The economics of providing new medicines and treatments

Michael Barry

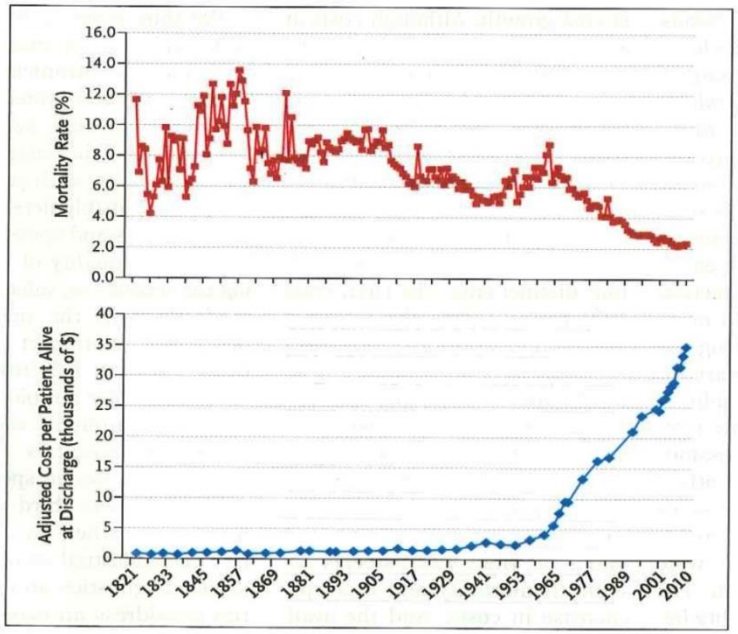
Department of Pharmacology & Therapeutics,
Trinity College Dublin

April 2018

"the reality that for the first time, improvements in inpatient mortality may be coming at unsustainable increases in cost"

Two Hundred Years of Hospital Costs and Mortality — MGH and Four Eras of Value in Medicine

Gregg S. Meyer, M.D., Akinluwa A. Demehin, M.P.H., Xiu Liu, M.S., and Duncan Neuhauser, Ph.D.



MGH's Inpatient Mortality Rate (Brown) and Adjusted Cost per Patient Who Was Discharged Alive (in 2010 Dollars; Blue), 1821–2010.

The four eras of value in medicine

1821-1910 – stable mean mortality, flat costs

1911-1960 – modest decreases in mortality, modest increases in costs

1961-2000 – steeper decline in mortality, steeper increase in costs

2000-date – mortality level, costs escalated dramatically

NEJM 2012;366: 2147-2149

Access to medicines – media and public awareness

9/12/2016

HSE runs out of money needed to provide new medicines to patients

Department says it is considering three medicines for approval

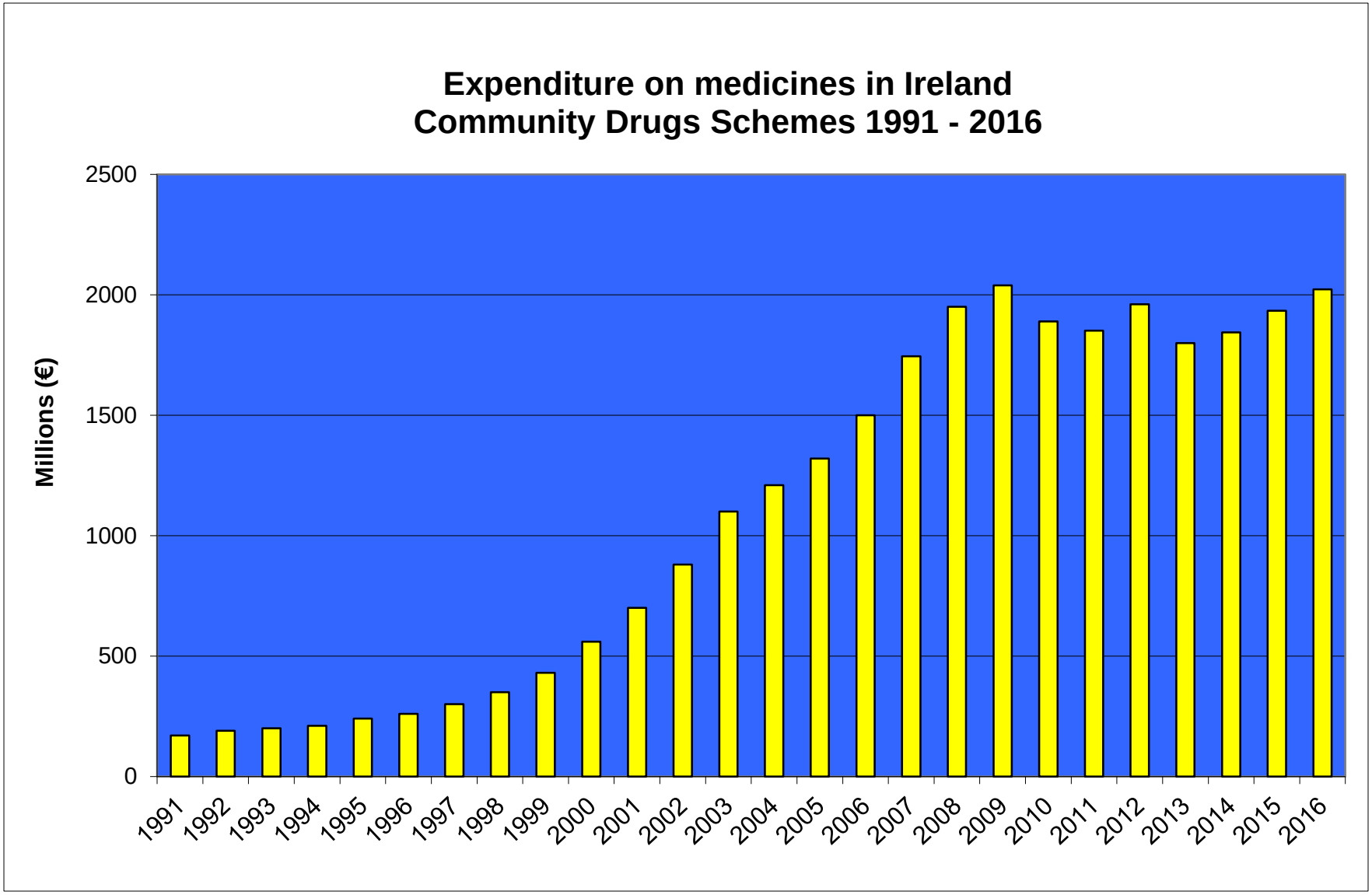
Paul Cullen
Sat, Jun 24, 2017, 14:04

2/9/2011

1/6/2016

21/1/2013

Total expenditure on medicines over €2.0 billion in 2016

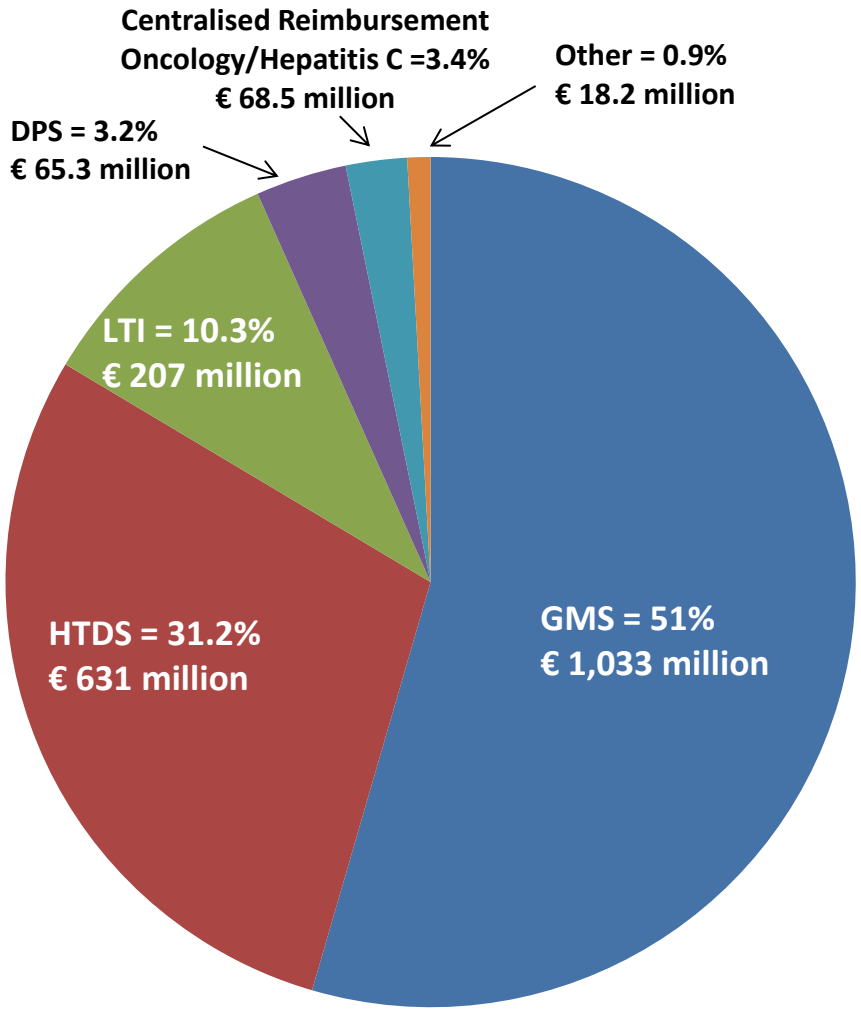


Drug expenditure in Ireland 2016

The GMS accounts for approx 59 million (78%) of all items dispensed. The DPS 10%, LTI 10%.

The HTDS accounts for 0.9% of items dispensed

Expenditure under the HTDS for 2016 is € 631 million (approx 31% of total)



Total expenditure under the Community Drugs Schemes was € 2,023 million in 2016 which represents a 4.6% increase as compared with 2015

From the HSE perspective there are two important considerations

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

Value for money

&

Affordability

HTA

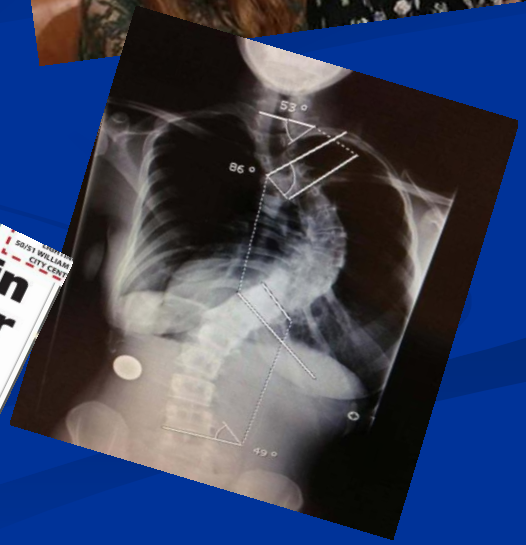
"studies the medical, social, ethical, and economic implications of the development, diffusion and use of a health technology"

INAHTA: 1998

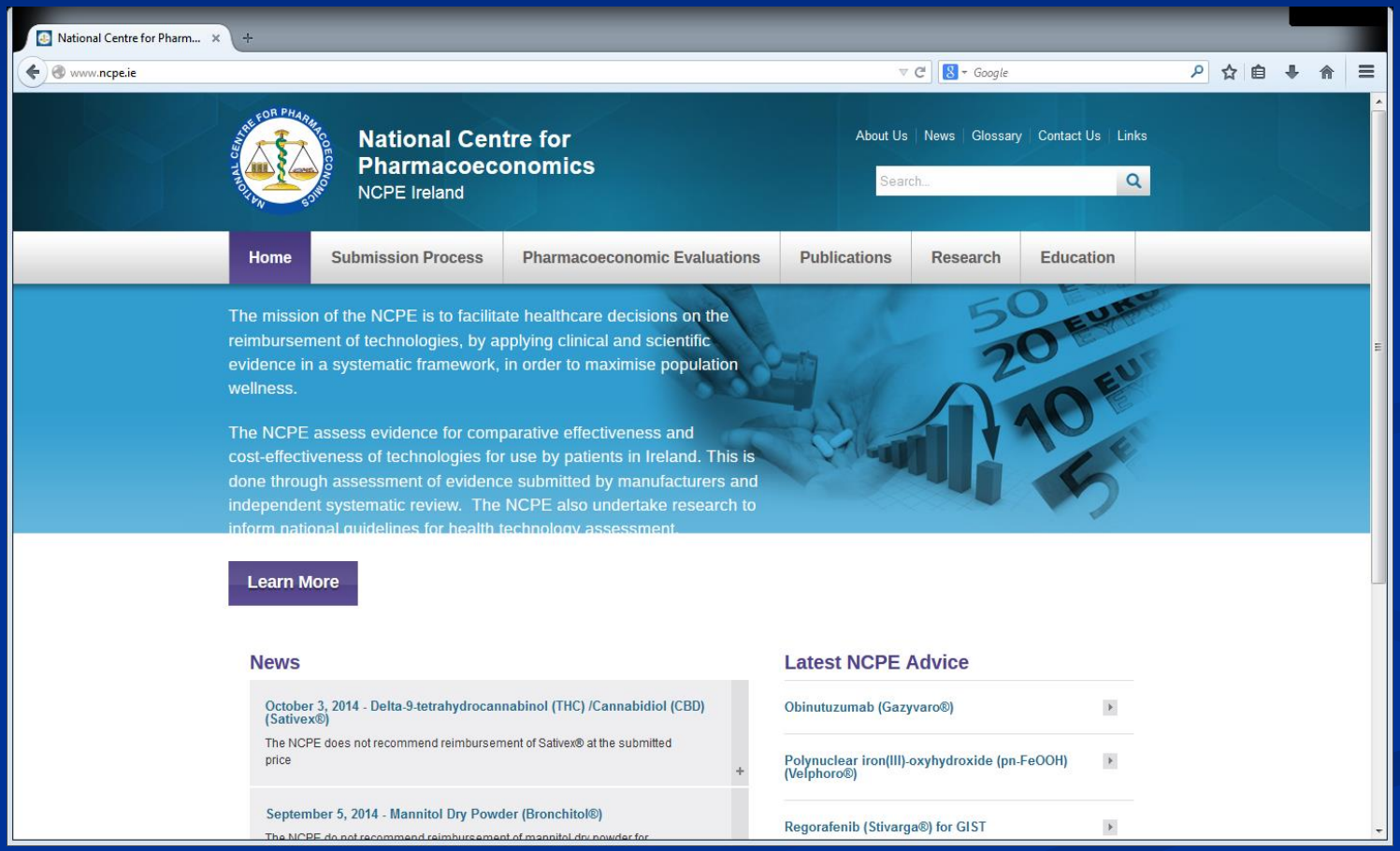
Budget impact analysis

Why bother with economic evaluation ?

Opportunity cost !!



The NCPE conducts the health technology assessment (HTA) of pharmaceutical products for the Health Service Executive (established April 1998)



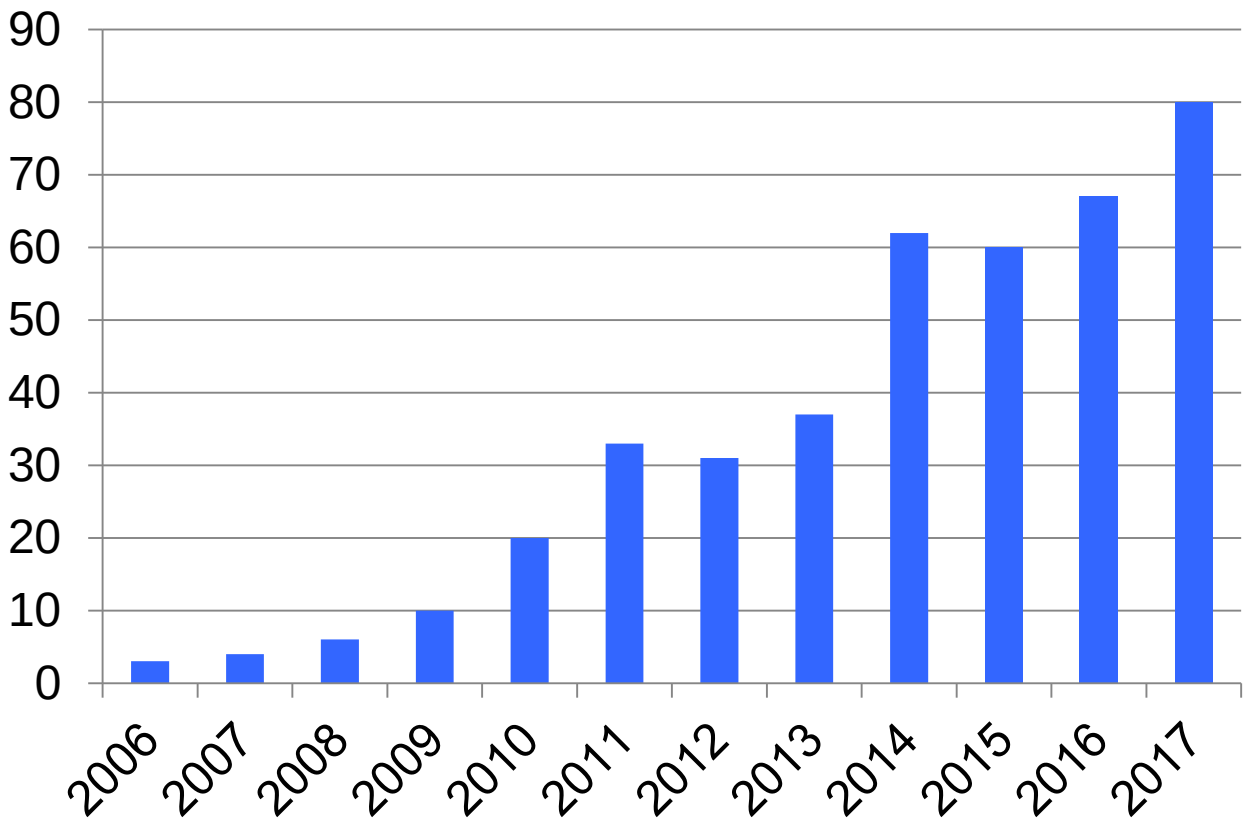
Over 375 recommendations on products since 2006

Affordability – funding very high cost drugs !

Eculizumab is a humanized monoclonal antibody that blocks the activation of terminal compliment at C5. It is indicated for the treatment of paroxysmal nocturnal haemoglobinuria (PNH) and atypical haemolytic uraemic syndrome (aHUS)

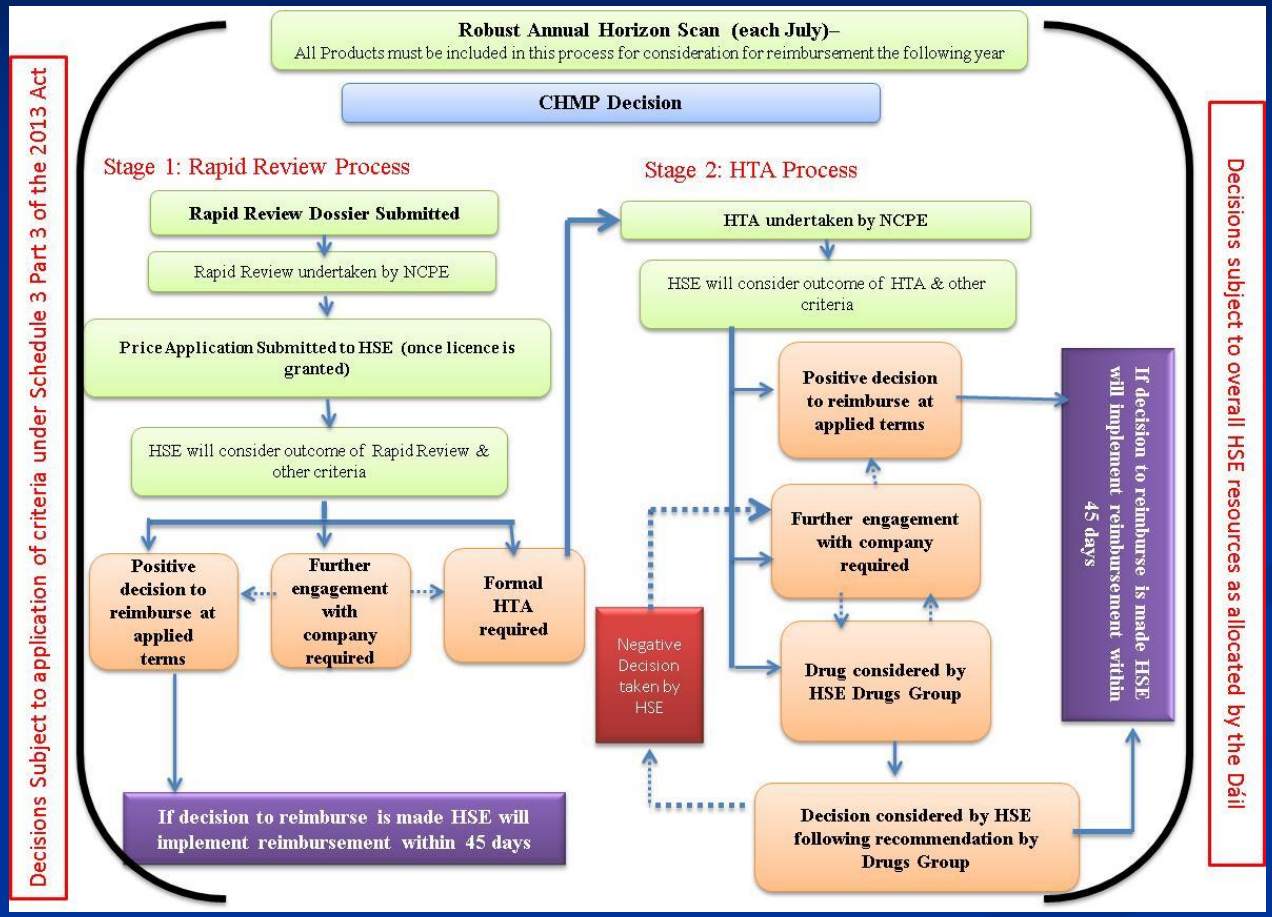
Eculizumab (Soliris) costs € 582,400 per patient per annum for aHUS

Number of products appearing on the NCPE website 2006 - 2017



2017
RR = 64
Full HTA = 16

Assessment process following 2016 IPHA/HSE/DoH discussions



Determining the Incremental Cost-Effectiveness Ratio (ICER)

What added value do we get for the increased cost as compared with the standard of care ?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

Cost-effectiveness of sacubitril + valsartan (Entresto)

$$\text{ICER} = \frac{\text{Costs for sacubitril+valsartan – costs associated enalapril}}{\text{Health outcomes with sacubitril + valsartan - outcomes with enalapril}}$$

(drug costs, hospital costs, primary care costs, investigations…)

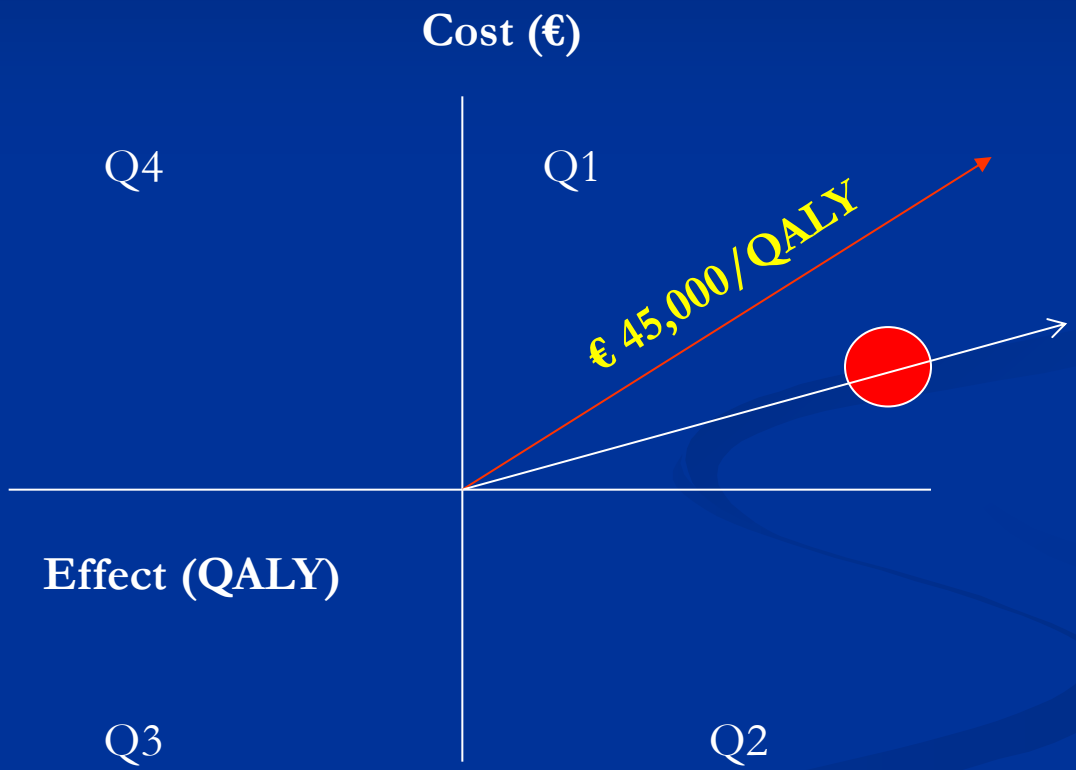
(deaths from CV causes, hospitalisations for HF, symptoms and physical limitations associated with heart failure…)

=

€ 25,234/QALY

Cost-effectiveness threshold

The line passing through the origin represents our 'acceptable' cost-effectiveness ratio. That is our maximum (or threshold) willingness-to-pay for a unit of effect (life year or QALY).



The QALY threshold to be used in the HTA process is € 45,000

Examples – you decide !

Health Technology Assessment of Ippi

Ipilimumab

'Ippi'

Ipilimumab is a monoclonal antibody that blocks cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), a negative regulator of T cells, thereby augmenting T-cell activation and proliferation. It is indicated for the treatment of advanced melanoma in adults who received prior therapy.

Price: € 85,000/patient

Budget impact: € 4,800,000 - € 7,400,000 per annum

Δ median overall survival = 3.6 months

Basecase ICER: € 147,899/QALY or € 92,443/LYG

NATIONAL CENTRE FOR PHARMACOECONOMICS

September 2011

What would you do ??

Expensive !

Significant budget impact – could I invest over € 7 million better ??

Price: € 85,000/patient

Budget impact: € 4,800,000 - € 7,400,000 per annum

Is this health outcome enough to justify the expenditure ?

Δ median overall survival = 3.6 months

Basecase ICER: € 147,899/QALY or € 92,443/LYG

This is not remotely cost-effective (value for money)

Health Technology Assessment & the public

Ipilimumab

'Ippi'

"We believe the Company has failed to demonstrate the cost-effectiveness of ipilimumab for the treatment of advanced melanoma in adult patients who received prior therapy. We cannot recommend reimbursement at the submitted price".

Price: € 85,000/patient

Budget impact: € 4,800,000 - € 7,400,000 per annum

Δ median overall survival = 3.6 months

Basecase ICER: € 147,899/QALY or € 92,443/LYG

Final ICER approx € 116,000/QALY

NATIONAL CENTRE FOR PHARMACOECONOMICS

September 2011

The Ippi controversy !

Final ICER ~ € 116,000/QALY

Reimbursement of Ipilimumab (Yervoy®) – opportunity cost !

Original price – revised price: implications for the treatment of other patients with serious medical conditions such as hepatitis C & MS e.g.

We could treat an additional 65 patients with Fingolimod (Gilenya) or

We could treat an additional 60 patients with Telaprevir (Incivo)

Ivacaftor (Kalydeco)

Ivacaftor – the evidence

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 3, 2011 VOL. 365 NO. 18

A CFTR Potentiator in Patients with Cystic Fibrosis and the *G551D* Mutation

Bonnie W. Ramsey, M.D., Jane Davies, M.D., M.B., Ch.B., N. Gerard McElvaney, M.D., Elizabeth Tullis, M.D., Scott C. Bell, M.B., B.S., M.D., Pavel Dřevínek, M.D., Matthias Griese, M.D., Edward F. McKone, M.D., Claire E. Wainwright, M.D., M.B., B.S., Michael W. Konstan, M.D., Richard Moss, M.D., Felix Ratjen, M.D., Ph.D., Isabelle Sermet-Gaudelus, M.D., Ph.D., Steven M. Rowe, M.D., M.S.P.H., Qunming Dong, Ph.D., Sally Rodriguez, Ph.D., Karl Yen, M.D., Claudia Ordoñez, M.D., and J. Stuart Elborn, M.D., for the VX08-770-102 Study Group*

Outcomes: 1. Δ from baseline predicted FEV1% was 10.6% greater for ivacaftor at 24 weeks
2. patients were 55% less likely to have a pulmonary exacerbation over 48 weeks
3. the treatment group scored 8.6 points higher on the respiratory symptoms domain of the Cystic Fibrosis Questionnaire at week 48 (a 100 point scale).
4. weight gain of 2.7 kg over placebo group by 48 weeks

Cost: priced over € 234,000 per patient per year

Submitted economic evaluation

Primarily on the basis of a 24 week study it was assumed that ivacaftor would prolong median survival by 29.2 years !!!

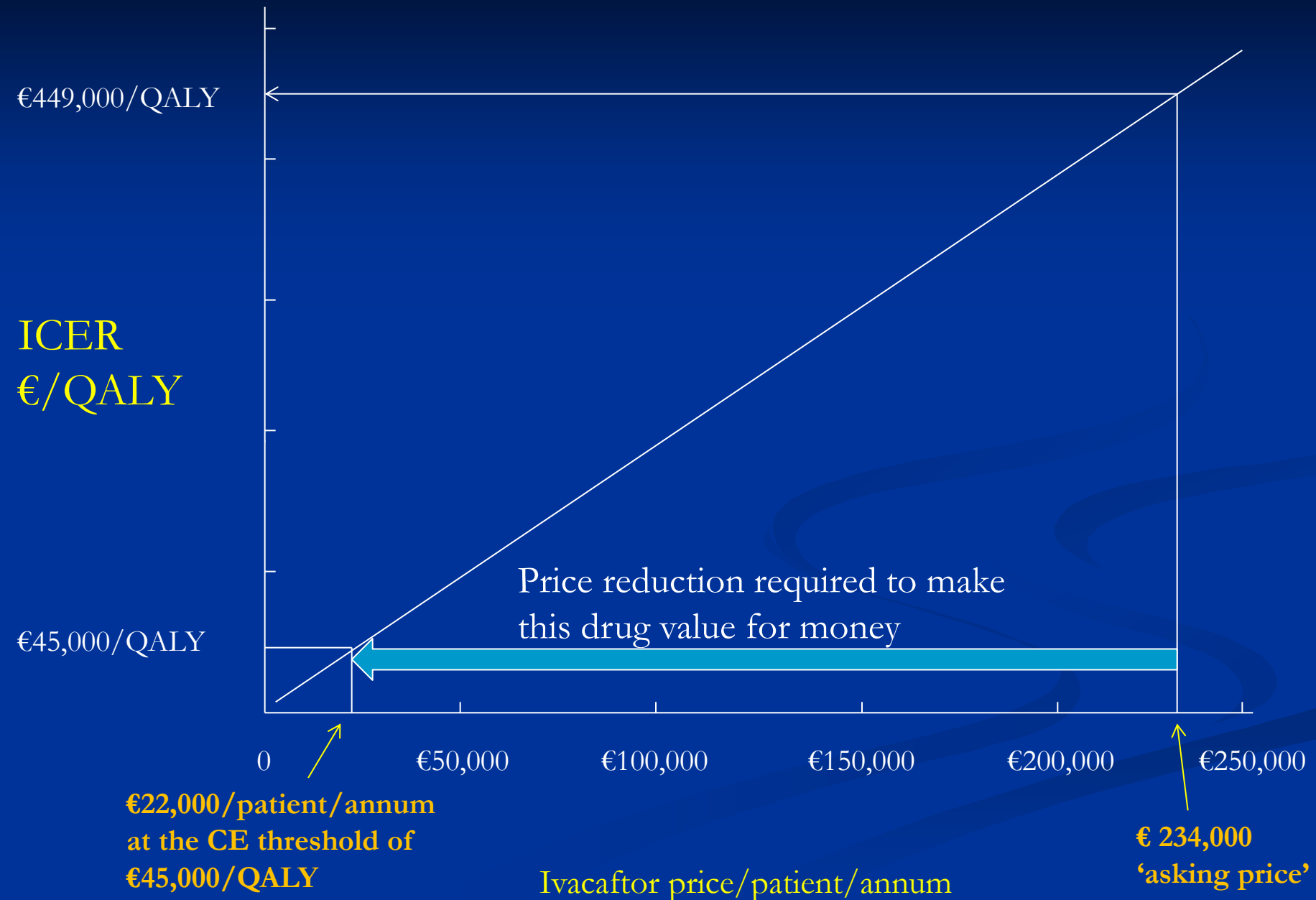
Cost-effectiveness of Ivacaftor (Kalydeco) for the treatment of cystic fibrosis in patients age 6 years and older who have the G551D mutation

Price: € 234,804/patient

Budget impact: € 28,000,000 per annum

Basecase ICER: € 449,035/QALY or € 443,825/LYG

Ivacaftor - Price vs ICER relationship



Ivacaftor – correct decision ???

Minister approves CF drug despite concerns over cost

Officials expressed concern over claimed benefits and impact of price on budget

Drug's approval universally welcomed by CF patients and all parties yesterday

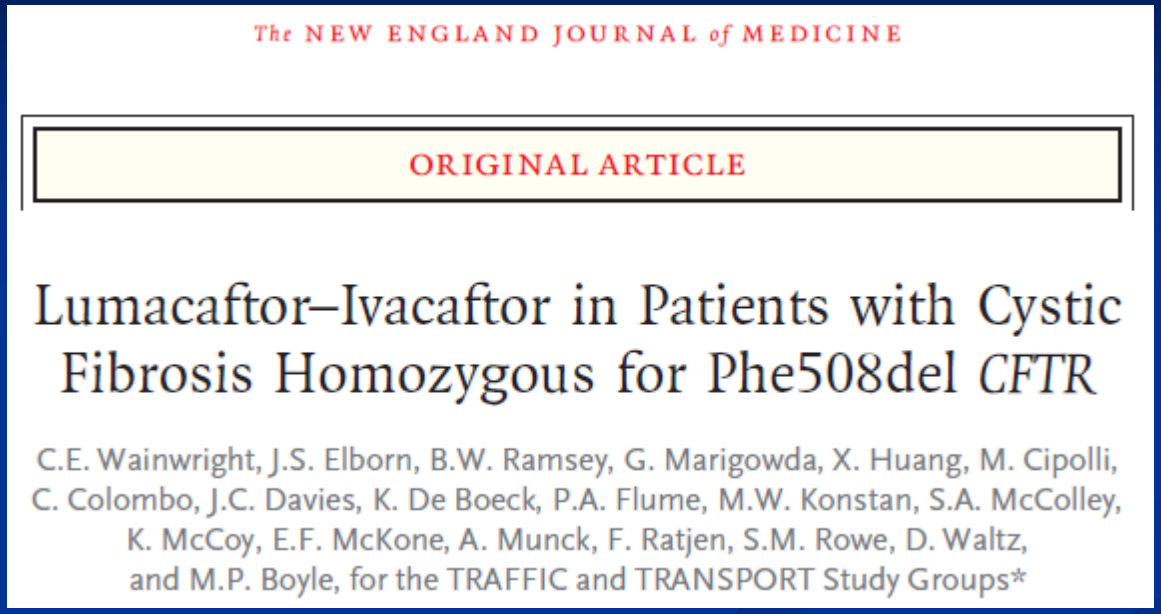
Price of CF drug may be health cuts elsewhere

'About one-third of the entire budget for new drugs this year will go towards making new CF drug available'

Irish Times 2nd February 2013

What about Orkambi ??

Lumacaftor - Ivacaftor – the evidence



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lumacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del *CFTR*

C.E. Wainwright, J.S. Elborn, B.W. Ramsey, G. Marigowda, X. Huang, M. Cipolli, C. Colombo, J.C. Davies, K. De Boeck, P.A. Flume, M.W. Konstan, S.A. McColley, K. McCoy, E.F. McKone, A. Munck, F. Ratjen, S.M. Rowe, D. Waltz, and M.P. Boyle, for the TRAFFIC and TRANSPORT Study Groups*

Outcomes: 1. Δ from baseline predicted FEV1% was ~ 3% greater for LUM-IVA at 24 weeks
2. patients were 39% less likely to have a pulmonary exacerbation over 48 weeks
3. 56% reduction in the annualised rate of pulmonary exacerbations requiring i.v. antibiotics
4. No clinically important difference in Cystic Fibrosis Questionnaire .
5. Small improvement in BMI = 0.24 kg/m²

Cost: priced over € 158,000 per patient per year

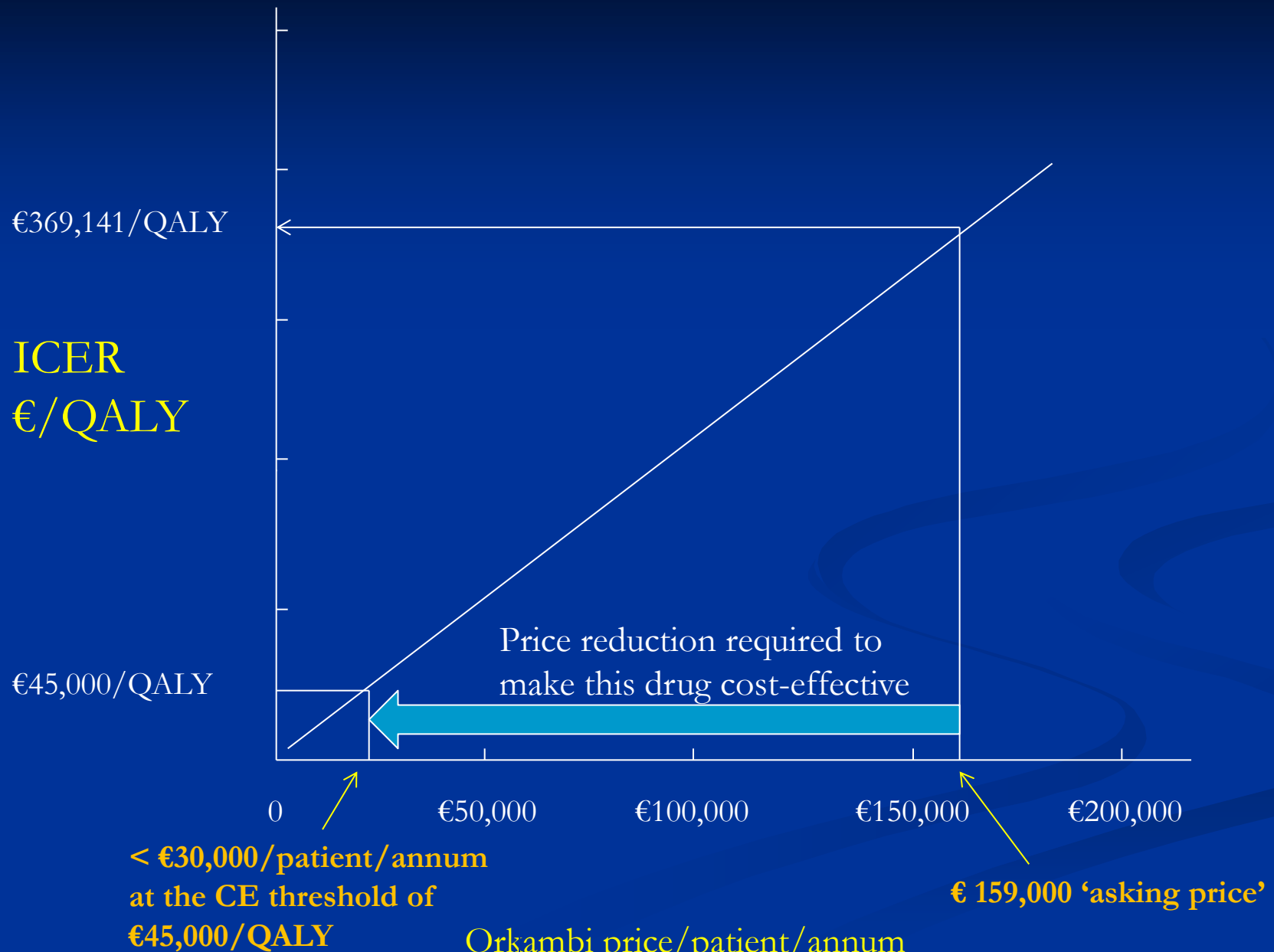
Lumacaftor + Ivacaftor (Orkambi)

Price: € 159,050 per patient

Budget impact: € 391,892,681 over 5 years

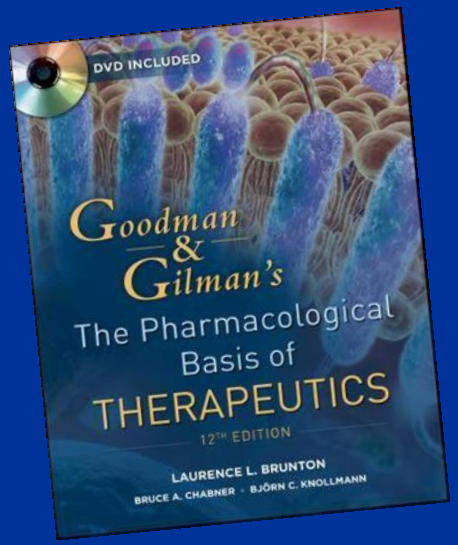
Basecase ICER = € 369,141/QALY

Orkambi - Price vs ICER relationship



The fundamental problem with Lumacaftor + Ivacaftor (Orkambi)

Type equation here.

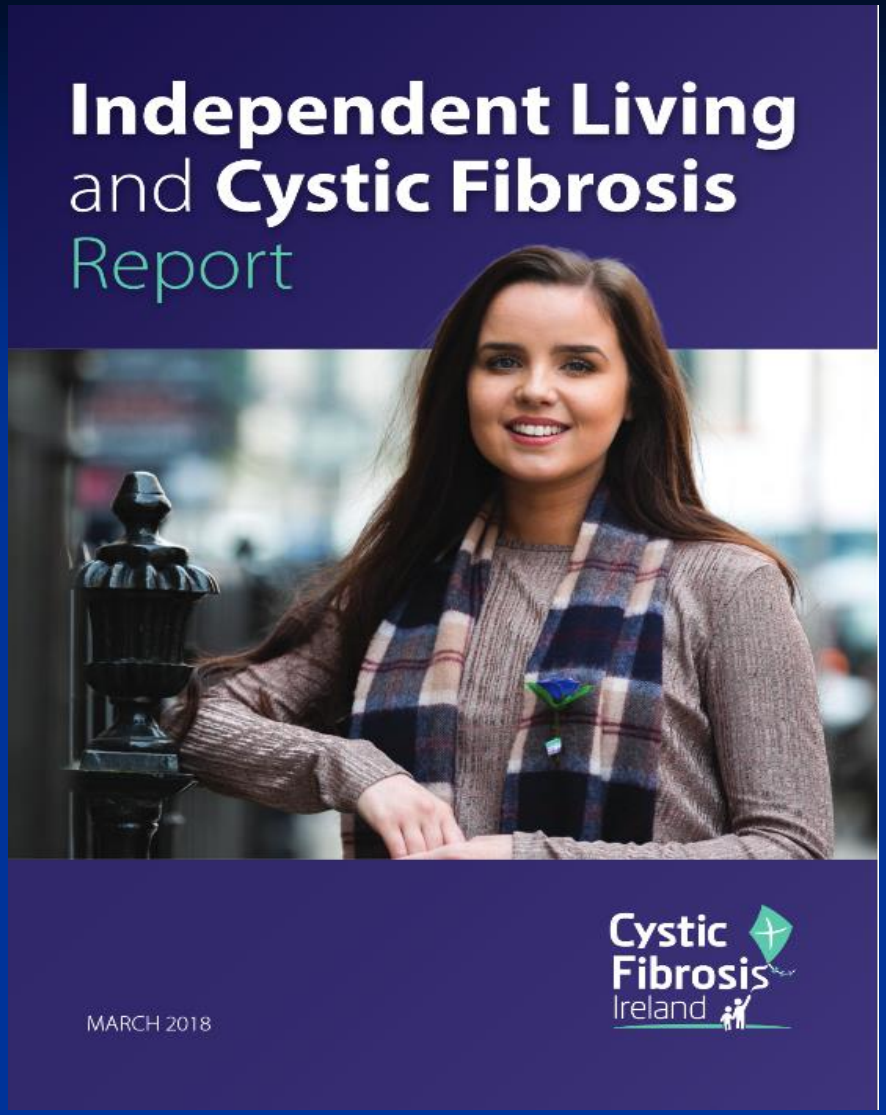


Lumacaftor is an enzyme inducer

Ivacaftor is a substrate

Lumacaftor

Ivacaftor → **metabolites**



Adults with CF are aspiring to and are increasingly living significantly more fulfilled and independent lives than 20 years ago

There have been dramatic changes in living arrangements for PWCF

There has been a significant increase in PWCF obtaining third level qualifications over the past two decades.

PWCF are increasingly in full-time and part-time employment

The median age of death in Ireland of people with CF has increased to 30 years of age in 2015 compared with 17 years of age in 1998

We await peer-reviewed scientific data to demonstrate the impact of ivacaftor (Kalydeco) and lumacaftor + ivacaftor (Orkambi) on CF morbidity and mortality

What about oncology drugs

DRUG REGULATION

Cancer drugs: high price, uncertain value

 OPEN ACCESS

A study published in The BMJ this week shows how most new cancer drugs are failing to deliver any clinically meaningful benefit. It's time for Europe to raise the evidence bar before market approval, finds **Deborah Cohen**

Deborah Cohen *associate editor, The BMJ*

Cohen D. BMJ 2017;359:j4543

RESEARCH

OPEN ACCESS

Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009-13

Courtney Davis,[1] Huseyin Naci,[2] Evrim Gurpinar,[2] Elita Poplavska,[3] Ashlyn Pinto,[2] Ajay Aggarwal[4,5]

To consider available data on overall survival and quality of life benefits of cancer drugs approved by the EMA from 2009 to 2013

- Over this time period the EMA approved 48 cancer drugs for 68 indications
- Eight indications (12%) were approved on the basis of a single arm study
- At the time of market approval there was a significant prolongation of survival in 24 of the 68 indications (35%)
- The magnitude of the benefit on overall survival ranged from 1.0 to 5.8 months (median 2.7 months)
- At the time of market approval there was an improvement in quality of life in seven of the 68 indications (10%).

RESEARCH

OPEN ACCESS

Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009-13

Courtney Davis,[1] Huseyin Naci,[2] Evrim Gurpinar,[2] Elita Poplavska,[3] Ashlyn Pinto,[2] Ajay Aggarwal[4,5]

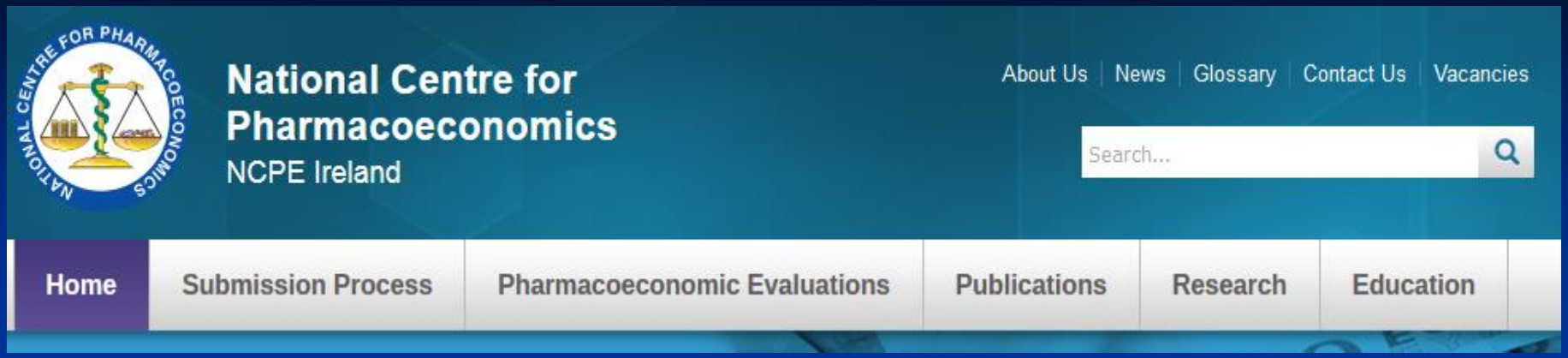
- Out of the 44 indications for which there was no evidence of a survival gain at the time of market authorisation, in the subsequent post-marketing period there was evidence for extension of life in three (7%) and reported benefit on quality of life in 5 (11%).

- Of the 68 cancer indications with EMA approval, and with a median of 5.4 years follow-up only 35 (51%) had shown a significant improvement in survival or quality of life, while 33 remained uncertain.

"most drugs entered the market without evidence of benefit on survival or quality of life"

"at a minimum of 3.3 years after market entry, there was still no conclusive evidence that these drugs either extended or improved life for most cancer indications"

Davis C et al. BMJ 2017;359:j4530



There were 21 full Health Technology Reports on cancer drugs published between January 2016 and December 2017

20 of the 21 cancer drugs were deemed not cost effective at the submitted price (95%)

The gross budget impact for the 21 products exceeded € 600,000,000 over 5 years

Example:

DRUG REGULATION

Cancer drugs: high price, uncertain value

OPEN ACCESS

A study published in The BMJ this week shows how most new cancer drugs are failing to deliver any clinically meaningful benefit. It's time for Europe to raise the evidence bar before market approval, finds **Deborah Cohen**

Deborah Cohen *associate editor, The BMJ*

This drug slows disease progression by 4.3 months

It is too early to say if it prolongs overall survival

There was no meaningful improvement of quality of life

It costs approximately € 140,000/patient/year

The ICER = € 96,376/QALY

The probability of being cost effective is less than 1%

The 5 year budget impact is € 65,000,000

Example:


DRUG REGULATION

Cancer drugs: high price, uncertain value

OPEN ACCESS

A study published in The BMJ this week shows how most new cancer drugs are failing to deliver any clinically meaningful benefit. It's time for Europe to raise the evidence bar before market approval, finds **Deborah Cohen**

Deborah Cohen *associate editor, The BMJ*

This drug slows disease progression by 4.3 months

It is too early to say if it prolongs overall survival

} Clinically effective ??

There was no meaningful improvement of quality of life

} Quality of life !

It's expensive

} It costs approximately € 140,000/patient/year

The ICER = € 96,376/QALY

} It is not cost-effective

We are reasonably sure that it is not cost effective

} The probability of being cost effective is less than 1%

The 5 year budget impact is € 65,000,000

} Large budget impact !!

THE IRISH TIMES

LATEST NEWS MOST READ MEDIA IRELAND WORLD SPORT

‘Politicisation’ of expensive drugs has led to cuts in community care, committee told

GP organisation calls for ban on radio and TV advertising by private hospitals, pharmas

‘We spend €700 million on high tech drugs. We spend €1.4 billion on all other pharmaceutical products. It’s astronomical’

Dr Mark Murphy – Oireachtas Committee on Health 2018

"for something like NICE …. It takes a political spark"

The Beta – interferon issue !

"how the hell am I meant to make that decision ?"

"Look, we have got away with this on this occasion. But I never want a minister to be put in this position again. Go away and devise some scheme where ministers do not have to take these decisions"

Gerry Malone 1995
(Minister of State for Health 1994-1997)

"They are not political or ministerial decisions"

Nivolumab (Opdivio)
"game – changer"

"Decisions on which medicines are reimbursed by the taxpayer are made on objective, scientific and economic grounds by the HSE on the advice of the National Centre for Pharmacoeconomics. They are not political or ministerial decisions"

Kathleen Lynch
Oireachtas debate 2/2/2016

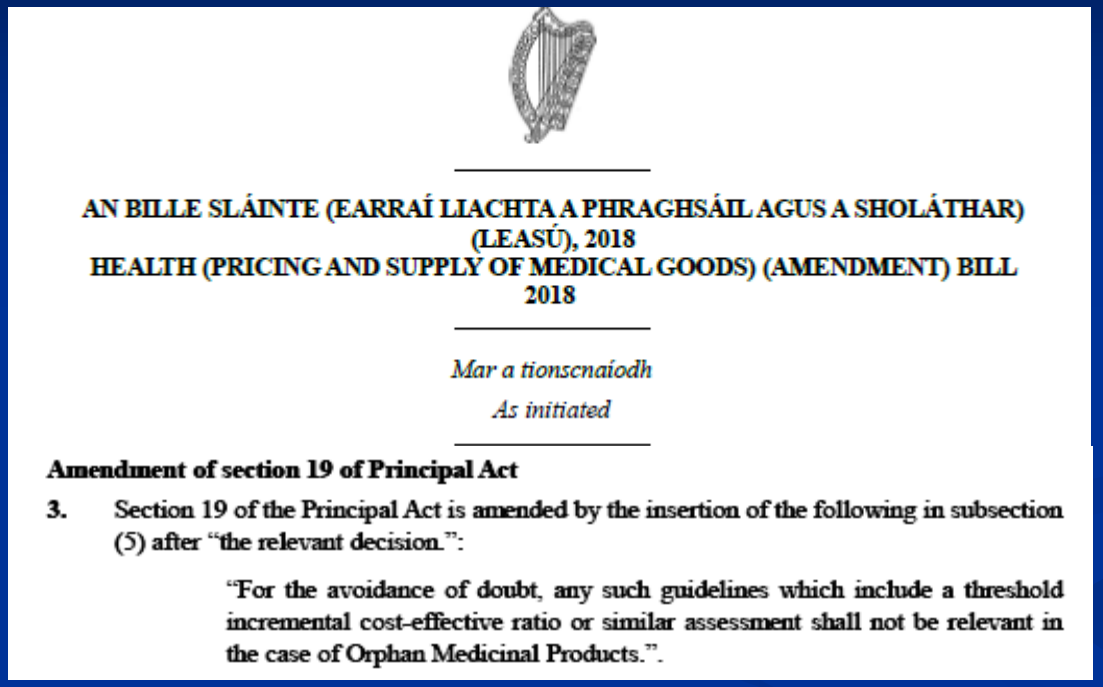
Assessment process following 2016 IPHA/HSE/DoH discussions

The HSE has statutory responsibility for decisions on pricing and reimbursement of drugs, in accordance with the Health (Pricing and Supply of Medical Goods) Act 2013.

Where the HSE approves reimbursement of a drug, reimbursement will be implemented within 45 days.

In a situation where the HSE cannot fund the drug from within existing resources it may inform the Department of Health. The Department of Health may bring a memorandum to Government in relation to the funding implications.

Proposed amendment to the Health Act 2013



AN BILLE SLÁINTE (EARRAÍ LIACHTA A PHRAGHSÁIL AGUS A SHOLÁTHAR) (LEASÚ), 2018
HEALTH (PRICING AND SUPPLY OF MEDICAL GOODS) (AMENDMENT) BILL 2018

Mar a tionscnaíodh
As initiated

Amendment of section 19 of Principal Act

3. Section 19 of the Principal Act is amended by the insertion of the following in subsection (5) after "the relevant decision.":

"For the avoidance of doubt, any such guidelines which include a threshold incremental cost-effective ratio or similar assessment shall not be relevant in the case of Orphan Medicinal Products.".

'assessment of the value for money of very high cost orphan medicines is not relevant'

The Pharmaceutical Industry

Adaptive pathways – early access

Adaptive pathways – concerns

- Adaptive pathways constitute a lowering of evidence standards
- Driven by commercial interests
- In effect mandate the funding of poorly tested expensive drugs

Bouvy et al. 2017

Compassionate access

α – 1 antitrypsin deficiency

Human α – 1 proteinase inhibitor

Respreeza

Price: ~ € 81,120 per patient per year (weight based 70kg)

Budget impact: € 37,650,000 over 5 years

The primary endpoint i.e. the annual rate of lung density loss at TLC and FRC combined did not differ between the placebo and Respreeza groups

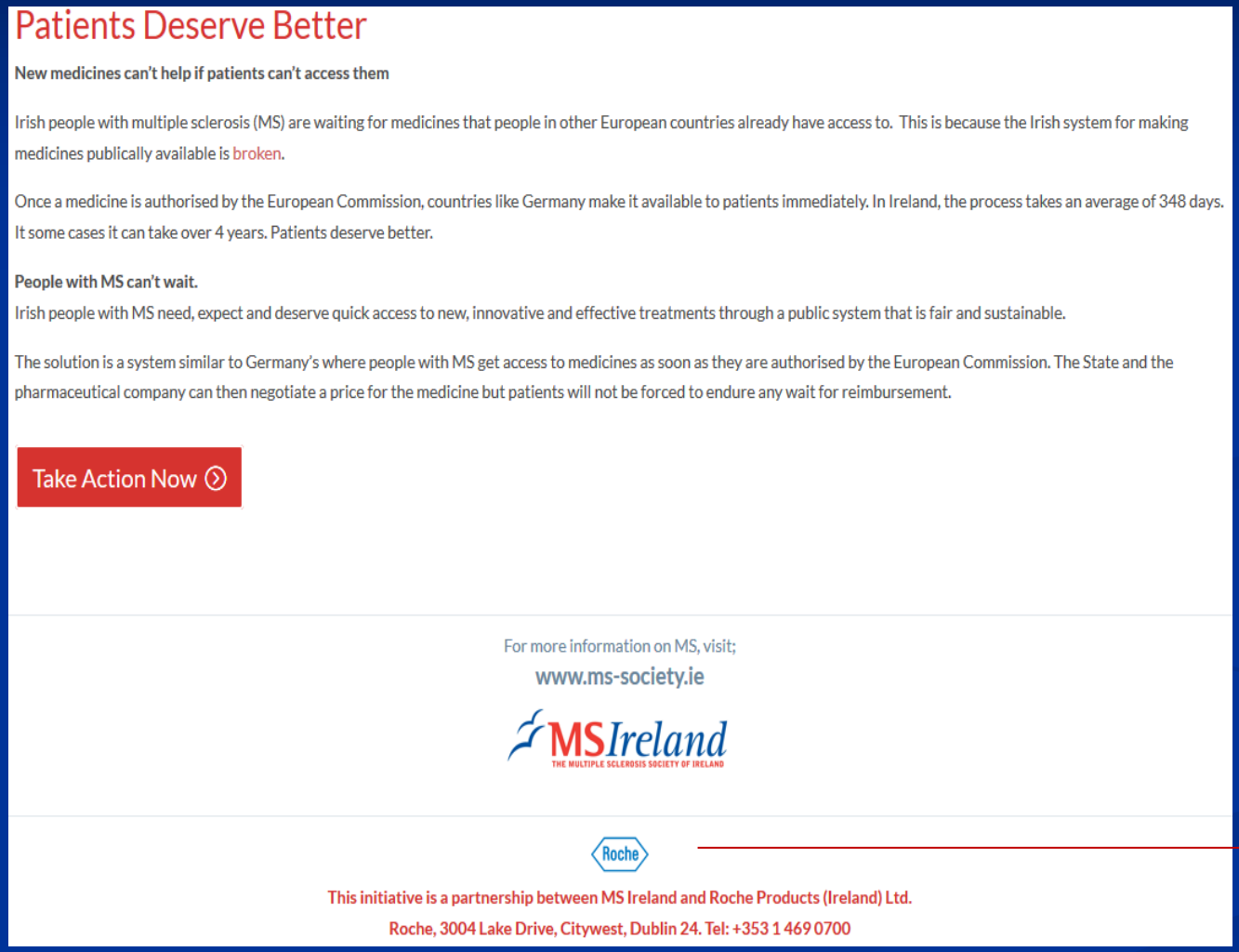
ICER: € 581,322/QALY

December 2016

Compassionate access

- Linking compassionate access schemes to the reimbursement decision can leave patients in a very difficult position when the reimbursement decision is negative.
- Pharma should not consider that such schemes guarantee reimbursement

Pharmaceutical Industry – Advocacy groups



Patients Deserve Better

New medicines can't help if patients can't access them

Irish people with multiple sclerosis (MS) are waiting for medicines that people in other European countries already have access to. This is because the Irish system for making medicines publically available is broken.

Once a medicine is authorised by the European Commission, countries like Germany make it available to patients immediately. In Ireland, the process takes an average of 348 days. It some cases it can take over 4 years. Patients deserve better.

People with MS can't wait.

Irish people with MS need, expect and deserve quick access to new, innovative and effective treatments through a public system that is fair and sustainable.

The solution is a system similar to Germany's where people with MS get access to medicines as soon as they are authorised by the European Commission. The State and the pharmaceutical company can then negotiate a price for the medicine but patients will not be forced to endure any wait for reimbursement.

Take Action Now

For more information on MS, visit;

www.ms-society.ie

MS Ireland

THE MULTIPLE SCLEROSIS SOCIETY OF IRELAND

Roche

This initiative is a partnership between MS Ireland and Roche Products (Ireland) Ltd.

Roche, 3004 Lake Drive, Citywest, Dublin 24. Tel: +353 1 469 0700

'The Irish system for making medicines publicly available is broken'

'Irish people with MS need, expect and deserve quick access to new, innovative and effective treatments through a public system that is fair and sustainable'

'The solution is a system similar to Germany's'

Yet more challenges on the way !!!

Gene therapies

EDITORIAL

A Cure for Hemophilia within Reach

H. Marijke van den Berg, M.D., Ph.D.

A cure for Haemophilia …….at what cost ?

A recent evaluation of gene therapies in late-stage clinical development indicated that 23 gene therapies are in phase III clinical trials

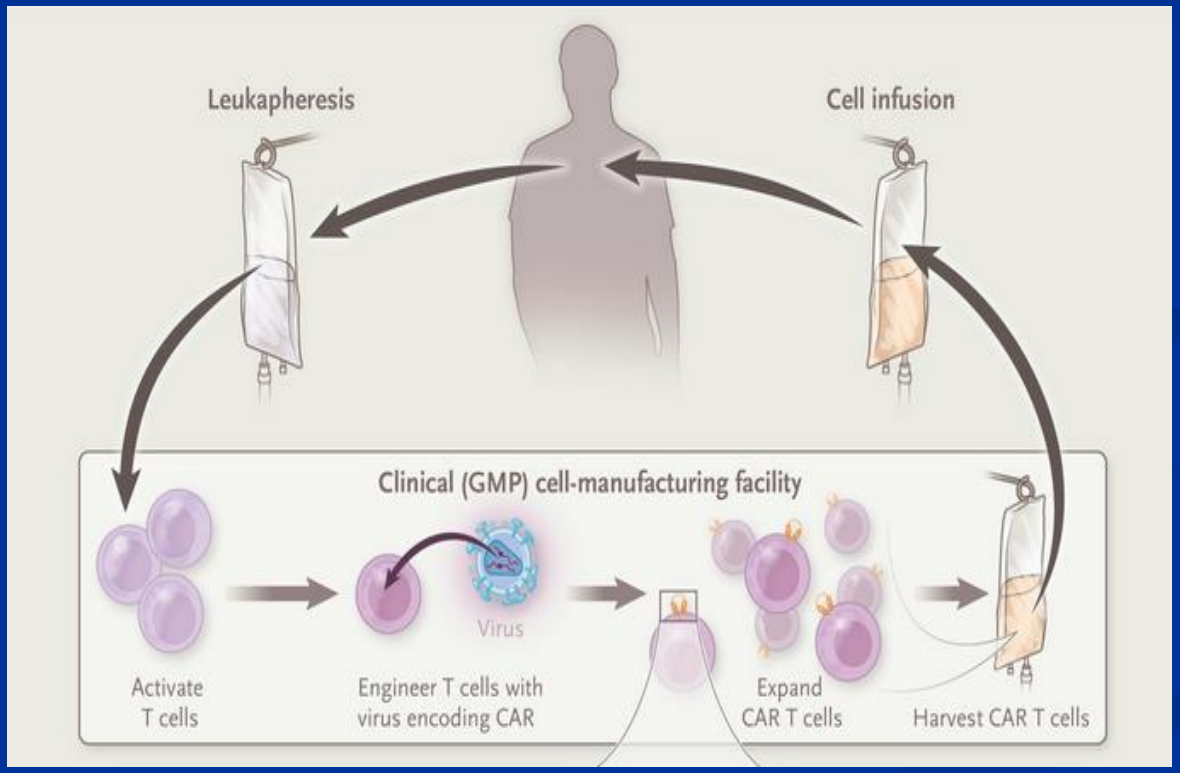
The anticipated prices range between $ 500,000 to $ 1,000,000 per treatment

1.New Engl J Med 2017;377:2592-2593
2. Value & Outcomes, Spotlight 2018;4:31-34

EDITORIAL

A Milestone for CAR T Cells

Eric Tran, Ph.D., Dan L. Longo, M.D., and Walter J. Urba, M.D., Ph.D.



T cells are engineered to express a chimeric antigen receptor (CAR) targeting the CD19 antigen expressed on the surface of B cells

This personalised therapeutic approach involves (a) removal of peripheral blood T-cells followed by (b) in vitro activation, genetic modification and expansion of the T cells and (c) infusion of the cells back into the patient.

N Engl J Med 2017;377:2593-2596

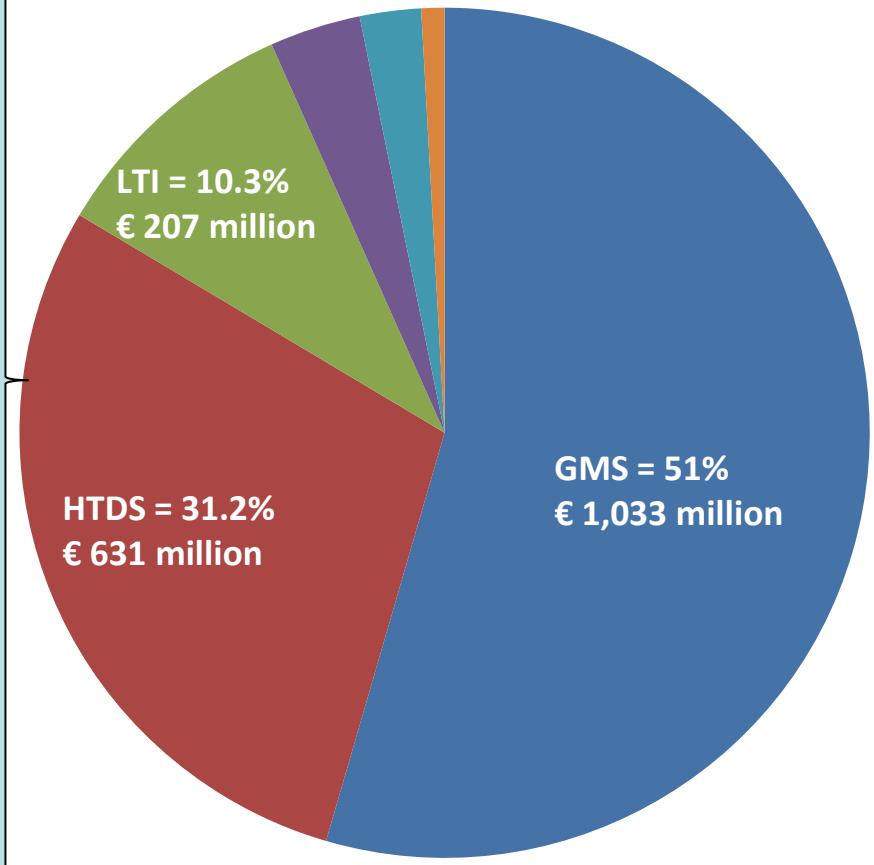
So what can we do ?

Only reimburse above €45,000/QALY in exceptional circumstances

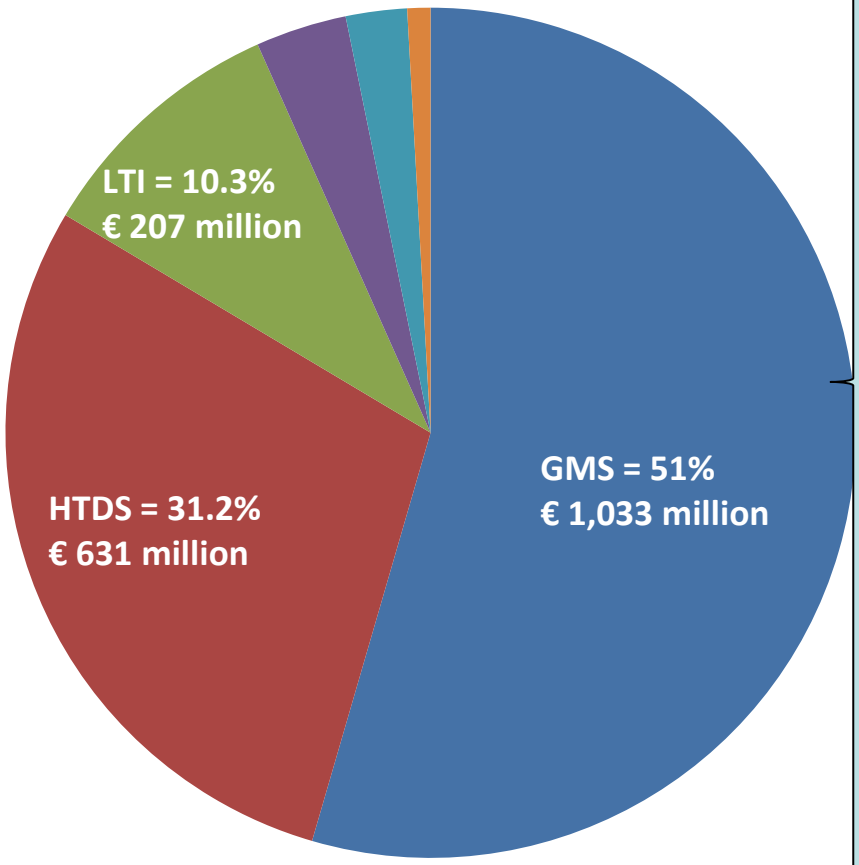
Introduce a pay for performance strategy for very high cost drugs

Mandatory collection of health outcome data following reimbursement

Insist on the use of biosimilar medicines when they are available



So what can we do ?



Alter our prescribing eg. Prescribing incentive scheme

Consider the introduction of Phase II reference pricing

Review of the Community Drugs Schemes e.g LTI scheme

Review payments to pharmacies

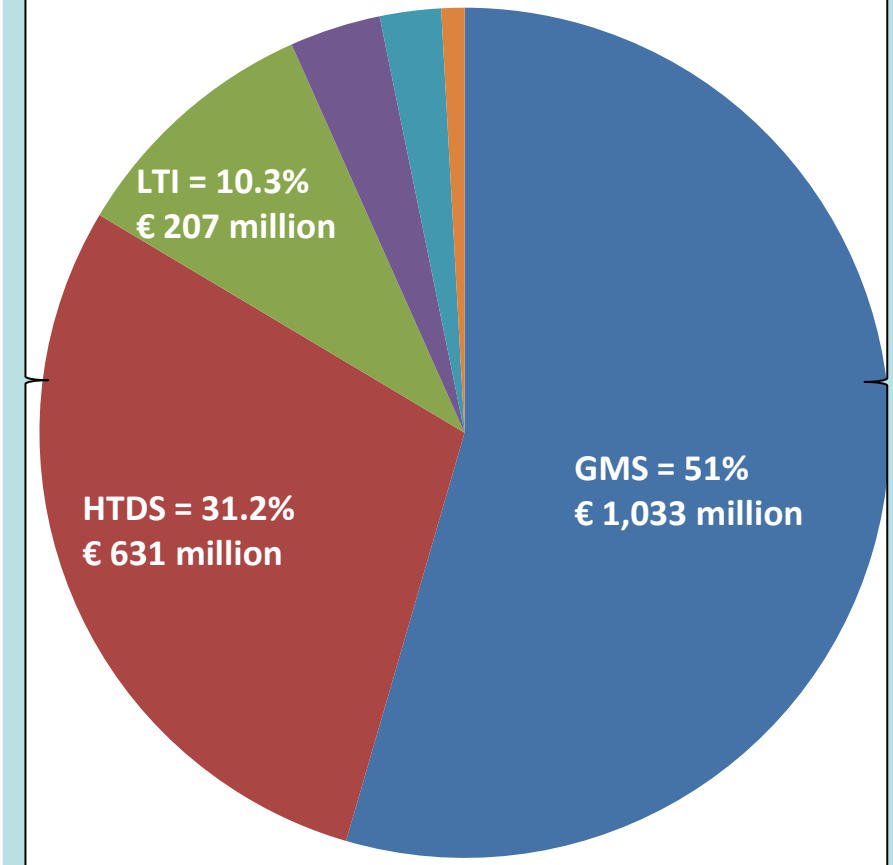
So what can we do ?

Only reimburse above €45,000/QALY in exceptional circumstances

Introduce a pay for performance strategy for very high cost drugs

Mandatory collection of health outcome data following reimbursement

Insist on the use of biosimilar medicines when they are available



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Preferred Drugs
THE RIGHT CHOICE, RIGHT NOW.
MEDICINES MANAGEMENT PROGRAMME

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

‘fair prices….real value’