Risk sharing arrangements/ managed entry agreements: Experiences in Europe

Prepared by Brian Godman

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2. Programmes across Europe

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There is increasing pressure on medicine budgets across Europe leading to increasing use of MEAs for new premium priced medicines

- Pharmaceutical budgets are under pressure across countries driven by new premium priced medicines (e.g. cancer and those for orphan diseases), changing demographics with the increasing prevalence of chronic diseases and associated medicine costs, stricter clinical targets especially with single disease model guidelines, and rising patient expectations
- Health authorities are becoming more business like to deal with these challenges including developing new models to better manage their entry and subsequent utilisation especially in Europe
- This includes new ways of managing the budget impact of new medicines – incorporating risk sharing arrangements (RSAs)/ managed entry agreements (MEAs) in Europe as part of reimbursement discussions to help maintain universal healthcare – and this will continue

Expenditure on medicines is rising across countries including Europe driven by cancer and hepatitis C

- Total expenditure on medicines among OECD countries in 2015 was over US$800 billion and rising

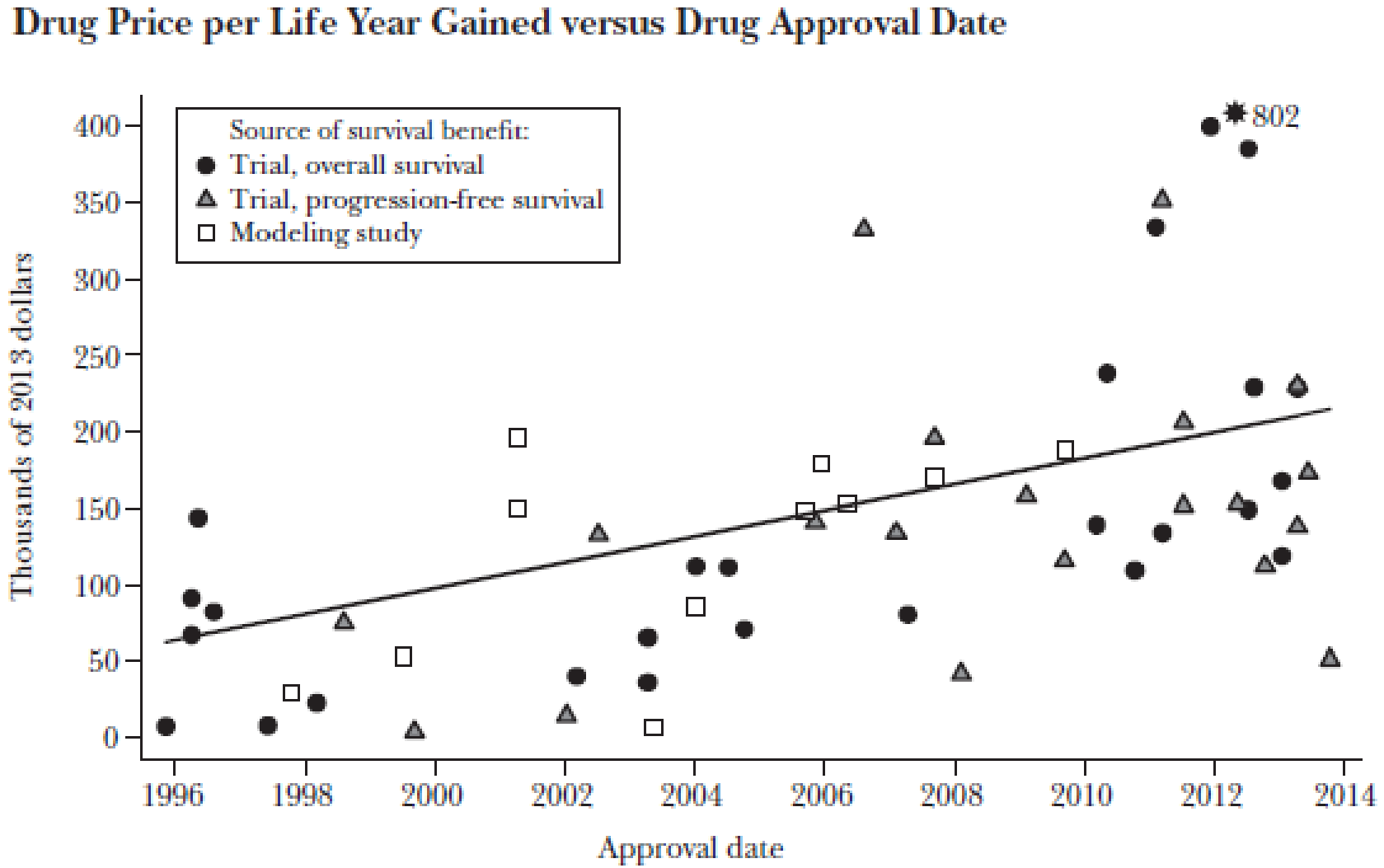
- In Europe, total sales in ambulatory care in 2016 was Euro210billion, an increase of 5% (nominal) from 2010 - helped by new medicines for cancer and Hep C. Hospitals sales are in addition - approx. 20% of ambulatory care expenditure

- Global sales of cancer medicines were $107billion in 2015 and rising over 11%/ year with the global spend on orphan medicines anticipated to reach US$178billion per year by 2020

- This is despite limited health gain with a number of new medicines including those for cancer and orphan diseases (increasingly inter-linked with cancer with small patient populations)

Ref: OECD 2017; Godman et al 2018

New cancer medicines now averaging US$207,000/ life year gained. Likely an underestimate as modelling and concerns between PFS and overall survival in solid tumours



Ref: Henshall et al 2013; Howard et al 2015; Godman et al 2015 2018

Ongoing concerns with the value of new cancer medicines at ever increasing prices

- Of the 12 drugs approved by the FDA for various cancers in 2012:
  - ❑ 9 were priced at more than US$10,000/patient/ month
  - ❑ Only 3 prolonged survival, 2 by less than 2 months

- Of the 7 targeted therapies for renal cell carcinoma approved in the US between 2005 and 2012:
  - ❑ all improved progression-free survival (PFS) by typically 3 to 6 months
  - ❑ However, minimal or no impact on overall survival at a cost of US$70,000 to US$140,000/ patient annually

- Recent studies have shown that the cost of goods of some new cancer medicines can be as low as 1% of the selling price, reflected also in the appreciable discounts that are already being seen for imatinib across Europe following generic availability

Ref: Kantarjian et al 2013; Godman et al 2015-2019; Hill et al 2017

Increasing concerns with the price and value of new medicines for cancer helped by its emotive nature

FEATURE

DRUG REGULATION

Cancer drugs: high price, uncertain value

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*

There is a similar trend for new OMPs with some now priced at over US$500k/patient/year – leading to blockbuster status in some (annual worldwide sales over US$1billion/ year)

Orphan drug	Indication	Average annual cost/ patient (US$)
Teduglutide (GATTEX)	Short bowel syndrome	295,000
Imiglucerase (CEREZYME)	Type 1 Gaucher disease	300,000
Ivacaftor (KALYDECO)	Cystic fibrosis	325,000
Galsulfase (NAGLAZYME)	Mucopolysaccharidosis VI	441,000
Idursulfase (ELAPRASE)	Mucopolysaccharidosis I and II	475,000
Eculizumab (SOLIRIS)	Paroxysmal nocturnal hemoglobinuria	486,000- 500,000
C1 esterase inhibitor (CINRYZE)	Hereditary angioedema prophylaxis	487,000
Alglucosidase alfa (MYOZYME)	Pompe disease	575,000

Ref: Cohen and Felix 2014; WHO Europe 2015; Godman et al 2015, 2016

There are also concerns with the prices for new medicines for orphan diseases (cont.)

Outrageous prices of orphan drugs: a call for collaboration

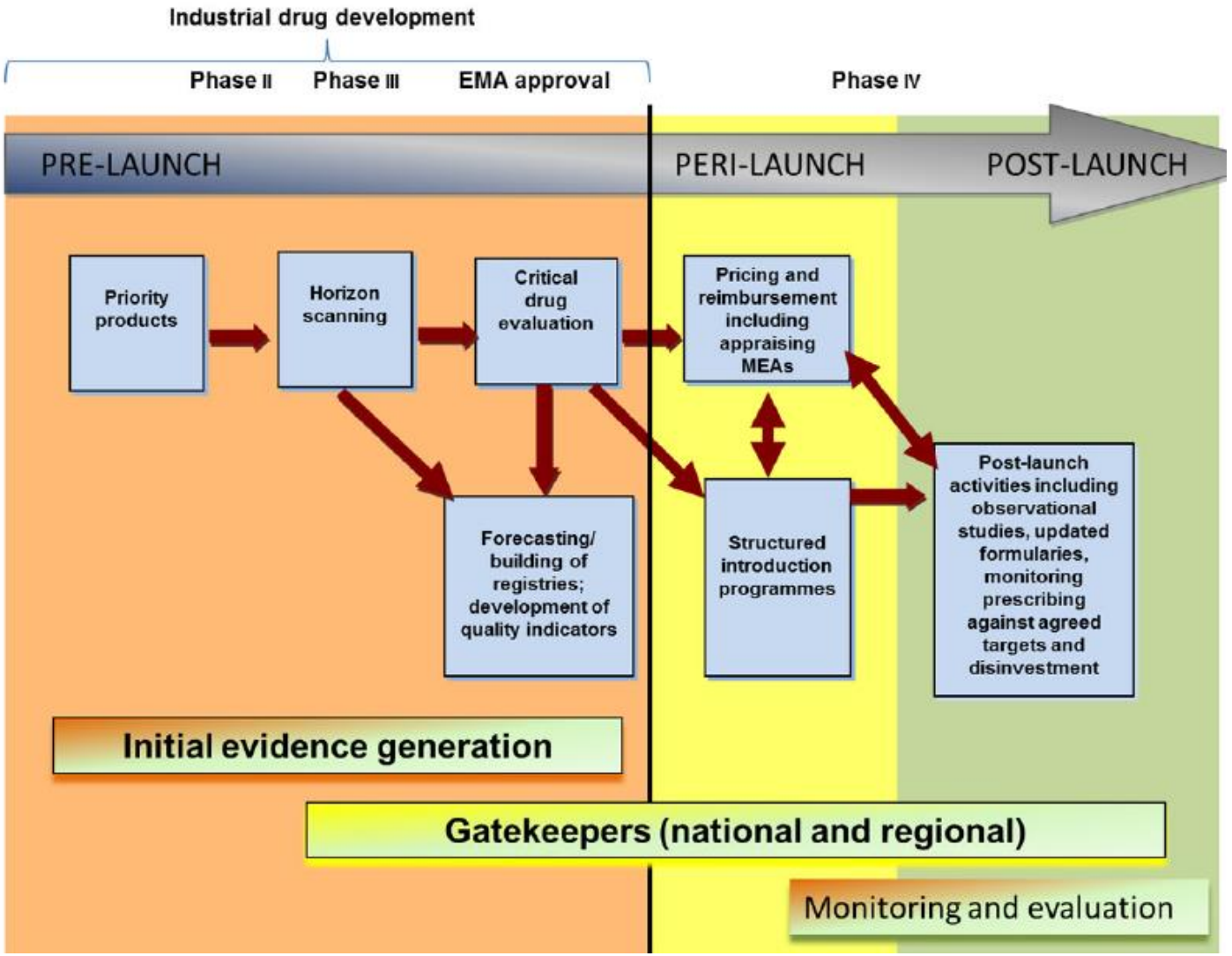
Lucio Luzzatto, Hanna I Hyry*, Arrigo Schieppati, Enrico Costa, Steven Simoens, Franz Schaefer, Jonathan C P Roos, Giampaolo Merlini, Helena Kääriäinen, Silvio Garattini, Carla E Hollak, Giuseppe Remuzzi, on behalf of the Second Workshop on Orphan Drugs participants*

Lancet 2018; 392: 791–94
Published Online
July 20, 2018

Few instances of a single act of legislation have shifted industrial policy in the pharmaceutical industry like the Orphan Drugs Act did when it was signed in the USA in

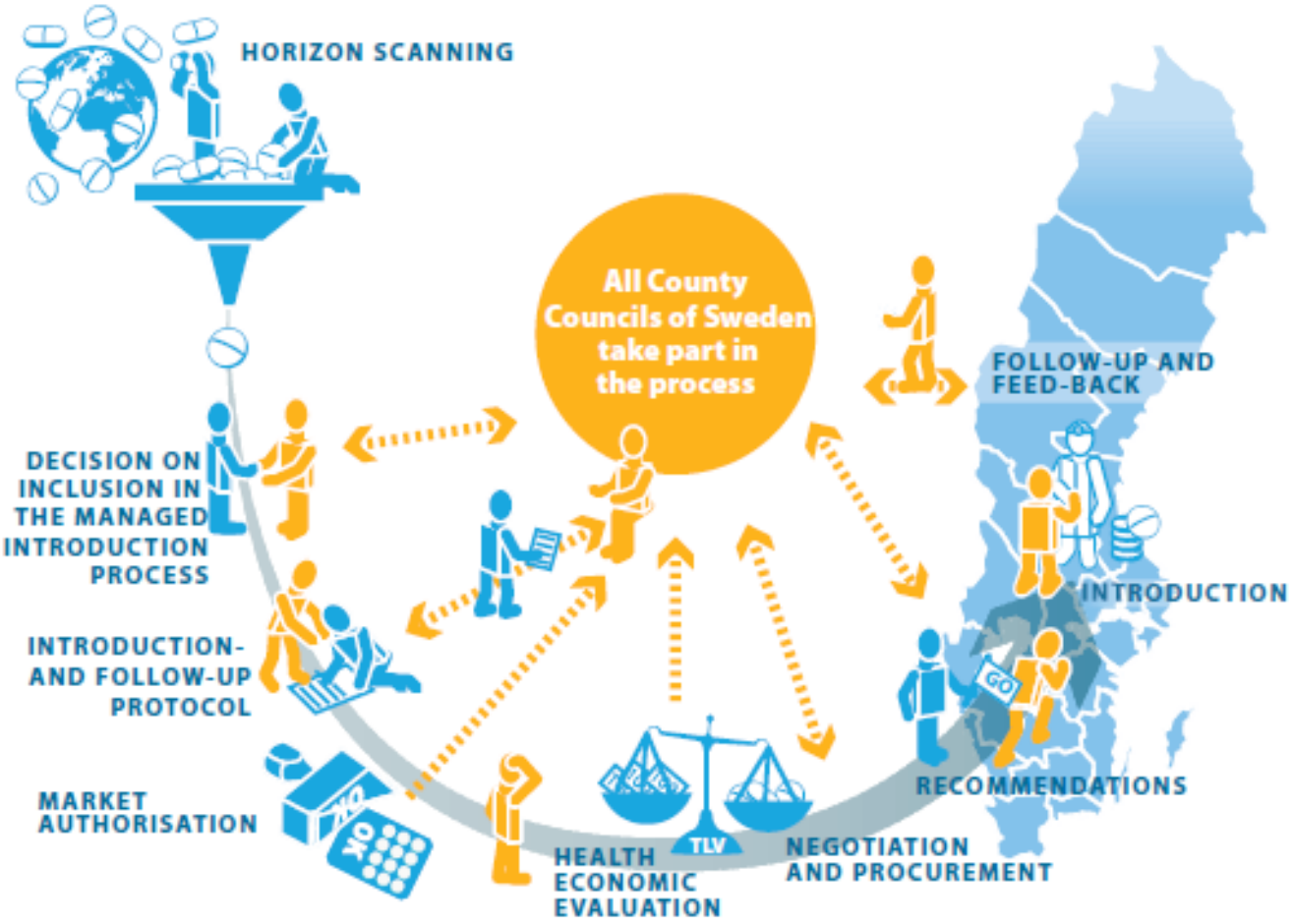
diseases. So-called orphanisation of common disorders, which is a direct result of the genomics era, enhances the scope for precision medicine and is expected to expand

Models to optimize managed entry of new premium priced medicines can be broken into 3 pillars



Ref: Godman et al 2012 - 2018; WHO Europe 2015

Currently a national collaboration model is in place in Sweden for the managed introduction and follow-up of new medicines that brings together the county councils, DTCs, governmental agencies and interaction with pharmaceutical companies



Ref: Ericksson et al 2017

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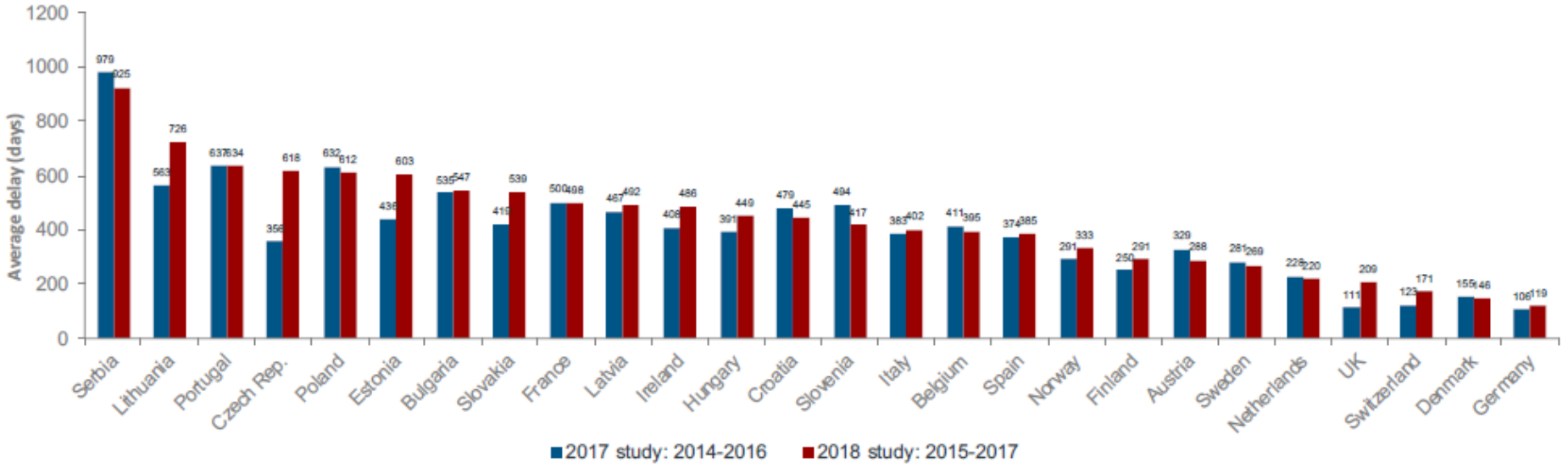
Managed Entry Agreements (MEAs) are well established across Europe and this will remain

- As mentioned, MEAs are used to facilitate reimbursement and access to new medicines in Europe, and are reasonably well established across Europe – although variations
- Their use has increased over time in response to:
  - high prices for new medicines, particularly those for cancer and orphan diseases (which are the predominant areas for new medicines in Europe)
  - the need for payers to work within finite budget limits
  - uncertainty regarding the effectiveness of new medicines in routine clinical care (real-life) especially with studies using surrogate markers and 'ideal' patients
  - European payers wish to address areas of unmet need, which can be facilitated by new medicines at appropriate prices given current delays in reimbursement
- Many definitions are currently being used for managed entry agreements (now predominating)/ risk sharing arrangements

Ref: Adamski et al 2010; Godman et al 2014 – 2018; Ferrario et al 2017

There can be appreciable reimbursement delays for new medicines in Europe causing concern



The graph shows typical time periods (days) between EMA authorization and reimbursement for new medicines among European countries

Ref: IQVIA 2019

MEAs typically have a common objective and can be typically be divided into two groups

- Despite the many definitions for MEAs/ risk sharing arrangements (RSAs)/ coverage with evidence schemes, all these schemes typically have a common objective, i.e. to facilitate access to new medicines in a context of uncertainty (around effectiveness and/or use in real-life) and high prices

- The different names used in different countries relate to the objectives they are trying to achieve, e.g. patient access schemes in the UK, the nature of the agreements (e.g. conventions in Italy), and the type of agreement

- As Alessandra has mentioned, MEAs can typically be divided into two:
  - ❑ outcome based schemes
  - ❑ financial based schemes

Ref: Adamski et al 2010; Godman et al 2014 – 2018; Ferrario et al 2017

MEAs typically have a common objective and can be typically be divided into two groups

- Financial/financial-based models include:
  - Price: volume agreements (PVAs) for both new and existing drugs
    - These typically include pay back/ rebate mechanisms if volumes and/ or expenditure exceed agreed limits for the drug, class, or overall pharmaceutical expenditure
    - Prevalent where currently limited demand side measures such as France and Italy as well as in a number of CEE countries
  - Patient access schemes involving free or discounted medicines – often discounts are confidential
  - Price cap/ expenditure cap schemes – whereby companies will cover the additional costs themselves above agreed limits, e.g. Lucentis in the UK. In addition in Australia they agreed 5 year expenditures for all suitable patients to receive second generation DAAs for Hepatitis C irrespective of usage in practice with the pharmaceutical companies

Ref: Adamski et al 2010; Godman et al 2014 – 2018; Ferrario et al 2017; Moon et al 2018

MEAs typically have a common objective and can be typically be divided into two groups

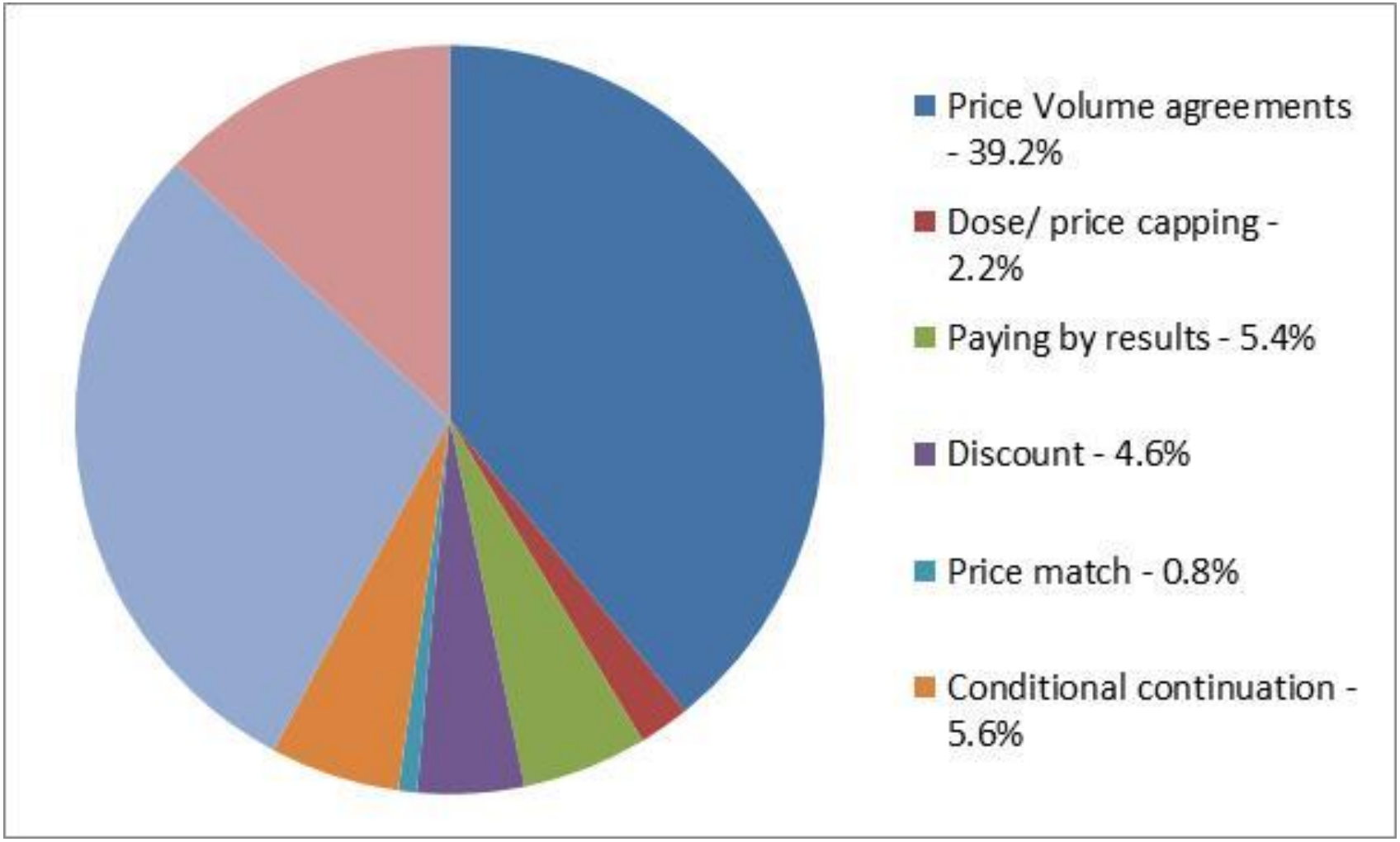
- Performance based or outcome models include:
  - 'No cure, no pay' schemes including rebates if the new medicine fails to produce the desired outcomes – concerns though that typically surrogate vs. outcome measures
  - Medicines provided free until their effectiveness is demonstrated in reality using biomarkers and other markers
  - Prices modulated if the new medicine does not produce the desired patient benefits (health gain) in clinical practice

- In reality, it is difficult to follow up outcome based schemes unless there are comprehensive IT systems in place (currently only applies to a few European countries and regions). Otherwise extensive administrative support reducing their applicability in practice, e.g. Velcade scheme in the UK

- There are also concerns if potential patient populations are large without means of stratifying patients

Ref: Adamski et al 2010; Godman et al 2014 - 2016; Clopes et al, Ferrario et al, Toumi et al 2017; Antonanzas 2018

Not surprisingly, price: volume agreements are the most common form of MEA in Euope with limited outcome based schemes



Ref: Ferrario and Kanavos 2013; WHO Europe 2015

Italy has implemented a number of performance based schemes (outcome based schemes) but concerns exist

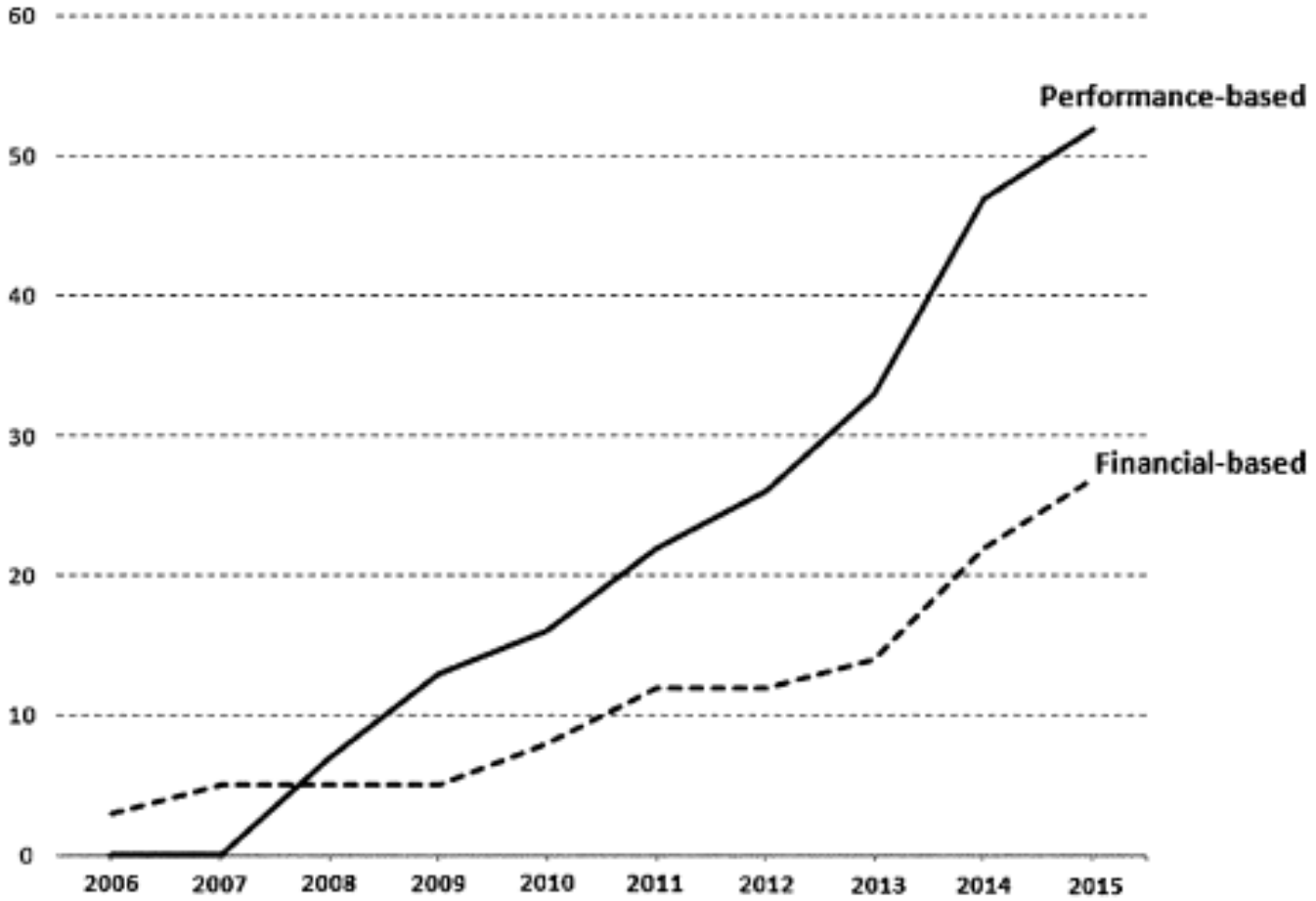
- Carlson et al (2017) identified 85 MEAs in Italy between 2007 and 2016, with 31 reimbursement conditional to performance, 23 financial agreements or volume of use, 17 conditioned continuation of treatment, and four of coverage linked to evidence generation

- Overall, performance based schemes have predominated in recent years in Italy – which is unlike other European countries

- However, Garattini noticed that despite physicians being asked to undertake an intermediate evaluation of pathology after a fixed number of therapy cycles and a final evaluation, in reality '**information collected seems to be mainly a self-certified validation of appropriate prescription by the physician**' rather than any '**additional information that might be useful for an extended clinical assessment of the treated patients**'

Ref: Garattini et al 2016; Carlson et al 2017

Performance based schemes (outcome agreements) have predominated in Italy in recent years

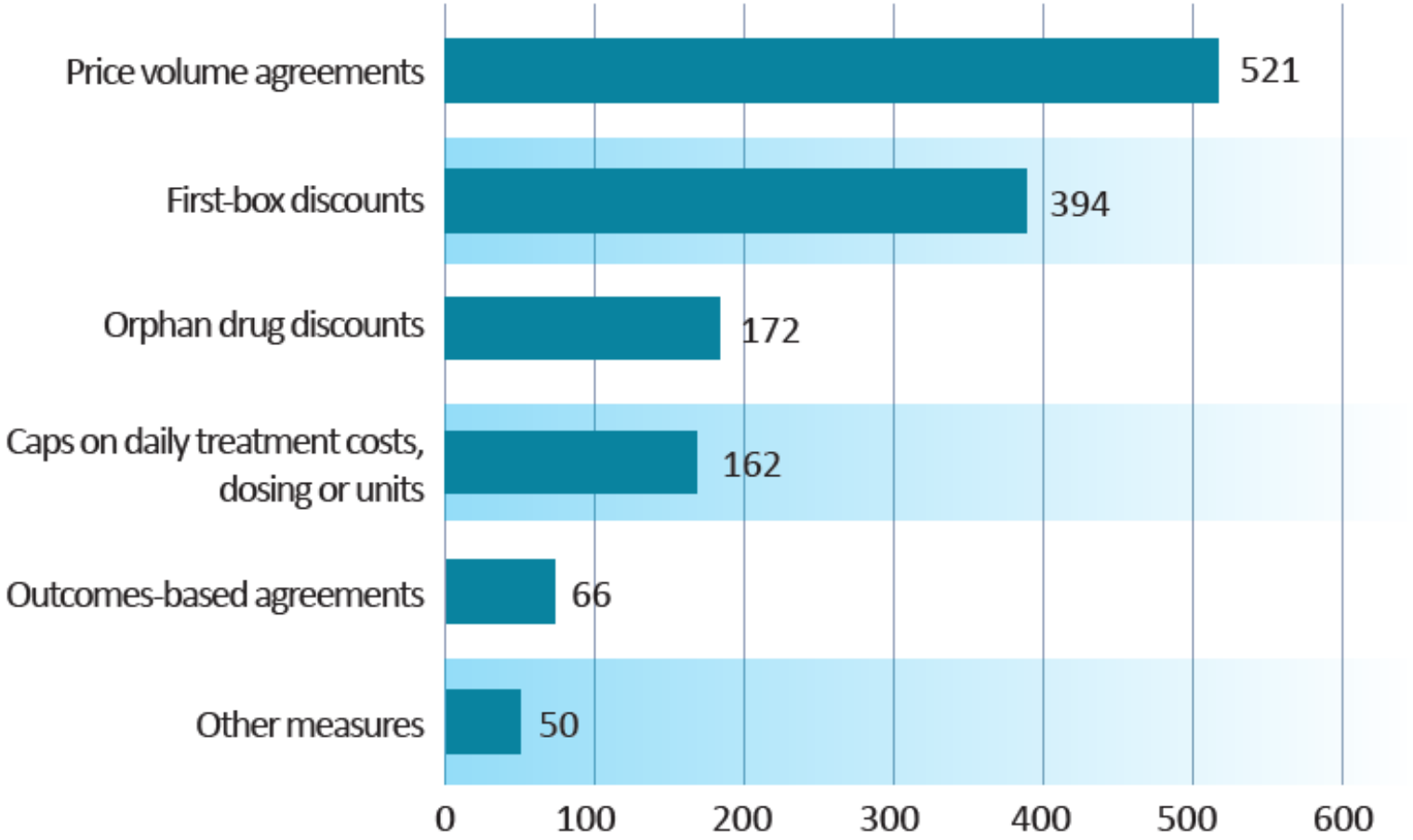


FbA, Financial-based agreement; PbA, performance-based agreement.

Cumulative trend of FbAs and PbAs

Ref: Garattini et al 2016

The savings from MEAs can be substantial especially for price and volume agreements, e.g. France (€millions)



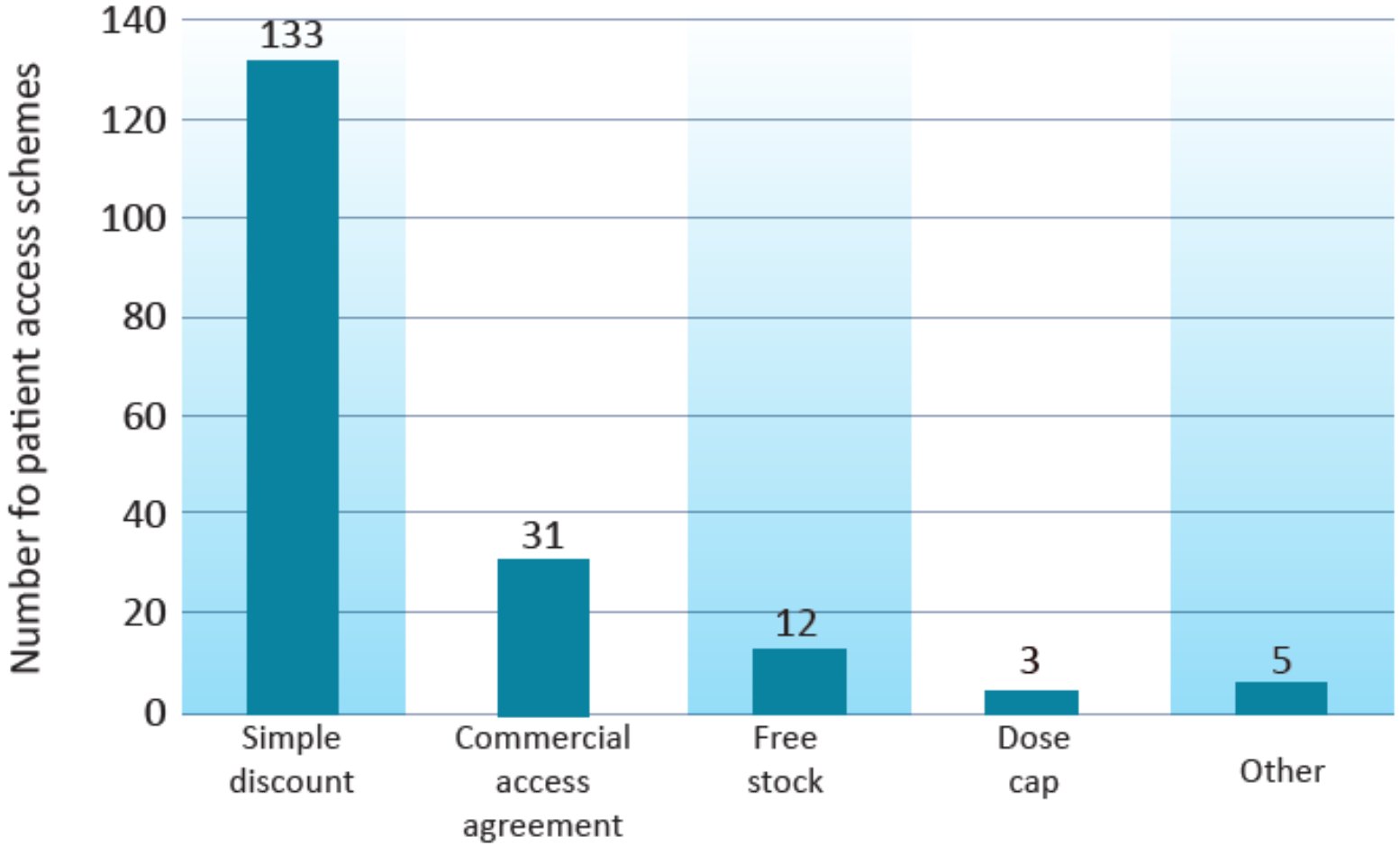
Ref: Grubert and Morse Consulting 2018

NICE in the UK has a Patient Access Unit to help facilitate the funding of new medicines where concerns – with a similar system in Scotland

- The Patient Access Scheme Liaison Unit (PASLU) was established by NICE to work with pharmaceutical companies
- PASLU evaluates the proposals and determines whether such schemes would work in the NHS (England)
- Simple discount schemes, either a lower fixed price or a percentage discount, are easier to implement and the review can be conducted rapidly by PASLU - usually within 4 weeks
- Complex schemes including outcomes schemes, dose caps, rebates, and upfront free stock, are more difficult to implement and take longer – consequently discouraged where possible by appreciably longer time periods for decision making (building on the experiences with beta interferons and Velcade)
- To date, NICE has entered into over 210 arrangements with companies (https://www.nice.org.uk/About/What-we-do/Patient-access-schemes-liaison-unit/List-of-technologies-with-approved-Patient-Access-Schemes)

Ref: NICE and SMC websites 2019

Typically NICE in the UK seeks to encourage simple discounts where possible by the length of time for negotiations (status of PAS October 2018) - changing with new regulations for the cancer drug fund



Ref: Grubert and Morse Consulting 2018

Pharmaceutical companies applying to the cancer drug fund for funding for their new cancer medicine in England must submit an MEA including details of data collection via Systemic Anti-Cancer Therapy (SACT) Data (mandated dataset as part of the Health and Social Care Information Standards in England)

Appraisal and Funding of Cancer Drugs from July 2016 (including the new Cancer Drugs Fund)

A new deal for patients, taxpayers and industry

Ref: NHS England 2016

There have been concerns with the MEA for beta interferons in the UK

- The beta interferon scheme was established in the UK in 2002 following initial rejection by NICE of the beta interferons for MS
- Under the scheme, the four manufacturers of beta interferons agreed that a cohort of approximately 10,000 patients would be followed for over 10 years with the cost of the beta interferons reduced or refunds given if the cost/ QALY was over an agreed limit
- The initial assessment after 2 years showed poor outcomes with concerns with slow recruitment (time consuming form filling during busy clinics and delays in neurology units being accredited)
- However more recent data suggests benefit; however, responses wane over time

Ref: Zampirolli et al – being submitted

The concerns with the beta interferon scheme in the UK were highlighted by slow recruitment and limited effectiveness initially – now eased

BMJ

RESEARCH

Multiple sclerosis risk sharing scheme: two year results of clinical cohort study with historical comparator

Mike Boggild, consultant neurologist,[1] Jackie Palace, consultant neurologist,[2] Pelham Barton, senior lecturer in mathematical modelling,[3] Yoav Ben-Shlomo, professor of clinical epidemiology,[4] Thomas Bregenzer, director, biostatistics,[5] Charles Dobson, senior projects officer,[6] Richard Gray, director[7]

Ref: Boggild et al 2009

By 10 years of follow-up, there was a beneficial effect of the beta interferons when used first line. However, the effect wanes over time

Multiple sclerosis

OPEN ACCESS

RESEARCH PAPER

Assessing the long-term effectiveness of interferon-beta and glatiramer acetate in multiple sclerosis: final 10-year results from the UK multiple sclerosis risk-sharing scheme

Jacqueline Palace,[1] Martin Duddy,[2] Michael Lawton,[3] Thomas Bregenzer,[4] Feng Zhu,[5] Mike Boggild,[6] Benjamin Piske,[4] Neil P Robertson,[7] Joel Oger,[5] Helen Tremlett,[5] Kate Tilling,[3] Yoav Ben-Shlomo,[3] Richard Lilford,[8] Charles Dobson[9]

Ref: Palace et al 2019

The NHS in Scotland has produced guidance for MEAs (Patient Access Schemes) again encouraging discounts

NHS National Services Scotland

NHS Scotland

Patient Access Scheme (PAS) Guidance

Ref: NHS Scotland 2019

Simple discount schemes are also prevalent in Scotland (UK for the NHS is divided into 4 regions)

- By the end of 2018, there were over 100 MEAs (Patient Access Schemes) established in NHS Scotland
- The vast majority of MEAs are simple discount schemes (discount at the point of invoicing)
- Less than 10% of MEAs are complex financial schemes
- Currently there is only one ongoing outcome based scheme in Scotland
- This trend is likely to continue – however, we may see the growth in outcome based MEAs in the future in Scotland especially for new cancer medicines as the CMOP programme roles out

Ref: Zampirolli et al – being submitted

Scotland is also looking to collect minimum data sets for cancer patients which could also result in more outcome based schemes in Scotland

- The Scottish Government in 2017 announced it is investing £300,000 this year in a programme which investigates whether medicines are as effective in the 'real world' as they are in clinical trials

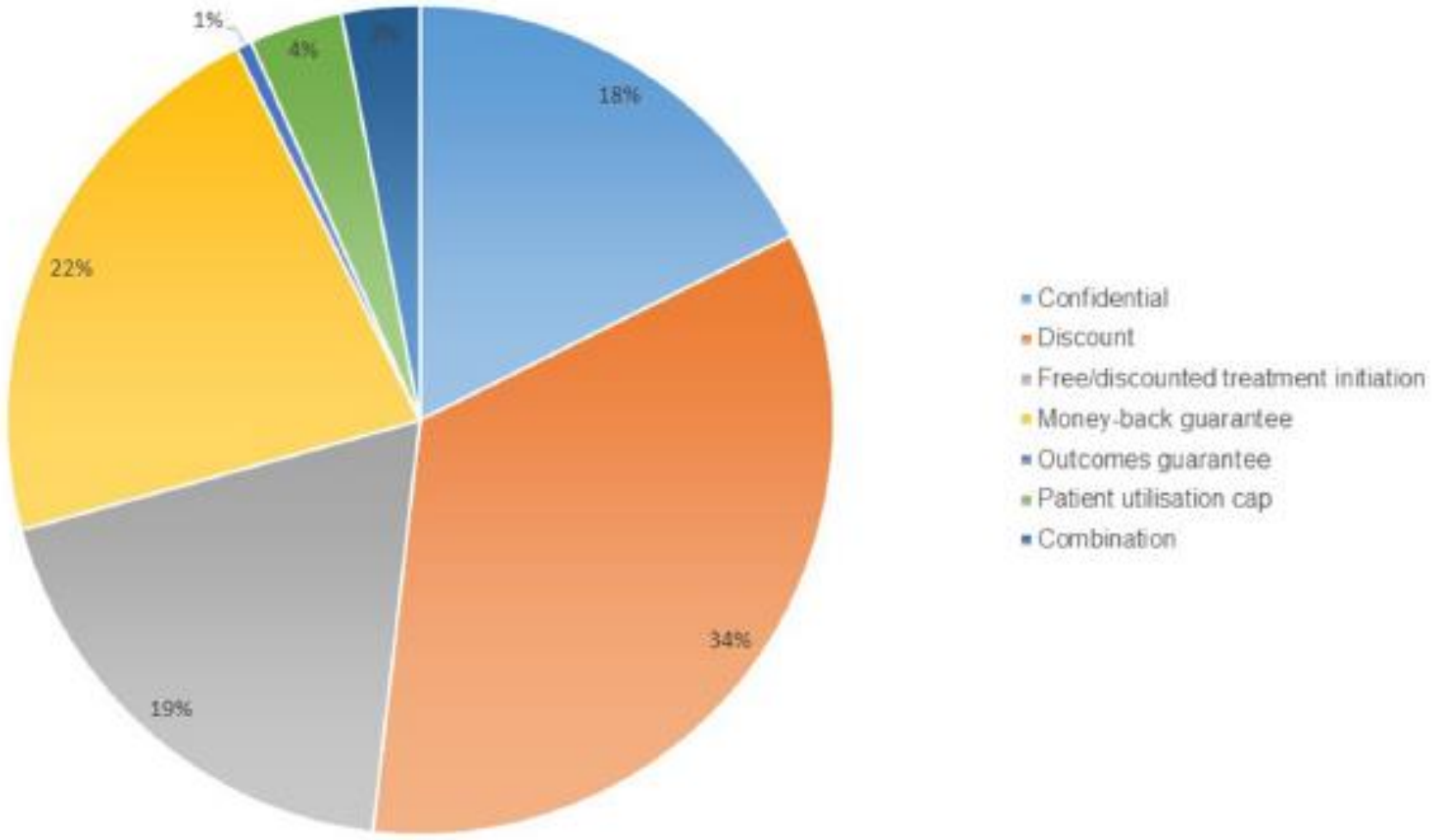
- The Cancer Medicines Outcome Programme (CMOP) is a three year collaboration between NHS Greater Glasgow and Clyde and the University of Strathclyde

- This involves developing, agreeing and implementing data sets for cancer to help better manage patients - Our vision is '**to develop a process which provides feedback to our cancer care clinicians on local outcomes. This real life data on the benefits, and side effects, of cancer medicines can then be used to identify supportive care needs as well as inform shared clinical decision-making between clinicians and patients**'

Ref: NHS Scotland website 2017

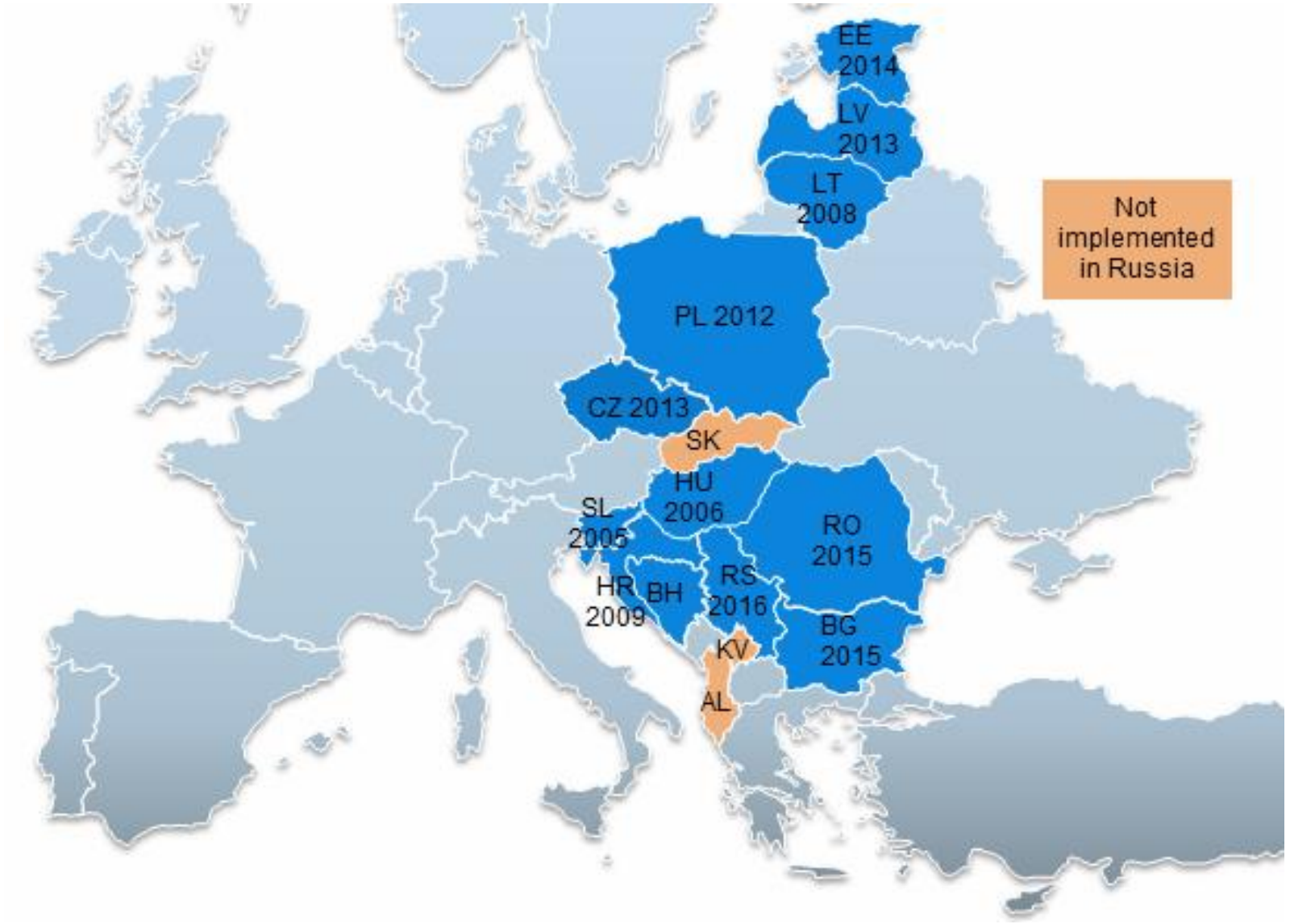
Financial based schemes are also more prevalent in oncology rather than outcome schemes in Europe

Number of MEAs and their type for oncology across Europe in recent years(n=164)



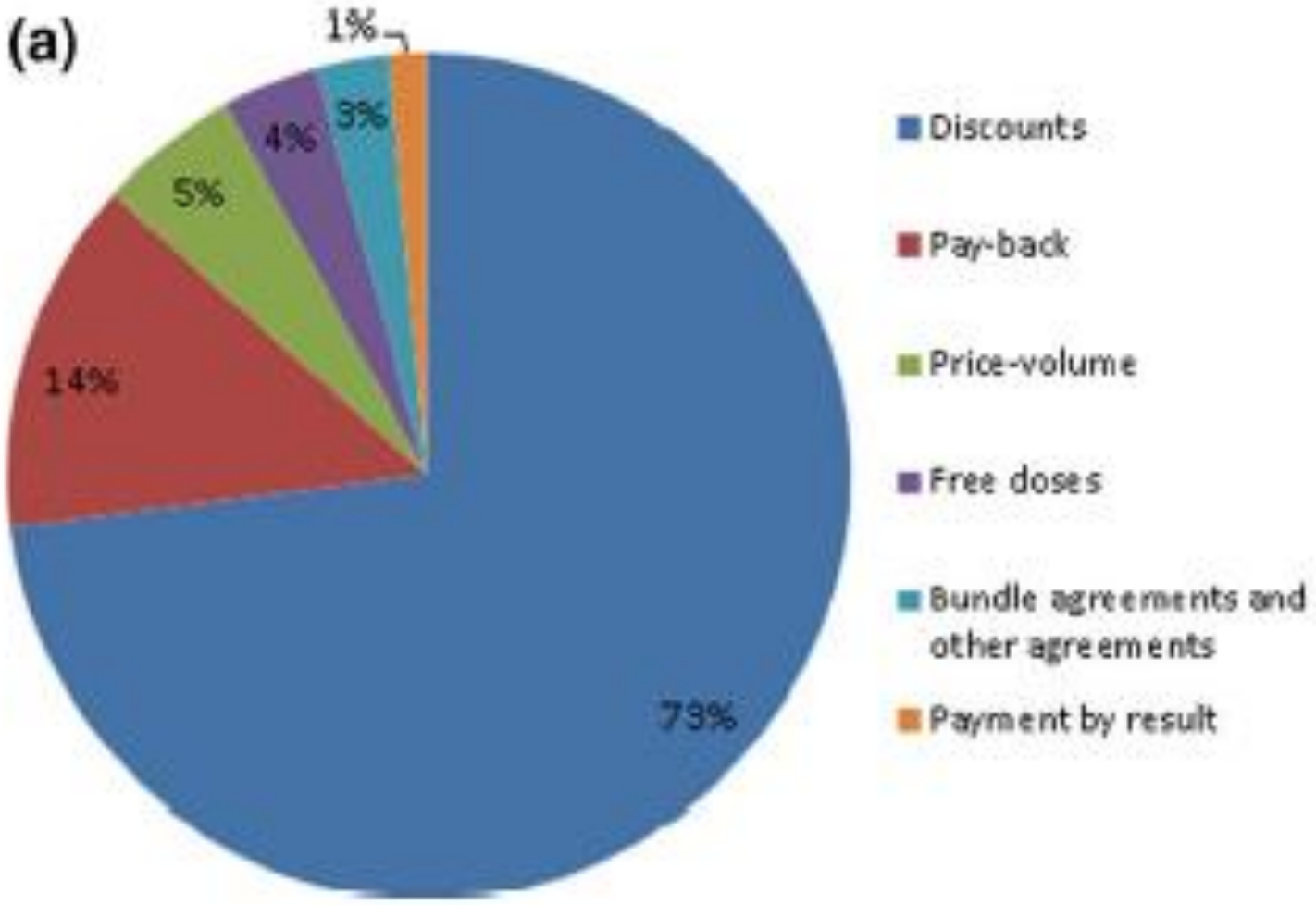
Ref: Pauwels et al 2017

MEAs are also growing among CEE countries – Implementation of MEAs as of February 2017



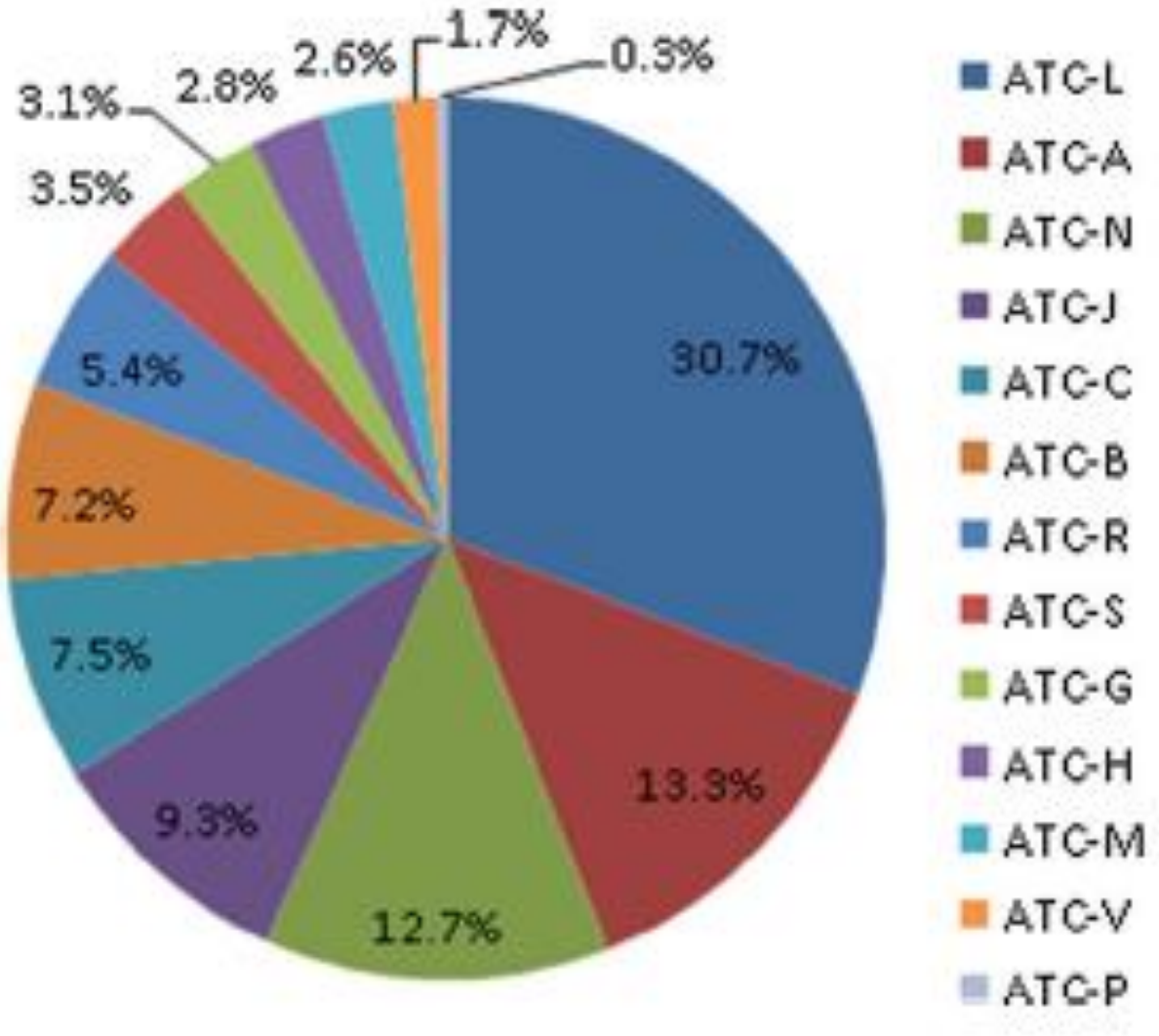
Ref: Ferrario et al 2017

Similarly, most MEAs in CEE countries are financially based, e.g. agreed discounts



Ref: Ferrario et al 2017

Not surprisingly most MEAs in CEE countries are also in the cancer area (ATC L)



Ref: Ferrario et al 2017

However there are examples of successful outcome based schemes, e.g. Catalonia

- An outcome based scheme was negotiated for the introduction of gefitinib in the treatment of patients with advanced EGFR-mutation positive non-small-cell lung cancer in Catalonia
- The pharmaceutical company agreed to reimburse the total treatment costs for patients that failed treatment, which was defined as progression at 8 or 16 weeks
- The scheme resulted in total savings of approximately €36,000 for the 41 patientsenrolled (approximately €880 per patient)
- The recent initiatives with the CDF in England and CMOP in Scotland are looking to build on schemes such as these

Ref: Clopes et al 2017

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There are positive considerations with MEAs as well as concerns. Key issues need to be addressed in the future

- There are a number of positive considerations regarding MEAs in Europe including aiding reimbursement/ funding for new medicines that would have otherwise not be reimbursed. In addition, helping health authorities stay within budget

- There are also concerns including high administration and transaction costs, the confidential nature of any discount (potentially penalising smaller European countries) as well as whether countries/ regions have the necessary infrastructure to undertake outcome based schemes

- Key considerations before undertaking MEAs include current capacities, clear objectives for any MEA, will the proposed MEA reduce uncertainty with the value of a new medicine especially if surrogate measures are used (outcome based schemes) and the length of time of any scheme

There are both Pros and Cons with financial based schemes:

Benefits with financial-based schemes

- Enhances the opportunities for reimbursement as well as for payers to work within defined budgets
- Shifts cost/ usage considerations to pharmaceutical companies – essential where concerns of excessive utilisation
- Limits 'off label' usage/ indication creep in practice – especially important for expensive biological drugs and new orphan drugs

Concerns with financial-based schemes

- The schemes may not always factor in issues such as compliance and dosage creep, e.g. now advocating 80mg atorvastatin in the UK for high risk patients
- Pharmaceutical companies may benefit from early access of 'unproven' technologies
- Can be complex to administer reducing savings in reality – especially if countries are operating multiple schemes at once
- Potentially issues of patient confidentiality and follow up, e.g. dose capping schemes
- Concerns if co-payments based on list rather than actual prices

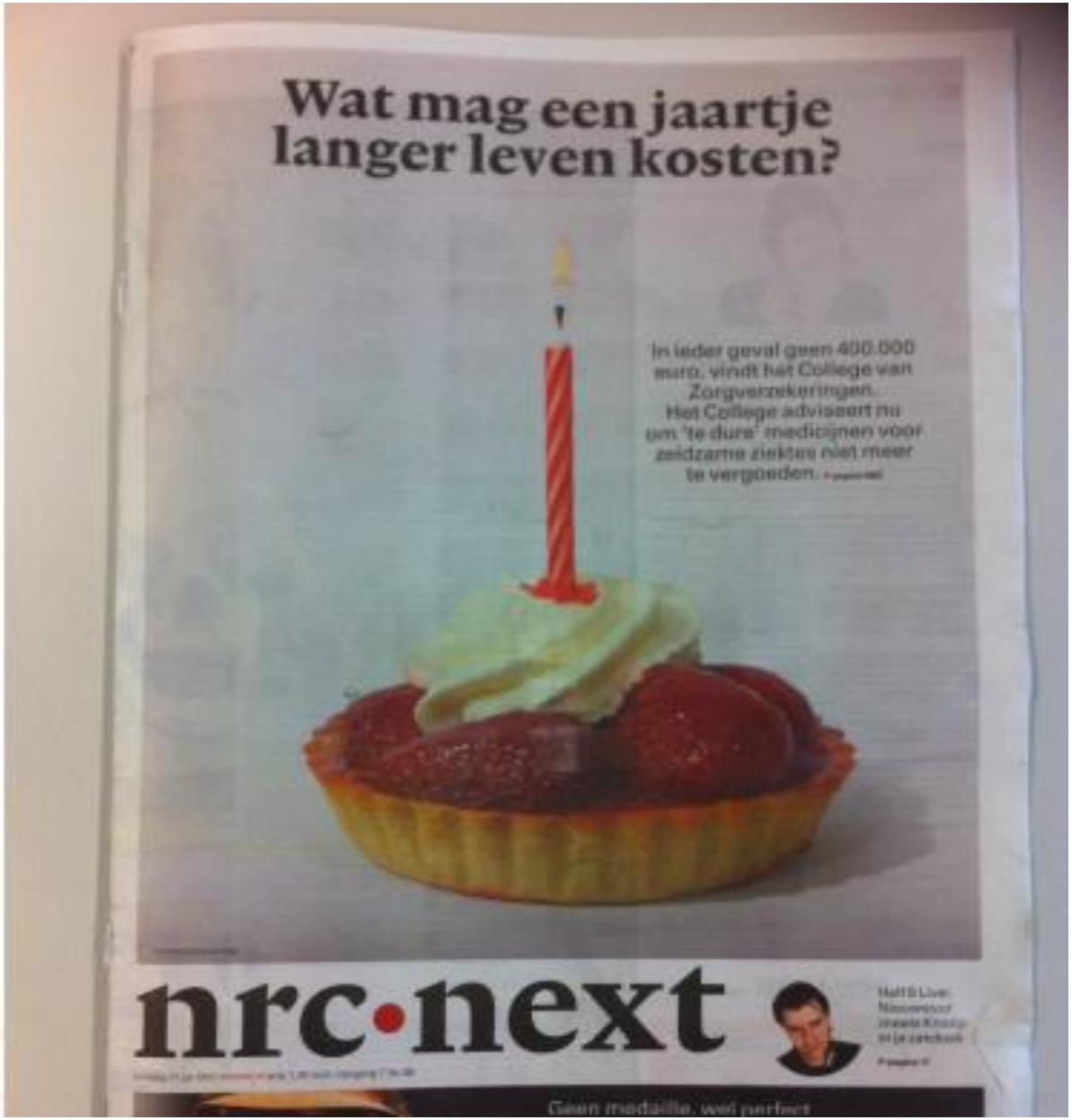
Similarly, there are both Pros and Cons with outcome based schemes:

Benefits of outcome based schemes

- Payers only fund treatments that produce desired health gain
- Treatments can potentially be targeted to those patients where health gain is greatest (if there is an appropriate marker)
- Payers can monitor usage in practice against agreements, as well as monitor safety in practice especially given the selective nature of Phase III clinical trials
- Enhances the chances of successful reimbursement and funding

Concerns with performance based/ outcome based schemes

- Whether the objective is fully explicit and transparent, and the level of evidence sufficient to make robust decisions
- Who will end up funding any necessary registries/ databases in reality, and can such schemes be introduced in practice with current regulations/ staff
- Length of follow-up – impacting especially on issues such capacity and compliance in practice as well as who funds the new medicine and at what price until such schemes are analysed (if open ended)
- General administration burden in practice unless comprehensive IT systems
- Whether the system can cope with time scales for refunds, e.g. time between monitoring disease progression and the next physician visit
- Potentially accelerating the uptake of new medicines in practice
- Whether refunds/ rebates are passed back to the payers in reality – especially within DRG systems, and what happens if companies refuse to reduce their price if the value is not seen in reality – difficult to disinvest on price (Pompe)



Pressure from the media in the Netherlands resulted in pressure on the MoH to ignore the advice of the reimbursement agency about funding enzyme replacement therapy for Fabrys' disease (up to €3.3 million incremental cost / QALY) and up to €15million for alglucosidase alfa to treat Pompe's disease

Ref: Godman et al 2015, 2016

MEAs will continue – but will need to look at alternative models as confidential discounts difficult

- We are likely to see MEAs continuing especially with ever increasing pricing requests for new medicines against a backdrop of increasing availability of standard medicines as low cost generics and biosimilars
- Companies can help by ensuring as robust data as possible during pricing negotiations and having realistic pricing expectations given the limited number of new medicines that are truly innovative – currently more hype than substance especially for new cancer medicines/ those for orphan diseases
- Companies can be potentially more transparent in their pricing structure/ negotiations given for instance low prices seen for some new cancer medicines and the situation with hepatitis C (new ones looking initially for over 99.5% gross profitability)
- Companies and others can assist with looking at alternative pricing models, e.g. TVF for new medicines for orphan diseases, as confidential discounts difficult to sustain within public health systems in Europe
- All key stakeholders need to start researching appropriate models, especially outcome schemes, early at pre-launch ready for marketing authorisation. Such activities will grow with increasing prevalence of NCDs across Europe and continued new premium priced medicines

Thank You

Any Questions!

Brian.Godman@ ki.se; Brian.godman@strath.ac.uk;
Brian.Godman@liverpool.ac.uk;
briangodman@outlook.com