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

Examples of Health Technology Assessment

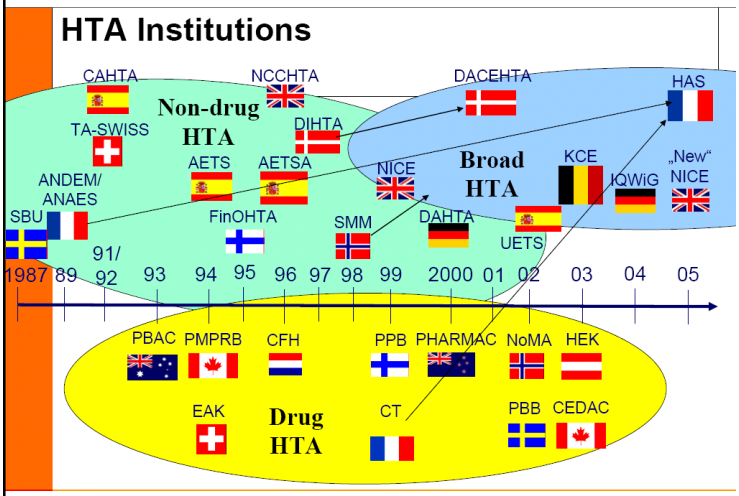
Frank Hulstaert, MD, MSc, FBCPM
KCE senior researcher
JAN 2016

.be

Disclaimers

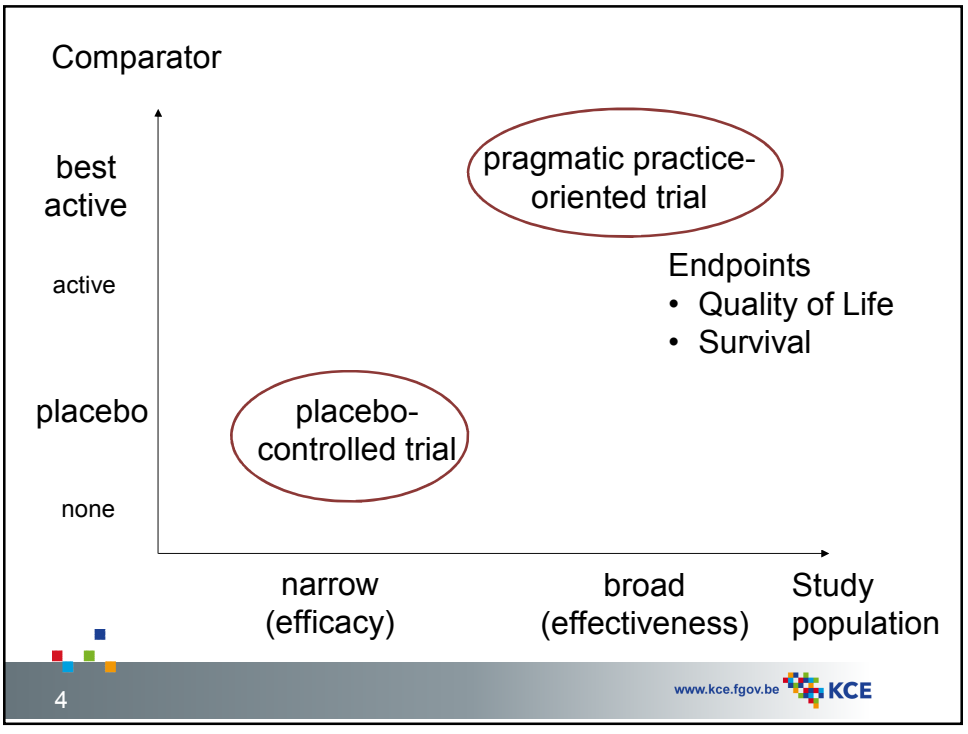
- **The views expressed in this presentation are of the speaker and do not necessarily reflect the opinions or beliefs of the KCE.**
- **The mention of any specific commercial product (s) does not constitute an endorsement by the KCE.**

The evolving landscape of HTA in Europe



Role of EUnetHTA and EMA?

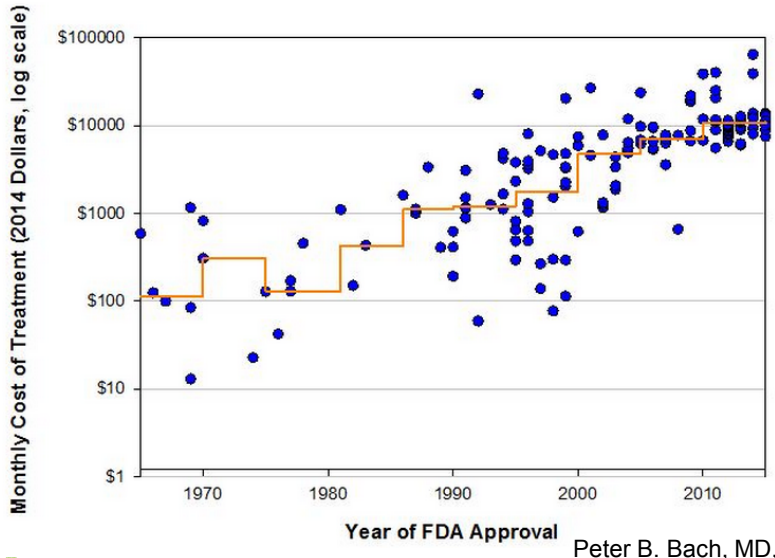
HTA and adaptive pathways



Clinical development and HTA

Clinical development		Health Technology Assessment
Exploratory trials	Confirmatory trials (RCTs)	
	• internal validity • safety • efficacy	• external validity • comparative effectiveness • cost-effectiveness • budget impact

The increase in new drug costs

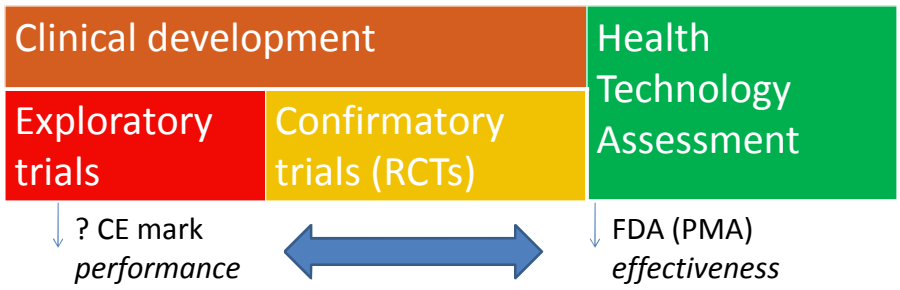


Peter B. Bach, MD, MSKC

Coverage with(out) evidence generation or the conflict of interest of the parties involved

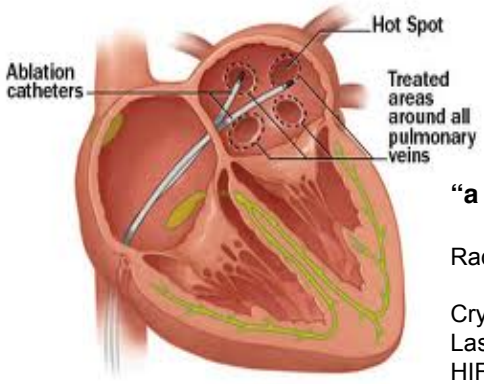
- **Before market authorisation / coverage:**
  - **RCT (if required) is performed timely**
  - **Coverage can be gained if efficacy is demonstrated**
- **After market authorisation / coverage:**
  - **RCT design is avoided, studies are delayed**
  - **Coverage can be lost if efficacy is not confirmed**
  - **Difficult decisions, also under adaptive pathways**

Innovative high-risk medical devices



Growing tension between
- fast market introduction based on device **performance** data
- payers requiring **efficacy/effectiveness** data, preferably based on RCTs.

Catheter ablation



"a knife is a knife"?

Radiofrequency waves
*HD Mesh Ablator®, Bard Inc.**
Cryo-ablation
Laser balloon ablation
HIFU balloon ablation
*HIFU ProRhythm Inc**
...
**Proven unsafe and stopped, years after CE mark was obtained, KCE report 184*

Why do we need RCTs?

The case of renal denervation to treat hypertension

- **EUnetHTA report based on non-RCT data:**
  - **"renal denervation using the Symplicity® system appears to decrease blood pressure, whereas the effects of other systems on blood pressure are uncertain."**
- **Reimbursed in 13 countries in Europe**
  - **in most cases regardless of the type of device.**
- **RCT versus sham procedure for FDA**
  - **NO EFFICACY, all trials put on hold.**

	Commercial clinical trials	Practice-oriented non-commercial clinical trials	Other clinical trials
Funding	Company	Healthcare deptm. (+university, charity)	Scientific research (+university, charity, industry)
Aim	For profit, development cycle	Optimize practice, comparative effectiveness	Create knowledge; proof of concept, translational
Interventions	Medicines, medical devices	+ surgery, lifestyle, psychotherapy, screening,…	+ surgery, lifestyle, psychotherapy, screening,…
International	Confirmatory (phase 2b/3)	If appropriate	Rarely
Risk level	++/+++	+/++	++/+++

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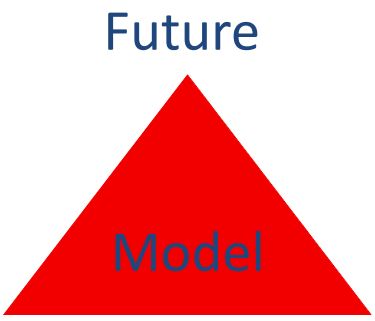
How to estimate an ICER?



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Data and models

- **Can systematic reviews be comprehensive?**

Reporting bias in medical research - a narrative review.
McGauran et al., IQWiG. Trials 2010.

- **Access to all study reports for HTA agencies?**
- **Meanwhile: trial registries, FDA/CDC website, …**

Level of information and transparency of pre-market clinical data

	Devices	Medicines
Europe	Trial registry (Eudamed) **not public** Trial results **not public** (in conflict with Directive and Declaration of Helsinki)	**Public** trial registry (Eudract) **Public** trial results (EPAR)
US	**Public** trial registry **Public** trial results	**Public** trial registry **Public** trial results

BMJ

RESEARCH

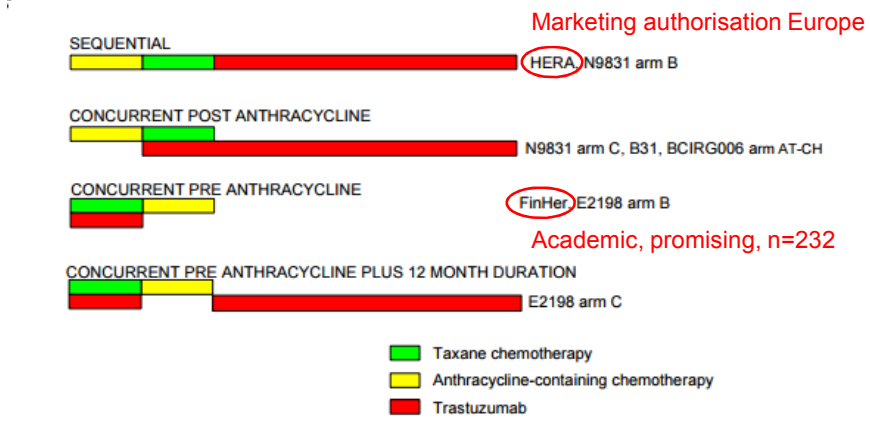
Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials

Dirk Eyding, project manager,[1] Monika Lelgemann, senior researcher,[2] Ulrich Grouven, statistician,[3,4] Martin Härter, head of department of medical psychology,[5] Mandy Kromp, statistician,[3] Thomas Kaiser, head of department of drug assessment,[3] Michaela F Kerekes, data manager,[3] Martin Gerken, researcher,[6] Beate Wieseler, deputy head of department of drug assessment[3]

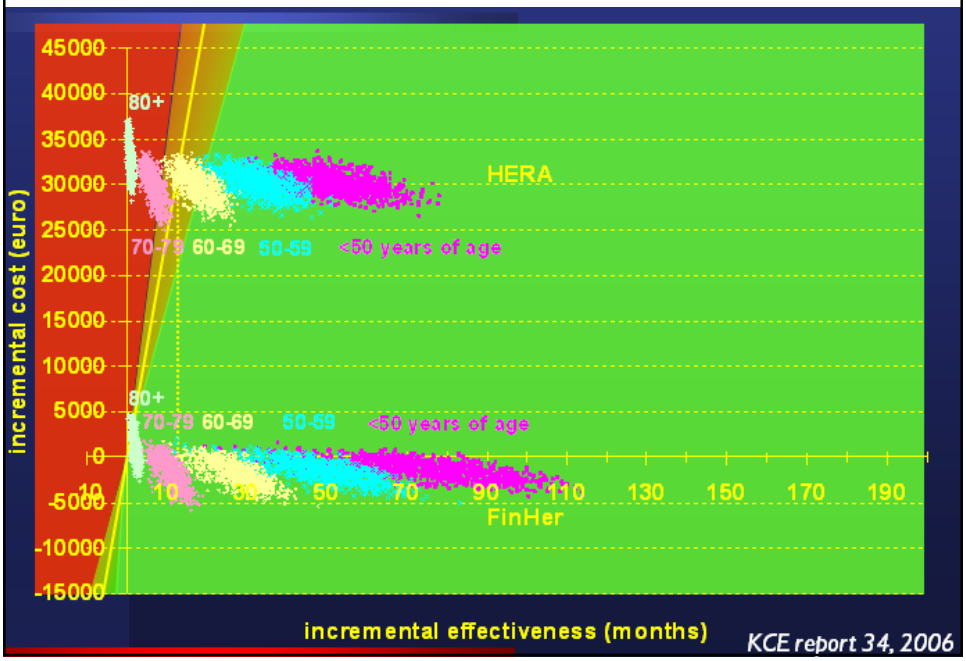
Conclusions Reboxetine is, overall, an ineffective and potentially harmful antidepressant. Published evidence is affected by publication bias, underlining the urgent need for mandatory publication of trial data.

BMJ. 2010 Oct 12;341:c4737.

The importance of trial registries
The case of trastuzumab (Herceptin)



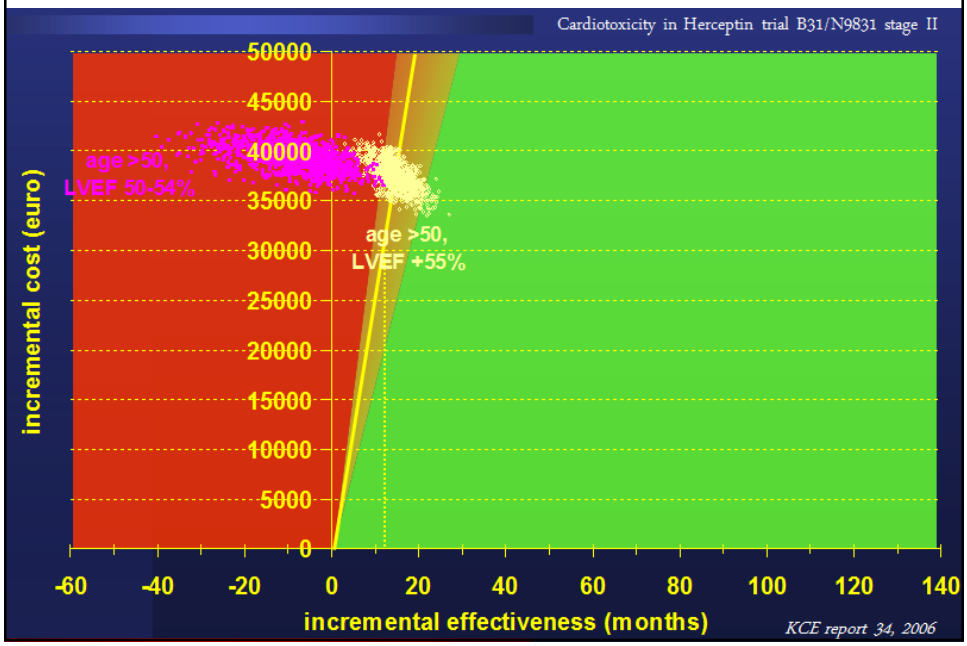
Targeted therapy in oncology - Herceptin



Trial registries, and choices made during clinical development, the case of trastuzumab (Herceptin) - continued

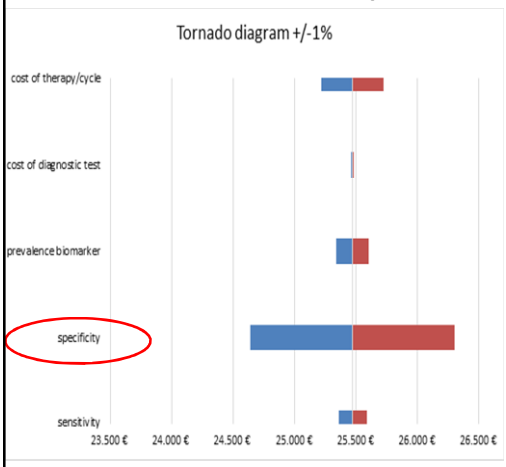
- **Found: study E2198, started in 1999. RCT in 2x100 patients of 10 weeks regimen versus 1 year of trastuzumab. Only short term safety published as abstract, but no survival data despite the long follow-up.**
- **Sponsor (Eastern Cooperative Oncology Group) was kindly requested to analyse and make public the survival data of E2198 ("was no priority").**
- **2006, after KCE report: no 5y survival benefit shown for one year of trastuzumab (83%) over 10 weeks (88%, p=0.29).**
- **Sledge GW, O'Neill A, Thor A, et al.: Adjuvant trastuzumab: long-term results of E2198. [Abstract] Breast Cancer Res Treat 100 (Suppl 1): A-2075, S106, 2006.**

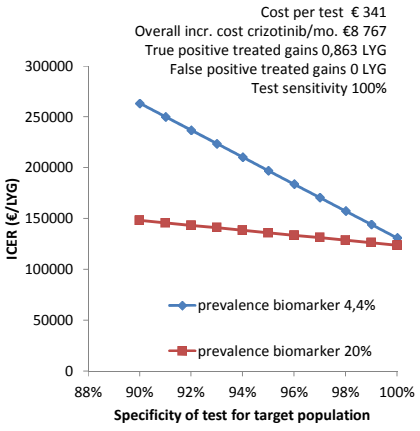
Modelling effects and side-effects



Test specificity of companion diagnostic impacts ICER

% false positives = 1 - specificity





Herceptin (trastuzumab) in early breast cancer

Xalkori (crizotinib) in NSCLC

San Miguel L, Hulstaert F. J Comp Eff Res. 2015 Nov;4(6):569-77

Low frequency of alterations in NSCLC
→
Importance of test specificity

http://www.mycancergenome.org/content/disease/lung-cancer/

Gene	Alteration	Frequency in NSCLC
AKT1	Mutation	1%
ALK	Rearrangement	3–7%
BRAF	Mutation	1–3%
DDR2	Mutation	~4%
EGFR	Mutation	10–35%
FGFR1	Amplification	20%
HER2	Mutation	2–4%
KRAS	Mutation	15–25%
MEK1	Mutation	1%
MET	Amplification	2–4%
NRAS	Mutation	1%
PIK3CA	Mutation	1–3%
PTEN	Mutation	4–8%
RET	Rearrangement	1%
ROS1	Rearrangement	1%

HPV vaccine, overall effect versus type specific

- **KCE report 64. 2007**
- **HPV genotype 16 and 18 detected in 70% of the cervical cancers.**
- **The message: vaccine prevents nearly 100% of 16/18 infections.**
- **This does not necessarily mean that when 16 and 18 type infections are completely eliminated there will be 70% less cervical cancer.**
  - **Efficacy is higher because of cross-protection?**
  - **Efficacy is lower because of multiple HR infections?**
- **The endpoint that integrates both effects is the overall reduction of cervical intraepithelial neoplasia grade 2+ (CIN2+) lesions in women negative for all HR HPV types at baseline (similar to vaccinating 12 y olds girls).**
  - **This result (46%) could only be found at CDC website (for a while).**

Modify assumptions when real data become available The case of HPV vaccination

	Overall % CIN2+ reduction	Overall % cervical cancer reduction
Model 1 (Smith JS, 2007)	49%	61%
Model 2 (Van de Velde N, 2007)	52%	68%
Model 3 (Kohli M, 2007)	66%	76%
RCT Gardasil, subgroup neg. for 14 HR HPV types, 3y data (company presentation for CDC)	46% (24-62%)	?

Letter to the Editor: How many CIN2+ lesions can be avoided through HPV 16/18 vaccination?

Vaccination against human papillomavirus - an impact on preterm delivery? Estimations based on literature review. *Sjøborg KD, Eskild A. Acta Obstet Gynecol Scand. 2009;88(3):255-60.*

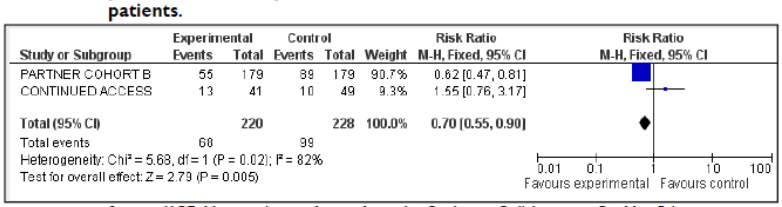
Letter to the Editor: How many CIN2+ lesions can be avoided through HPV 16/18 vaccination?

"One of the important assumptions in this paper is that women who are vaccinated have a 65% reduced risk of CIN2+ lesions. However, the most reliable estimate publicly available for overall CIN2+ reduction after vaccination is 46% (95% confidence interval 24%-62%). This estimate is based on a pooled analysis after 3 years of follow-up of all subjects who tested negative at baseline for 14 high-risk HPV types and who were randomly assigned to receive Gardasil® or placebo."

Unpublished data in FDA meeting materials or transcripts
The case of transcatheter aortic valve insertion (TAVI).

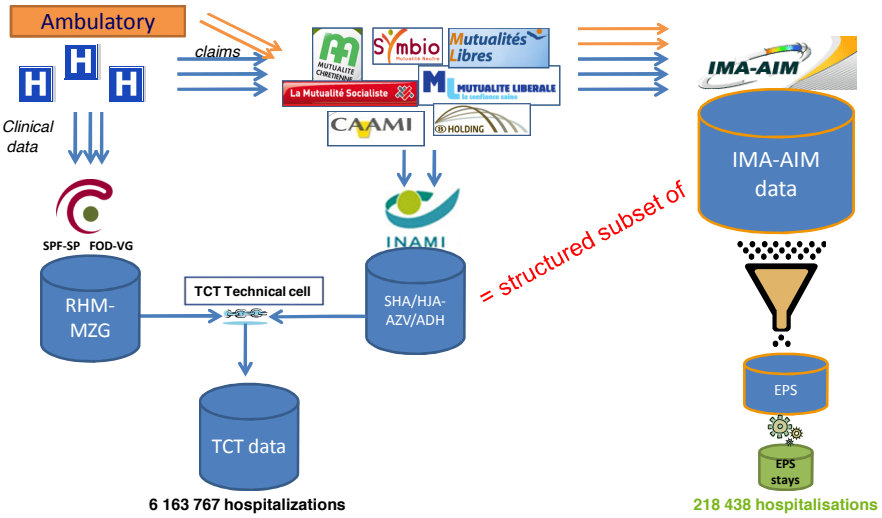
- **KCE report 163. 2011**
- **Unpublished data related to the randomised Continued Access Cohort B subgroup of the PARTNER RCT were presented by the sponsor at the July 20, 2011 FDA meeting and results are depicted in Figure 4.**

Figure 4. Risk ratio for all-cause 1-year mortality of TAVI in inoperable patients. Meta-analysis of PARTNER Cohort B and Continued Access patients.



Source: KCE. Meta-analysis software from the Cochrane Collaboration, RevMan 5.1

Databases and data flows



KCE REPORT 184C

KCE
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Belgian Health Care Knowledge Centre

Europace
doi:10.1093/europace/eut004

CLINICAL RESEARCH

Effectiveness of catheter ablation of atrial fibrillation in Belgian practice: a cohort analysis on administrative data

Hans Van Brabandt*, Mattias Neyt, and Carl Devos

Belgian Health Care Knowledge Centre, Brussels, Belgium

Received 25 October 2012; accepted after revision 30 December 2012

IMA data 2006-2010, plus some registry data BeHRA

KCE report 184, 2012

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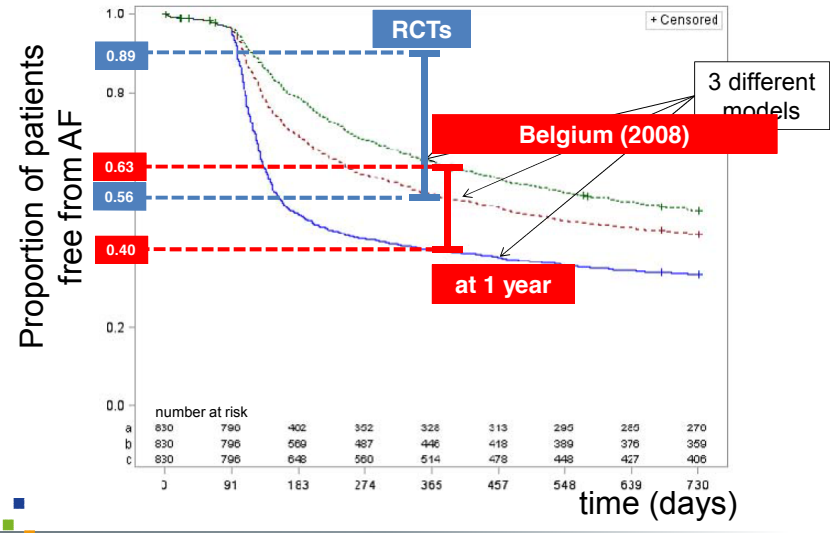
Freedom from AF



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Model for Trisomy 21-testing in Belgium

- Most variables based on up to date local data.
- for Belgium
  - National Institute for Statistics,
  - RIZIV-INAMI,
  - Minimal clinical data of hospitalizations,
  - Permanent population sample,
- for Flanders
  - Studiecentrum Perinatale Epidemiologie,
- for 40% of Flanders: AML laboratory,
- or a hospital: Ziekenhuis Oost-Limburg.

KCE report 222, 2014

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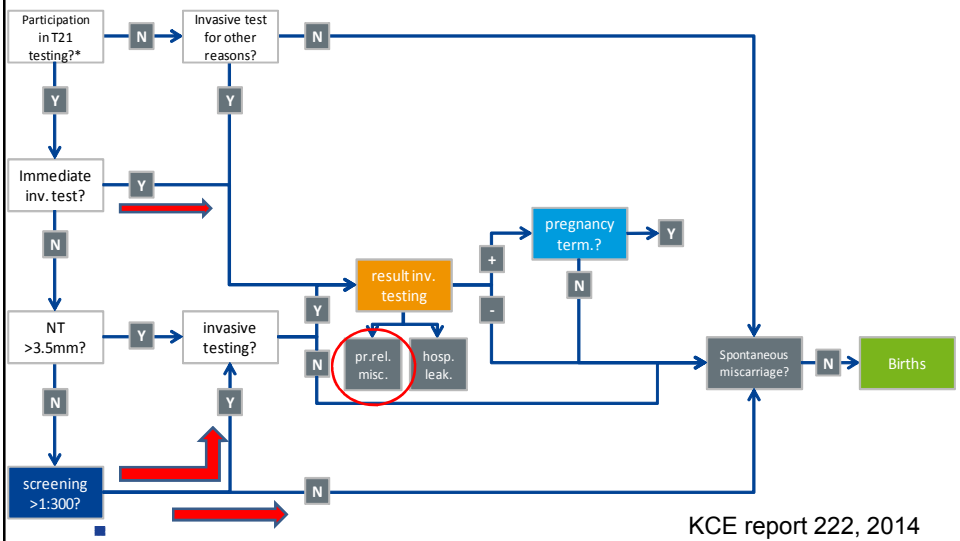
Model for Trisomy 21-testing in Belgium

✓ local data
✓ calibration



KCE report 222, 2014

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Harms compared to current situation for NIPT options

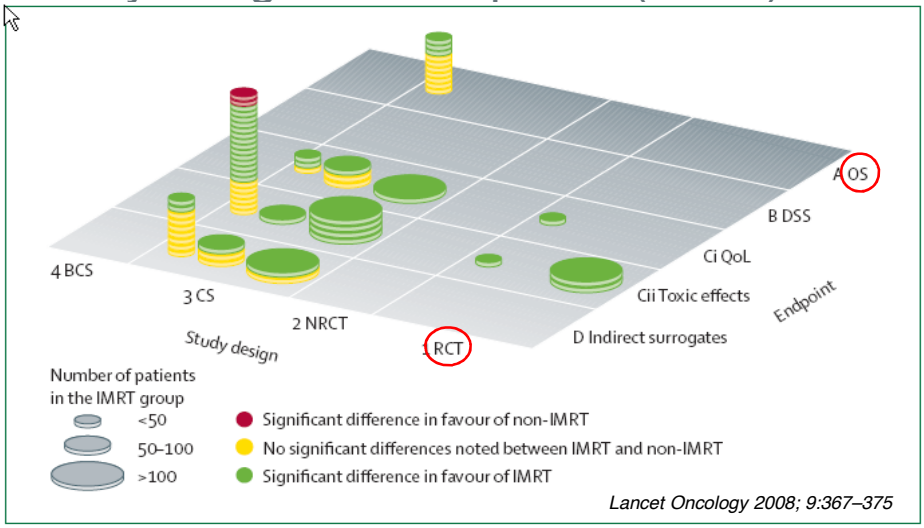
HARMS	Triage 1:300 5%	Triage 1:600 9%	Triage 1:1700 20%	Primary NIPT
Procedure-related miscarriages	↓↓	↓↓	↓↓	↓↓
False-negative tests (T21 missed)	= (+1)	↓	↓↓	↓↓↓

Table 5 – Scenario's of introducing NIPT

Scenario	Sensitivity (%)	Specificity (%)	T21 detected (n)	T21 born, after false neg. screen (n)	Invasive tests T21 related (n)	Procedure-related miscarriages T21 related (n)	Max. cost NIPT for €86 944 per T21 diagnosed (€)
Current screening >1:300 risk	72.5	95.0	170	41	5772**	58	none
Triage NIPT for >1:300 risk	72.5	95.0	169	41 +1 NIPT	1615**	16	>€460
Triage NIPT for >1:600 risk	81.0	90.9	184	28 +1 NIPT	1706**	17	>=€460
Triage NIPT for >1:1700 risk	87.3	80.2	194	19 +1 NIPT	1915**	19	€289
Primary NIPT same uptake	99.3*	99.84*	215	2	793***	8	€152
Primary NIPT 90% uptake	99.3*	99.84*	240	2	848***	8	€152

*sensitivity and specificity of NIPT after excluding NIPT with 'no result'.
**including 1000 invasive tests without screening and 398 invasive tests for NT>3.5mm
***including 398 extra invasive tests for NT>3.5mm; and assuming all 2000 women will accept current screening after a repeated 'no result' NIPT

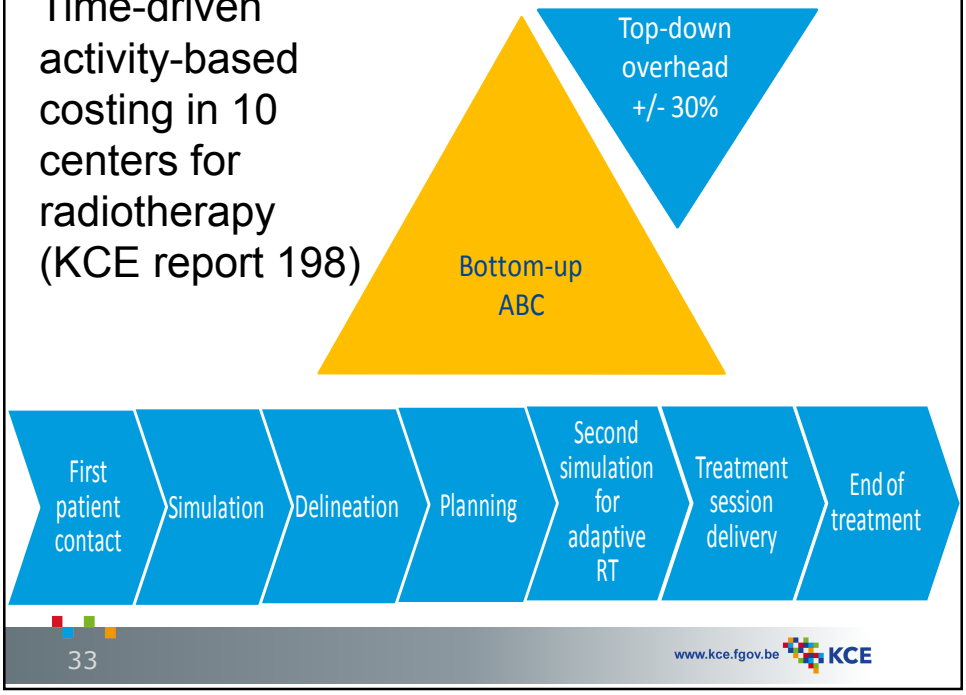
Study design and endpoints (IMRT)



Lancet Oncology 2008; 9:367–375

Figure 3: **Evaluation tool for relevance of clinical statements reported in 56 studies of IMRT**
BCS=best case series. CS=case series. NRCT=non-randomised controlled trial. RCT=randomised controlled trial. OS=overall survival. DSS=disease-specific survival. QoL=quality of life.

Time-driven activity-based costing in 10 centers for radiotherapy (KCE report 198)



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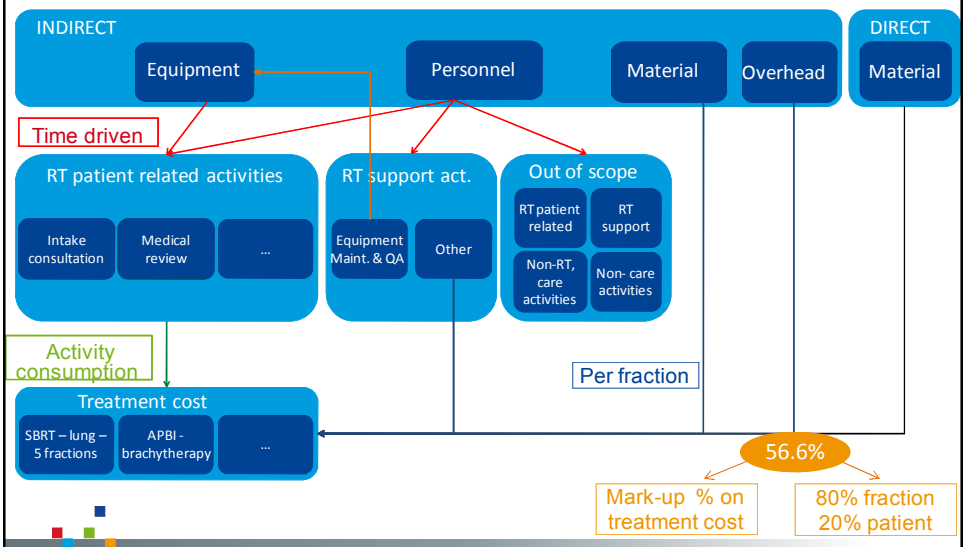
Time-driven activity-based costing



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Patients and costs in the 10 centres

Treatment group	Average cost (euro)	Patients in 10 centres (N/year)	(%)	Total cost in 10 centres (Mio euro)	(%)
Breast	4675	5133	28%	24,0	31%
Head Neck	7153	1131	6%	8,1	10%
Prostate	6995	1250	7%	8,7	11%
Lung	5422	1458	8%	7,9	10%
Rectum	4810	834	5%	4,0	5%
Other	4392	3620	20%	15,9	20%
Palliative	1916	4839	26%	9,3	12%
Overall	4266	18265	100%	77,9	100%

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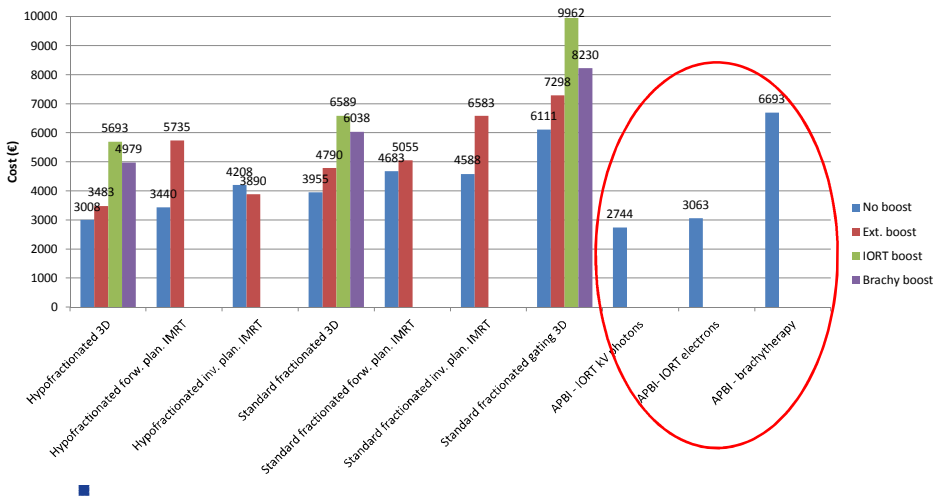
Cost of radiotherapy of early breast cancer



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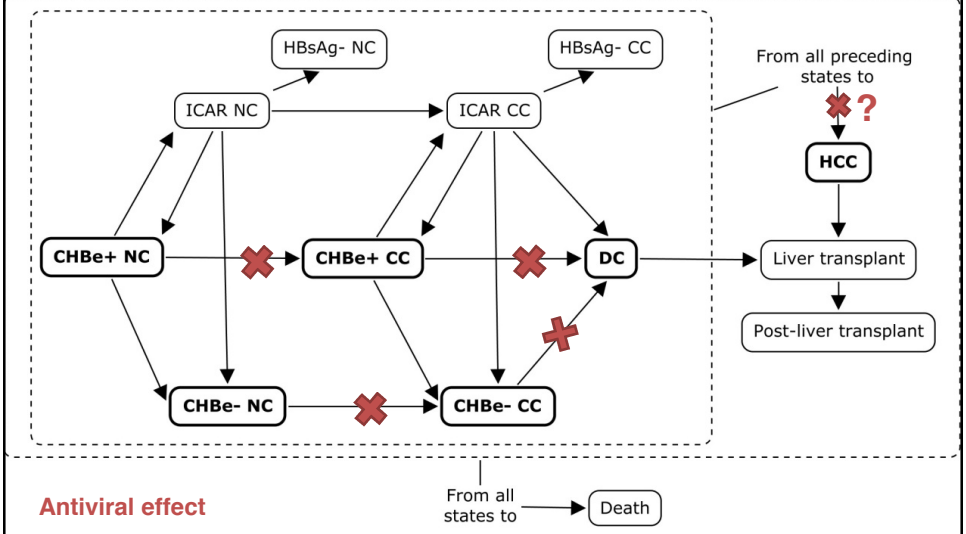
Chronic hepatitis B model

KCE Report 127, 2010



Treated states are in bold; ICAR= inactive carrier; CHB= chronic hepatitis B; NC= no cirrhosis; CC= compensated cirrhosis; DC= decompensated cirrhosis; HCC= hepatocellular carcinoma

Model input

	Source	Important findings
Patients / disease state	Survey in 18 centres, >500 patients	25% of CHB patients have cirrhosis
State transitions	Literature plus Leuven untreated cohort (n=278)	Cirrhosis age-dependent CHBe+ with normal ALT
Treatment effect	Single arm studies, expert opinion	tenofovir = entecavir effect cirrhosis > effect HCC
Cost / disease state	Survey patients linked to IMA through TTP, cost attribution by expert	Year of LT: €100,000
Quality of life/ disease state	Multicenter survey, literature: DC, HCC, LTy1	No change after drop in viral load

Patient numbers, annual cost and utility by disease state

Disease state	Patients visiting a specialist in Belgium °	Mean annual cost per patient, HBV related		Mean utility value (95% confidence interval)
		No antiviral strategy (euro)	Tenofovir strategy (euro)	
ICAR	1266	115	115	0.83 (0.82-0.87)
CHBe+/- NC	1197	591*	591+4970**	0.82 (0.78-0.86)
CHBe+/- CC	383	1115*	1115+4970**	0.78 (0.73-0.84)
DC§	10§	6814*	6814+4970**	0.49 (0.46-0.51)#
HCC	49	10816*	10816+4970**	0.52 (0.49-0.54)#
Liver transpl. y1	19	99998	99998	0.71 (0.69-0.74)#
Post liver transpl.	181	7518	7518	0.82 (0.75-0.88)

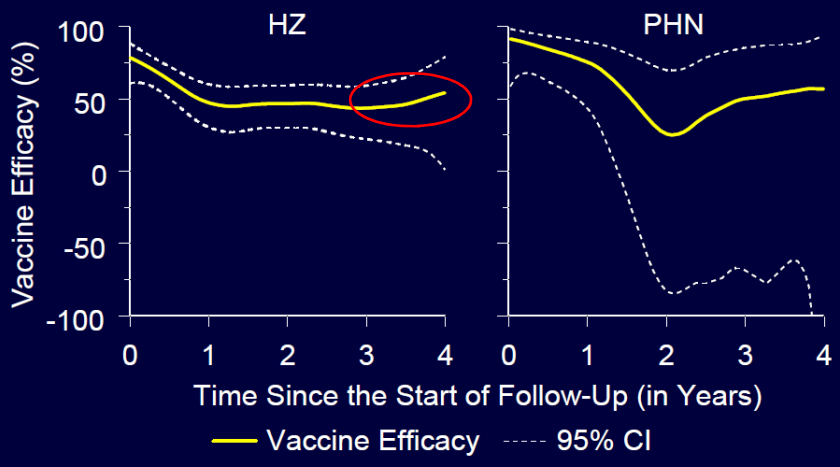
°excluding HIV or HCV co-infection; *excluding antiviral drug costs; **annual cost of tenofovir reduced by 17% in 2015 and by 19% in 2018. #based on the absolute decrease in utilities from CHB, as reported by Levy et al. 2008. §underestimated

Critical determinants of ICER

	Literature Lower ICER	KCE Higher ICER
QoL improvement if low DNA or e seroconversion	Yes (assumption)	No (measured)
Duration of treatment in CHBe- patients	Stop if low DNA	Continue (= guidelines)
Natural progression rate to cirrhosis	Uniform 5% to 9% (not compatible with survey results)	1%, 2%, 5% age dependent (measured)
Assumed reduction of HCC under treatment	Based on untreated cohort (REVEAL)	50% reduction, highly uncertain

Hulstaert F et al. Int J Technol Assess Health Care. 2013 Jan;29(1):35-41

Duration of ZOSTAVAX™ Efficacy



- After initial drop during the first year, point estimates for VE_{HZ} and VE_{PHN} were stable through 48 months of follow-up
- Subject follow-up is continuing (persistence substudy) at 12 of 22 study sites

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ZOSTAVAX™ lots administered

Protocol 004

	Grp 1*	Grp 2**	Grp 3**	Grp 4**
N	835	978	8720	8737
PFU/ Dose (10^3)	50-62	34-42	26-33	21-26
Dates	11/98 11/99	04/99 11/99	07/99 12/00	07/00 09/01
Avg. F/U (days)	1400	1400	1200	900

*Group 1 comprised of 3 unaged clinical lots

**Each group comprised of 3 of the 9 accelerated aged clinical lots

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Data and models

- Surrogate endpoints without validation
- Modify assumptions when real data become available
- Risks of extrapolations
- Assumptions without measurements eg EQ5D
- The problem of the fake references
- Also model the side-effects of the intervention
- Validation and transparency of source code
- Importance of discount rate for costs and benefits

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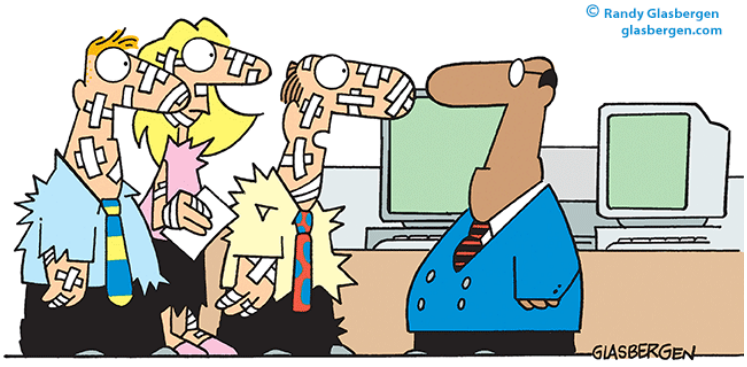

"Frankly sir, we're tired of being on the cutting edge of technology."

CCC CoCanCPG
eunethta
European Observatory on Health Systems and Policies
INAHTA