Discrepancies between Regulators and HTA bodies

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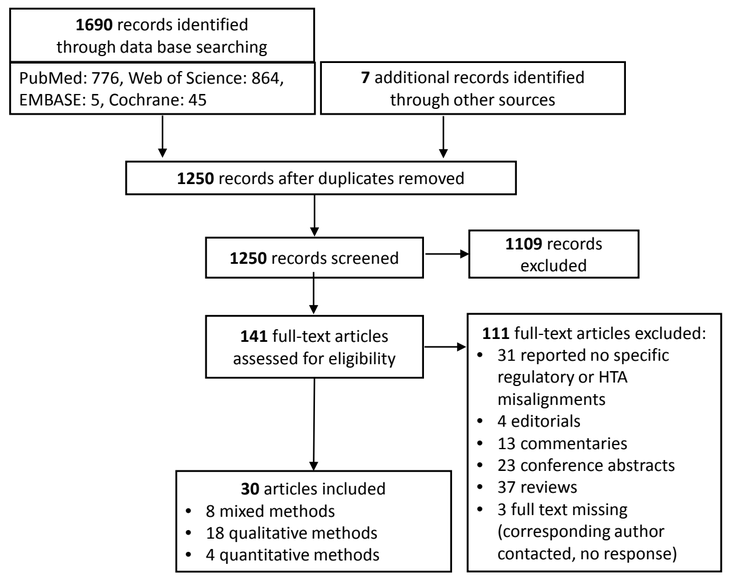
Introduction

- Regulatory approval grants market access, indeed, through coverage decisions, HTA-bodies rule about real patient access
- Despite their different objectives, HTA-bodies largely depend on evidence that was created for the market authorization
- Potentially causing that technologies are approved but not reimbursed
- Additionally there are discrepancies among HTA-bodies' evidence requirements
- Early dialogue meetings aim to align the different evidence requirements that pose a great challenge for manufacturers

Methods

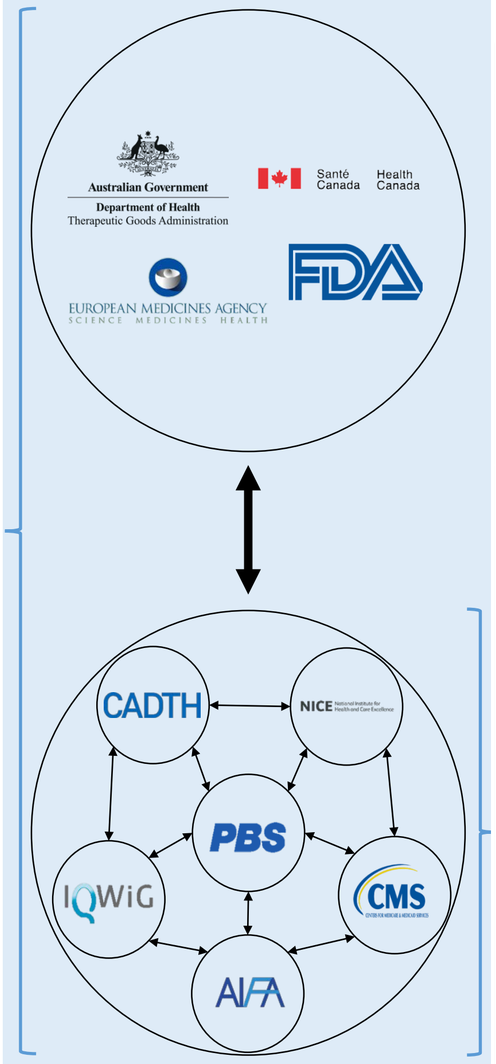
- We systematically searched literature that was published until 07.02.2018
- The search term built around the three main blocks 1) regulator; 2) HTA and 3) alignment or misalignment
- Articles that cover properties that influence regulatory or reimbursement processes; regulators' or HTA-bodies' evidence requirements; third and fourth hurdle pathways were included
- Further articles were classified in qualitative, quantitative or mix-methods research according to Starr
- Findings were categorized in 1) discrepancies between regulators and HTA bodies; and 2) misalignments among HTA-bodies evidence requirements

Results



Regulators & HTA bodies

Misalignment		Regulator	HTA bodies
Objective		Quality, safety, efficacy Non-inferiority Does the technology offer more benefit than harm compared to placebo?	Relative-/ cost-effectiveness, Superiority Does the technology offer more benefit than harm compared to alternatives under consideration of price for the population.
Evidence sources		RCT	RCTs, partially RWD (registries, EHRs, claims data)
Validity		Internal validity	External validity, generalizability
Study design	Study length	Relatively short trials to demonstrate efficacy	Longer lasting trials to assess true effectiveness
	Study population	Relatively small, homogenous, comorbidity free population	Larger, heterogeneous general population
	Study setting	Controlled ideal conditions	Actual health care practice
	Comparator	Active (non-inferiority) or placebo (superiority)	Active (superiority)
	Endpoints	Broader acceptance of surrogate, intermediate, mechanistic endpoints	"Hard" patient relevant endpoints, validated surrogate endpoints (show correlation with patient relevant endpoints)



Among HTA bodies

Misalignment			Characteristic
Methods			**Relative- /comparative- effectiveness** The effect of the new therapy in comparison to the standard of care **Cost-effectiveness** The effect of the new therapy in relation to its price
Source of evidence			**Mostly RCT data** **Also RWD (non-RCT data)** e.g., observational studies, electronic health records, claims data
Assessment	Clinical effectiveness	Comparators	comparator corresponding to **health systems standard of care**, used indication and dosage (narrowly defined) various comparators **use in practice** (broadly defined)
		Endpoints	Broader acceptance surrogates. Generally reject surrogate, possibly accept validated surrogates in certain conditions or if validated (correlation with patient relevant endpoint)
Appraisal	Cost and economic evaluation	Methods	**No economic methods** (rely on relative effectiveness) **Various economic methods** e.g. costs/QALY, Budget impact analysis, economic modeling, multi-criteria decision analysis
		Criteria	Patient population size, willingness to pay thresholds

Discussion

- Regulators' and HTA bodies' aims implicate different or even mutually exclusive evidence requirements
- HTA bodies share similar goals but adopted different methodologies and consult different data
- Early dialogues between regulators, HTA bodies and manufacturers offer possibilities to create synergies in the evidence generation
- Alignment in the evidence requirements should respect professional or national priorities

Conclusion

- There are limits to the alignment of regulatory and HTA evidence requirements
- HTA bodies should strive for a stronger alignment of clinical evidence requirements
- In non-clinical evidence requirements there are limits to an alignment

Acknowledgements
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 779306.