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

UNIVERSITY OF EXETER | MEDICAL SCHOOL

Surrogate Endpoints In HTA:
A Methods Guidelines Review Across Europe

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Context

- Ever increasing pressure to ensure faster access to new, more complex health technologies
- HTA agencies everywhere have to rely on evidence based on surrogate outcomes
- Surrogate outcomes can help speed the process, but poorly validated surrogate outcomes carry the risk of harm and waste
- A previous review[(1)] identified a relatively limited number of guidance documents considering surrogate outcomes

(1) Garrido MV, Mangiapane S. Surrogate outcomes in health technology assessment: an international comparison. International journal of technology assessment in health care. 2009;25(3):315-22

Our review

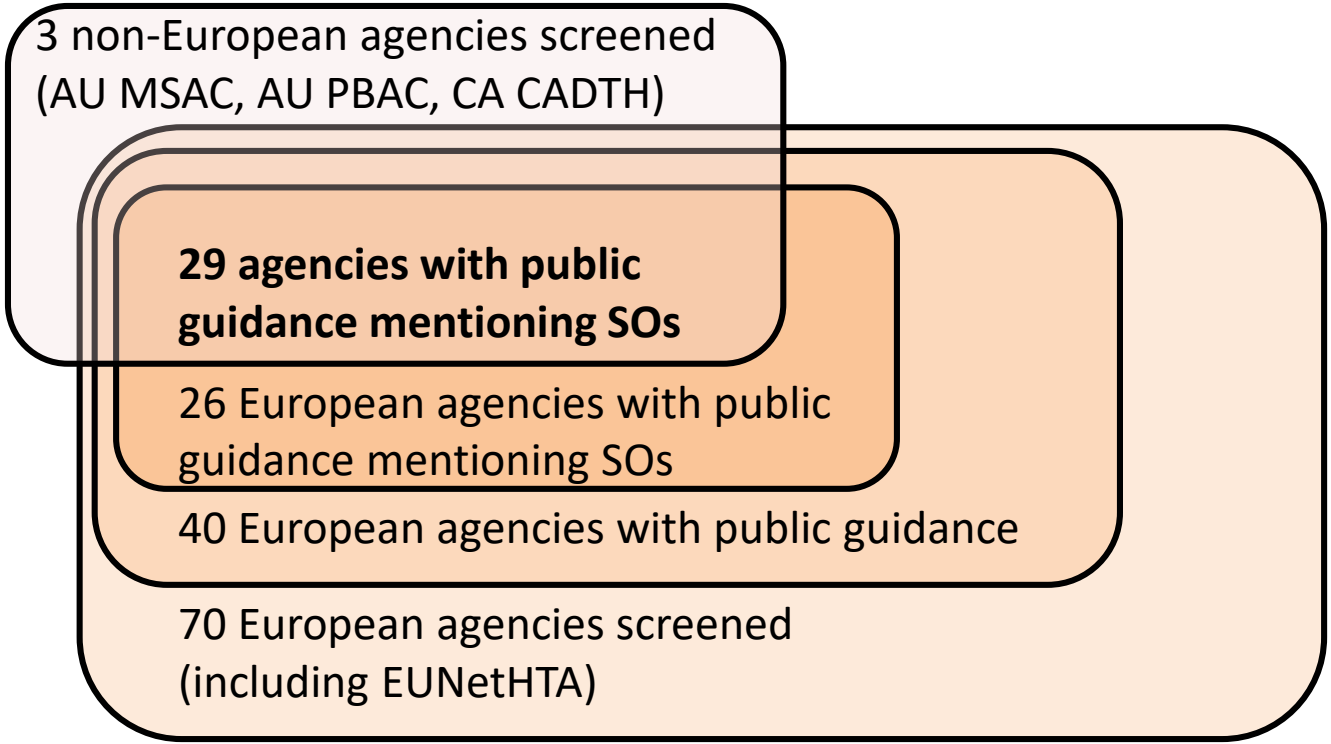
- **Methodology:**
  - Identify relevant HTA agencies from:
    - Health Technology Assessment International (HTAi),
    - European network for Health Technology Assessment (EUnetHTA) and
    - International Network of Agencies for Health Technology Assessment (INAHTA).
  - Identify relevant methods guidelines
  - Screen guidelines and extract info specific to SOs

Identify relevant HTA agencies

- Two main criteria followed for the update:
  - **Geographical:** only agencies located in either the European Union (EU) or the European Free Trade Association (EFTA) were included,
  - **Methodological:** only agencies with a role in methods guidance development were included.

- **Exception**! Australian PBAC, MSAC and Canadian CADTH, even if *non-European* agencies, were purposefully kept in the sample as known examples of established HTA agencies

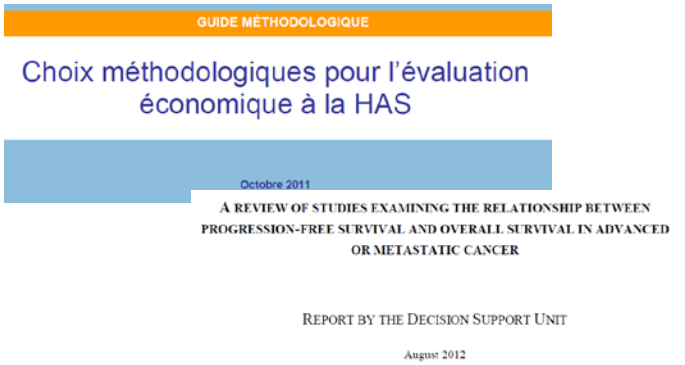
Identify methods guidance



Documents identified

- **40 guidance documents** from **26 European agencies in 18 countries** were included
- **Five guidance documents** from **three agencies** in AU and CA

- documents were official guidelines, but also support documents



Scope of included documents (EU)

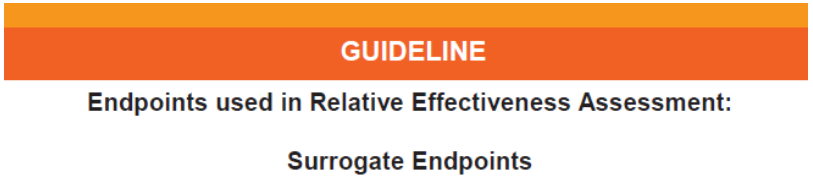
- The majority of the documents were not technology-specific
- 15 (37%) referred specifically to pharmaceuticals and ***only one*** (2%) (UK NICE:MTEP) was intended for medical devices
- 2 documents (all dedicated documents from DE IQWiG, UK NICE) were intended for **oncology medicines only**

Documents specifically on surrogate outcomes (EU)

- Extent to which SO were treated in the document varied greatly:
- from **single mentions** (CR AAZ, ES AVALIA-T, NO NIPH) in generic terms,

> *(1) In view of the therapeutic importance […], the medicinal product could be:*
> *- with proven positive effects on final clinical outcomes,*
> *- with proven positive effects on **alternate outcomes**,[…]* (CR AAZ)

- to **full documents** dedicated to SO (EUnetHTA, DE DIMDI, DE IQWiG, UK NICE,)



Content analysis

Domain	Explanation
Definition	Is a definition of surrogate outcomes provided as part of (or annex to) the document?
Examples	Are example of surrogate outcomes provided in the text of the document (e.g.. progression-free survival as SO for overall survival)?
Use of surrogates considered	Are considerations on the use of surrogate outcomes included in the guidelines, such as recommendations to caution when including SO in the analysis?
Acceptability criteria	Are there acceptability criteria included in the guidelines? (e.g.. requirements to validate the SO used)
Evidence strength assessment	Is there a framework for quantifying the evidence on the surrogate-final outcome relationship? (e.g.. level 3 for only evidence of biological plausibility; level 1 for evidence of correlation between SO and clinical outcome of interest from meta-analyses (Ciani et al. 2016, DOI: 10.1016/j.jval.2016.10.011))
Validation methods	Are any validation methods prescribed? (eg. correlation of the effects on the surrogate and the effects on the clinical endpoint from meta-analysis of randomised trials)
Validation values	Are there cut-off values of the surrogate-final outcome association suggested?

Content analysis: results (1)

Data analysis showed that:

- 34 (83%) documents contained **general considerations (eg. recommend caution) on the use of SOs**
- 18 (49%) documents **defined acceptability criteria for SOs in evaluations** (eg. requirements to justify the value of the SO in the analysis)
- 14 (34%) documents **provided examples of SO** (eg. *progression-free survival as SO for overall survival*)
- Nine (22%) documents provided a ***definition* of SO**

Content analysis: results (2)

- Six (15%) provided a **framework for quantifying the quality of evidence** (eg. level 3 for only evidence of biological plausibility, level 1 for evidence of correlation between SO and clinical outcome of interest from meta-analyses)
- Four (10%) documents (IQWiG, EUnetHTA, INFARMED) **prescribed validation methods**
- *Only two documents* (IQWiG, EUnetHTA) mention **cut-off values** (eg. R^2_{trial} >0.85) for the acceptability of correlation evidence between SO and clinical outcome of interest

Discussion

	Velasco-Garrido review	Our review
Year	2009	2018
Scope	international	Mostly European
Screened agencies	55 international agencies	70* European agencies + three international agencies
Included documents	20 documents from 23 (42%) agencies	40 documents from 26* (39%) agencies + five documents from three non-European agencies
Similarities between findings	- general preference for final outcome - only use SO in justified circumstances - no -/+ list of 'established SO'	
Differences	-also included an analysis of HTA reports	- a more detailed extraction and appraisal framework - new dedicated documents

* Including EUNetHTA guidelines

Discussion

- A minority of HTA agencies formally deal with SOs consideration with sufficient level of detail
- Where SO were addressed, there was a considerable similarity in recommendations across agency guidelines
  - probably driven by the existing EUnetHTA guidelines on SOs
- PBAC/MSAC and CADTH had similar recommendations on the use of SO (caution and justification) and acceptability criteria (need for evidence of connection between the SO and the clinical outcome of interest)

Discussion

- Most of the guidelines were not technology-specific, or referred to pharmaceuticals; *very little specific to medical devices*;

- Consideration of SO quality assessment/ validation/ threshold setting was limited to a few agencies and generally lacked detail, ie. guidance given is very generic and unclear in terms of what constitutes a reliable surrogate marker

Conclusion

- The EUNetHTA guidelines have provided an opportunity for harmonisation for the evaluation of SOs

- However, further prescription of validation remains challenging in the absence of adequate evidence/methods (eg. are particular cut-off values reasonable?)

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Thank you!

Q&A

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