Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

Single-arm trials

a good step towards faster access/reimbursement of drugs?

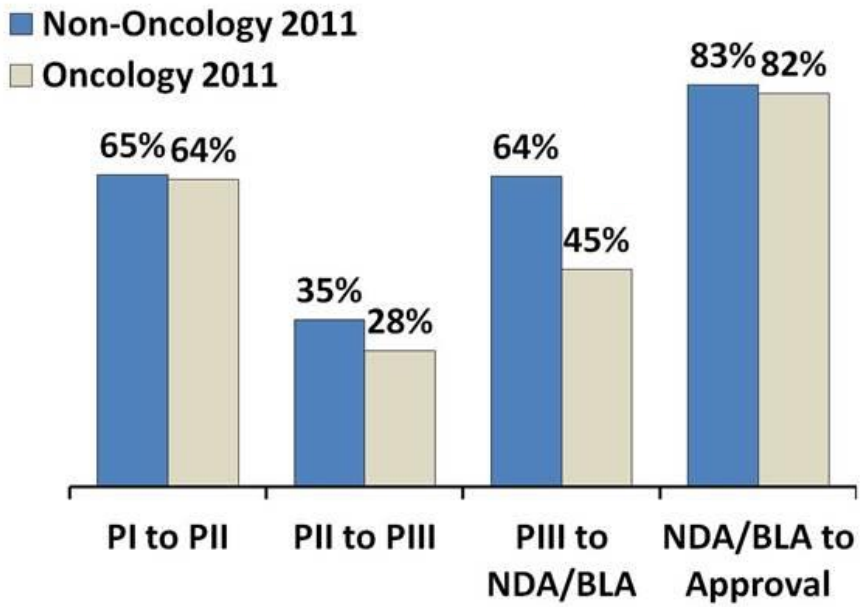
(with an added value for 'all' patient…)

Mattias Neyt, MSc, PhD
Senior health economist
mattias.neyt@kce.fgov.be

Overview

- Are you aware of…
  - Development success rate of drugs
  - Prices vs. added value
  - Impact on surrogate endpoints vs. survival & QoL
  - Registration vs. reimbursement
  - (Small?) impact on inefficient use of limited resources
  - Importance of HTA
- Some things to think about…
- Open question: are single-arm trials (and other systems to provide faster access) the best way to provide added value to all patients?

Phase III development success rate



Source: www.biotech-now.org

LOA from	phase I	phase III
- Non-oncology:	12%	53%
- Oncology:	6.6%	37%

NDA: New Drug Application
BLA: Biological License Application
LOA: Letter of Authorization

Huge prices for cancer drugs vs. modest gains

Every patient with cancer or another life-threatening disease wants the most effective treatment, but drug prices have become staggering. Twelve of the 13 new cancer drugs approved last year were priced above $100,000 annually (Table 1), The added-value argument for unaffordable prices is not supported by objective data. Most new cancer drugs provide few or no clinical advantages over existing ones. Only one of the 12 new anticancer drugs approved in 2012 provides survival gains that last more than 2 months (Table 1). Source: Light, Cancer, 2013

Surrogate vs. survival (& QoL)

Many cancer drugs recently approved in US do not improve overall survival, study finds

Michael McCarthy

Seattle

In recent years most cancer drug approvals by the US Food and Drug Administration have been made on the basis of a surrogate endpoint, such as tumour response rate or progression-free survival. When such approvals are made the agency typically advises or requires that post-approval studies be conducted to clarify the drug's effect on overall survival.

However, a new US study has found that, in most cases, cancer drugs that have recently secured FDA approval on the basis of surrogate endpoints either do not—or have not yet been shown to—improve overall survival.

In the study[1] Chul Kim, of the National Cancer Institute in Bethesda, Maryland, and Vinay Prasad, of Oregon Health and Science University in Portland, Oregon, identified all cancer drugs that the FDA had approved from 2008 to 2012. They then identified those that were approved on the basis of a surrogate endpoint and conducted a literature review to identify any follow-up reports into each drug's effect on overall survival.

They found that, of the 54 drugs approved by the FDA during that time period, 36 (67%) were approved on the basis of a surrogate endpoint. The primary measure of efficacy for 19 (53%) of the 36 surrogate based approvals was rate of response, measured by a reduction in tumour size or volume. For 17 (47%) of the 36 approvals the primary measure of efficacy was progression-free or disease-free survival.

However, the researchers also found that, after a median follow-up of 4.4 years, only five of these 36 drugs were subsequently shown to improve overall survival in randomised studies, 18 failed to improve overall survival, and the survival effects of the remaining 13 were unknown because the necessary studies either had not been done or had not been reported.

Thus, after several years of follow-up, 86% (31/36) of the drugs approved on the basis of surrogate endpoints—accounting for 57% (31/54) of all cancer drugs approved during the study period—had unknown effects on overall survival or did not show gains in survival, the researchers wrote.

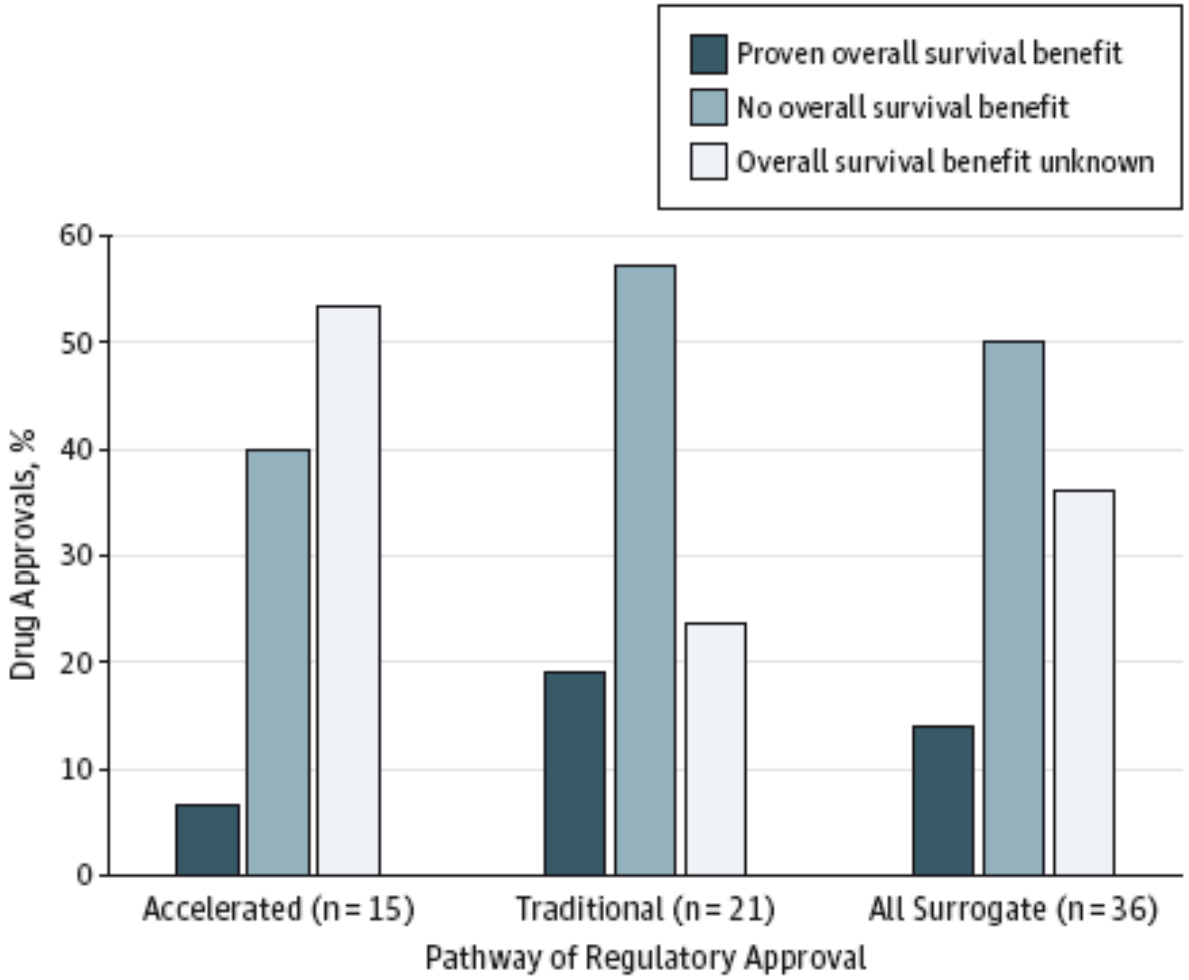
They concluded, "Our results suggest that the FDA may be approving many costly, toxic drugs that do not improve overall survival. Enforcement of postmarketing studies is therefore of critical importance."

1 Kim C, Prasad V. Cancer subsequent overall surviv approvals. *JAMA Intern M*

Request better evidence before widespread use…

Cite this as: *BMJ* 2015;351:h5634

Figure 2. Overall Survival Results for Cancer Drug Approvals Granted on the Basis of a Surrogate End Point



Source: Kim, JAMA, 2015

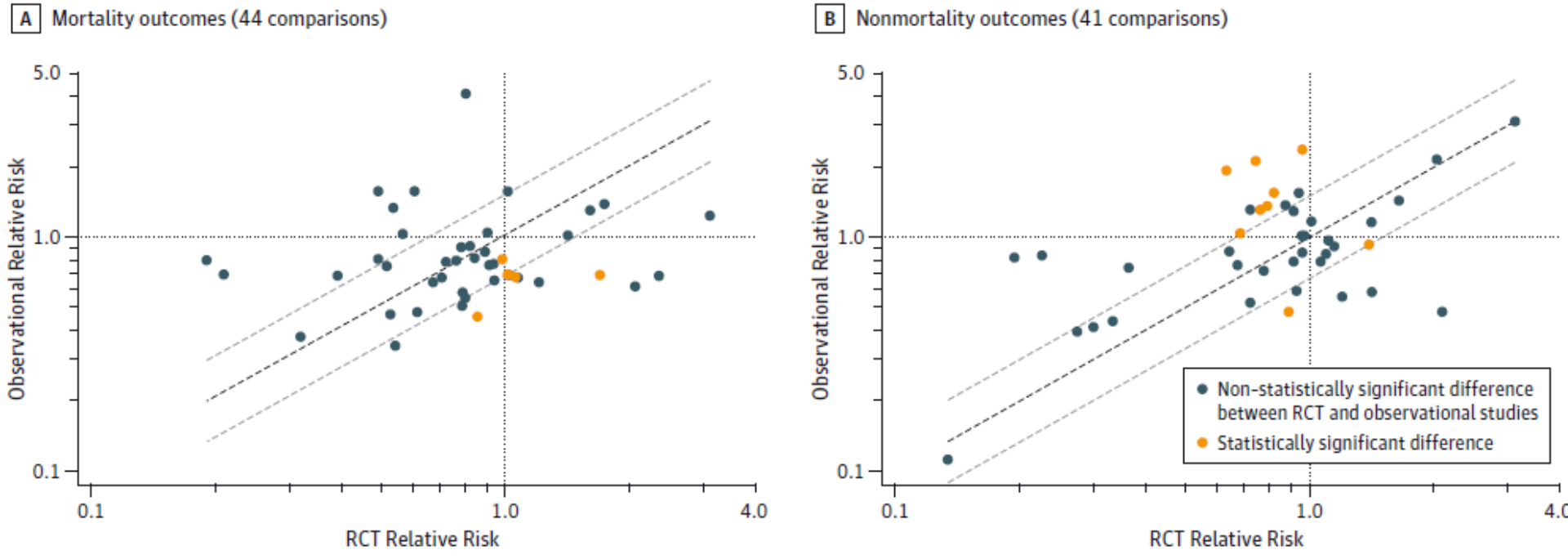
Propensity score

- Major concern: no good estimate of treatment effect → misinformation

The Figure indicates that in a few cases estimates are in almost perfect agreement, sometimes they point in the same direction but differ in magnitude, and sometimes they conflict in direction (markers in the top-left or bottom-right quadrants of each graph). Despite strong support for propensity-based methods from rigorous theory and simulations, the data to date show no clear improvement in agreement relative to previous comparisons of RCTs vs observational studies analyzed with conventional adjustment methods.[6]

Even more concerning than the overall lack of agreement across designs is the absence of a clear pattern

Figure. Comparison of Propensity Score Analyses and RCT Results From 3 Recent Empirical Assessments[3-5]



Source: Dahabreh, JAMA, 2014

Registration vs. reimbursement

Awareness, early dialogues, guidelines…

The 4th hurdle

Budget impact (Affordability)
A 5th hurdle

Cost-effectiveness (Acceptability)

Comparative effectiveness (comparator, endpoints, …)

Efficacy

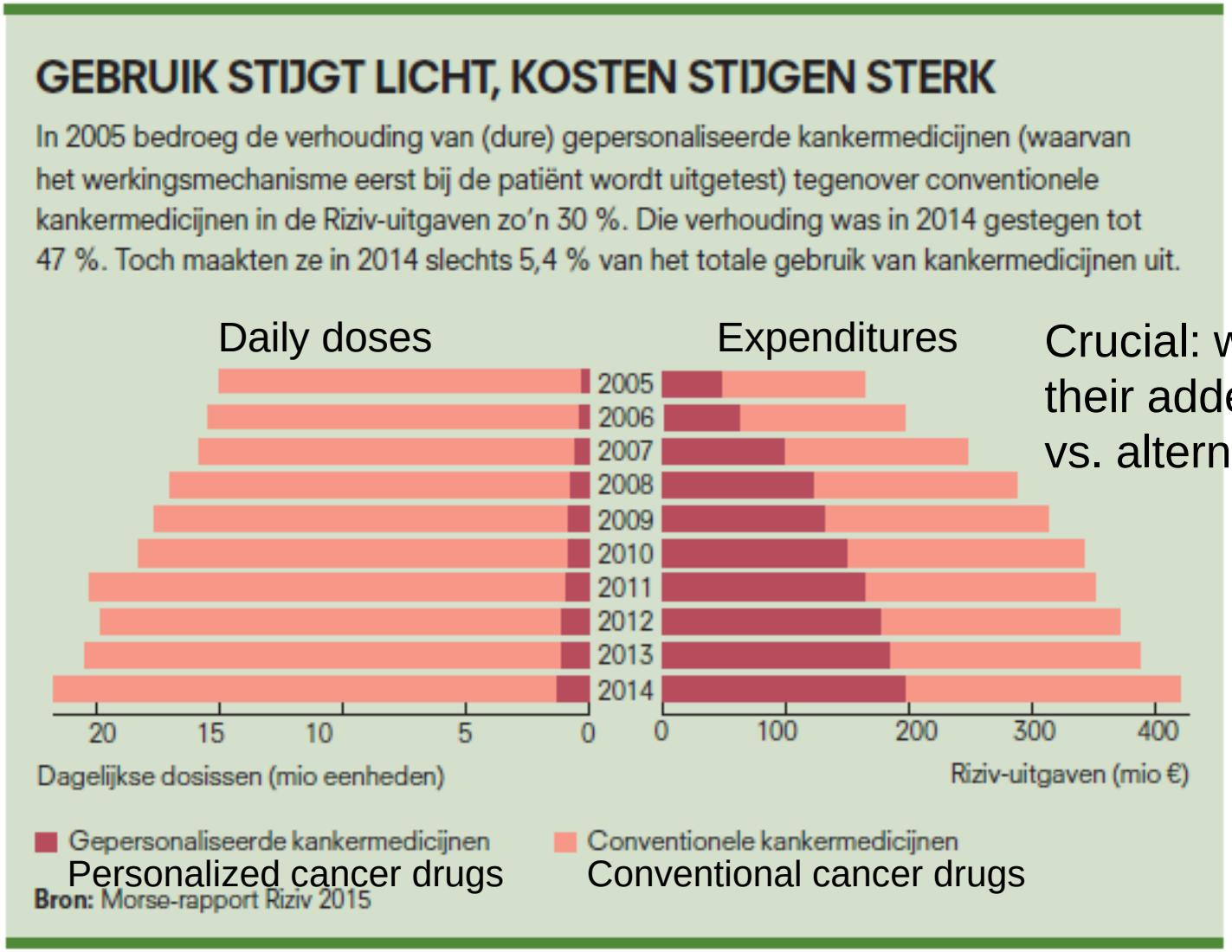
Safety

Quality

Regulatory procedure – Registration

HTA – Reimbursement

Small population ~ small BI?



Crucial: what is their added value vs. alternatives?!?

Personalized cancer drugs

Conventional cancer drugs

Source: Van Hecke, Test Aankoop, 2016

Why HTA?

Goal:

- Micro level (ST)
  Support decision makers by providing them objective, transparent, and scientifically based information.

- Macro level (LT, 'all' patients)
  - Accessibility,
  - High quality,
  - Affordability / sustainability (LT!)

Something to think about…

- Some concerns with SAT
  - Reliable info on therapeutic added value?
  - Causing recruitment problems in other studies?
  - Faster access vs. faster/better reimbursement?

  ➔ Without reliable evidence: possible harm & waste of money (on societal level: try to do the best for ALL patients)

  - Can we do better? SAT should not be the standard, only in exceptional well-considered cases (e.g. >>> treatment effect)

For your information

- EUnetHTA guideline "Internal validity of non-randomised studies (NRS) on interventions"

1st recommendation:

As the inclusion of non-randomised studies (NRS) in an HTA report requires large efforts (but often fails to increase the validity of the report's conclusion), the decision to do so should be made only after careful consideration of all advantages and disadvantages.

The inclusion of NRS evidence might mislead researchers into the false belief that RCTs are not worthwhile to perform. Thus, HTA might act as a barrier in finding out the 'true' effect of an intervention.

In the assessment of safety, however, non-comparative studies may play a greater role (37).

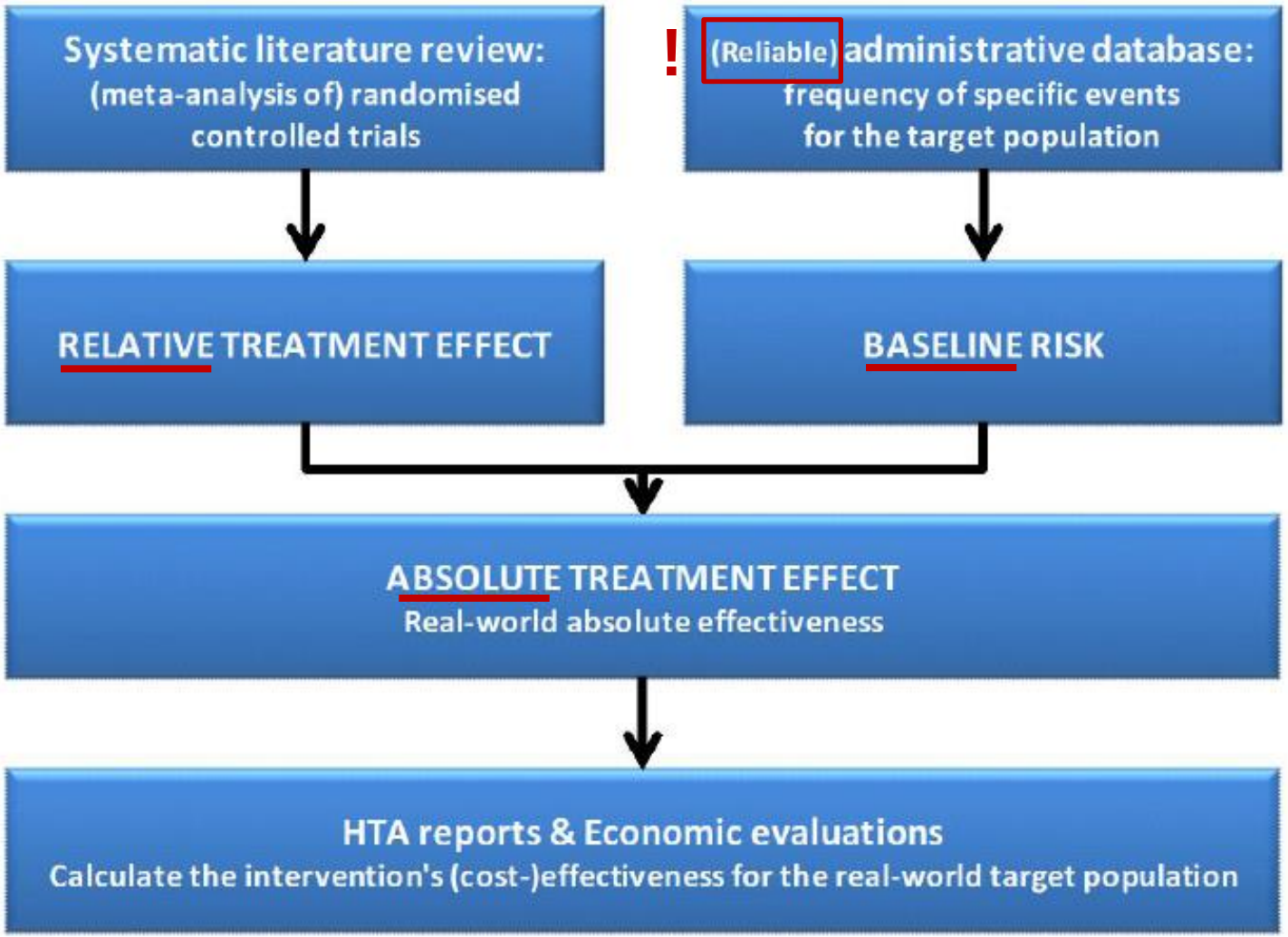
Something to think about…

- Steps in the good direction that need further support
  - International collaboration: better organisation of clinical trials (ECRIN, IRCI, EORTC, …)
  - Early dialogues: valuing cancer treatments with a focus on both regulatory approval AND HTA/reimbursement
  - More transparency of clinical trial results (theory vs. practice)
  - Pragmatic comparative effectiveness trials
  - Use appropriate research design for appropriate purposes (example: see next slide)

- If we have some time… possible approach:

Combine strengths of both
RCTs and observational data…

Source: Neyt et al., Health Policy, 2012



KCE

Open for discussion

- What is your definition of ‘innovation’?
- What is your goal (faster access vs. added value)?
- Do you achieve this with single-arm trials?

- HTA/reimbursement is national responsibility
  … BUT major influence of European policy
  - Lowering standards → shifting the problem
  - Is it wise to shift the burden of generating evidence from pre-marketing to post-marketing?

THANK YOU!

KCE

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

CCC CoCanCPG

eunethta
EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

European Observatory on Health Systems and Policies 1998-2008

INAHTA