Medical Evaluation
Technology Assessment

Economic evaluations in the Belgian reimbursement system and public funding of clinical trials

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Who am I …

- (Health) economist, MSc, PhD
- Since 2005 - …: working at KCE
  Senior health economist
  (www.kce.fgov.be)
- Since 2010 - …: partner in ME-TA
  CoI: To avoid any potential conflict of interest, we limit our activities to non-profit organisations. Education and training is open to everyone.

GHENT UNIVERSITY

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

ME-TA
Medical Evaluation
Technology Assessment

About the KCE (www.kce.fgov.be)

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OUR MISSION

KCE's mission is, on the basis of scientific analysis and research, to advise policymakers on decisions relating to health care and health insurance.

KCE is not involved in the decision-making or implementation process. Instead, its role is to identify and shed light on the best possible solutions, in the context of an accessible, high-quality health care system with due regard for growing demand and budgetary constraints. Further, KCE supports care providers by developing clinical guidelines, gearing these towards the evolving body of scientific knowledge and publishing on methodologies that serve as a guide for other health care researchers.

KCE IS INVOLVED IN FOUR MAIN DOMAINS + KCE Trials

- Good Clinical Practice: developing clinical practice guidelines
- Health Technology Assessment: evaluating medical technologies and medicinal products
- Health Services Research: investigating the optimal means of organising and funding health care
- Methods: developing effective research instruments

Overview

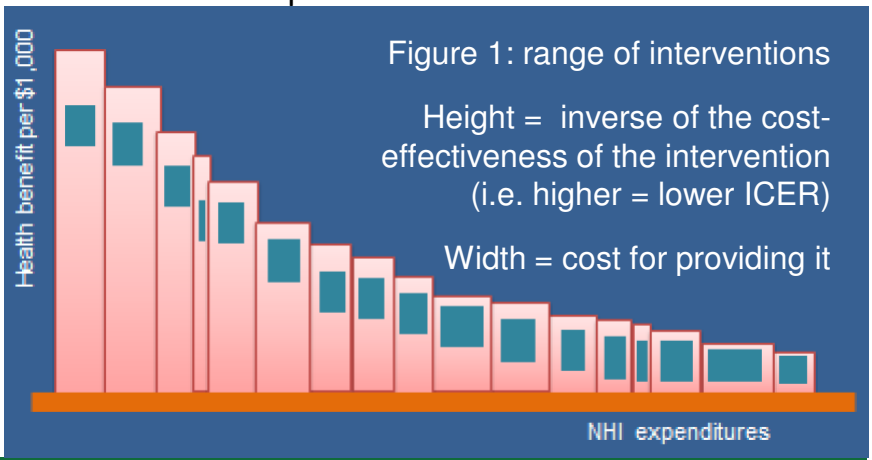
- Why economic evaluations
- Economic evaluations in the Belgian system (~Royal Decree - KB)
  → (problems with) confidential contracts
- Government-sponsored trials

Why economic evaluations

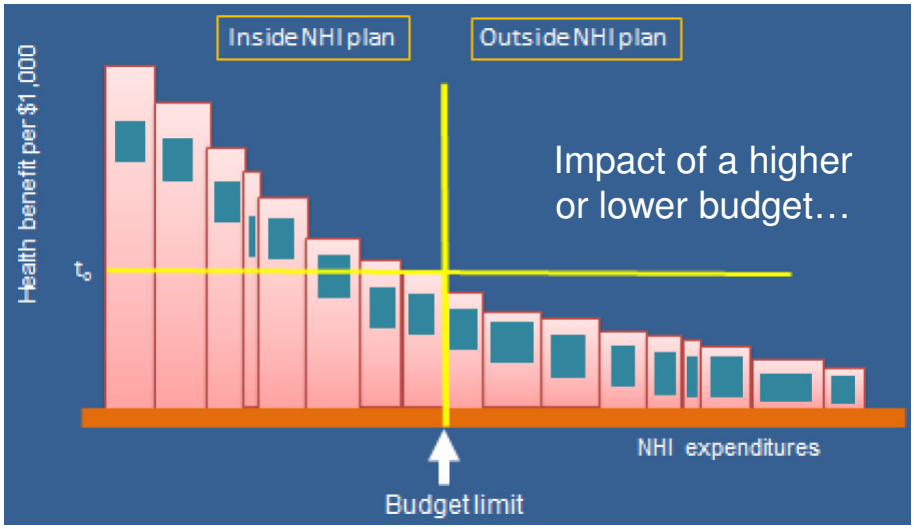
- The bookshelf approach – to avoid misunderstandings
  - ICER threshold ~~=~~ budget
  - Cost-effectiveness/utility: one criterium

Bookshelf approach…

- Culyer A. Cost-Effectiveness Thresholds in Health Care: A Bookshelf Guide to their Meaning and Use. CHE Research Paper 121. December 2015.



- The budget & the ICER threshold



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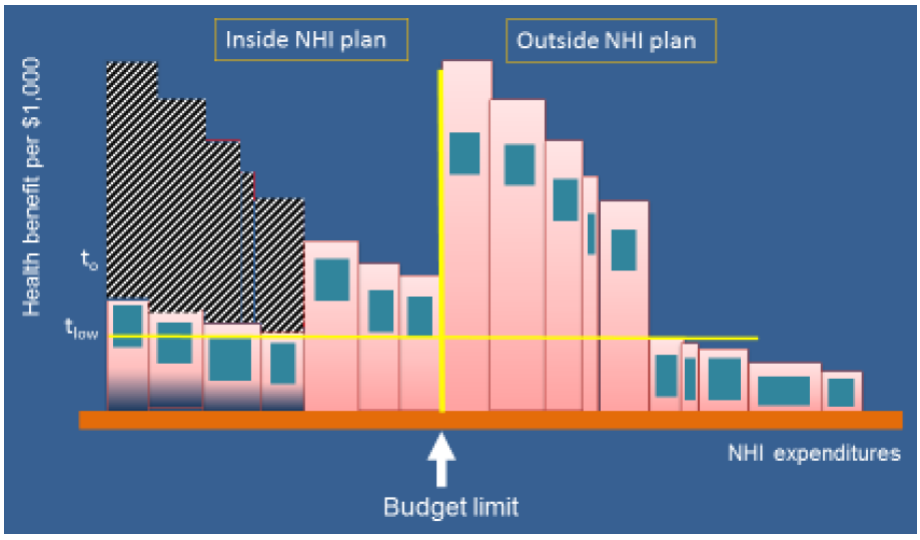
- Figure 7: Extreme health loss from threshold set too low (too high ICERs!)



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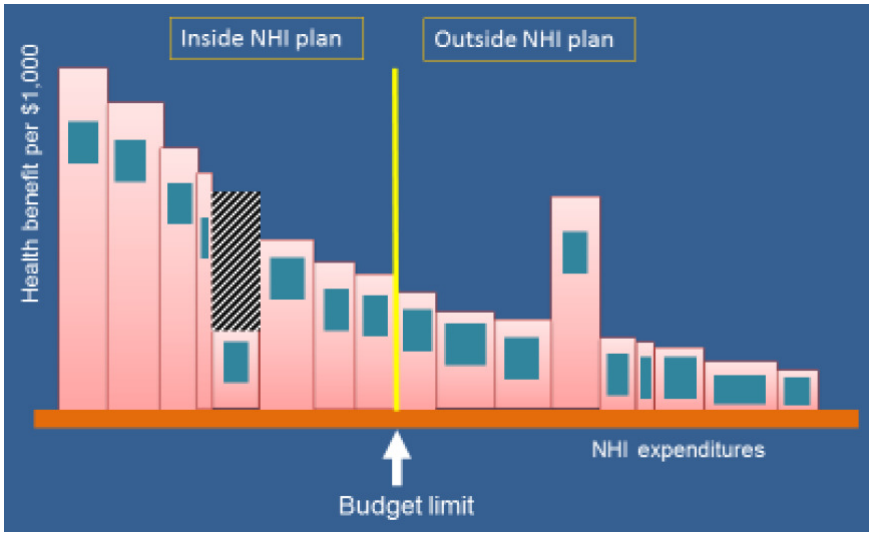
- Figure 5: Health loss from 'poor' technology selection



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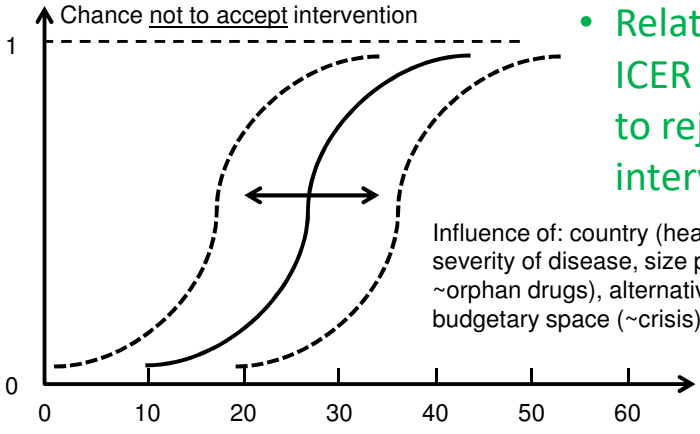
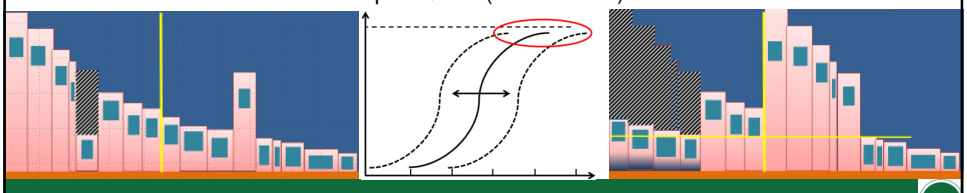


- Relationship ICER & chance to reject intervention

Influence of: country (health budget), severity of disease, size population (~BI, ~orphan drugs), alternatives, lobby, budgetary space (~crisis), etc.



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Seems logic… however…

The $640 Billion Question — Why Does Cost-Effective Care Diffuse So Slowly?

Victor R. Fuchs, Ph.D., and Arnold Milstein, M.D., M.P.H.

- CE is not applied automatically
  - ≠ point of views of stakeholders… → regulation!

• Reimbursement criteria: for drugs

Art. 4. De beslissing omtrent het al dan niet opnemen, het wijzigen of het schrappen omvat een beslissing over de vergoedingsbasis, de vergoedingsmodaliteiten en desgevallend de termijn en de te evalueren elementen voor de individuele herziening en wordt genomen na een evaluatie van één of meer van de volgende criteria, zoals bepaald in artikel 6:

1° de therapeutische waarde ;

2° de prijs van de specialiteit en de door de aanvrager voorgestelde vergoedingsbasis ;

3° het belang van de specialiteit in de medische praktijk in functie van de therapeutische en sociale noden, met inbegrip van de relevantie en de adequaatheid van de grootte van de verpakking in dagdosissen in functie van de beoogde therapie ;

4° de budgettaire weerslag voor de verzekering, rekening houdend met de begrotingsdoelstellingen ;

5° de verhouding tussen de kosten voor de verzekering en de therapeutische waarde.

Art. 6. Indien een specialiteit door de aanvrager gerangschikt is in klasse 1, worden alle criteria vermeld in artikel 4 in de beoordeling gehanteerd. Indien een specialiteit door de aanvrager gerangschikt is in klasse 2, subklasse 2B of subklasse 2C of klasse 3, subklasse 3B of subklasse 3C worden de criteria vermeld in artikel 4, 1° tot en met 4° in de beoordeling gehanteerd. Indien een specialiteit door de aanvrager gerangschikt is in klasse 2, subklasse 2A of klasse 3, subklasse 3A, worden de criteria vermeld in artikel 4, 2° en 4° in de beoordeling gehanteerd.

De definitieve vaststelling van de meerwaardeklasse gebeurt door de Minister, op voorstel van de Commissie, behoudens in de gevallen waar de Commissie niet tijdig een voorstel formuleert in welk geval de Minister beslist en in de gevallen waar de Minister niet tijdig een beslissing neemt in welk geval het meest recente voorstel vanwege de aanvrager geldt.

Reglementering

K.B. van 21.12.2001 (geldig voor alle dossiers ingediend voor 1 april 2018)

KB van 1 februari 2018 (geldig voor alle dossiers ingediend vanaf 1 april 2018)

- Reimbursement criteria: also for devices!

1° Therapeutic value

2° price

3° importance in medical practice

4° budget impact

5° cost effectiveness

Art. 16. De beslissing met betrekking tot de aanvraag tot aanpassing van de lijst wordt door de Minister genomen, na een evaluatie van één of meerdere van de volgende criteria bedoeld in artikel 35*septies*/2, § 3, van de wet :

1° de therapeutische waarde van het hulpmiddel, uitgedrukt in één van de twee klassen die uitgebreid worden gedefinieerd in artikel 17;

2° de individuele prijs van het hulpmiddel, en de voorgestelde vergoedingsbasis;

3° het belang van het hulpmiddel in de medische praktijk in functie van de therapeutische en sociale noden;

4° de budgettaire weerslag voor de verzekering;

5° de verhouding tussen de kosten voor de verzekering en de therapeutische waarde van het hulpmiddel.

Klasse 1

Art. 17. De therapeutische waarde en de eventuele therapeutische of gezondheidseconomische meerwaarde van een hulpmiddel worden uitgedrukt in één van de volgende klassen :

1° Klasse 1 : hulpmiddel met een aangetoonde meerwaarde tegenover bestaande therapeutische alternatieven.

Art. 18. § 1. Indien in de aanvraag tot aanpassing een hulpmiddel wordt gerangschikt in klasse 1, worden alle criteria vermeld in artikel 16 in de beoordeling gehanteerd.

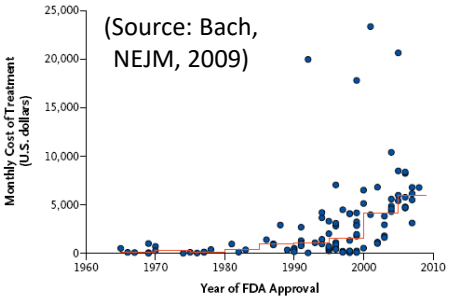
K.B van 25.06.2014: Procedures, termijnen en voorwaarden inzake de tegemoetkoming van de verplichte verzekering in de kosten van implantaten en invasieve medische hulpmiddelen

Market Spiral Pricing of Cancer Drugs

Light, Cancer, 2013

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: Bach, NEJM, 2009)

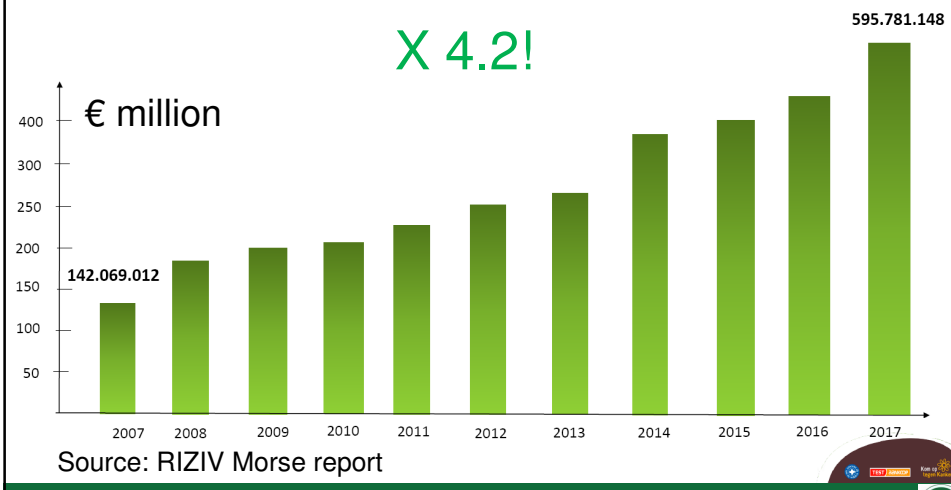
Figure 1. Monthly and Median Costs of Cancer Drugs at the Time of Approval by the Food and Drug Administration (FDA), from 1965 through 2008.

Shown are costs for 1 month of cancer treatment for a person who weighs 70 kg or has a body-surface area of 1.7 m². The red line indicates median prices during a 5-year period. Prices have been adjusted to 2007 dollars and reflect the total price for the drug at the time of approval, including both the amount of Medicare reimbursement and the amount paid by the patient or by a secondary payer. (For details about the costs of individual drugs, see the Supplementary Appendix, available with the full text of this article at NEJM.org.)

In 2012:

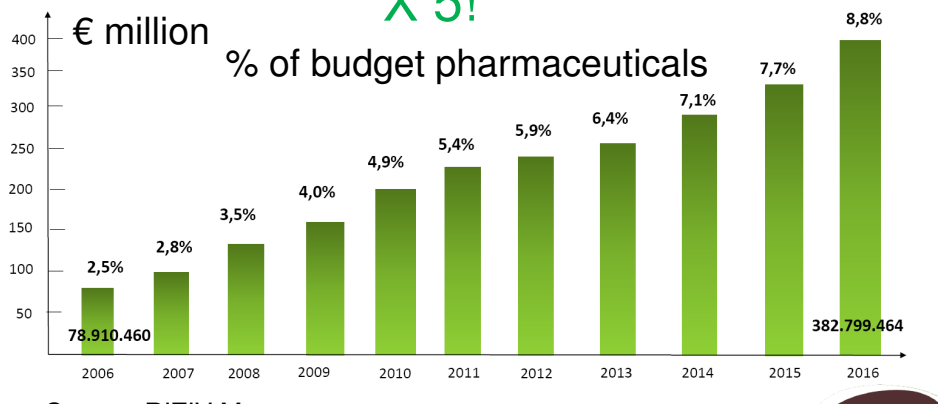
Drug (Trade Name; Company)	Monthly or Per-Cycle Cost
Axitinib (Inlyta; Pfizer)	$10,584 (up to $21,168)/mo
Enzalutamide (Xtandi; Astellas)	$8,940/mo
Ziv-aflibercept (Zaltrap; Sanofi-Aventis)	$15,360/mo (two 200-mg vials per dose; 80 kg)
Regorafenib (Stivarga; Bayer)	$11,220/mo
Pertuzumab (Perjeta; Genentech)	$4,890/3 weeks
Cabozantinib (Cometriq; Exelixis)	$11,880/mo
Vismodegib (Erivedge; Genentech)	$9,000/mo
Carfilzomib (Kyprolis; Onyx)	$11,937/mo (1.8 m²)
Bosutinib (Bosulif; Pfizer)	$9,817/mo
Ponatinib (Iclusig; ARIAD)	$12,900/mo
Omacetaxine (Synribo; Teva)	$28,056/mo for 14-day cycles; $14,028/mo for 7-day cycles (1.8 m²)
Vincristine sulfate liposome (Marqibo; Talon)	≈$12,000/cycle
Glucarpidase (Voraxase; BTG International)	$108,000 (80 kg)

Expenditures innovative cancer drugs



Source: RIZIV Morse report

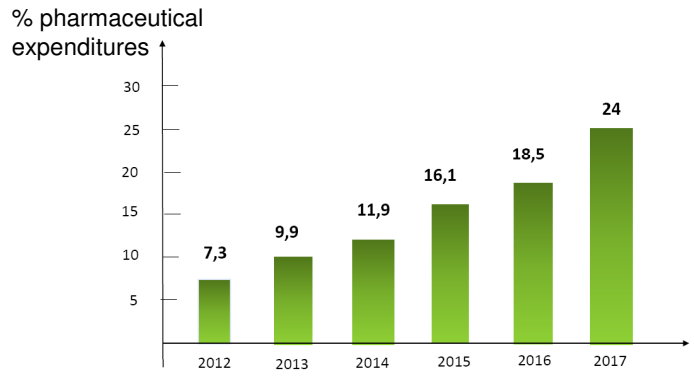
Expenditures orphan drugs



Source: RIZIV Morse report

Market-entry agreements as a solution?

Pharmaceuticals with confidential price discounts



Source: RIZIV (2018)

Market-entry agreements (MEAs)

Challenges:

- Insufficient evidence e.g. on relative effectiveness and cost-effectiveness
  - ➢ Faster access to innovation
  - ➢ ~~Evidence generation~~
- Prices increasingly high and limited resources
  - ➢ Better prices

Short term vs. long term? (see further)

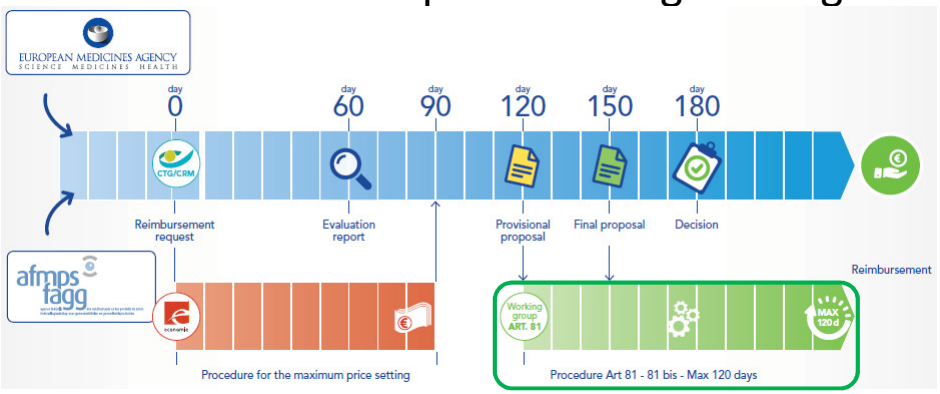
MEAs: study objective

- Study objective:
  - Evaluation of the Belgian system of conventions “article 81”

  Requested by: TEST ACHATS / TEST AANKOOP, Kom op tegen Kanker
- FYI: Managed Entry Agreements (article 81(bis) → article 111-113)
  - Available in Belgium since 2010

MEAs: the evaluation process

- Reimbursement request for drugs in Belgium



Art. 111: if no final proposal CRM on day 150 (~art.81)
Art. 112: if suggested by CRM on day 120 (~art.81 bis)
Art. 113: initiative by the Minister (new)

MEAs: methods

- European experience
- Belgian experience
  - Analysis of current contracts
  - Stakeholder consultation

- Limitation: public access ←→ confidentiality

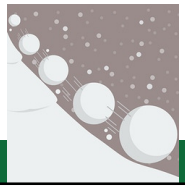
MEAs: advantages

- Reimbursement &
- Lower price/refunds

However… → what's the meaning of a x% reduction?

MEAs: Long-term risks

- ~~Evidence generation~~
  - (Not enough) data in initial submission file
  - Additional data in new submission file?
    (see next slide)
    → Negotiation power of Belgium…
- Withdrawal of reimbursement?
  - Incentive to collect additional data…
- Number of MEA:
  snowball effect



MEAs: Long-term risks

- 16 expired conventions: (source – KCE report 288)

Unfortunately, in most cases, we observed that the new submission files for the CTG-CRM contain not much extra information. In several new evaluation reports (day 60 of the new submission procedure, see section 3.3.3), RIZIV – INAMI experts indicate e.g. that:

- no new clinical studies were provided,
- the present reimbursement request dossier is largely identical to the initial dossier (of 4 years before),
- the clinical uncertainty on the added therapeutic value of X versus Y still exists,
- there are still insufficient data to judge whether X has a therapeutic added value,
- there are no (long-term) comparative studies between X and Y,
- the convention has not permitted to remove uncertainties,
- the effect on QoL has not been investigated,
- etc.

MEAs: Long-term risks

- (confidentiality of) prices
  - Impact future evaluations
  - External reference pricing
  - Impact generics & biosimilars
  - Impact on price setting

- Currently no win-win situation

MEAs: However, potential if…

- Potential if:
  - Selective use (e.g. unmet need)
  - Link uncertainty & type of MEA (& consequences if conditions not fulfilled)
  - Transparent communication
  - International collaboration (further research & price negotiations)

- To create a high quality, accessible & financial sustainable health care system (with justifiable facial prices)

More information: KCE report 288

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HOW TO IMPROVE THE BELGIAN PROCESS FOR MANAGED ENTRY AGREEMENTS? AN ANALYSIS OF THE BELGIAN AND INTERNATIONAL EXPERIENCE

2017 www.kce.fgov.be

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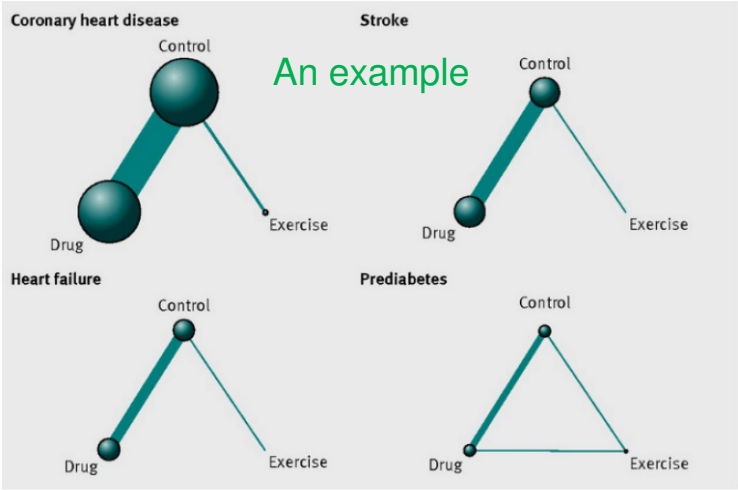
KCE Trials

- Open question: why is there a need for public funded clinical trials?
  - (Pragmatic) comparative trials with medicinal products
  - (Optimization of) use drugs in children and rare diseases
  - Trials with 'old' (cheap) pharmaceuticals
  - Trials with medical devices (under conditions…)
  - Trials on diagnostics and screening
  - Trials in medical areas not owned by private companies: surgical techniques, lifestyle, psychotherapy, etc.
  - …

Figure 7 – Network of available comparisons between exercise and all drug interventions in coronary heart disease, stroke, heart failure, and prediabetes.



Source: Naci et al., BMJ, 2013[74]
Size of node is proportional to number of trial participants, and thickness of line connecting nodes is proportional to number of participants randomised in trials directly comparing the two treatments.

KCE Trials

- KCE report 246: publicly funded practice-oriented clinical trials → succes factors
  - Topic selection
    - Pragmatic, practice-oriented, practice-changing
      - Programme management team + independent experts
      - Top down and bottom up proposals
  - Infrastructure and network
    - Local (to be developed) & International (ECRIN)
  - Implementation
    - Publication & implementation projects

What is KCE Trials?

Many questions in healthcare are currently not or not sufficiently studied in clinical trials, despite their high societal importance. The KCE concluded in the summer of 2015 that public funding of such trials would be beneficial (Report 246-2015) under certain conditions. These trials not only contribute to better patient care but also to a more efficient use of public resources.

The Minister of Public Health Maggie De Block decided in the autumn of 2015 that KCE should launch and manage a programme of pragmatic practice-oriented clinical trials. The available budget for KCE Trials in 2016 and 2017 is 5 million €, increasing to 10 million € from 2018 onwards.

For an efficient international and multilingual cooperation, English was adopted as a working language. For that reason all publications, communications and activities will take place in English.

Which trials are funded?

KCE Trials focuses on comparative effectiveness trials which show clear value for money and have the potential for return on investment. Comparative effectiveness trials compare the benefits and harms of different treatment options that are already in use in the health care system but which have never been adequately compared directly (i.e. which of 2 treatments work better in a real-life situation).

Accepted study interventions are not limited to drugs or medical devices but also include a broad range of interventions for example psychotherapy, diet, life-style interventions, diagnostic tests, surgery or ways to deliver health care.

...

KCE Trials

- **SELECTION CRITERIA KCE TRIALS 2017**

Specific criteria investigator-led call 2017

Expected return on investment (ROI)	Highest score: substantial cost savings are expected. Either substantial savings per patient for small populations as well as savings for large populations that are substantial because of the size of the population fall within this category. Interventions with an equivalent effectiveness that result in relevant cost savings compared with existing alternatives also fall within this category. High score: Increased patient benefit comes at acceptable extra expense for society. Low score: It is very questionable whether the increased patient benefit comes at an acceptable extra expense for society. Research outlines that contain insufficient information to judge the expected ROI will receive a low score.

- Often: RoI - unclear

KCE Trials: Previous submissions

Research proposal

- No information on costs initial interventions
- No information on probability events

  (~potential absolute treatment effect)

➔ Difficult to assess potential RoI

KCE Trials: Open question

- Which elements would you include in your research if you would like to perform an economic evaluation in the future?

ST *C&E (+/-)* LT

- Where, when & how are you going to gather this information…

FYI: Do's & don'ts

- Do not only focus on the medical aspect → also economic, organisational issues, etc.
- Research proposals:
  - Do include info on costs initial intervention and comparator
  - Do include info on possible impact & consequences (relative vs. absolute treatment effect → importance of the baseline risk)

FYI: Do's & don'ts

- Research protocols
  - Do not gather all data on costs → overload
    - (retrospective) access financial data?
  - Do focus on the (most important) incremental elements
    - Something to think about: how to gather/access relevant information (~e.g. AEs, QoL)
- Importance of literature review
- FYI: http://www.ichom.org/ & → HRQoL!!! http://www.comet-initiative.org/

Further information

Managed entry agreements

- Gerkens S, Neyt M, San Miguel L, Vinck I, Thiry N, Cleemput I. How to improve the Belgian process for Managed Entry Agreements? An analysis of the Belgian and international experience. Health Services Research (HSR) Brussels: Belgian Health Care Knowledge Centre (KCE). 2017. KCE Reports 288.

Public funding:

- Neyt M, Christiaens T, Demotes J, Hulstaert F. Publicly funded Practice-oriented Clinical Trials. Health Services Research (HSR) Brussels: Belgian Health Care Knowledge Centre (KCE). 2015. KCE Reports 246.
- Neyt M, Christiaens T, Demotes J, Walley T, Hulstaert F. Publicly funded practice-oriented clinical trials: of importance for healthcare payers. J Comp Eff Res. 2016 Nov;5(6):551-560.
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