Positional and collaborative negotiations: The key to healthy competition

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Overview

- Challenges for health care systems
- Principled negotiation
- A toolkit for robust negotiations

Challenges for health care systems

"IT'S A NEW MIRACLE DRUG. IT'LL BE A MIRACLE IF YOU CAN AFFORD IT."

Observation 1: Significant challenges of applying HTA in managing the introduction and use of new health technologies

Key challenges

- Ensuring equitable access to high cost health technologies
- Advancing methodological approaches to improve efficiency in allocation of resources
- Consideration of efficacy in trials versus relative effectiveness in clinical practice (limited data on outcomes)
- Increased pressure to conduct assessment early in the clinical development process[1]

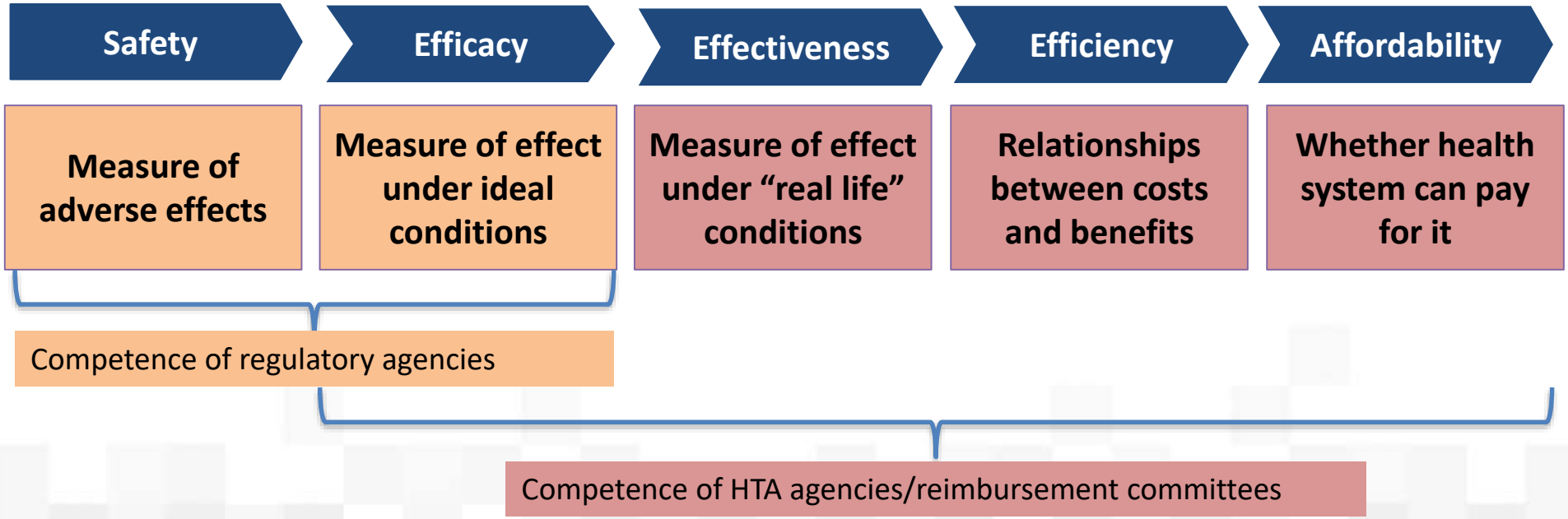
Product / therapeutic area –specific issues

- **Products with multiple indications**
  - FDA – 154 approved indications for 124 oncology drugs (1.25 indications/drug) with an original or supplemental indication approved 2006-2015[2]
  - IMS projects that by 2020, most oncology products will have 3+ indications[3]
- **Combination therapies**
  - Primary route of development for a new molecular entity is use in combination with existing therapies from another manufacturer[3]
  - How to assess the value of the individual components
- **Targeted therapies (e.g. oncology) and personalized/precision medicine (e.g. gene therapy)**
  - Complexity of assessment
  - Narrow therapeutic margin between benefit and harm
- **Transition of anticancer medicines into chronic treatments[3]**

Source: 1 - http://clincancerres.aacrjournals.org/content/19/1/6; 2 – OECD (2015), Heath at a Glance 2015: OECD indicators; 3 – IMS (2015) – Global Medicines Use in 2020, Outlook and Implications, November 2015

Observation 2: What do decision-makers want?

- Safety and Efficacy are *first* steps to provide evidence for a new treatment;
- Effectiveness and Efficiency need to be proven;
- Affordability is increasingly becoming a requirement for coverage and may result in access restrictions



- Efficacy does not imply effectiveness and effectiveness does not imply efficiency
- Safety and efficacy are the competence of regulators, effectiveness, efficiency and affordability are the competence of payers/insurers
- Use of HTA to assess value for money and affordability; increasing use of RWE now/in future

Observation 3: Requirements to deliver value for money

- Assessing (new) medical technologies **requires**
  - Skilled human resources in sufficient numbers
  - A **principled approach**
    - Legal framework
    - Criteria
    - Ways of assessing
    - Procedures
    - Metrics

✓ Different degrees of acceptance & sophistication

Observation 4: HTA bodies vary in how value dimensions are assessed… do we rely on assessments in other settings?

		France	*Germany*	*Sweden*	*England*	*Italy*	*Netherlands*	*Poland*	*Spain*
Burden of disease									
	Severity	***	**	**	**	*	**	**	**
	Availability	***	*	*	***	*	**	*	**
	Prevalence	*	**	*	*	**	**	**	**
Therapeutic									
	Direct endpoints	***	***	***	***	***	***	***	***
	Surrogate endpoints	**	**	**	**	**	**	**	**
Safety									
	Adverse events	***	***	***	***	***	***	***	***
	Tolerability	**	**	**	**	**	**	**	**
	Contraindications	**	**	**	**	**	**	**	**
Innovation									
	Clinical novelty	***	*	*	*	**	**	***	**
	Nature of treatment	***	*	*	**	x	*	***	**
	Ease of use & comfort	*	*	**	*	x	*	x	*
Socioeconomic									
	Public health	**	**	*	**	*	***	***	*
	Budget impact	*	***	**	***	**	**	***	**
	Social productivity	*	**	***	**	*	**	*	**

***	mandatory/ formal/explicit/ planned/ directly/ grading system
**	"considered", e.g. recommended, informal/implicit but planned, formal/explicit but ad-hoc/indirectly, etc.
*	optional/ informal/implicit/ad-hoc/ indirectly/ no grading system
x	not considered in any way

Source: Angelis and Kanavos, *Social Science & Medicine* 2017.

Observation 5: Divergent *HTA recommendations occur because of differences in data interpretation AND other considerations*

HTA recommendation – the case of Aubagio® teriflunomide

Aubagio® (teriflunomide) Indication: treatment of relapsing multiple sclerosis

Clinical uncertainties

	Australia	Canada (CADTH)	Canada (Quebec)	England	France	Germany (IQWiG)	Scotland	Sweden
Recommendations/ decisions	LWC	DNL	L	LWC	ASMR V	No additional benefit shown	LWC	L
Country setting generalizability				✓				
Age of patients included in the trial							✓	
Pre-treated patients		X						
Number of patients	✓							
No strong clinical benefit shown	✓							
Appropriateness of endpoints	✓		✓	✓			✓	
Lack of comparisons with main medicine used					O		O	
Indirect comparison not well designed	X	X	✓	✓		X	X	✓
Main trial not well powered for outcomes		X	X					
Long-term safety profile and monitoring time of AEs		O		✓			O	
Differences in safety profile with comparators	✓							✓
Position in the current clinical practice				✓				
Lack of data for RRMS subgroups					O			

Economic uncertainties

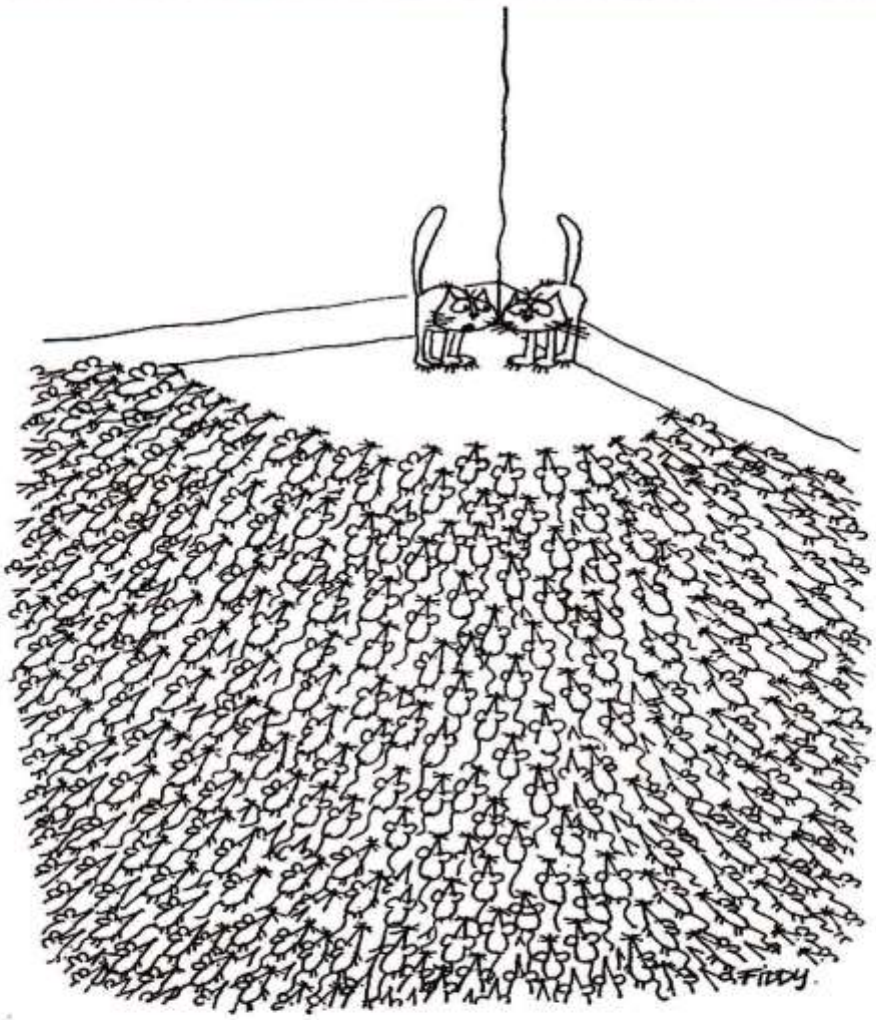
	Australia	Canada (CADTH)	Canada (Quebec)	England	France	Germany (IQWiG)	Scotland	Sweden
Recommendations/ decisions	LWC	DNL	L	LWC	ASMR V	No additional benefit shown	LWC	L
Validity of the model considered				✓				
Modelling disease progression		X		✓				
Inclusion of the waning effect		X		✓				
Lack of appropriate sensitivity analysis							O	
Lack of direct comparative trial data		X					✓	
Reliability of relapse rate in the main informing indirect comparison				✓				
Comparison with too expensive comparators	O							
Costs of hospitalized relapse		X						
Costs of adverse events		X					✓	
Reliability of utility included		X		✓				

✓ = Uncertainties raised and overcome X = Uncertainties raised not overcome O = Uncertainties raised and with no effect or not addressed.

Abbreviations: AE, adverse event; ASMR, improvement in actual medical benefit; CADTH, Canadian Agency for Drugs and Technology in Health; DNL, do not list; IQWiG, Institute for Quality and Efficiency in Health Care; L, list; LWC, list with criteria; RRMS, relapsing-remitting multiple sclerosis.

Source: LSE, September 2017.

So, what's the strategy to achieve optimal resource allocation based on evidence submitted?



"Well, don't just stand there -
NEGOTIATE!"

Different approaches in negotiations

Positional bargaining

- Partisan perceptions

Principled negotiation

- Satisfies **interests**, not positions
- No waste: the best of many **options**
- **Legitimate**: no one feels "taken"
- Better than your best **alternative** (BATNA)
- Well-planned **commitment**
- Process is efficient: good **communication**
- Process improves the working **relationship**

How do we negotiate?

Assessing and interpreting clinical & economic evidence in the context of HTA

- How to interpret clinical & economic evidence

  A. Clinical vs. surrogate endpoints, comparators
  B. Relative vs absolute effects
     A. **The relationship between the observed and true treatment effects involves testing the hypothesis using statistical analysis**. Three key measures: point estimate, confidence interval, p-value
  C. When trials are not big enough
  D. Understanding subgroup analyses
  E. Challenges of single arm trials
  F. Type of analysis (ITT vs. per protocol)
  G. Data cross-overs
  H. Economic evidence

Clinical evidence – therapeutic impact assessment

Example: clinical endpoints for cancer – EMA guidance

Acceptable clinical endpoints

- Clinical outcomes: cure rate, overall survival (OS)
- Surrogate endpoints: progression free survival (PFS), disease free survival (DFS)[1]
  - the comparative importance of OS and PFS to patients is uncertain, live longer or without progression?
- Demonstrated favourable effects on survival are the most persuasive outcome of a clinical trial with prolonged PFS/DFS considered to be of benefit to the patient[1]
- Alternative primary endpoints, such as time to tumor progression (TTP) or time to treatment failure (TTF) have to be fully justified
- Recently, two frameworks for assessing cancer drugs by payers, clinicians and patients (ASCO and ESMO) both always give a higher weight for OS than PFS
- Hence a drug with a remarkable effect on PFS would be assigned a score lower than a modest or even small effect on OS

Surrogates justification

- Often selected as a primary endpoints in oncology trials because:
  - may be more readily demonstrable (more number of events)
  - may be detected earlier, and
  - often has a larger effect size because of the observed effect on survival can be diluted by subsequent treatment post-progression
    - Trials can involve unblinding patients at (i) end of trial or (ii) when they relapse, at which point the control patients are allowed to cross over to the experimental treatment - can make OS difficult to interpret

Source: 1 – EMA: Guideline on the evaluation of anticancer medicinal products in man

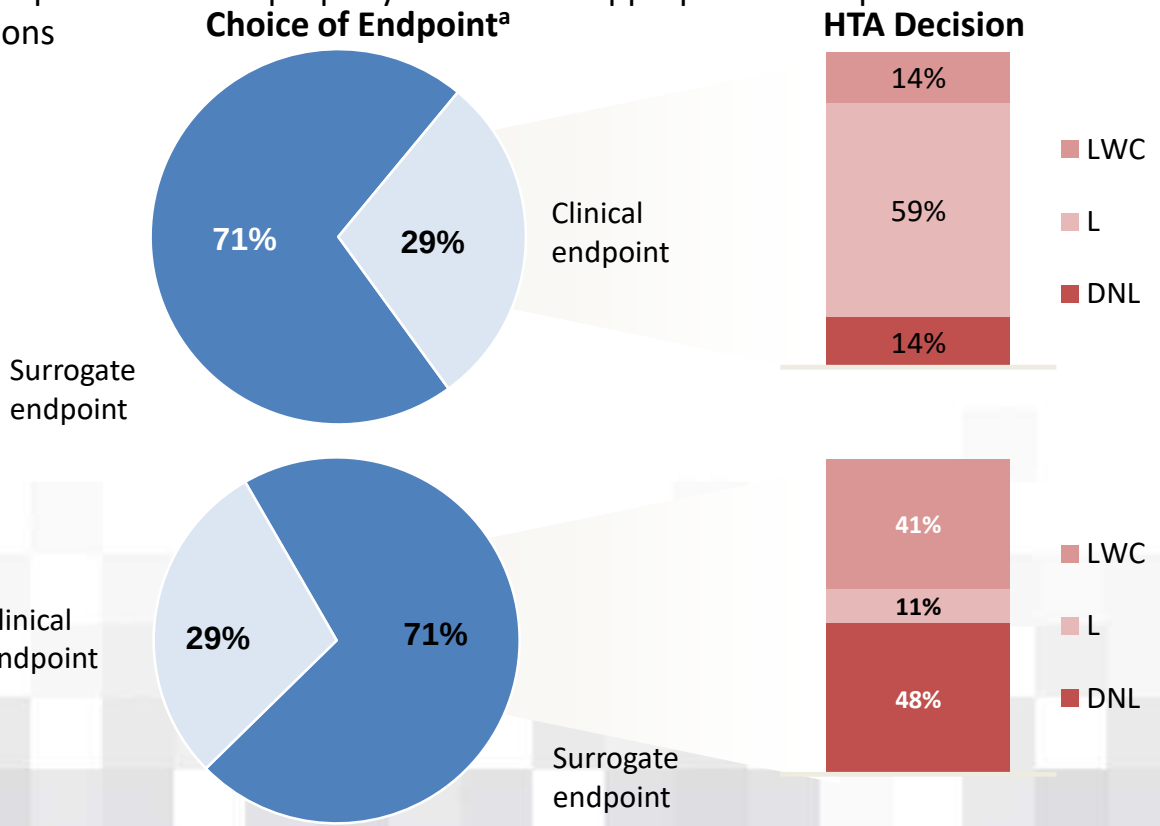
Clinical evidence – therapeutic impact assessment

Use of clinical endpoints have increased the probability of positive HTA recommendations

- **Use of surrogate endpoints is far more likely to lead to negative recommendations (i.e. either do not list or list with criteria)**
- Dependence on surrogate endpoints must be properly validated in appropriate therapeutic context to avoid outright HTA rejections

[The National Authority for Health] is quite tough on criteria, they prefer to have actual clinical endpoints and not surrogate endpoints and outcomes. – France

No manufacturer has ever properly validated its surrogate endpoints, so we don't use them. Our decision is always based on clinical endpoints. – Germany

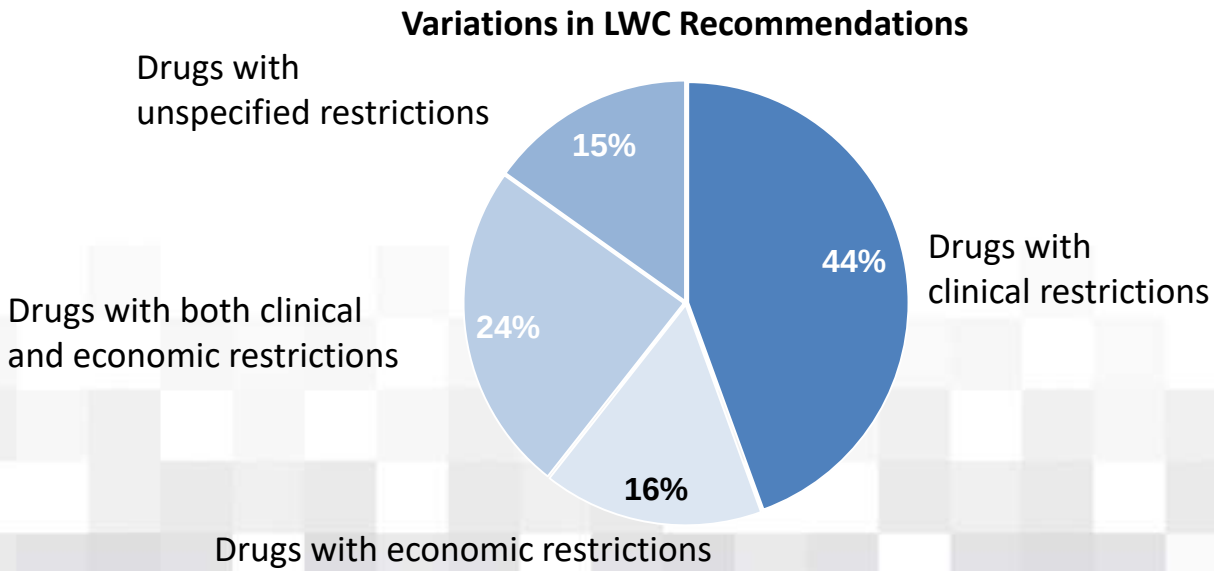


Abbreviations: DNL, do not list; L, list; LWC, list with criteria.
[a] Clinical endpoint, overall survival; surrogate endpoint, progression-free survival.
N=24 cancer drug-indication pairs across Australia, Canada, England, France and Scotland (2012-2016).
Source: LSE, March 2017.

Clinical evidence – therapeutic impact assessment

HTA agency restrictions to protect budgets from new drugs with clinical/economic uncertainties

- **Over 53% of the drug-indication pairs analyzed across seven countries achieved List With Criteria (LWC) recommendations, subject to various clinical and economic restrictions on product usage and taking into account budget impact**
- Most of the restrictions placed on drugs receiving LWC recommendations are clinical in nature rather than economic, highlighting the importance of high quality clinical evidence (e.g., trial design, evidence on hard endpoints, comparators) that HTA agencies place on new evidentiary submissions.



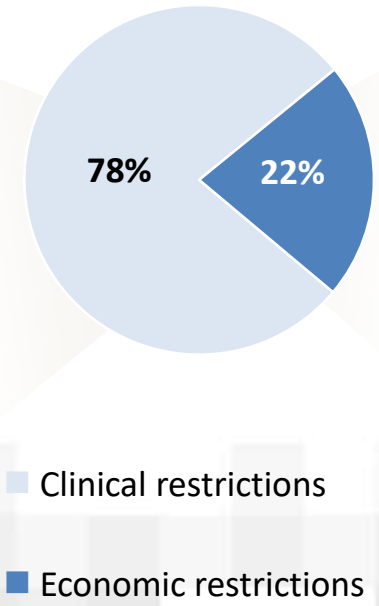
Abbreviation: LWC, List with criteria.
N=502 data points across Australia, Canada, England, France, Germany, Scotland, and Sweden (2012-2017).
Source: LSE, September 2017.

Clinical evidence – therapeutic impact assessment

List with criteria restrictions on product utilization emphasize HTA agency focus on quality clinical evidence

Variations in LWC Recommendations

Clinical restrictions	
Limited to specific patient subgroup	59%
Limited to use within therapeutic pathway	13%
Restricted to specialist prescribing	9%
Special monitoring required	7%
Subject to special status/exception list	5%
Subject to dosing regimen restrictions	4%
Restrictions similar to other drugs in same class	2%



Economic restrictions	
Subject to managed entry agreement	53%
Funding conditional to improved cost-effectiveness	13%
Limited reimbursement	12%
Cost similar to other drugs in same class	10%
Funding conditional to drug price reduction	7%
Subject to duration/administration restrictions	4%

Abbreviation: LWC, List with criteria.
N=814 restrictions across Australia, Canada, England, France, Germany, Scotland, and Sweden (2012-2017).
Source: LSE, September 2017.

Relative versus absolute effects

Example: Sunitinib vs Interferon Alfa in Metastatic Renal-Cell Carcinoma

Trial details –

- **Population**: Randomised trial of 750 patients
- **Intervention**: sunitinib vs interferon-α
- **Outcome measure**: progression-free survival

Key results

- Big separation between the progression-free survival (PFS) curves
- Hazard ratio=0.42
- The risk of progressing or dying is reduced by 58% with sunitinib, compared to interferon-α (risk is approximately halved)
- NB: all effect sizes must compare one group with another

Key Issue

- Is the effect of sunitinib small, moderate, or big?
- Median PFS time: 11 months (sunitinib) versus 5 months (interferon-α)
- On average, sunitinib patients lived without progression by 6 months more than the control group

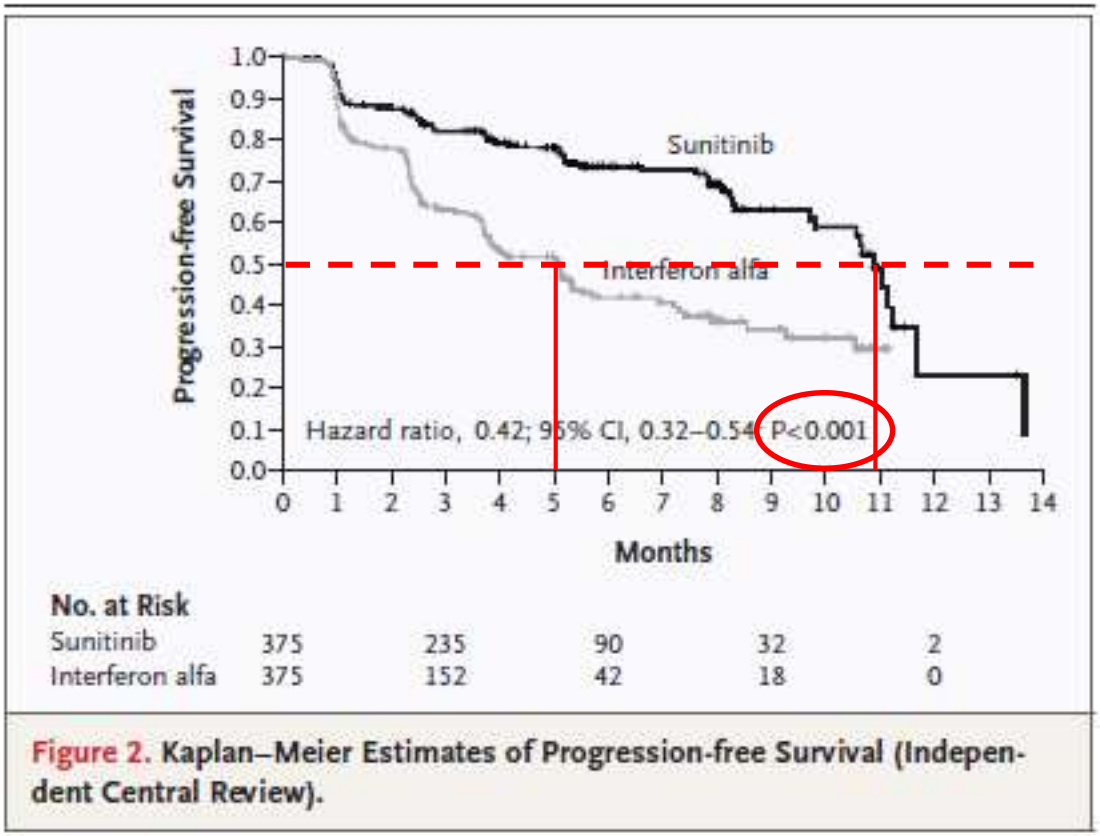


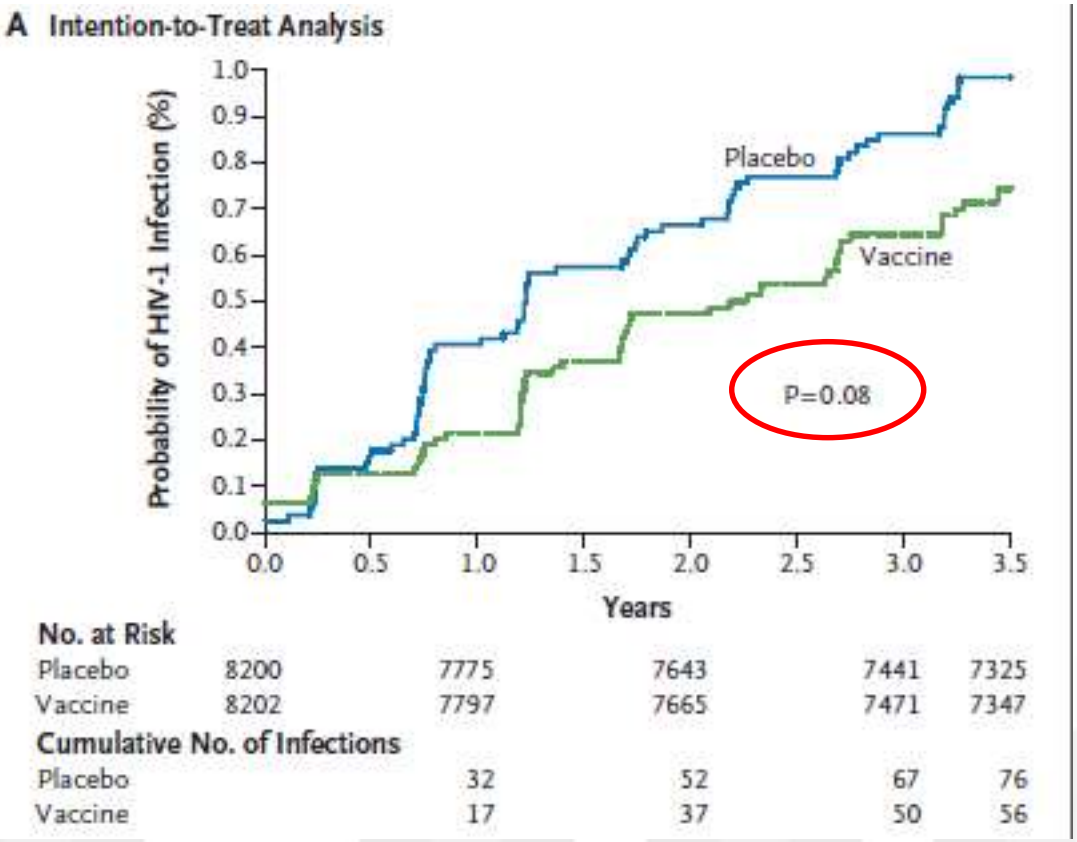
Figure 2. Kaplan–Meier Estimates of Progression-free Survival (Independent Central Review).

When trials are not big enough

Example: Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand

PRIMARY END POINTS

We established the presence of HIV infection on the basis of repeated positive results on enzyme immunoassay and Western blotting, with two confirmatory HIV nucleic acid tests: the Amplicor HIV Monitor (version 1.5) assay (Roche) in Thailand and the Procleix HIV discriminatory assay (Novartis) in the United States. We performed three



Key results

- Effect size: Vaccine reduced risk of HIV infection by 26%
- 95% CI 48% reduction up to 4% increase
- [Hazard ratio for HIV infection is 0.74, 95% CI 0.52 to 1.04]

Key Question

What is the issue here?

When trials are not big enough

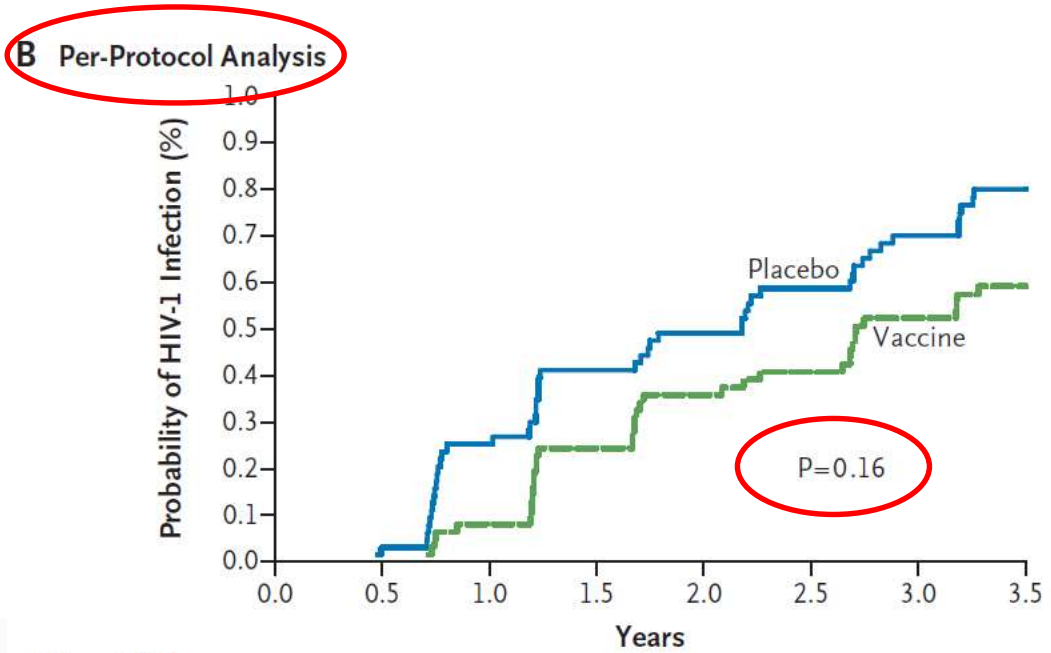
Example: Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand

Key results

- Effect size: Vaccine reduced risk of HIV infection by 26%
- (but should really be >50% to be considered worthwhile)
- All vaccination visits were completed on schedule, and excludes n=7 who were HIV positive at baseline

Conclusion

The ALVAC-HIV and AIDSVAX B/E regimen may reduce the risk of HIV infection in a community-based population with a largely heterosexual risk



No. at Risk					
Placebo	6366	6283	6220	6089	6002
Vaccine	6176	6140	6068	5958	5874
Cumulative No. of Infections					
Placebo		16	31	44	50
Vaccine		5	22	32	36

Note: all vaccination visits completed on schedule and excludes n=7 who were HIV positive at baseline

Understanding subgroup analyses

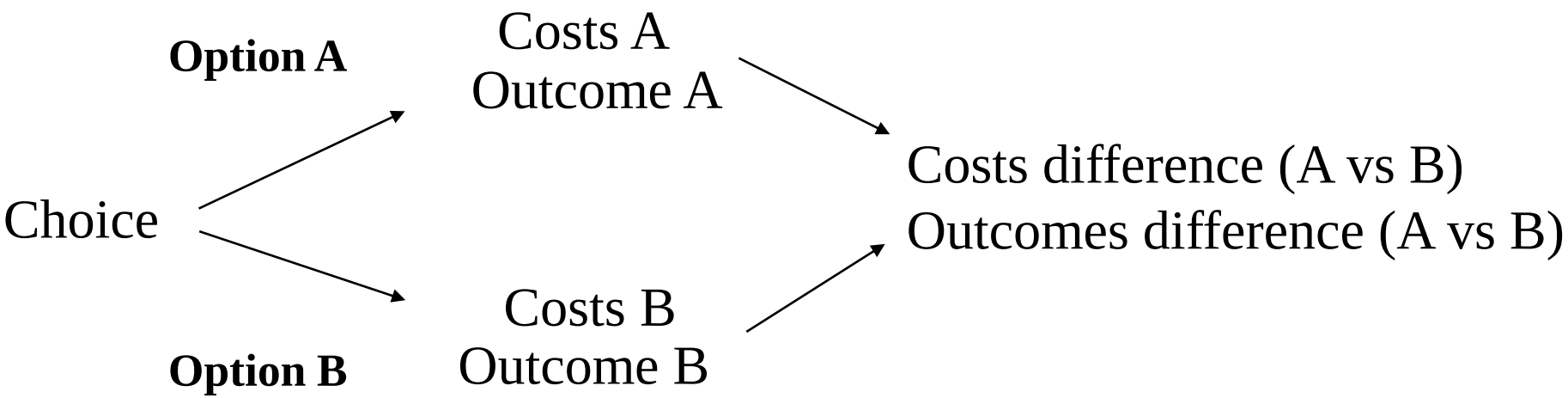
- What are the 4 possible outcomes of subgroup analyses?
- Need to think carefully about what information they provide:
  i. Treatment works equally well in different subgroups (i.e. no subgroup effect)
  ii. Treatment works better in one group than another, but works in all groups
  iii. Treatment works in one group but ineffective in another
  iv. Treatment works in one group but is harmful in another
    - (i) and (ii) are OK; they just provide some interesting information
    - But for (iii) and (iv) we would need good evidence if the recommendation is that some future patients should <u>not</u> receive the new treatment

➢ Subgroup analyses is often done when there is no overall treatment effect and the researchers conduct a lot of analyses to find an effect - a 'fishing expedition'

➢ Differentiate between pre-specified (usually ok to present) vs. exploratory/*post hoc* (often difficult to interpret)

Economic evidence

Economic evaluation approach



The difference in costs is compared with the difference in outcomes, to assess the cost per unit of outcome of the intervention of interest

$$ICER = \frac{C_a - C_b}{E_a - E_b} = \frac{\Delta C}{\Delta E}$$

But, what's our WTP threshold?

Source: McGuire, LSE 2015

Economic evidence

Budget impact represents the most prevalent economic criterion in shaping HTA decisions

- While most agencies will aggressively challenge the economics of new products to protect their national budgets, HTA agencies that require cost-effectiveness assessments as part of a drug submission generally place higher importance on economic criteria

Economic Criterion Importance Towards HTA Decision-Making

	Australia	Canada (CADTH/ pCODR)	Canada (Quebec)	England	France	Germany	Scotland	Sweden
Appropriate economic model	●	●	●	●	●	○	●	◎
ICER acceptable	●	●	◎	●	○	○	●	◎
Budget impact analysis	●	●	●	●	◎	◎	◎	●
Suitable modelling approach adopted[a]	●	●	◎	●	◎	○	●	◎

○ = Low ◎ = Moderate ● = High

Abbreviations: CADTH, Canadian Agency for Drugs and Technology in Health; ICER, incremental cost-effectiveness ratio; pCODR, pan-Canadian Oncology Drug Review.
[a] e.g., decision analyses, Markov family, simulations.
N=26 online surveys with current and former HTA agency senior staff members.
Source: LSE, September 2017.

Interpretation of clinical trials

Summary

- Relative and absolute treatment effects provide quite different information about the same treatment (one is the effect of the treatment *per se*; the other is the effect when applied to a particular patient group)

- Increasing number of phase III trials with results that just miss statistical significance using conventional 5% level and are difficult to interpret – mitigate issue by making the trial large enough

- Subgroup analyses require great care when being done and interpreted; key consideration is to avoid recommending a new therapy in some patients, when the evidence is not strong enough to say so

- Be aware that many people do not understand how to properly interpret subgroup analyses

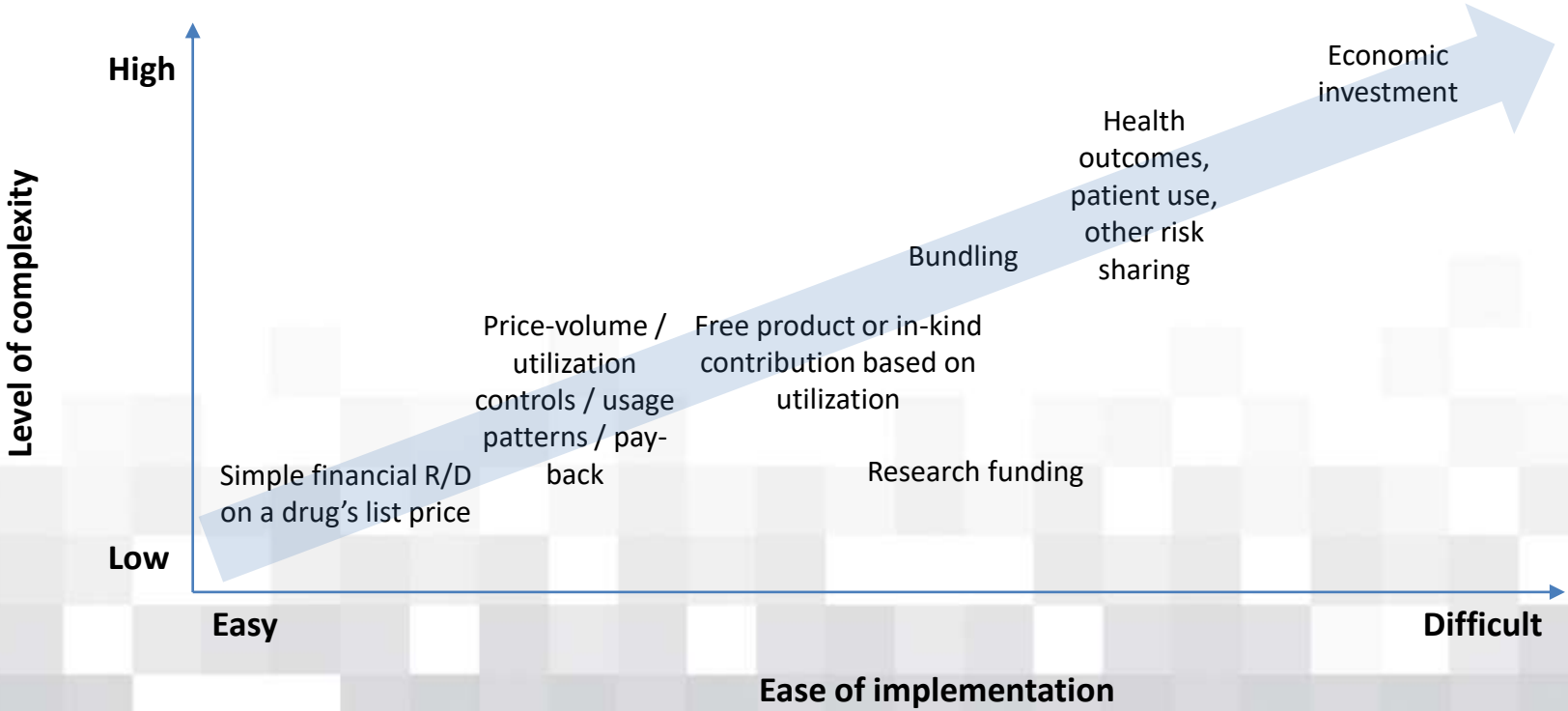
Source: Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women in osteoporosis: treatment of peripheral osteoporosis (TROPOS) Study
Journal of Clinical Endocrinology and Metabolism

Contracting mechanisms

An overview

- Volume- or expenditure-based contracts aim to provide budgetary predictability and limit budget impact
- Outcomes-based contracts are used to address clinical uncertainty about health outcomes for new products -- complexity
- Risk-sharing can include shared risk of potential overspend based on pre-defined budget, dose caps, and response rates

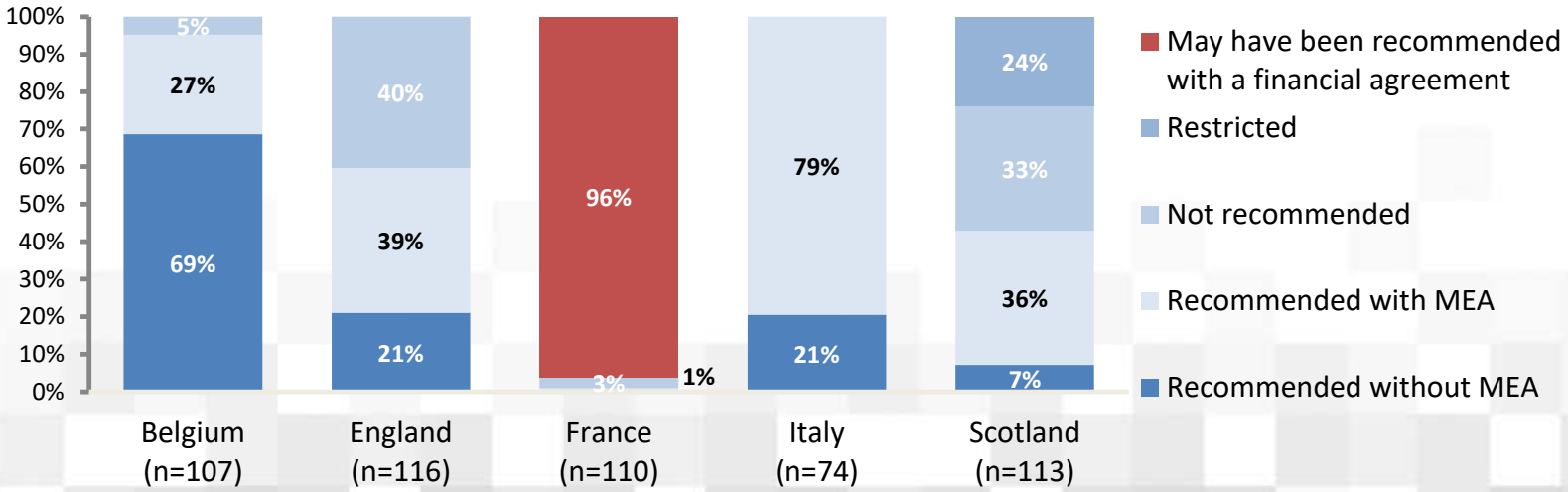
Select contracting mechanism (resulting in a rebate / discount "R/D")



Prevailing HTA uncertainties over evidence generate existence of managed entry agreements

- HTA agencies increasingly express doubts over clinical and economic impacts of new drugs, relying on managed entry agreements (e.g., financial, outcomes-based, or combination) to protect national budgets and share risk with biopharmaceutical companies
- Financial arrangements (e.g., price-volume, price discount, cap) account for the majority of MEAs

Most HTA agencies recommend fewer drugs without restrictions or managed entry agreements

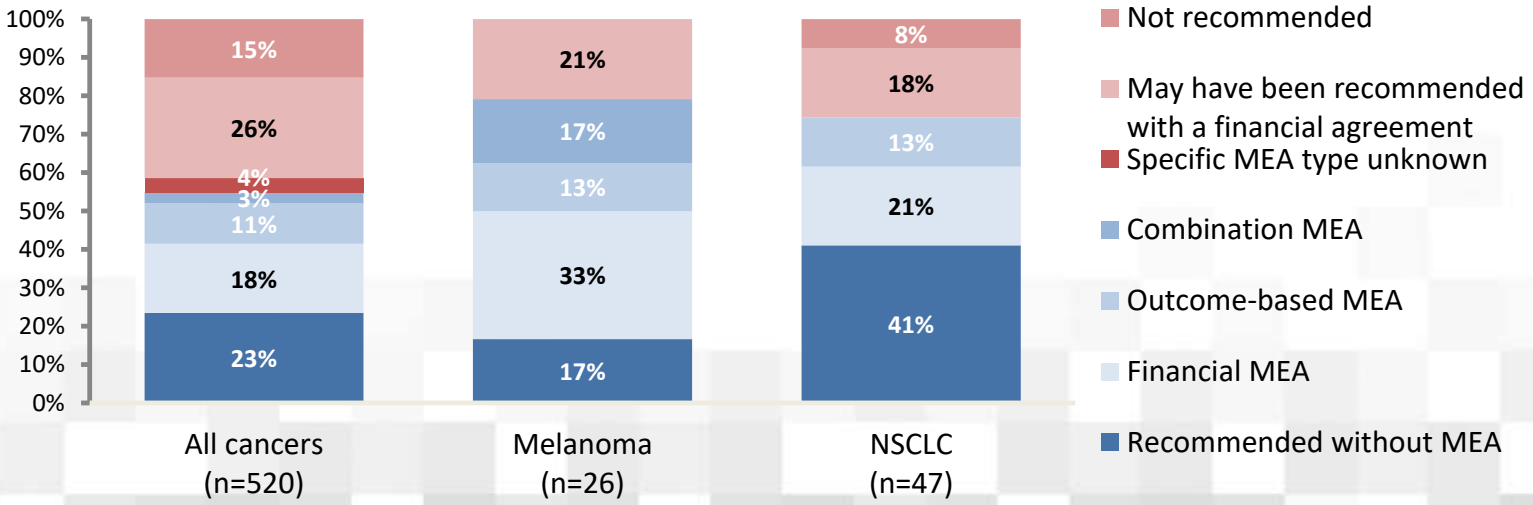


Abbreviation: MEA, managed entry agreement.
Note: France keeps evidence of financial MEAs confidential.
n=total number of drug-indication pairs studied 2012-2016.
Source: LSE, March 2017.

HTA agencies commonly recommend oncology drugs with managed entry agreements

- Managed entry agreements for oncology drugs (i.e., most often price-volume agreements) account for over one-third (37%) of all MEAs across analyzed countries and therapeutic areas
- Differences between melanoma and lung cancer therapies are due in combination to evidence strength, higher budget uncertainty, and changing HTA attitudes towards exercising MEAs
- Although HTA is increasingly used to make coverage and/or pricing decisions on medicines, many oncology products are accepted at higher ICERS than treatments for other diseases[1]

HTA decisions for oncology drugs often include some form of managed entry agreement



Abbreviations: MEA, managed entry agreement; NSCLC, non-small cell lung cancer.
Note: n=total number of drug-indication pairs studied, 2012-2016.
Source: LSE, March 2017.

Overall …

- Collaborative negotiation can lead to positive outcomes
- Robust data analysis can reveal significant opportunities to negotiate favourable outcomes for health insurers
- Appropriate benchmarks are needed (e.g. size of effect acceptable, WTP threshold)
- Simplicity in contracting
- Greater collaboration in data management, esp. in RWE