COMED PUSHING THE BOUNDARIES OF COST AND OUTCOME ANALYSIS OF MEDICAL TECHNOLOGIES

UNIVERSITY OF EXETER | MEDICAL SCHOOL

Surrogate Outcomes in Health Technology Assessment: are they as established as they seem?

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Definition of surrogate outcomes*

Disease-centered characteristics ⟷ *Patient-centered characteristics*

Biomarkers
A characteristic that is objectively measured and evaluated as an indicator of normal, pathogenic or pharmacologic responses to a therapeutic intervention.

Surrogate outcomes

A *biomarker* that is intended to substitute and predict for a *final outcome.*

Final outcome
A characteristic that reflects how patients feel, function or survive.

e.g. Carotid intima media thickness → **Cardiovascular Mortality**

e.g. Intraocular pressure → **Loss of vision**

**Biomarkers Definition Working Group, NIH 2001*

WP2 – Use of surrogate outcomes for medical devices

Overall objective and specific tasks

To improve the *decision-making* process concerning new or existing technologies whose evidence base is mainly supported by *surrogate outcomes*

1. To review and map use of surrogate outcomes in economic evaluations in HTA methods guidelines and reports

2. To use various sources of evidence (e.g. RCTs, registries) to validate putative surrogate outcomes

3. To develop a framework for surrogate outcomes-based value determinations and to identify potential levers and barriers to its implementation

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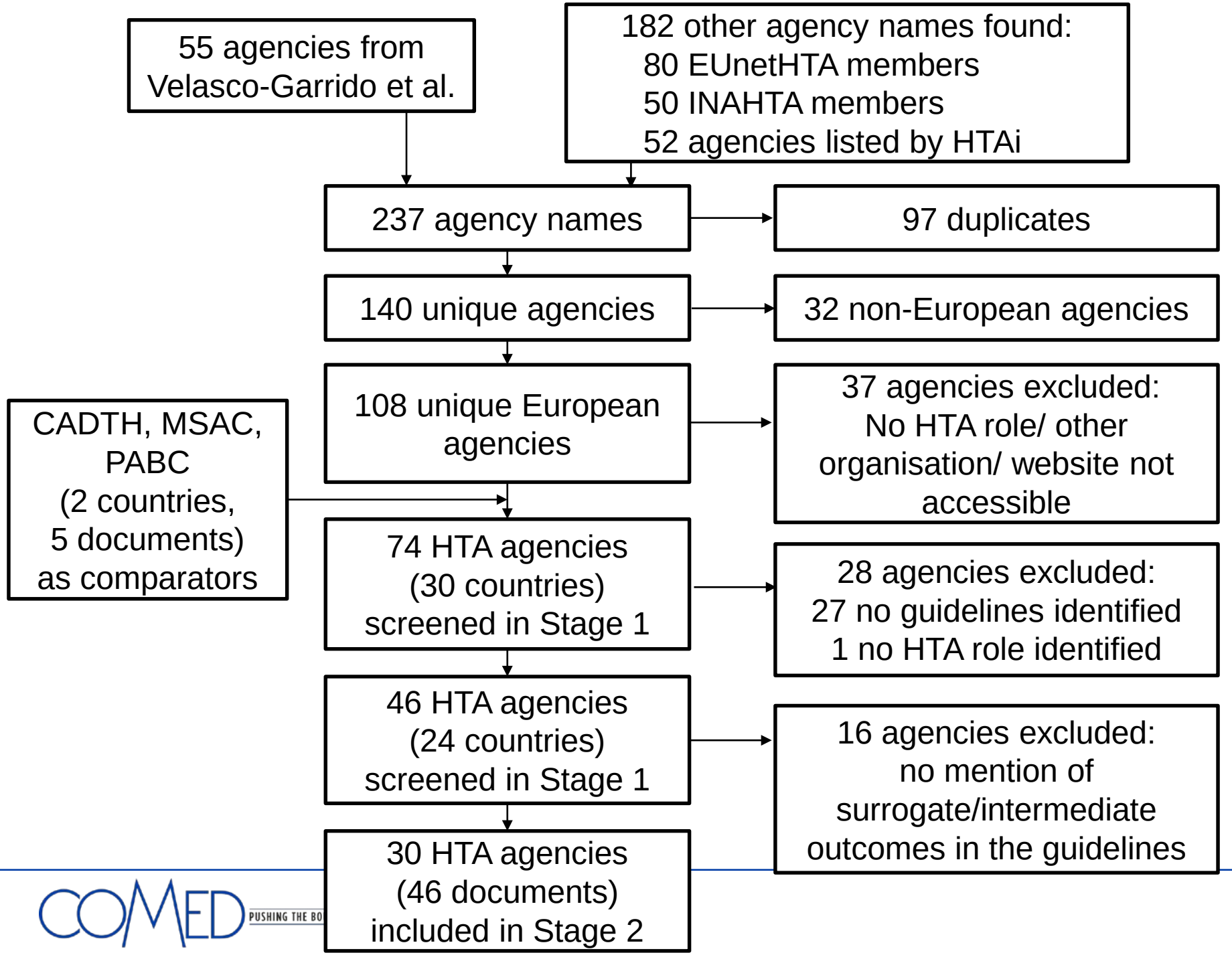
- A. Review of publicly available **methods guidance** from international HTA agencies
- B. Review of **HTA reports** from international agencies that rely on surrogate outcomes

A. Review of methods guidance from international HTA agencies

Summary of data extraction

Definition	Is a definition of surrogate endpoints provided?
Examples	Are example of “reliable” surrogate endpoints provided?
Use	Is use of surrogate endpoints recommended or discouraged in specific situations?
Evidence	What evidence is required for quantifying the the surrogate-final outcome relationship?
Validation methods	Are any validation methods prescribed?
Validation threshold	Are there accepted cut-off values for surrogacy presented?


55 agencies from Velasco-Garrido et al.
182 other agency names found:
80 EUnetHTA members
50 INAHTA members
52 agencies listed by HTAi
237 agency names
97 duplicates
140 unique agencies
32 non-European agencies
108 unique European agencies
37 agencies excluded:
No HTA role/ other organisation/ website not accessible
CADTH, MSAC, PABC
(2 countries, 5 documents)
as comparators
74 HTA agencies
(30 countries)
screened in Stage 1
28 agencies excluded:
27 no guidelines identified
1 no HTA role identified
46 HTA agencies
(24 countries)
screened in Stage 1
16 agencies excluded:
no mention of surrogate/intermediate outcomes in the guidelines
30 HTA agencies
(46 documents)
included in Stage 2

A. Review of methods guidance from international HTA agencies

Results

- **2 (4%)** documents provide **thresholds** for validation
- **6 (13%)** documents discuss **methods** for validation
- **7 (15%)** documents discuss **evidence** for validation
- **10 (22%)** documents provide **definition** of surrogates
- **15 (33%)** documents provide **examples** of surrogates
- **39 (85%)** documents discuss **use** of surrogates

“The acceptability of a surrogate endpoint in supporting effectiveness of a pharmaceutical is mostly based on its biological plausibility and empirical evidence (observational and RCT) for a patient relevant clinical endpoint [...]

*“A surrogate endpoint represents a special use of a biomarker since [illegible] biomarker [illegible] substitute for a clinical endpoint [...] biomarkers will be considered as surrogate endpoints if they can reliably substitute for a clinical endpoint and predict its clinical benefit”**

“[illegible] absence of evidence [illegible] glycaemic control as a surrogate for the avoidance of long-term complications in patients with diabetes”

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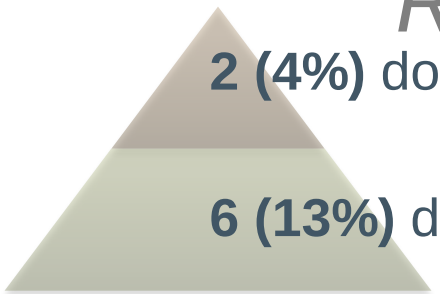
* Endpoints used in relative effectiveness assessment of pharmaceuticals Surrogate Endpoints, *EUnetHTA 2013*

A. Review of methods guidance from international HTA agencies

Results



2 (4%) documents provide **thresholds** for validation

6 (13%) documents discuss **methods** for validation

*"The majority of the procedures […] rely on **meta-analyses of several RCTs** and estimate **the correlation of the effects** on the surrogate and the effects on the clinical endpoint.*

*There is no clear consensus of which correlation values are sufficient to assume adequate surrogacy, but **values of between about 0.85 and 0.95 are often discussed**.*

*If there is no high correlation demonstrated, conclusions might still be made if the **surrogate threshold effect (STE)** is considered. Also based on an analysis of several RCTs, the STE defines **the minimum absolute value of the effect on the surrogate which has to be observed in a new trial to deduce an effect on the clinical endpoint**. In both cases, certainty of the conclusions depends on pre-specified levels of significance."*

* Endpoints used in relative effectiveness assessment of pharmaceuticals Surrogate Endpoints, *EUnetHTA 2013*

A. Review of methods guidance from international HTA agencies

Pharmaceuticals vs MDs guidance

	NICE TA guidance	NICE MTEP guidance
Definition	✓	✗
Examples	✓	✗
Use	✓	✓ (refers to intermediate outcomes and acknowledges the limited nature of evidence usually available for medical devices)
Evidence	✓ (evidence must be provided together with an explanation of how the relationship is quantified for use in modelling […] the uncertainty associated […] should be explored and quantified)	✗
Methods	✗	✗
Threshold	✗	✗

A. Review of methods guidance from international HTA agencies

Discussion

- Compared to Velasco-Garrido 2009 (20 documents) we identified 46 documents from 30 agencies
- 15 (33%) referred specifically to pharmaceuticals, 2 (4%) specific for oncology
- The level of consideration varied greatly, from single mention to entirely dedicated documents*
- Guidance regarding evidence, methods and threshold for surrogate validation was limited to a few agencies (IQWIG, G-BA, PBAC, EUnetHTA, INFARMED) and is still unclear in terms of what constitutes a reliable surrogate marker
- In the light of the EU joint HTA proposal, there is an opportunity for further methodological harmonisation on how to handle the uncertainty associated to surrogate outcomes

* Validity of surrogate parameters in oncology (Rapid report), IQWiG-Berichte 80, 2011

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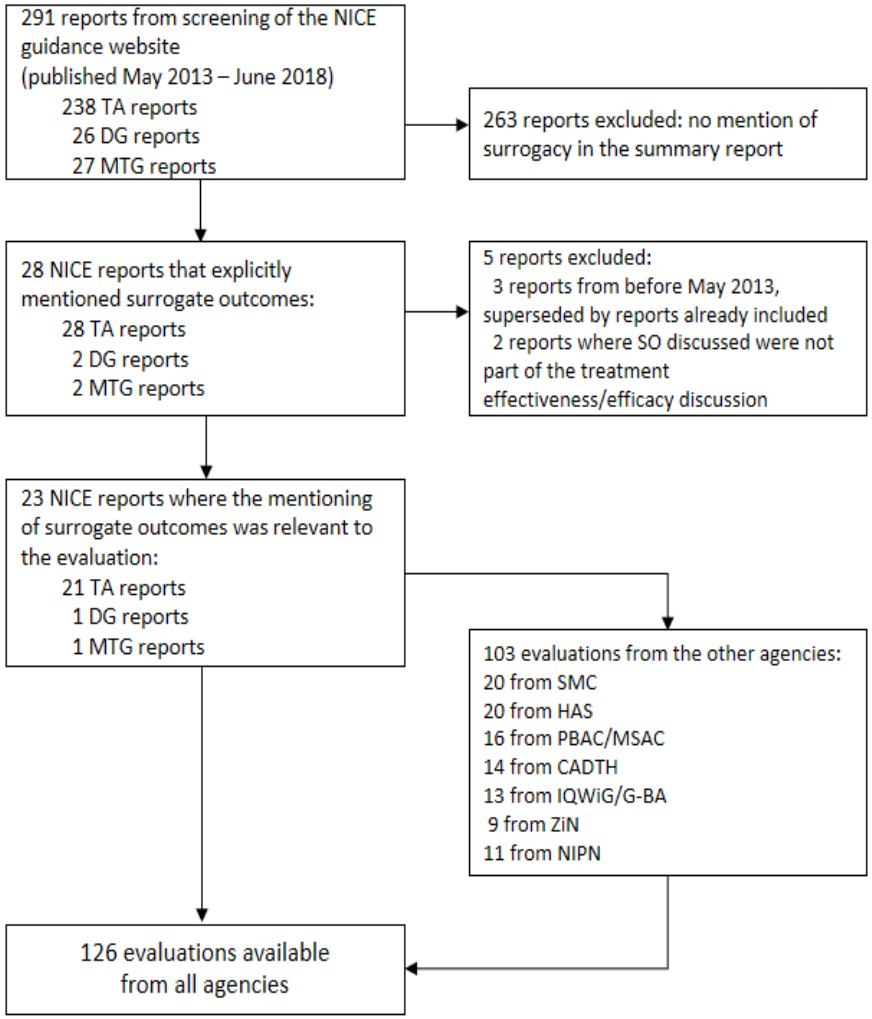
B. Review of HTA reports from international agencies that rely on surrogate outcomes

Objective

① to map the range of methodological approaches adopted *empirically* to the use of surrogate endpoints in HTA reports across international HTA agencies

② to assess how the uncertainty linked to surrogates influence the coverage or reimbursement decisions

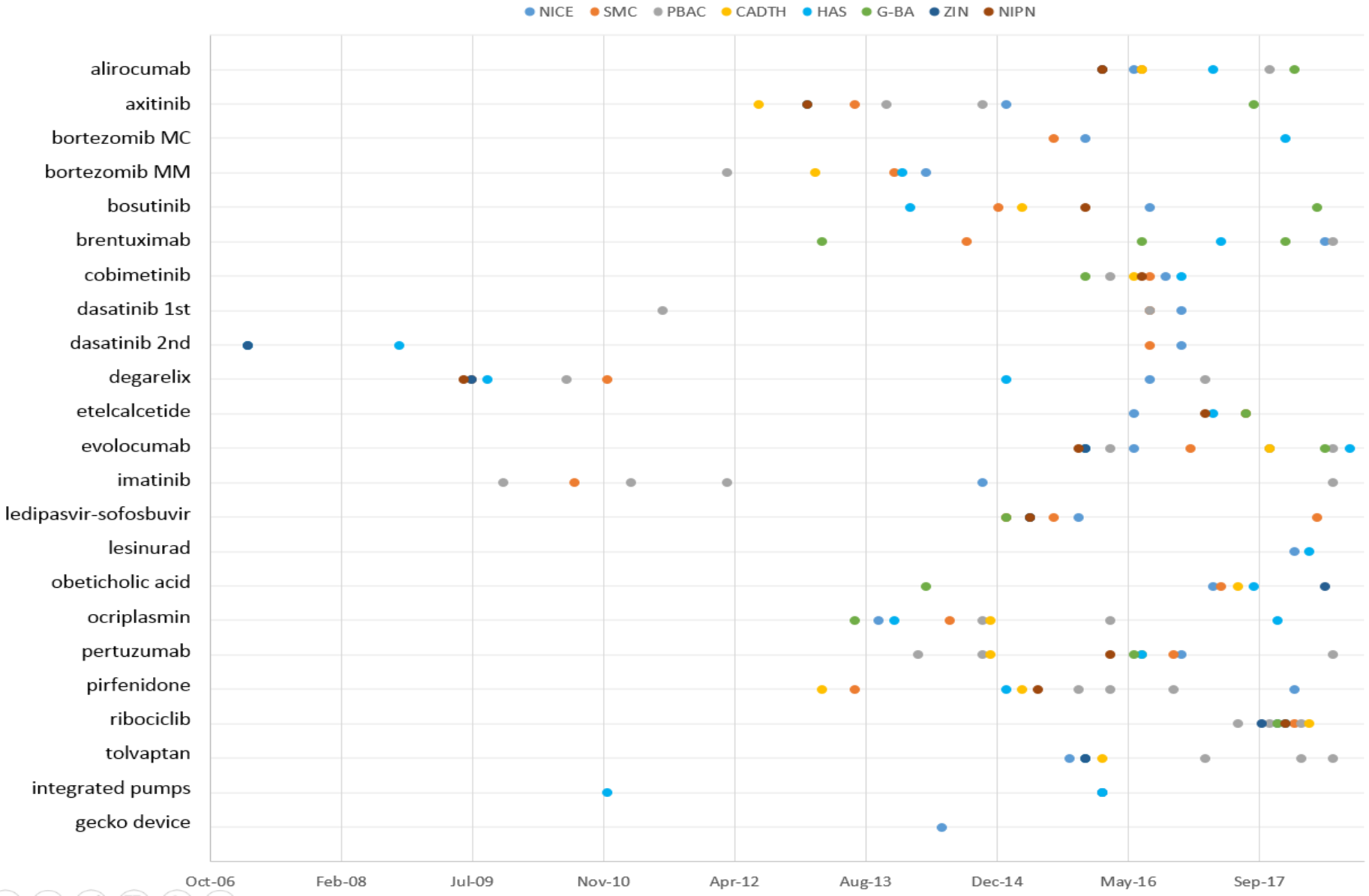


B. Review of HTA reports from international agencies that rely on surrogate outcomes

Agency sampling

Agency (country, acronym)	Guidelines	Mention	Definition	Examples	Use	Evidence	Methods	Threshold
FR HAS	✓	✓			✓	✓		
DE G-BA	✓	✓			✓	✓	✓	
DE iQWIG	✓	✓		✓	✓	✓	✓	✓
HU NIPN	✓	✓			✓			
NL ZIN	✓	✓		✓	✓	✓		
UK HIS	✓	✗						
UK NICE	✓	✓		✓	✓	✓		
EU EUnetHTA	✓	✓	✓	✓	✓	✓	✓	✓
AU MSAC	✓	✓			✓	✓	✓	
AU PBAC	✓	✓	✓	✓	✓	✓	✓	
CA CADTH	✓	✓		✓	✓		✓	

B. Review of HTA reports from international agencies that rely on surrogate outcomes



B. Review of HTA reports from international agencies that rely on surrogate outcomes

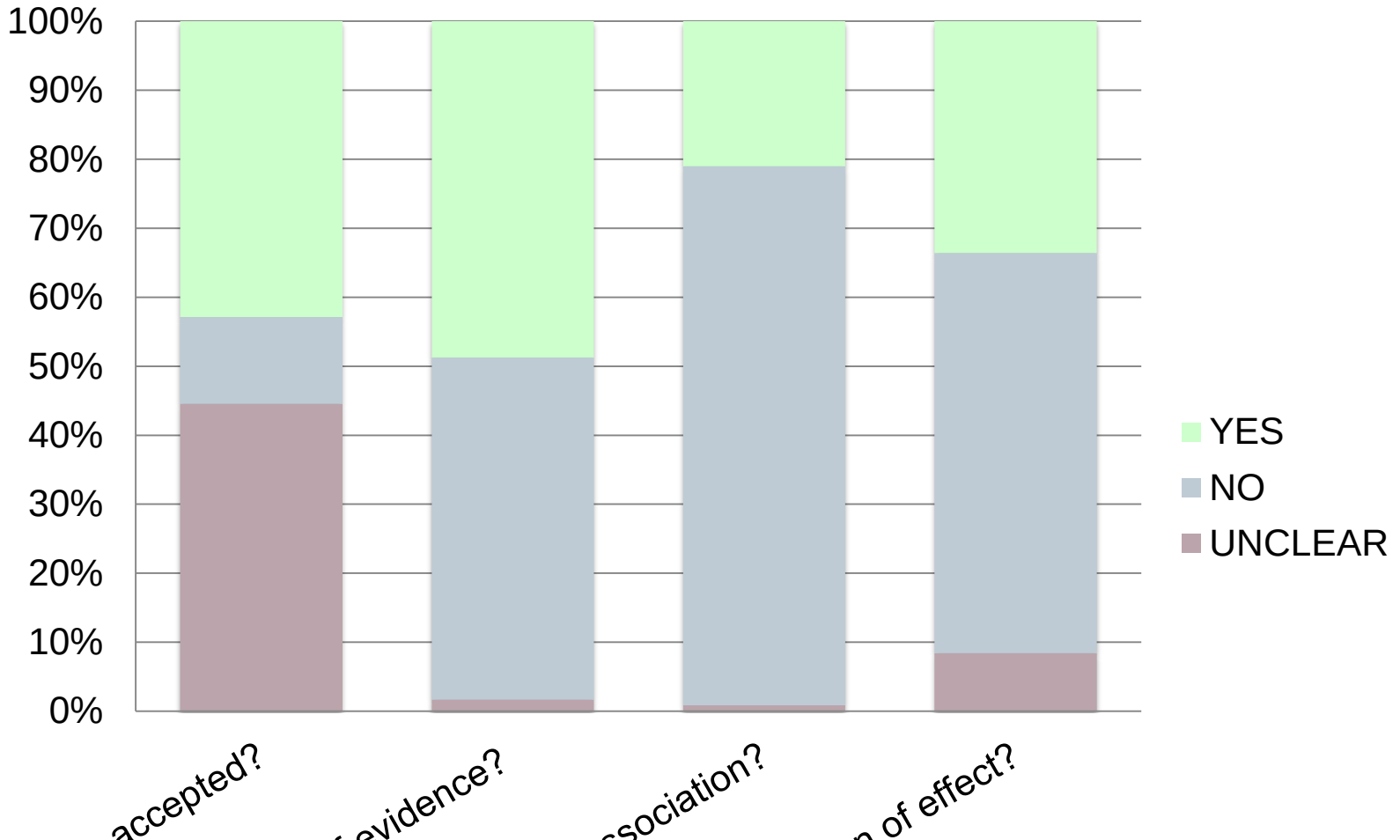
Results

Which surrogates considered?

- Progression-free survival: 7 (30%) (i.e. axitinib, bortezomib, brentuximab, cobimetinib, pertuzumab, ribociclib)
- Tumour or hematologic response: 4 (17%) (i.e. bosutinib, dasatinib first and second line, pertuzumab)
- Changes in LDL-C levels: 2 (9%) (i.e. alirocumab, evolocumab)
- Other surrogate endpoints:
  - Biomarkers: parathyroid hormone (PTH), testosterone, prostate specific antigen (PSA), alkaline phosphatase, bilirubin, glycated haemoglobin (HbA1c), sustained virologic response
  - Functional measurements: forced expiratory volume (FEV1), forced vital capacity (FVC), venous blood flow, change in total kidney volume (TKV)
  - Clinical rates (eg. proportion of patients with non-surgical resolution of focal vitreomacular traction)

B. Review of HTA reports from international agencies that rely on surrogate outcomes

Results



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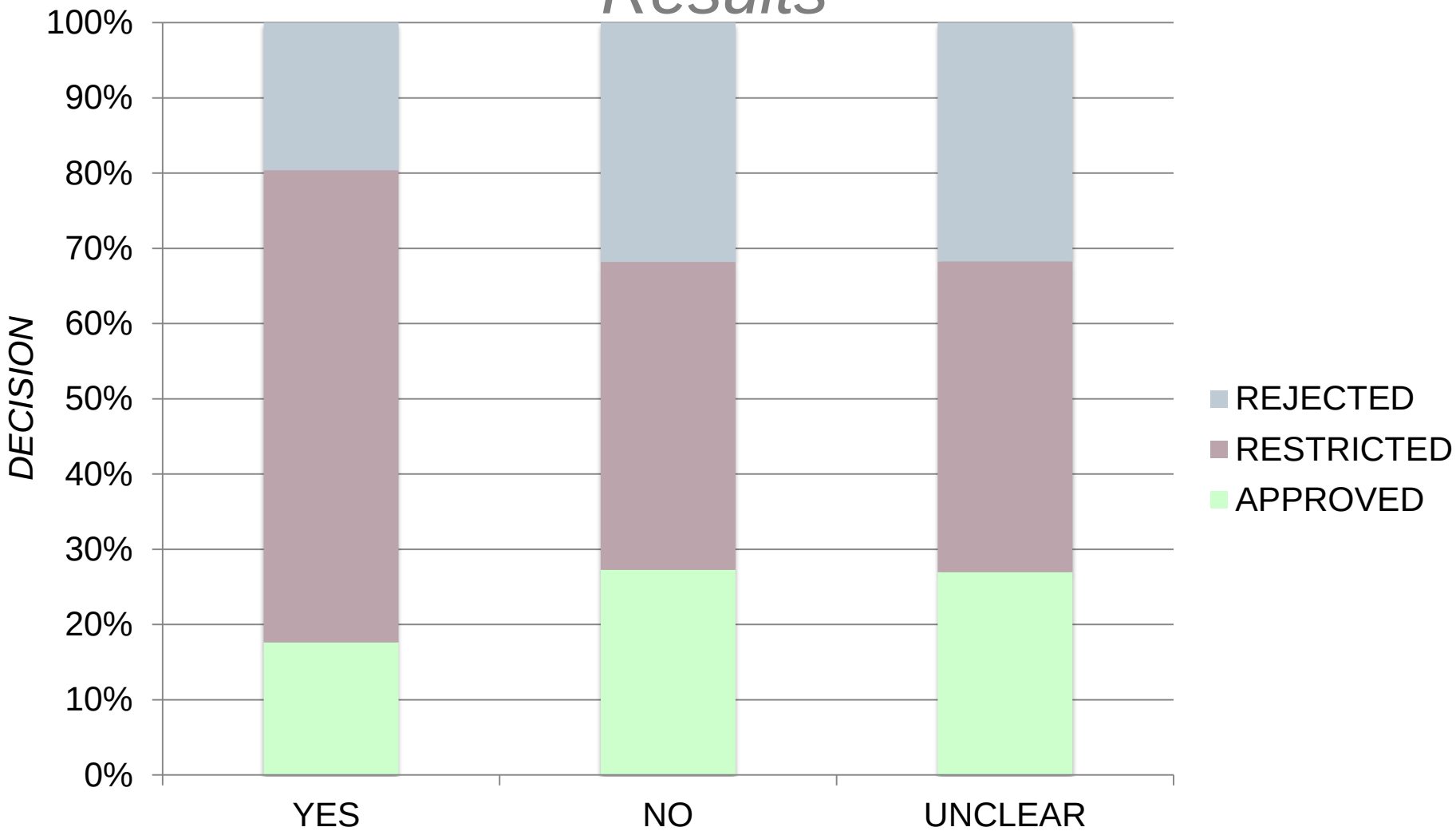

B. Review of HTA reports from international agencies that rely on surrogate outcomes

Discussion

- Little evidence of application of formal validation processes in HTA reports
  - acceptance of proposed surrogates often relies on previous assessments, regulatory assessments, expert opinion
- When CEA are included, surrogates are key model parameter
  - Models developed around immature survival data from short-term studies thus propagating the uncertainty of secondary endpoints (e.g. PFS/post-progression/death)
  - Surrogate endpoint as prognostic marker influencing transition probabilities
- The main approaches to handling decision uncertainty driven by surrogates evidence were
  - Price discount agreements/PAS (e.g. CDF);
  - Reject/Restrict approval;
  - Apply a different evaluation framework (eg. EOL, orphan…)
- Sampling framework and transparent and complete reporting

WP2 – Use of surrogate outcomes for medical devices

Next steps

- Further quantitative analyses on data extracted from Review B
- Access of different sources of IPD data (both RCT and registries) to pursue a statistical validation process on surrogate endpoints relevant to a MD-based technology (e.g. TAVI) *(Task 2)*
- Experimental study (i.e. DCE) to investigate relative value of attributes of the evidence that are relevant to surrogate-outcomes based decisions in order to develop an evidence-based framework useful for decision-makers and payers internationally *(Task 3)*

Thank you

Q&A

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