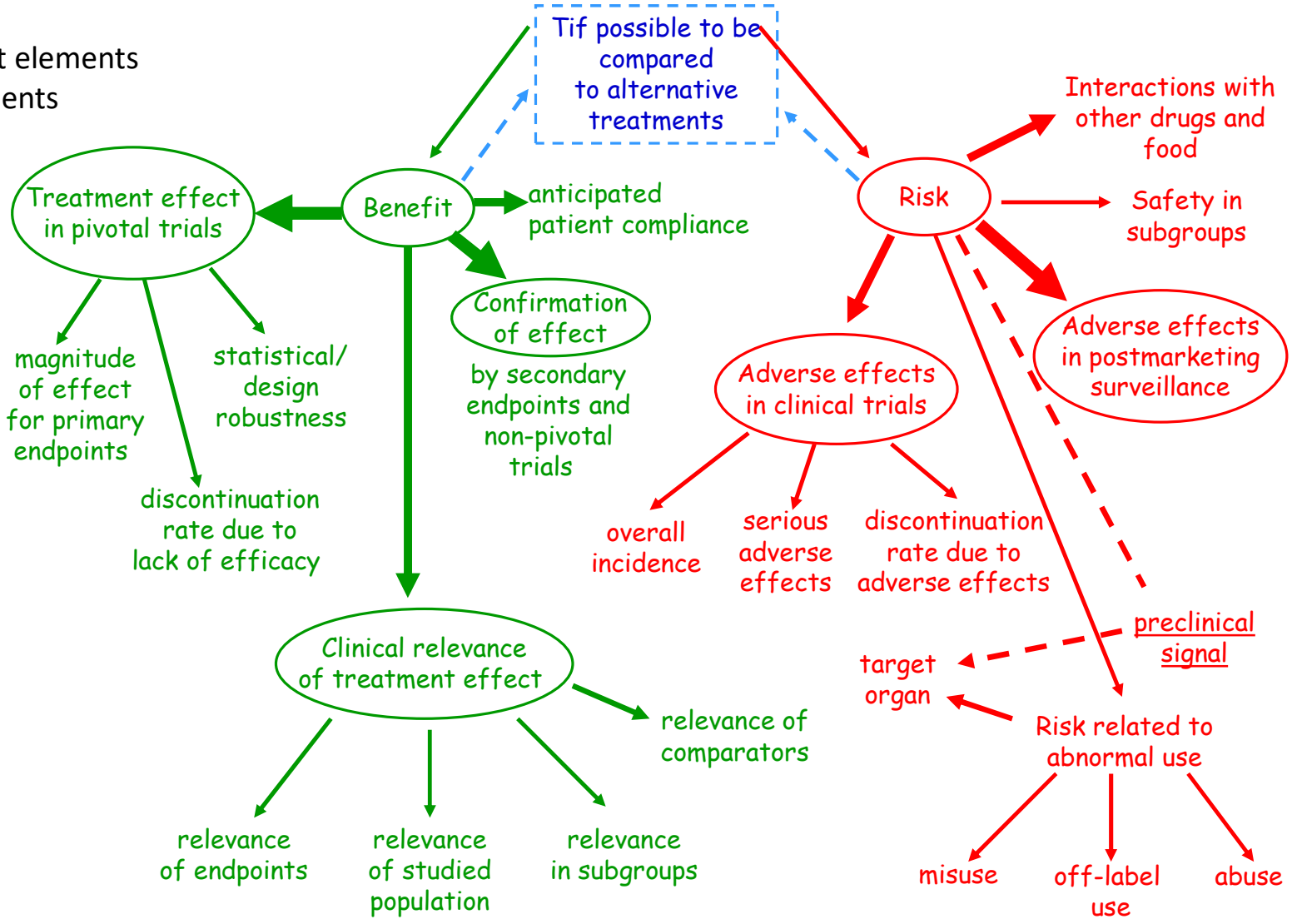
Graphic illustration of Decision tree elements for Benefit-Risk Assessment

GREEN=benefit elements
RED= risk elements



Elements for Benefit-Risk assessment

This task is extremely difficult and 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

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Elements for Benefit-Risk assessment

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

Definition of a benefit = favourable (clinical) 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

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Elements for Benefit-Risk assessment

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, vaccine failure, waning immunity, lower efficacy towards pathogen genetic variants on important efficacy endpoints or other undesirable effect.
- Describe the unfavourable effects themselves **and the uncertainty in the knowledge** about these unfavourable effects

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Conclusions

Benefit / Risk Balance:

- **Often clinical trial data are derived from a homogeneous setting, thus regulatory agencies need reflections on certainties and uncertainties of how such data can be applied to large and heterogeneous populations.**
- **It is a continuous process**
- **Needs to be repeated when new data become available**
  - ✓ **Collecting new data on benefits**
  - ✓ **Collecting New data on risks**
  - ⇒ **B/R evaluation is important even if the benefit is forgotten due to disappearance of the disease**
- **R/B remains a difficult exercise knowing that for many Adverse Events the causal relationship is unknown…**

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Thank you for your attention!

Questions

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