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# Discrepancy between clinical decisions and economic factors


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 & PharmacoEconomics **PE<sup>2</sup>**



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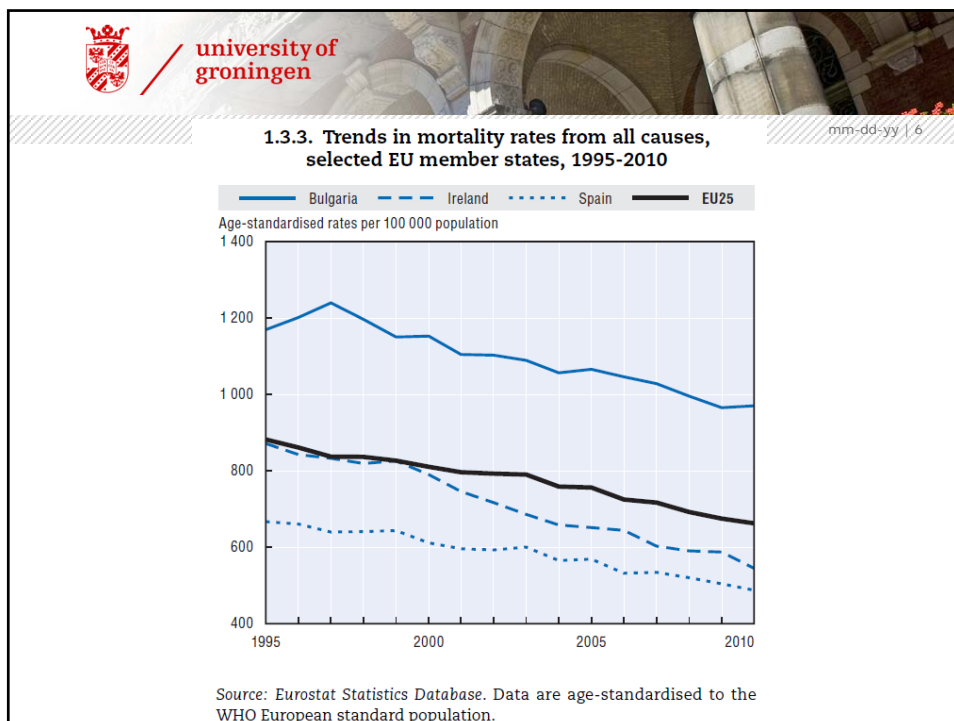
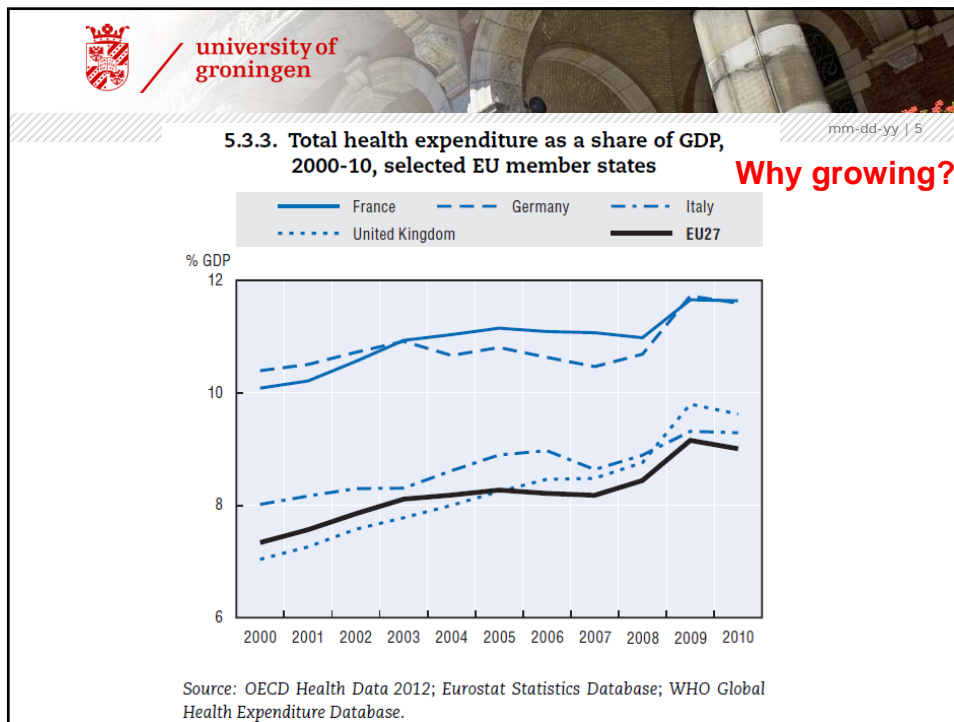
# Nothing to disclose

## Background Stefan Vegter

- Trained as pharmacist
- PhD in pharmaco-economics
- Researcher University of Groningen
  - Courses pharmaco-economics, pharmaco-epidemiology
  - Outcomes research of patient care in community pharmacies
- Vegter Health Economic Research
  - Reimbursement dossiers
  - Economic models, meta-analyses, ...

## Overview

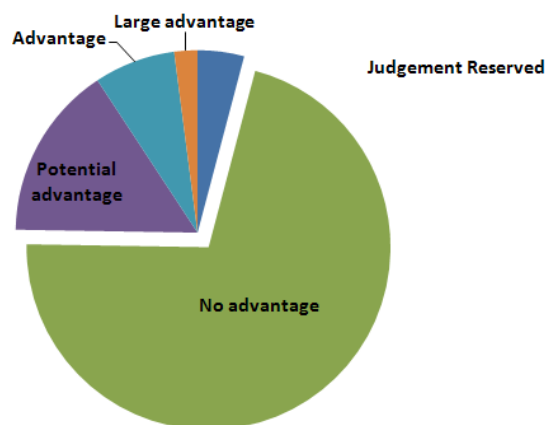
- **Reimbursement of drugs**
  - Reimbursement systems in the EU
  - Role of pharmaco-economics in drug reimbursement
- **Discrepancy between economics and clinical decisions**
  - Case studies
  - Thresholds, exceptions and patient-access schemes
  - New pharmaco-economics: outcomes research




## Healthcare cost drivers

- **“Good” reasons:**
  - Lower mortality -> population growth
  - Income growth -> more spending
  - Improved diagnostics -> earlier treatment
- **“Neutral” reasons**
  - Population is aging (e.g. post-WW 2 baby-boom)
- **“Decision pending” reasons**
  - ‘New’ diseases and ‘lifestyle’ drugs (medicalisation)
  - New drugs for existing diseases
  - Shift towards more expensive drugs

## Canadian Health Technology Assessments 1981-2005




Nakagawa. 2007

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## Reimbursement processes

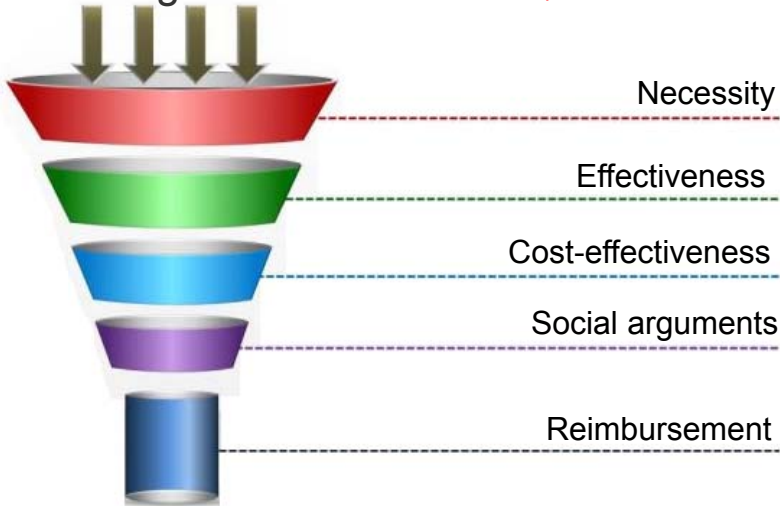
- **Differences**
  - Assessors can be government, healthcare providers or insurers
  - Funding can be taxes or insurance
  - Outcomes can be recommendations or decisions
- **Similarities in general structure**
  - Two main questions
    - Question 1: Medical value?
    - Question 2: *Added* medical benefit?

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## Medical value “Dunnings Funnel”

(not official in NL!)



Necessity

Effectiveness

Cost-effectiveness

Social arguments

Reimbursement

## Question 1: medical value

- **Necessity**
  - Is the care necessary to participate in society?
  - Can persons pay for it themselves?
- **Effectiveness / safety**
  - Does the intervention or care do what is to be expected of it (balance between effectiveness and adverse effects)?


## Question 1: medical value

- **Cost-Effectiveness**
  - Is the balance between the costs and (health) gains favorable?
- **Social arguments**
  - Does society *want* the drug to be reimbursed?
  - Is it practically doable to reimburse? (e.g. budget impact)
  - Knock-on effects of reimbursement
  - Own responsibility?

## Question 2: added medical benefit

- Assessment in comparison with existing therapies:
  - Effectiveness
  - Adverse drug effects
  - Experience
  - Applicability
  - Ease of use

## Outcome of assessment

- **No added therapeutic benefit (List 1A; 80%)**
  - Placed in clusters based on therapeutic similarity
  - Pharmacotherapeutic dossier required, but no economics
  - Reimbursement limit (≈average of other drugs)
- 
 • **Added therapeutic benefit (List 1B: 20%)**
  - For drugs without comparable drugs *or* with therapeutic superiority
  - Pharmacotherapeutic and Farmacoeconomic dossier required
  - No reimbursement limit (but maximum is price in GB, BE, GE and FR)
- **Conditional reimbursement (List 2): fear of high costs or abuse**
  - Only reimbursed when given as second/third-line (e.g. fingolimod for MS)
  - Only reimbursed for specific indications (e.g. sildenafil for pulm.hypert.)

## France

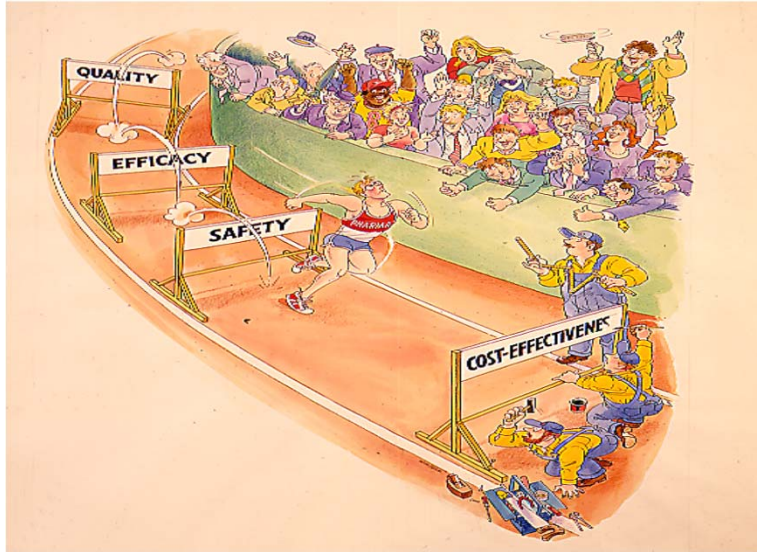
- Step 1: Medical benefit assessment (SMR):
  - Based on efficacy, safety, severity of disease, public impact
  - **Outcome determines reimbursement percentage:**
    - Important (100% hospital / 65% retail) (>85% of all drugs)
    - Moderate (35%)
    - Weak (15%)
    - Insufficient (0%)
- Step 2: Improvement over existing drugs (ASMR)
  - **Used for price negotiations**
  - 'Major innovation' to 'no improvement' (most get lowest rating)

## Overview

- **Reimbursement of drugs**
  - Reimbursement systems in the EU
  - **Role of pharmaco-economics in drug reimbursement**
- **Discrepancy between economics and clinical decisions**
  - Case studies
  - The costs of orphan drugs
  - Thresholds, exceptions and patient-access schemes
  - New pharmaco-economics: outcomes research




## Cost-effectiveness, the fourth hurdle?



## Role of pharmacoeconomics

- In several EU countries, CE is assessed during the reimbursement process
- **The actual role of health-economics is limited**
  - Only UK has official threshold for cost per QALY
  - NL: many reimbursed drugs (on list 1B) do not have pharmacoeconomic evidence (e.g. exceptions for orphan drugs and HIV drugs)
  - NL: several drugs are reimbursed despite negative CE evaluation
- The role of health-economics is increasing however


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## Status aparte for orphan drugs?

- Monetary incentives
  - Long market exclusivity
  - Reduced registration fees
- Regulatory incentives
  - Scientific advice
  - No requirements for health-economics in NL
- Incentives worked: >80 orphan drugs on the market in Europe




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## Status aparte for orphan drugs?

- Portugal, France, Belgium
  - All orphan drugs are reimbursed
  - In Belgium, some rejected because cheaper alternative exists (e.g. compounded)
- Netherlands:
  - No cost-effectiveness analysis required
  - Most (95%) orphan drugs are reimbursed (may change in future)
- Scotland:
  - Cost-effectiveness analysis required
  - Many (≈50%) orphan drugs are not reimbursed (too high cost/QALY)


Vegter. CT. 2010

## Overview

- **Reimbursement of drugs**
  - Reimbursement systems in the EU
  - Role of pharmaco-economics in drug reimbursement
- **Discrepancy between economics and clinical decisions**
  - **Case studies: phosphate binders in renal disease**
  - Thresholds, exceptions and patient-access schemes
  - New pharmaco-economics: outcomes research

## Case studies: phosphate binders

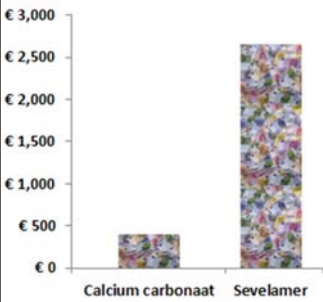
- Calcium carbonate, calcium acetate
  - + Cheap, long experience
  - Hypercalcemia, high pill burden (compliance)
- Non-calcium binders (sevelamer, lanthanum carbonate)
  - + No hypercalcemia, lower pill burden
  - Expensive!


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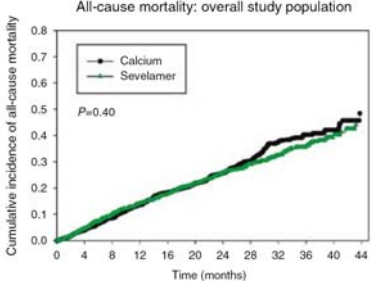
## Case study 1: expected versus real-life use

- Dutch reimbursement report Sevelamer (2000):
  - Similar effectiveness of sevelamer and calcium-based phosphate binders
  - In case of hypercalcemia, sevelamer (=calcium-free) may be given
  - Estimate of CVZ and manufacturer: 40% substitution in 2<sup>nd</sup> line



Calcium carbonaat    Sevelamer

All-cause mortality: overall study population




Cumulative incidence of all-cause mortality

Time (months)

$P=0.40$

| No. at risk | 1050 | 888 | 753 | 640 | 559 | 491 | 430 | 347 | 259 | 161 | 64 | 12 |
|-------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|
| Calcium     | 1050 | 888 | 753 | 640 | 559 | 491 | 430 | 347 | 259 | 161 | 64 | 12 |
| Sevelamer   | 1053 | 882 | 737 | 656 | 591 | 520 | 449 | 379 | 298 | 196 | 66 | 18 |

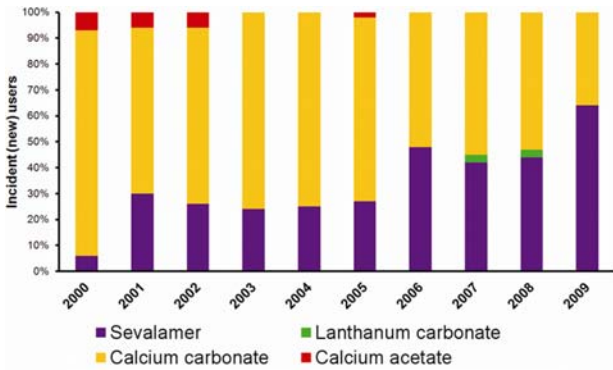
CVZ. 2000  
Suki. KI. 2007


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## ... and real-life costs...

- Observational study in Dutch prescription database (unpublished)
- **Real-life use: up to 60% in first line use**



Incident (new) users

2000 2001 2002 2003 2004 2005 2006 2007 2008 2009


■ Sevalamer    ■ Lanthanum carbonate  
■ Calcium carbonate    ■ Calcium acetate


Vegter. RuG. 2011

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## Case study 2: indirect medical costs


|  | Medical   | Non-medical                         |
|--|---|-------------------------------------|
| <b>Direct costs</b><br>   | Medication<br>Administration costs<br>Hospital admissions | Travel expenses<br>Home adaptations |
| <b>Indirect costs</b><br> | <b>Medical costs in gained life-years</b>                 | Productivity losses                 |

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## Indirect medical costs, unfair or logical?

- Dialysis patients with not regain renal function by using phosphate binders...
  - Life-years gained means extra dialysis (≈50-70K € per year!)
  - Inclusion of these costs will make *any* therapy non-CE
  - Solutions may be exclusion of these costs (illogical?) or judging by different thresholds



| Second line phosphate binder | Dialysis costs excluded | Dialysis costs included |
|------------------------------|-------------------------|-------------------------|
| Drug cost (€/day)            | ICER (€/QALY)           | ICER (€/QALY)           |
| €0.00                        | Cost-saving             | €0000                   |
| €7.00                        | €4500                   | €104000                 |

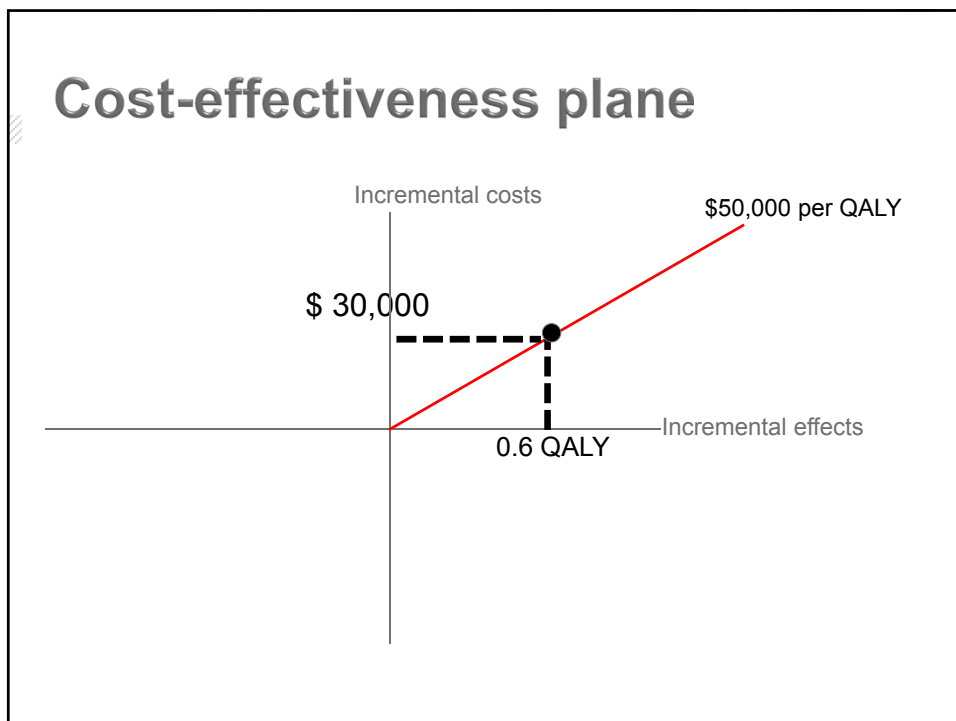
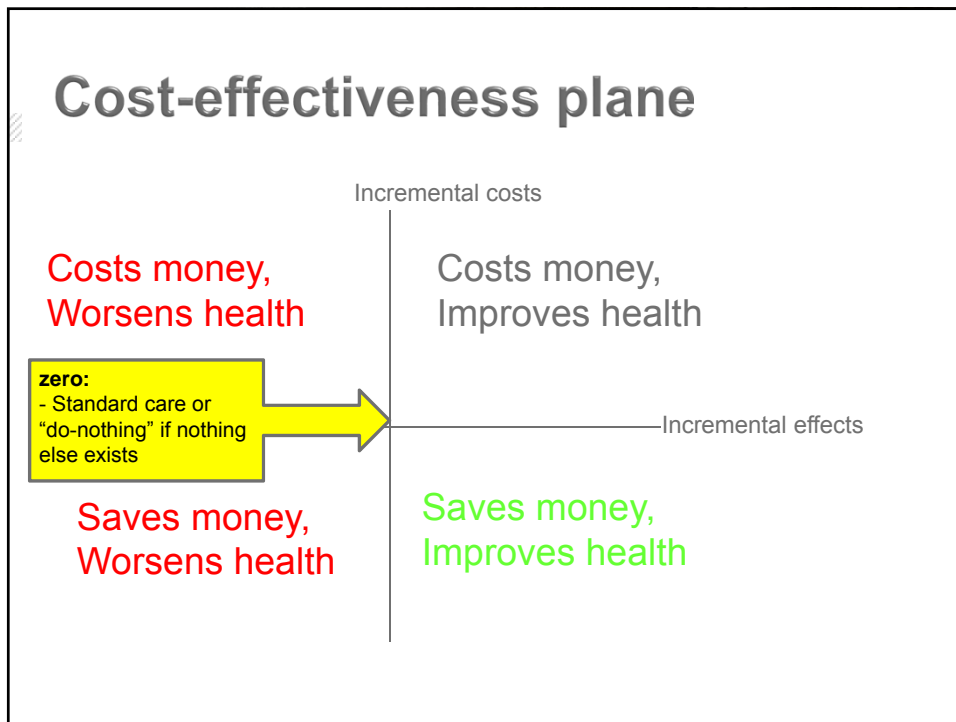
Vegter. RuG. 2011

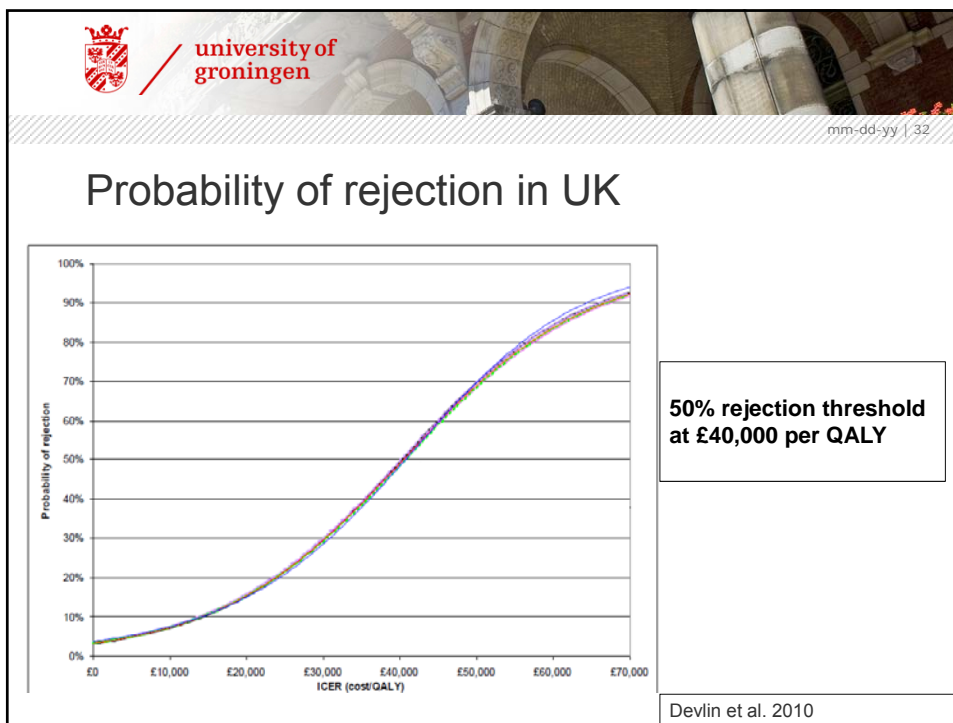
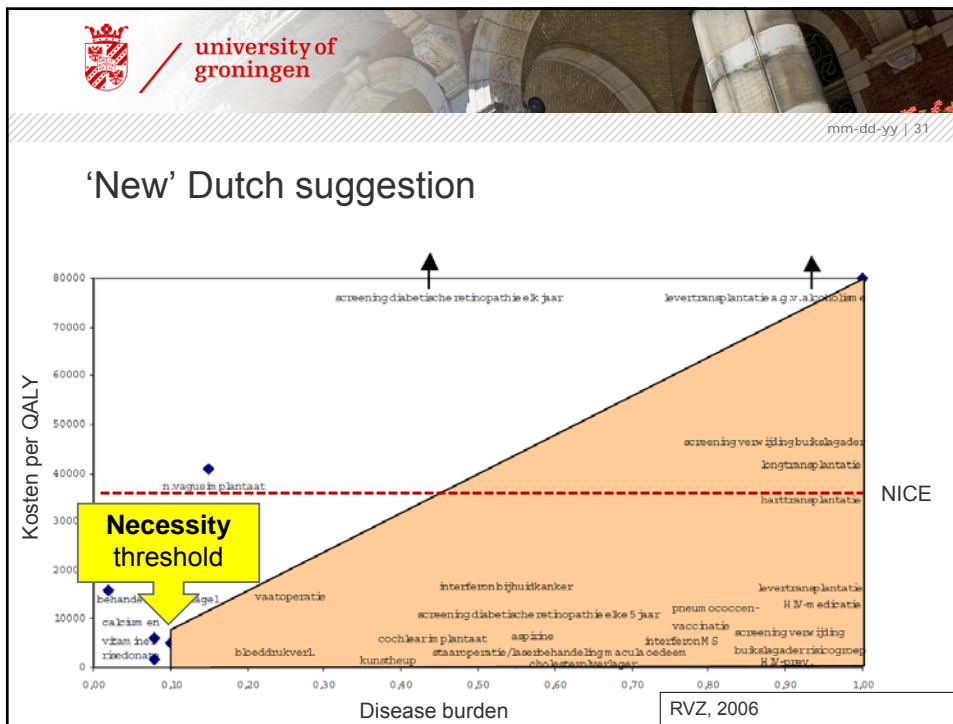
## Overview

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  - Reimbursement systems in the EU
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- **Discrepancy between economics and clinical decisions**
  - Case studies
  - **Thresholds, exceptions and patient-access schemes**
  - New pharmaco-economics: outcomes research

## Limits to cost-effectiveness?

- **Societies' willingness to pay for a QALY**
  - Canada: \$20.000 - \$100.000
  - US: \$50.000 - \$100.000
  - Netherlands: €20.000 / €50.000
  - Belgium: €50.000
  - UK: £20.000 - £30.000
  - WHO standard: 3 \* GDP per capita





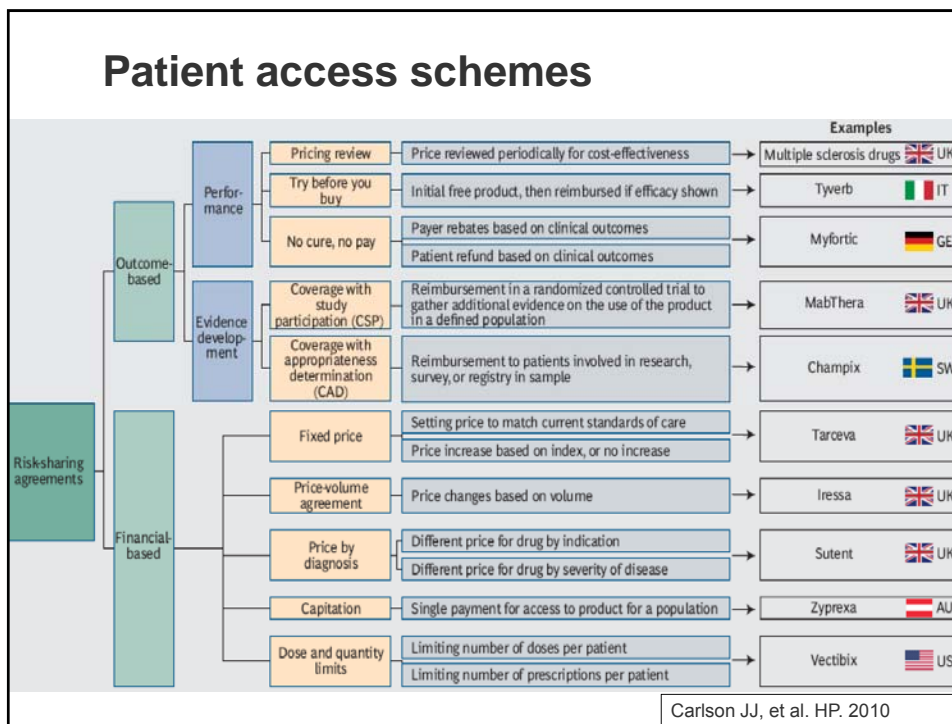


## Role of CE in UK

- The 'official' threshold is £20,000 - £30,000
- However, there are exceptions and co-factors:
  - Severity (e.g. Cancer = at least £10,000 higher ICER approved)
  - Significant innovation
  - Existence of treatment alternatives
  - Uncertainty in CE estimates
  - **End-of-life treatments**
    - For patients with limited life-expectancy (<2 years)
    - Treatments can gain at least 3 additional months of life
    - Small population, no treatment alternative

## Patient access schemes





## Overview

- **Reimbursement of drugs**
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## What is outcomes research

- Outcomes research focuses on real-life outcomes: drug use, quality, effectiveness, cost-effectiveness and positioning
- In potential, this may solve (some of) the discrepancy between clinical and economic factors!
  - Currently used for expensive drugs, e.g. TNF-alpha, anticancer, orphans

**Real-life safety**




**Real-life effectiveness**



**Real-life use**

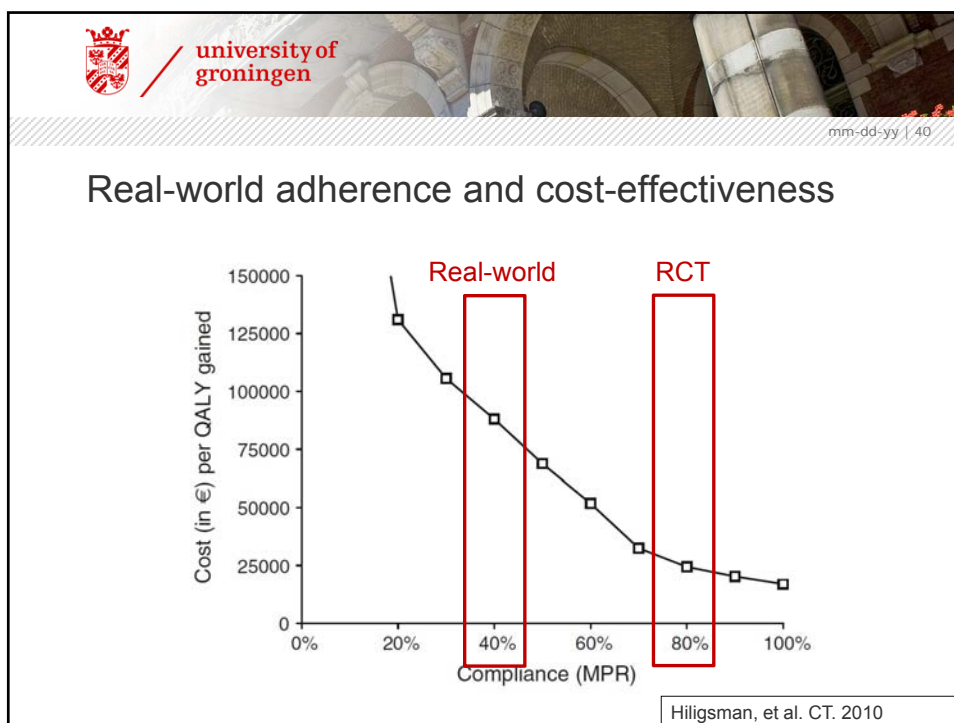
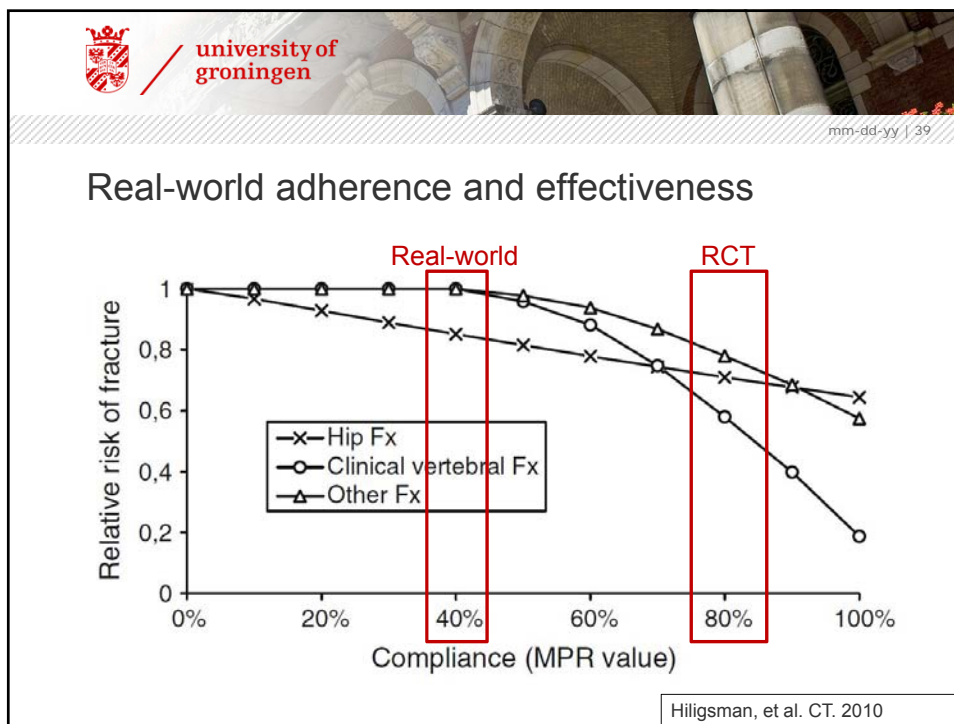


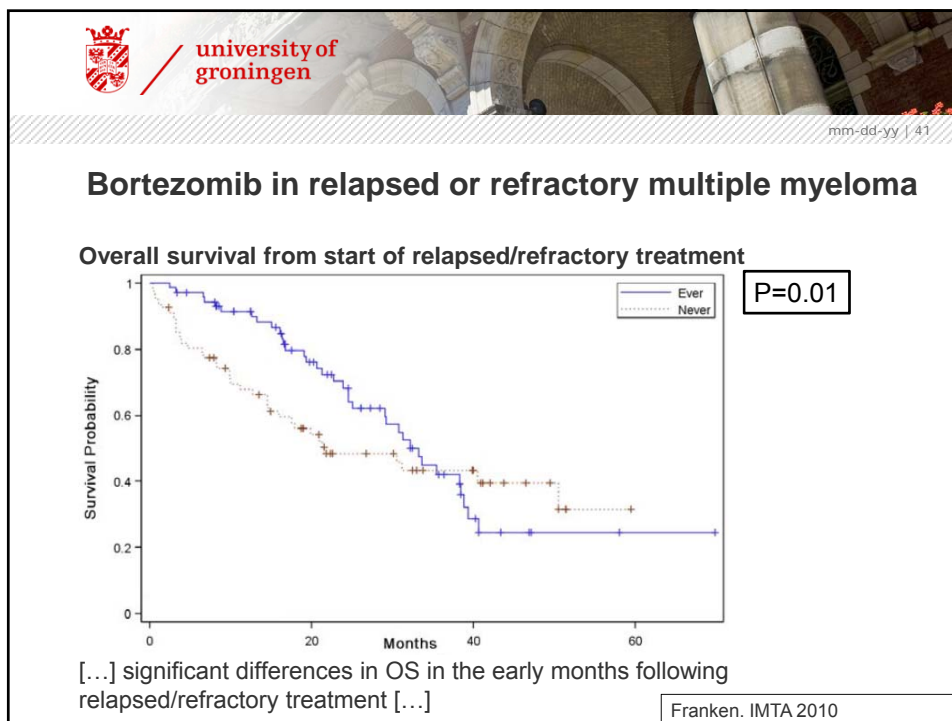

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## What answers does OR provide?

- Treatment is conditionally reimbursed for 4 years, after this time reassessment...
- **Therapeutic value**
  - Overview new data (effectiveness and safety)
  - Preferably country-specific data (hospital registries)
- **Real-life use**
  - E.g. Off-label use, variability in dosage, new guidelines
- **Real-life cost impact**
  - Differences between expected and real-life costs
- **Cost-effectiveness**
  - On the basis of real-life effectiveness and costs






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## Closing remarks

- Pharmaco-economics offers a formal frame to support health-care decisions
  - Role in reimbursement is limited but growing
- Discrepancies may occur!
  - Many non-economic and political arguments play a role
  - A fixed cost-effectiveness thresholds may not be desirable...
  - ... and/or price discounts and/or conditional reimbursement may increase
  - ... re-evaluations may be necessary and/or ....
- Shift to outcomes research
  - Pay-for-performance schemes
  - Hospitals will play a large role in 'real-life' cost-effectiveness studies

## Health Economics.... A New Toxicity?



*"The drug itself has no side effects - but the number of health economists needed to prove its value may cause dizziness and nausea"*

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# Discrepancy between clinical decisions and economic factors

## Workshop topics

Academy Seminar 2013 - Lisbon, Portugal, September 14 2013

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- **WORKSHOP 1**
- **PATIENT ACCESS SCHEMES**

## Patient access schemes

- **Discuss the pro's and cons of PAS**
  - Volume-price agreements
  - Outcomes based risk sharing
  - Direct discounts
- **Perspectives:**
  - Government/society (payer)
  - Healthcare professional
    - What would a hospital have to do to make the PAS possible (for example, PAS in Multiple sclerosis / Multiple myeloma)
    - Should a clinical expert have a veto on a PAS?
  - Manufacturer

- **WORKSHOP 2**
- **COMPOUNDED OR LICENCES DRUGS**



## Example 1


- Compounded medication versus registered orphan drugs
- Wilzin® - Wilson's disease (*prevalence 6:10,000*)
- = zinc acetate, first clinical study in 1978 (Lancet)
- Licenced drug costs 5 times more than compounded product.



Daphne Austin (UK Public Health Commissioning Network):  
 "The NHS is being ripped off."

## Example 2


- Firdapse® - Lambert-Eaton Myasthenic Syndrome (*prev. 3.4 per million*)
- Costs: £40,000-£70,000 per year
- = amifampridine ( $\approx$ diaminopyridine)
- Costs £800-£1,000 per year
- Manufacturer did not have to conduct any clinical trials (these were already done in 1984)

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### Comparison of purchase prices and compounding production costs of selected orphan drugs in Belgian hospitals (2011)

| Active substance                 | Orphan indication                          | Evidence | Quantity            | Cost to hospital (€) |          |
|----------------------------------|--|----------|---------------------|----------------------|----------|
|                                  |  |          |                     | Purchase             | Compound |
| <b>Amifampridinez (Firdapse)</b> | Lambert-Eaton myasthenic syndrome          | 1984     | 60 x 10 mg tablets  | 1380                 | 24       |
| <b>Betaine anhydrous</b>         | Homocystinuria                             | 1981     | 180 g solution      | 448                  | 92       |
| <b>Mercaptamine bitartrate</b>   | Nephropathic cystinosis                    | 1978     | 60 x 50 mg tablets  | 64                   | 25       |
| <b>Sodium phenylbutyrate</b>     | Urea cycle disorders                       | 1990     | 60 x 500 mg tablets | 187                  | 70       |
| <b>Zinc acetate (Wilzin)</b>     | Wilson's disease (hepatolenticular degen.) | 1978     | 60 x 50 mg tablets  | 84                   | 14       |



*"Pharmacies can consider compounding, rather than purchasing, these orphan drugs."*

Simoens. DTP 2011

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## Discussion suggestions

- What are the advantages and disadvantages of having a registered product versus compounding the product in the hospital?
- What could be potential advantages of having a registered product?
- Should (hospital) pharmacies always be allowed to prepare these orphan drugs themselves?



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- **WORKSHOP 3**
- **REIMBURSEMENT DECISIONS**



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## Reimbursement assessment

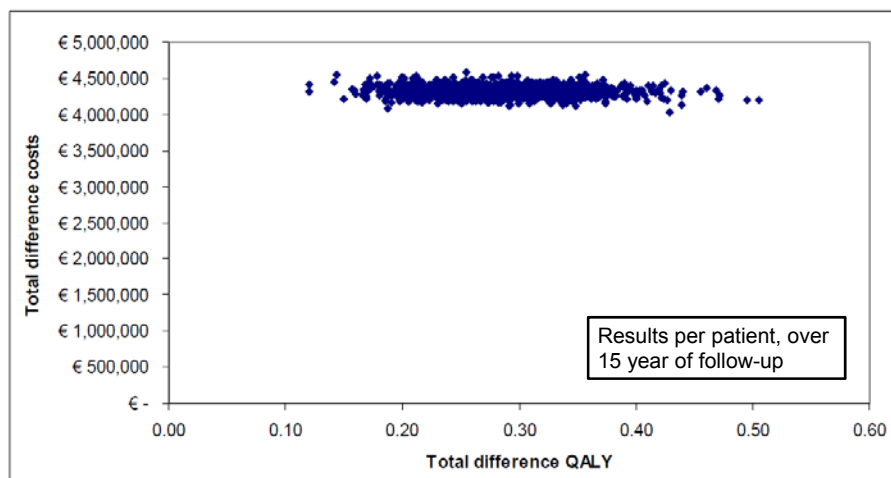
- Many factors come into play when deciding whether or not drugs should be reimbursed. Cost-effectiveness is only one of them!
- Discuss the pro's and cons of reimbursing the drugs
  - Use Dunning's Funnel elements
- Drugs:
  - Myozyme (alglucosidase alpha) for Pompe's Disease
  - Drugs for erectile dysfunction

## Alglucosidase alpha (Myozyme®)

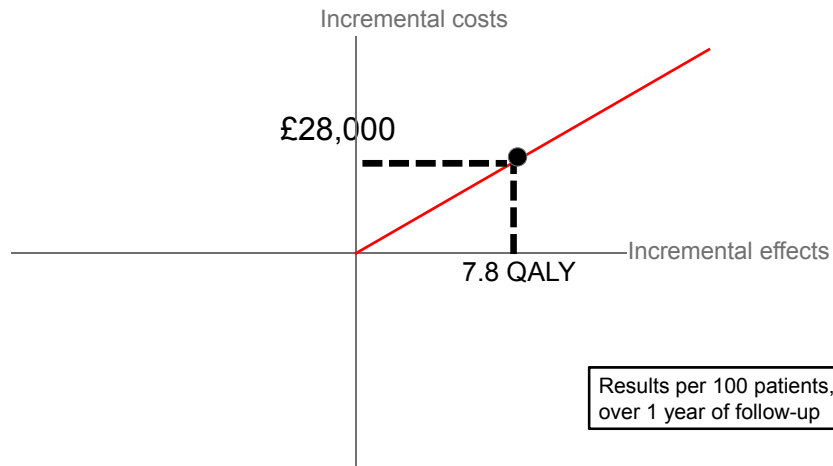
- Pompe disease
  - Enzyme deficiency; may be absent from birth (classic disease) or have reduced activity (adults; non-classic disease)
  - Leading to cardiovascular and respiratory problems
- Alglucosidase alpha (Myozyme)
  - Enzyme replacement therapy
  - Cost per patient per year: around €500.000
- Budget impact
  - +- 100 patients with Pompe in Netherlands
  - Similar to budget impact of all antidepressants in NL (>1 million patients)



## Cost-effectiveness of Myozyme for adult patients



## Cost-effectiveness plane



Stolk. BMJ. 2000

### Discussion suggestions

- How would you evaluate the two drugs according to “Dunnings Funnel”?
- What is the cost-effectiveness (range) of Myozyme?
- What is the cost-effectiveness of the erectile dysfunction drug?