Reflections on HTA and ways forward

Panos Kanavos
London School of Economics
HTA conference, Athens, 18 February 2020

THE LONDON SCHOOL OF ECONOMICS AND POLITICAL SCIENCE

Outline

1. Key trends and challenges with new therapies

2. Thoughts on options for future funding

Trends in bringing new drugs to market

- New therapies (including cell and gene therapies) are highly specific and tailored to an individual's immune system, offering **promising opportunities for previously terminal conditions**

- The first cell and gene therapy approved by the US Food and Drug Administration (FDA) was in 2017. In total, 17 cell and gene therapies were approved by the end of 2019, of which ten were novel agents. **Over 800 cell and gene therapies were in development at the beginning of 2019** (FDA, 2019)

- Despite potentially transformative benefits, high upfront costs lead to concerns over financial sustainability: **Currently, costs for one-time use range from $450,000 (Kymriah) to over $2 million (Zolgensma).**

FDA. 2019. *Statement from FDA Commissioner Scott Gottlieb, M.D. and Peter Marks, M.D., Ph.D., Director of the Center for Biologics Evaluation and Research on new policies to advance development of safe and effective cell and gene therapies*. U. S. Food and Drug Administration.

General Challenges

1. High levels of clinical uncertainty at the time of approval

- RCTs often unfeasible or unethical in the context of less common, rare and serious diseases, often leading to regulatory approval based on single arm trials with historical controls.
- Limited data on long-term clinical efficacy. Are cell and gene therapies actually cures?

2. High upfront costs

- Prices in excess of $2 million for one time use are with us already
- Budget constraints will become more problematic over time (10% of US citizens have a rare disease linked to a genetic defect)

3. High manufacturing and distribution costs: barriers

- Delivery and manufacturing process is very complex and highly regulated.
- Process can take several weeks between sample collection, transportation to and from manufacturing facilities, the manufacturing process and administration of the product.
- Manufacturing and administration facilities must be accredited limiting industrial scaling of the process (e.g. only 7 hospitals in England accredited to administer CAR-Ts).

1. Challenges to HTA

Challenge 1: Time to access

- Role of HTA committee

- Role of Negotiation committee
  - Critical stakeholder
  - Significant backlog of new products

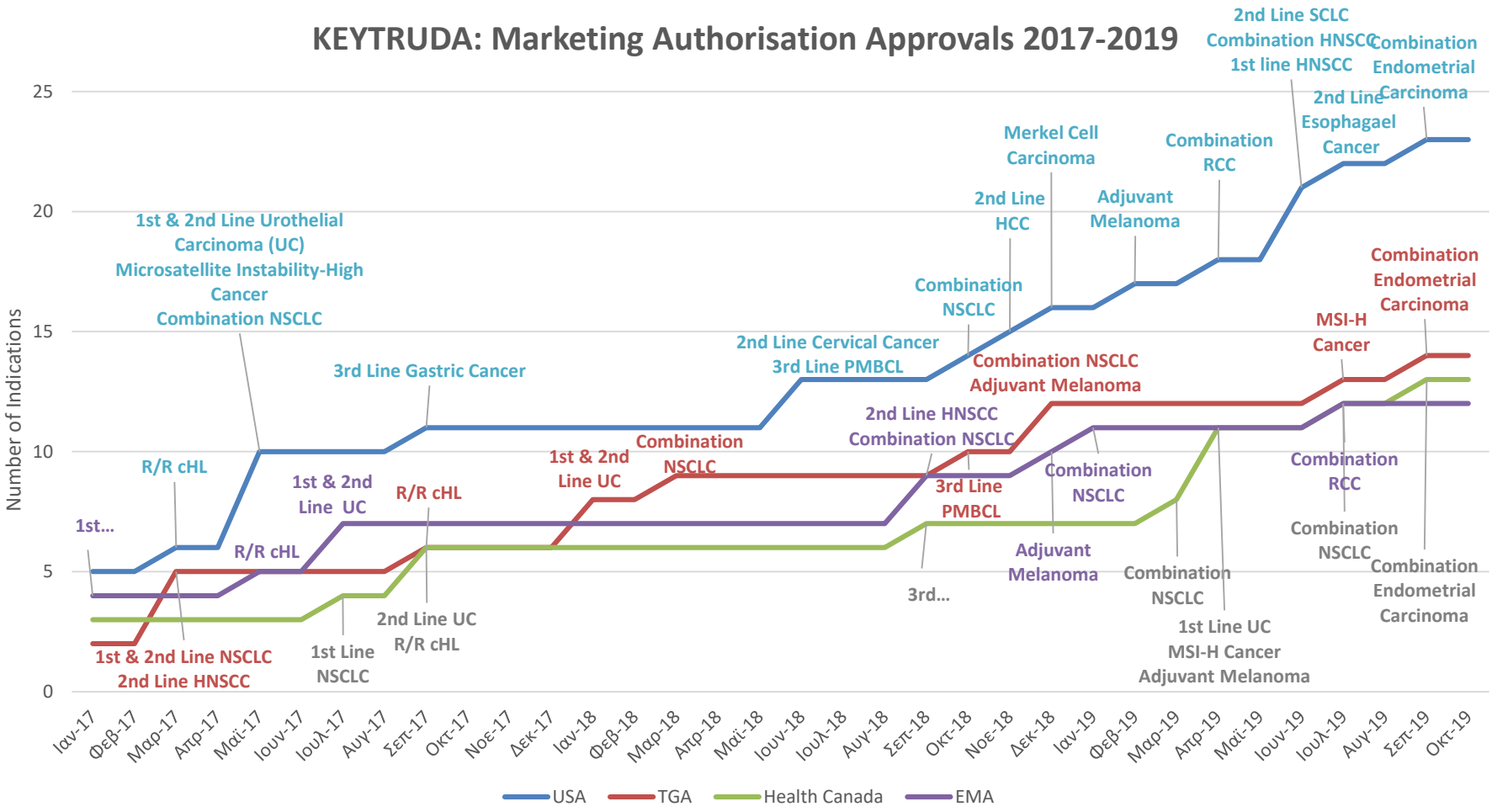
- Alternative routes to access to address backlog
  - E.g. direct importation

Challenge 1: Low quality evidence but high price

Social Value Judgement (SVJ) index[8]			
	Accelerated Approval	Non-Accelerated Approval	Total
$SVJ_{Low} \leq 4$	-	-	-
$5 \leq SVJ_{Moderate} \leq 8$	33 (75%)	45 (82%)	78 (79%)
$SVJ_{High} \geq 9$	10 (25%)	10 (18%)	20 (21%)
Orphan status[9]			
No	36 (82%)	41 (75%)	77 (76%)
Yes	8 (18%)	14 (25%)	22 (24%)
Disease severity			
No	20 (45%)	35 (64%)	55 (56%)
Yes	24 (55%)	20 (36%)	44 (44%)
Unmet need			
No	16 (36%)	27 (49%)	43 (43%)
Yes	28 (64%)	28 (51%)	56 (57%)
Key primary endpoint			
Surrogate	23 (52%)	34 (62%)	57 (58%)
Clinical	8 (18%)	6 (11%)	14 (14%)
Co-primary (clinical & surrogate)	13 (30%)	15 (27%)	28 (28%)
ICER (€ per QALY, 2017)[10]			
Mean (SD)	64,732 (± 37,413)	41,187 (±16,727)	N/A
Min	17,107	9,230	
Max	161,704	77,475	

- AAP drugs have a 57% higher submitted ICER than non-AAP drugs. Although in itself, it is not a definitive predictor of coverage, it is an important marker
- In the majority of cases, the clinical evidence submitted relied on surrogate endpoints, while clinical endpoints were used as primary endpoints in less than 15% of all cases. ALL FUNDED

Challenge 2: Number of indications is increasing, but often there is not a portfolio approach to pricing



Source: LSE database.

Challenge 3: Number of combination therapies is increasing, but there is no framework for combination pricing or comparative clinical benefit assessment

Issue	Definition
Value assessment & HTA	• How do HTA bodies assess combination therapies? • How do they measure and apportion the benefit to the combination's components? • What are the evidentiary requirements for value assessment of combination therapies? What is feasible vs what is desirable? • Do they assess the incremental benefit from the technologies' joint use, or the benefit of each technology in isolation?
Pricing models	How are pricing decisions made for drugs used in combination with another drug/diagnostic? Which pricing models work best in capturing value for combination therapies?
Coverage & reimbursement	How do payer bodies reach decisions on reimbursement and what are the implications for patient access?
Competition landscape	Does the field of combination therapies present challenges from a competition perspective, in the sense that the existing framework may result in an uneven playing field for competitors?

Challenge 4: Variability in how different value dimensions are assessed… some are important modifiers; but difficulty in providing link to price

Value framework

		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	*	**	***	**	*	**	*	**

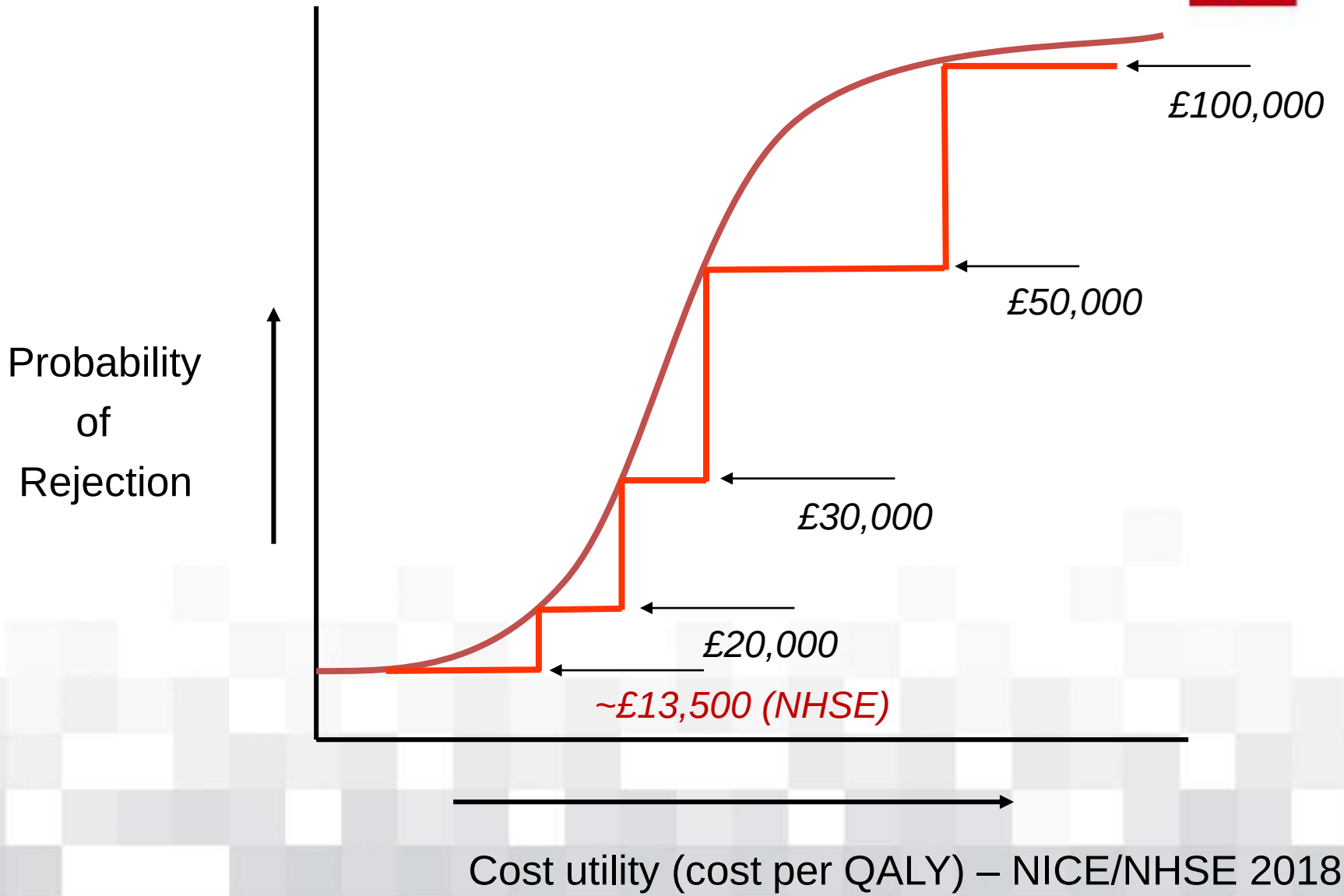
***	mandatory/ formal/explicit/ planned/ directly/ grading system
**	"considered", e.g. recommended, informal/implicit but planned, formal/explicit but ad-hoc/indirectly, etc.
*	optional/ informal/implicit/ad-hoc/ indirectly/ no grading system
x	not considered in any way

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

Challenge 5: How do we reimburse new therapies?

Therapy	FDA	EMA	Clinical Evidence	Price (USD)	Outcome
Glybera (alipogene tiparvovec)	N/A	Exceptional circumstances	3 phase III trials, under 30 patients enrolled	$1.2 million	- Withdrawn, lack of demand (under 5 years of market authorization in Europe) - Original manufacturer went bankrupt
Strimvelis (GSK-2696273)	N/A	Orphan Drug	Phase I/II trial, 12 patients (additional monitoring status – patients enrolled in long-term registry)	$648,000	- Sold by manufacturer due to lack of demand - Less than five patients treated since market authorization
Kymriah (tisagenlecleucel)	Priority Review, Breakthrough Therapy	Priority Medicines Scheme (PRIME)	Single arm phase II trial, Adverse events for 95% of patients	$475,000	- Outcome-based payment model with rebate for null treatment effect
Luxturna (voretigene neparvovec-rzyl)	Priority Review, Breakthrough Therapy, Orphan Drug	Orphan Drug	Open label phase III RCT, 41 patients	$850,000	- Outcome-based payment model with rebate for null treatment effect
Zolgensma (onasemnogene abeparvovec)	Fast Track, Priority Review, Breakthrough Therapy, Orphan Drug	Under evaluation (approval expected 2020)	Phase I open label trial, 12 patients	$2.1 million	- Amortized payment plan for health insurers over five years - 100 doses available through a managed-access program (lottery system for countries in which the drug is not yet approved)

Challenge 6: Multiple WTP thresholds for different types of drugs…



Where do we go from here?

Where do we go from here?

1. Evidence from other settings: Restrictions in use, risk share, rejections
2. Provisions around time-to-coverage negotiations (***access accelerator with clauses***)
3. Need for the health system to be ***demand-led*** rather than ***supply-driven*** (***paying for outcomes plus***)
4. Budget-setting as a risk-mitigation strategy (***price as a notional variable***)
5. Evidence generation and assessment
6. Funding options for new therapies

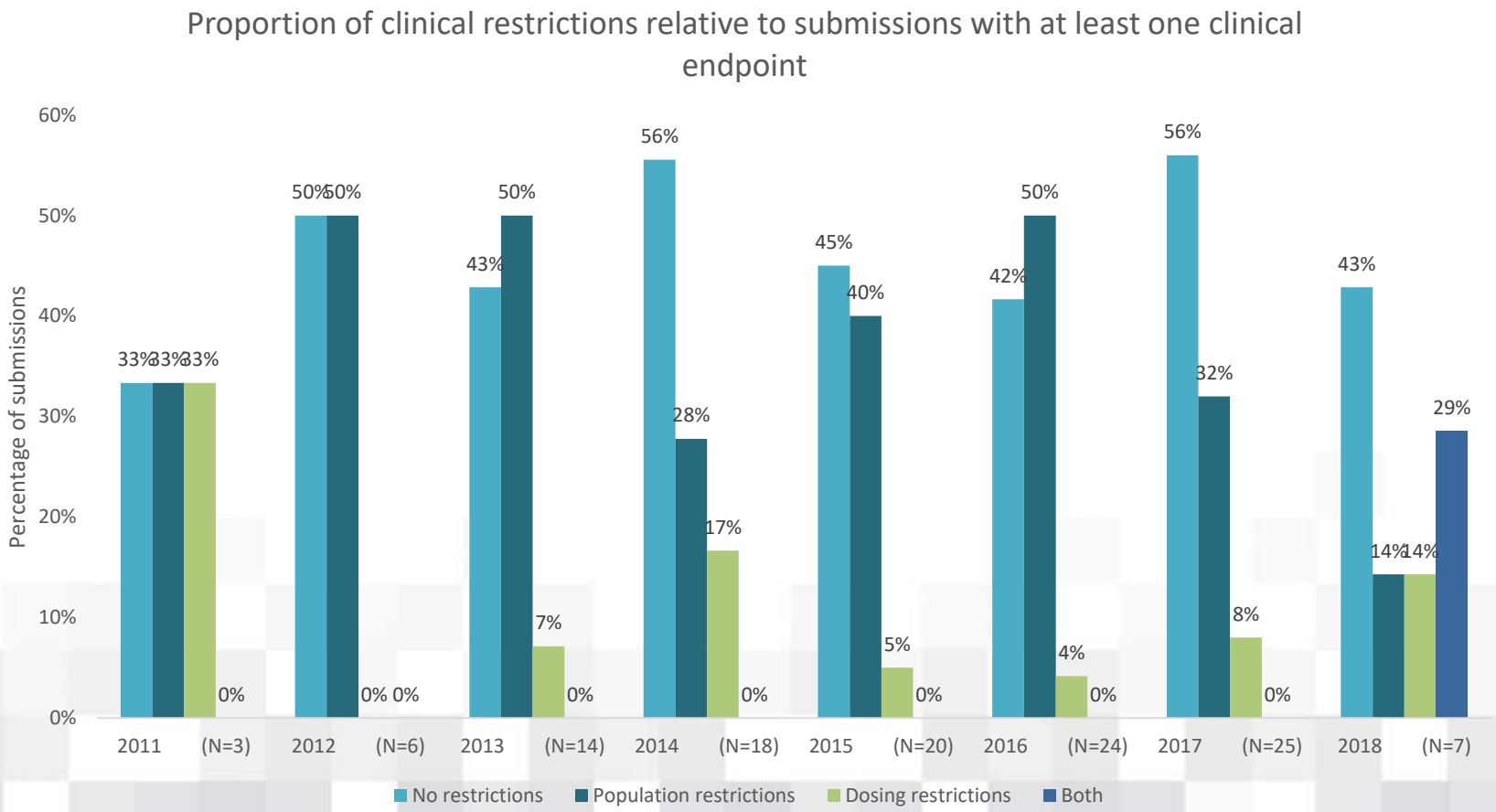
1. What is evidence from other settings showing us?

I. Restrictions in use

II. Risk shares a necessity

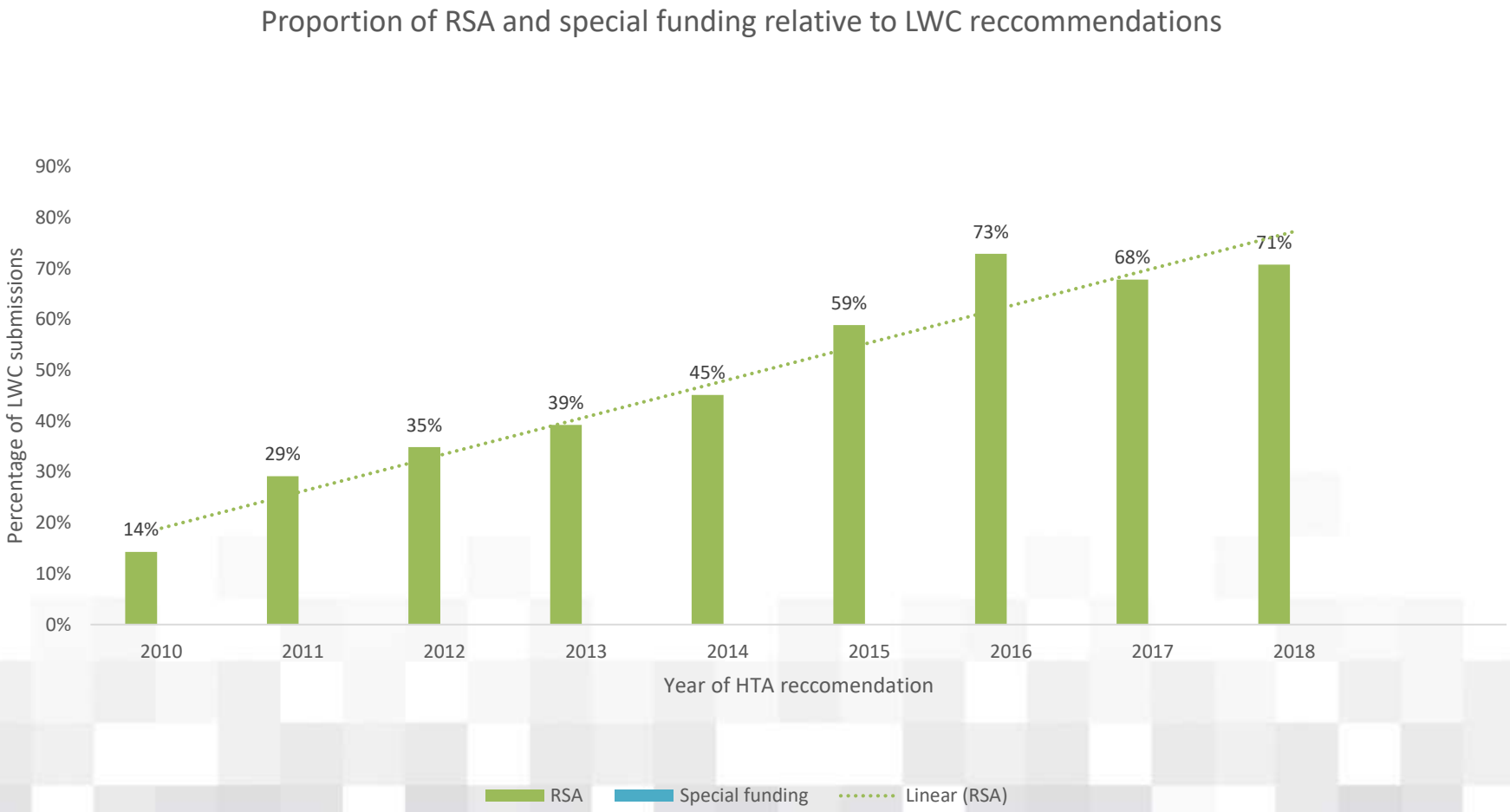
III. Saying ‘no’ is an option

I. Clinical restrictions as a means of "facilitating" coverage and reimbursement



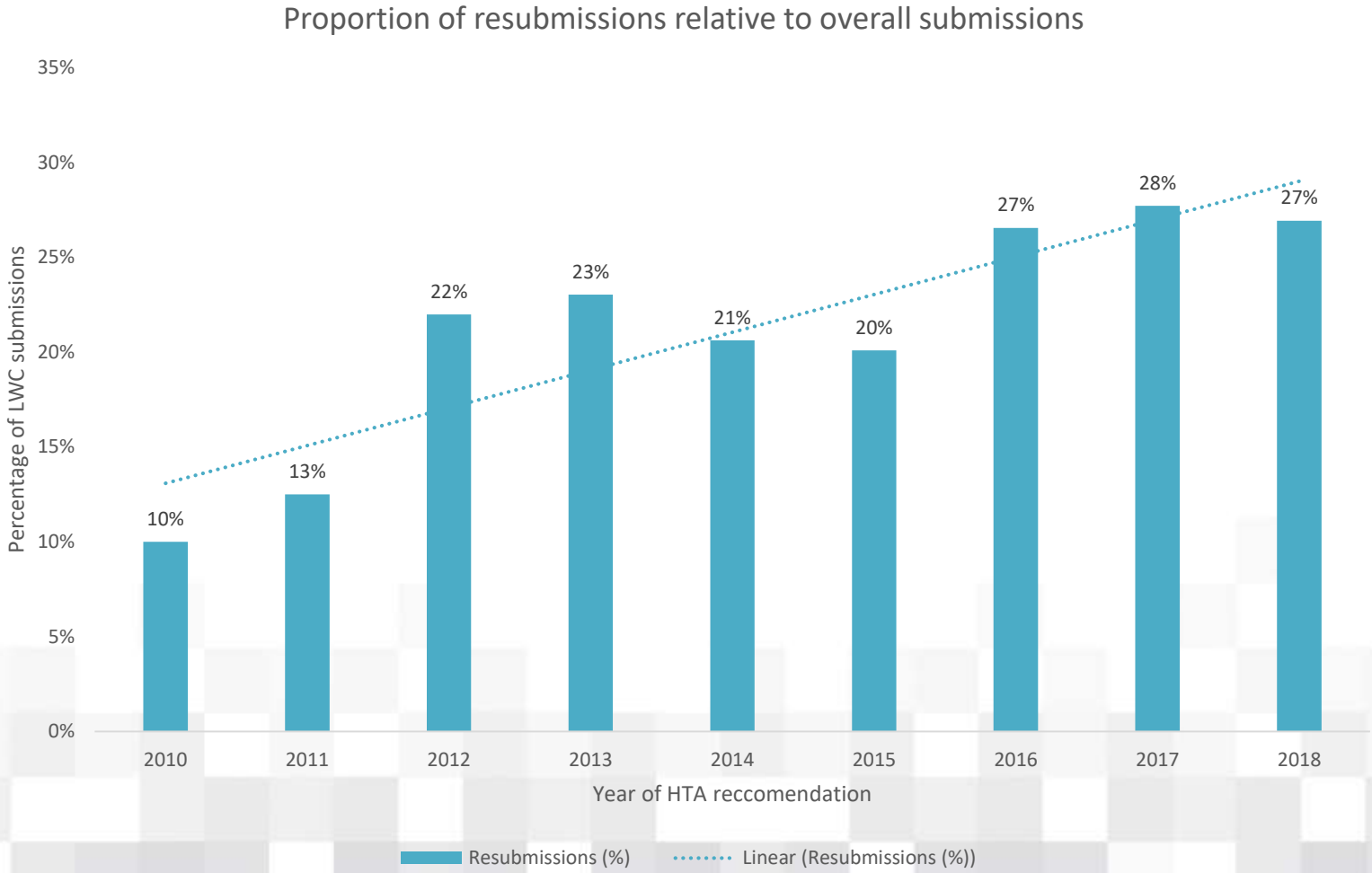
Note: Pooled data from England, Scotland, France, Germany, Sweden, Australia, Canada, Quebec; **n=1,415**
Source: LSE database, 2020.

II. Financial Risk Sharing as a facilitator of coverage and reimbursement



Note: Pooled data from England, Scotland, France, Germany, Sweden, Australia, Canada, Quebec; **n=1,415**
Source: LSE database, 2020.

III. Prior rejections by reimbursement committees or HTAs due to data inadequacies



Note: Pooled data from England, Scotland, France, Germany, Sweden, Australia, Canada, Quebec; **n=1,415**
Source: LSE database, 2020.

2. Provisions around time-to-coverage negotiations

- Long time lag between MA and access to medicines
- Perennial complaints from patients and industry

a) HTA/negotiation phase often too long and discussion on uncertainty mitigation complex

b) Parallel review process is a necessity

c) Additional evidence generation is a necessity (with cross-border collaboration)

d) Consider capping the length of time negotiations last

e) Consider compassionate use programmes for therapies under negotiation (a form of voluntary licensing?)

f) Need provide signal that negotiations are time-limited;

g) Eliminate IFET route: a paradox & an oxymoron

3. Need for health systems to be demand-led rather than supply-driven

- Health systems reactive to submission of evidence and price requests
- May be necessary to have an explicit and ex ante determined needs assessment strategy
- This means becoming more demand-led rather than supply-driven, which implies setting benchmarks

a) For chronic conditions one such benchmark could be the cost of illness (both direct and indirect)
   i. can aid in cost-effectiveness analysis
   ii. helpful in measuring the potential savings of averting a case of or mitigating the costs of an illness

b) New therapies to benchmark against aspects of societal "burden" they are addressing appropriately monetized (RoI approach)

c) Product premia to be compared against cost-of-illness

4. Budget-setting as a risk-mitigation strategy

- Cost-effectiveness only broadly useful as a means of providing steer for coverage purposes
- Increasingly provides an indication of the disproportionate investment health care systems need to make for obtaining a unit of additional health gain

a) Negotiating based on a budget is much more meaningful (including PVAs or O-B RSAs)

b) Assumes that health insurance/EOPYY is aware of patient numbers and current treatments

c) Can be seen is becoming irrelevant as a variable

d) Confidentiality is necessary

5. Evidence generation and assessment

- Robust evidence needs to be produced to ensure that there are indeed meaningful clinical benefits despite significant uncertainties.

a) Countries taking the lead in admitting such products to reimbursement can contribute important primary evidence on their effectiveness for the common good.

b) Registries, can be used where evidence from different countries and systems can be generated and leveraged.

c) Registries can be set up pro-actively, so that evidence on effectiveness becomes available within a reasonable timeframe.

6. Financing options for expensive drugs

- **Need to think now of alternative routes to coverage & payment**

1. Amortization, Installments and Annuities

- Spreading large upfront cost into installments payed over time.
- Used in multiple industries including housing (mortgages) and banking (interest rates and loans).

2. Outcomes-based Payments (OBP)

- More comprehensive models involve multiple years with payments spread over time based on achievement of pre-specified performance criteria (Higher degree of risk-sharing, but may be problematic in many settings)

3. Reinsurance and Stop-Loss Policies

- Insurance providers purchase reinsurance or stop-loss from another insurance company.
- Financial risk of “curative” therapies is transferred to the reinsurance company, which pools risk over a much larger scale
- Already used for healthcare financing in USA (e.g. organ transplants)

Σας ευχαριστώ!

LSE THE LONDON SCHOOL OF ECONOMICS AND POLITICAL SCIENCE