Improving synergy between HTA bodies and regulatory agencies

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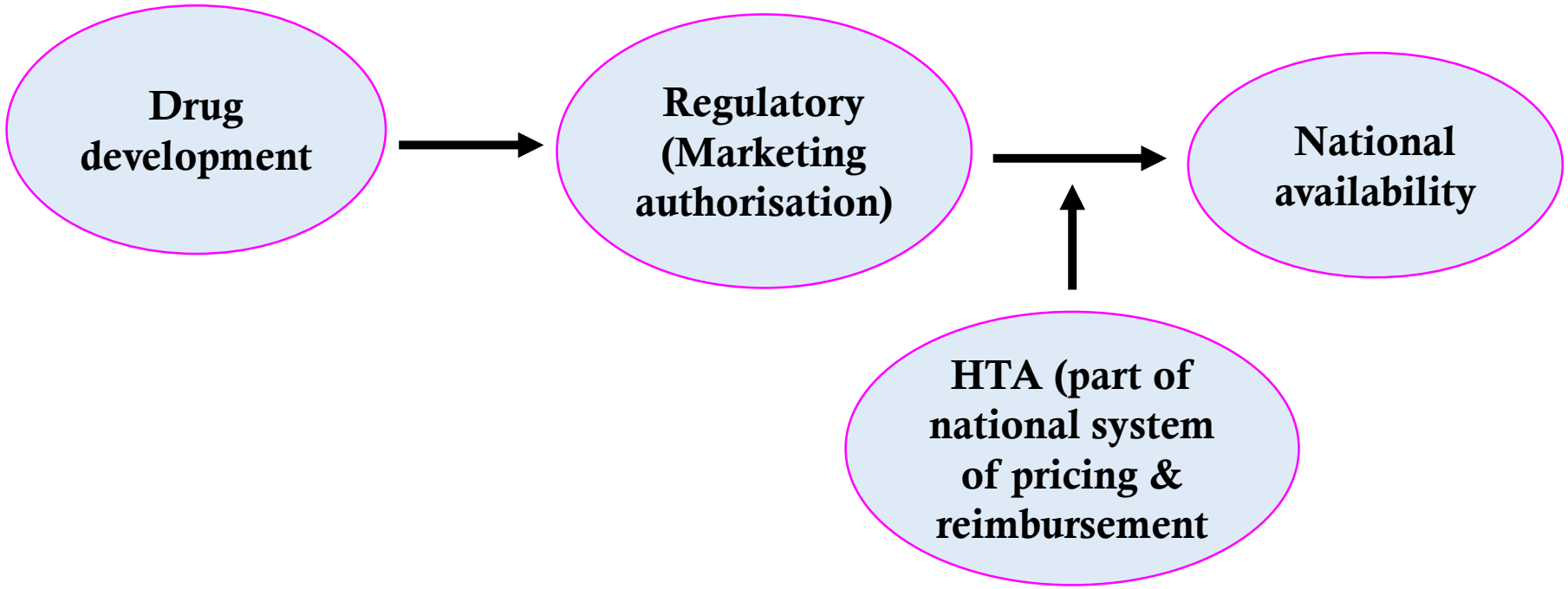
Is the silo-based model for medicine evaluation broken?



- Between March 2000 and March 2018, just 56% of drugs approved by EMA were recommended by NICE for reimbursement[1]
- <50% of new cancer medications assessed during 2013-2017 across 20 countries, received positive reimbursement recommendations[2]

[1]Grignolo A, Siu A. Improving Drug Development and Patient Access With the Right People, Processes, and Culture: What Needs to Happen Right Now to Bring Better Medicines to the Patients Who Need Them. *Ther Innov Regul Sci.* 2019;53(3):398-402.
[2]IQVIA Institute for Human Data Science. Global Oncology Trends 2018: Innovation, Expansion and Disruption. 2018; www.iqvia.com/institute/reports/global-oncology-trends-2018.

Study objective

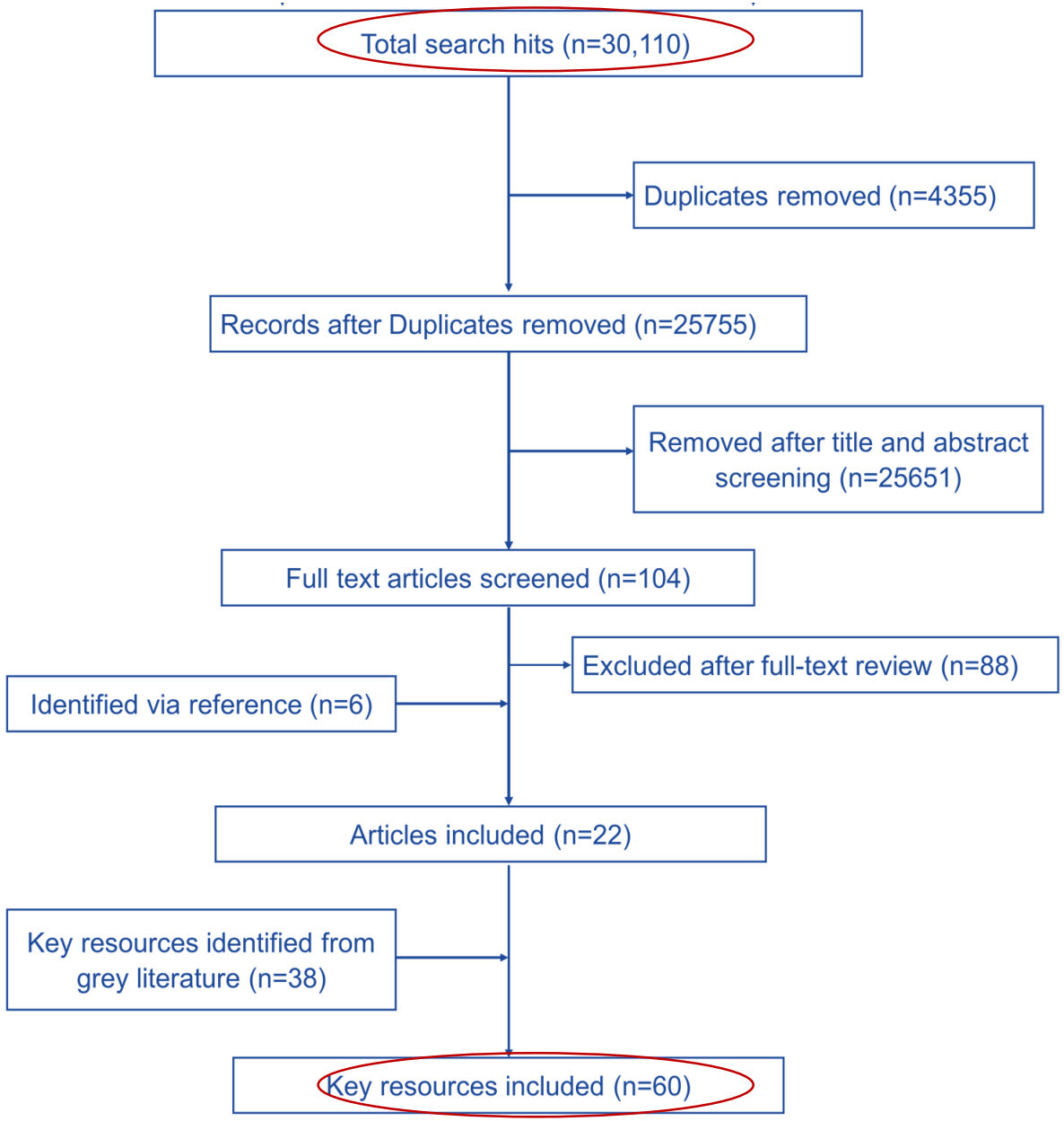
To provide insights into opportunities and outcomes of synergy initiatives between HTA and regulatory agencies

Methods

- Systematic review
  - ❖ *Medline, EMBASE, and the International Pharmaceutical Abstracts database were searched until 21 October 2019*
  - ❖ *We also searched for grey literature (working papers, commissioned reports, policy documents) via google scholar and several national and multinational institutional websites*

- Cross-sectional survey
  - ❖ Online-based from January to April 2020
  - ❖ HTA bodies and regulatory agencies in Europe only
  - ❖ The same set of questions seeking insight into HTA-regulatory interactions
  - ❖ Six (6) key questions
    - ✓ *Formal link of collaborating?*
    - ✓ *Types and examples of collaboration*
    - ✓ *Key outcomes and challenges*

Results



Results

Survey

- The online survey received responses from 22 HTA bodies (21 countries) and 6 regulatory agencies (5 countries)

- Response rates were 18% (6/34) and 61% (22/36) for regulatory agencies and HTA bodies, respectively.

- Of the regulatory agencies, one was from Western Europe, two from Northern Europe, two from Central and Eastern Europe, and a representative from the EMA.

- Among the HTA bodies, nine were from Western Europe, seven from Central and Eastern Europe, four from Northern Europe, and two from Southern Europe

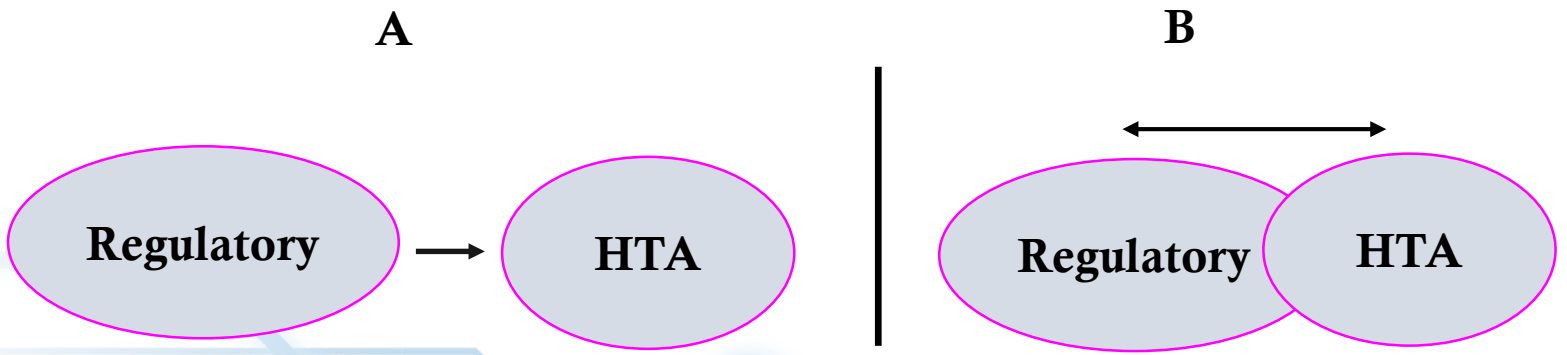
Understanding HTA-regulatory focus

	Regulatory approval	HTA assessment (to inform reimbursement decisions)
Legal mandate	Usually defined within national public health legislation	HTA may be undertaken by a group within and accountable to a payer
Primary role	Provide market authorization within the mandated jurisdiction based on an assessment of safety, quality, efficacy, and risk–benefit profile	Support for clinical and coverage decisions based on assessment of relative effectiveness, costs and, in some, system affordability, value for money, and values within the system
Decision	Evaluates whether the clinical benefits for patients outweigh the risks? Should this technology be available?	Assess whether the product offers useful, appropriate (and affordable) benefits for all or a select subgroup of patients compared to what is most commonly used in the disease area?
Assessment focus	Efficacy, safety, quality (e.g., GMP)	Effectiveness, safety, quality of life, economics, budgetary impact, social, ethical, legal, organizational
Strength of Evidence	Pre-launch: Efficacy and safety from RCTs (usually placebo-controlled) Post-launch: Relative efficacy or effectiveness may be considered when reviewing product's ongoing risk– benefit profile	Pragmatic RCT*, observational studies, decision-analytic techniques (modelling)
Characteristics of studies they prioritize		
Validity	Internal validity	External validity
Comparator	Placebo	Active control, ideally standard of care
Endpoints	Laboratory findings and surrogate endpoints	Quality of life; final clinical 'hard' outcomes such as death
Time horizon	Trial duration	Lifetime or at minimum the time needed to capture all risks and benefits of therapy

What is harmonization?

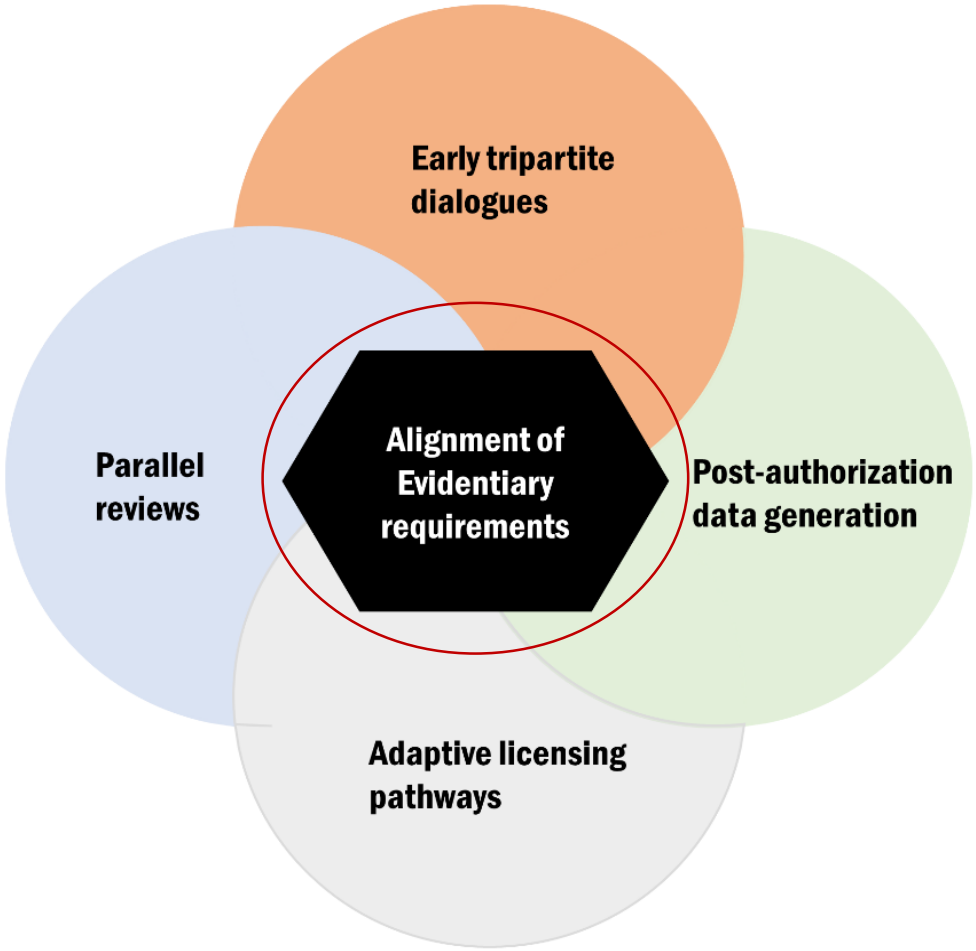
- Harmonization is broadly considered to encompass the streamlining of regulatory and reimbursement processes

- It is also deemed process-oriented and centered on reducing the time between regulatory and reimbursement decisions, and minimizing duplication of work



- From the survey, most regulatory agencies (4/6; 67%) and half (11/22, 50%) of the HTA bodies reported having a formal link for 'collaborating' with the other

Key avenues for HTA-regulatory collaboration



Alignment of evidentiary needs

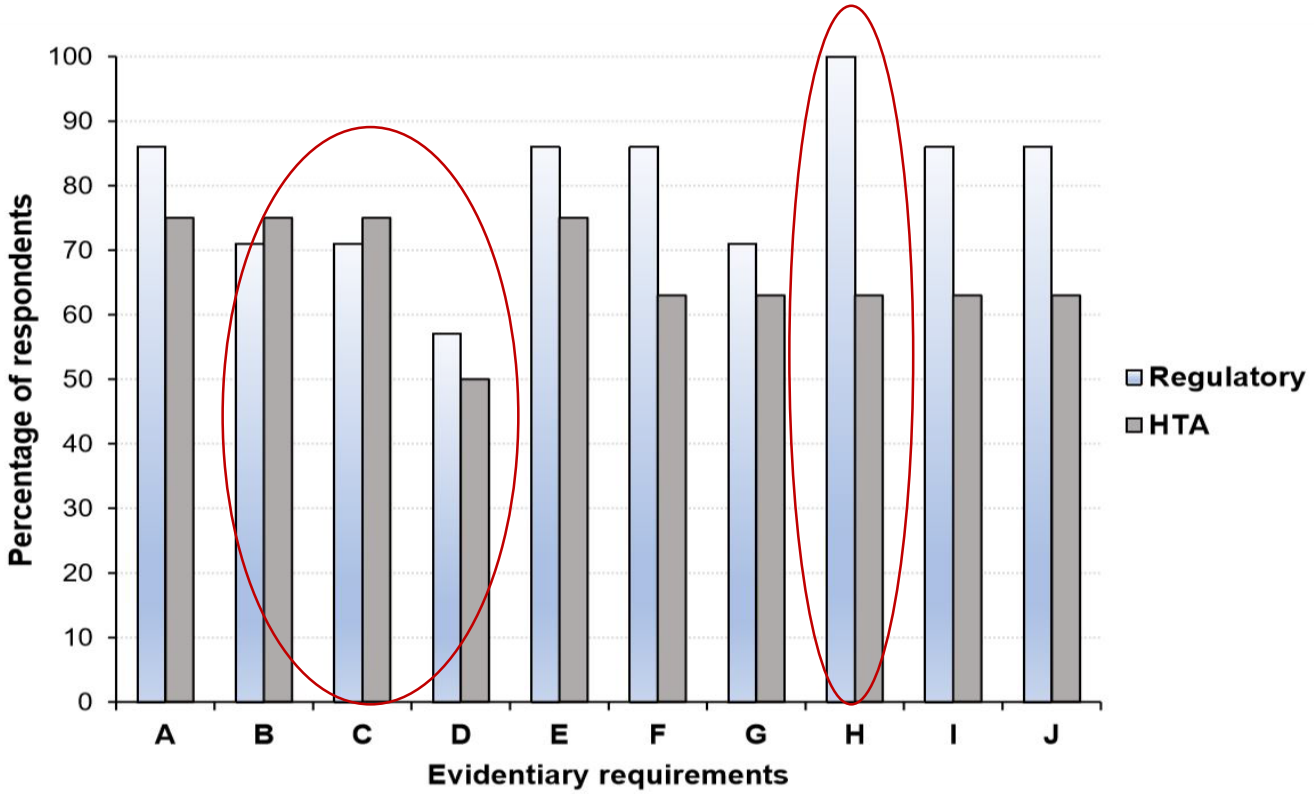
- Commonality of safety and efficacy assessment
- Increasing interest in relative efficacy and comparative effectiveness research (CER)
- Contextual issues
  - *Study design*
  - *Endpoint*
  - *Comparator*
- Perhaps differences are exaggerated??

Alignment of European Regulatory and Health Technology Assessments: A Review of Licensed Products for Alzheimer's Disease

Marieke J. H. J. Dekker[1*], Jacoline C. Bouvy[2], Diana O'Rourke[3], Robin Thompson[4], Amr Makady[5], Pall Jonsson[3] and Christine C. Gispen-de Wied[1]

There was a large overlap in inclusion of trials in regulatory and HTA assessments, although the focus on specific outcomes slightly differed

Alignment of evidentiary needs



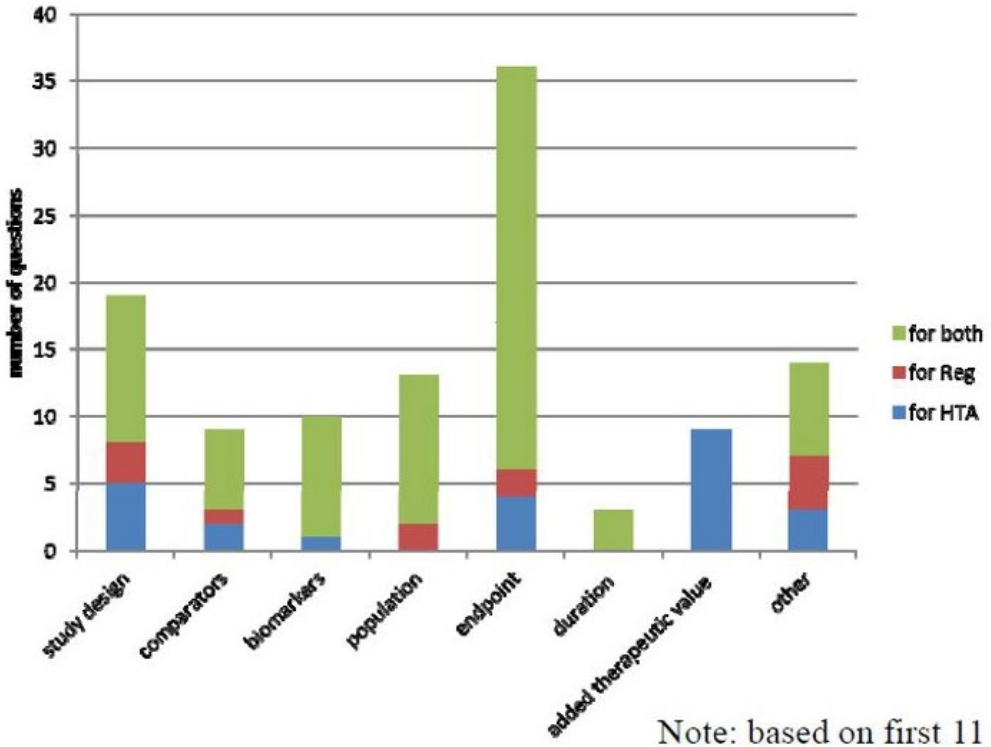
A = Acceptable primary end point; **B** = Inclusion of active comparator arm in the trial; **C** = Use of patient reported outcomes; **D** = use of health-related quality of life measures; **E** = Choice and use of surrogate measures; **F** = Criteria considered in choice of comparator: therapeutic; **G** = Use of subgroup analyses; **H** = Inclusion and choice of secondary efficacy parameters; **I** = Definition of unmet medical need; **J** = Use of biomarkers to monitor patient outcomes; sourced from Wang et al.2018

Promoting early tripartite dialogues

- Regulatory early dialogue has been in place for many years
- During 2008 -2012, 85% of applications that received and followed early EMA scientific advice were ultimately granted marketing authorization compared to only 41% that did not[1]
- Early dialogue with HTA relatively new
- Tripartite dialogues offer opportunity to define divergent data needs and align evidentiary requirements for developers
- Several tripartite dialogues exist both at national (UK, Sweden, Australia) or multi-country levels (EMA, Tapestry network, green park collaboration)

Promoting early tripartite dialogues

- EMA-HTA parallel scientific advice, 2010
- 63 PSAs completed by 2015



Note: based on first 11 procedures

Endpoint and study design

Promoting early tripartite dialogues

- 518 answers provided by regulators and HTA assessors in 31 PSAs revealed that full agreements, partial agreements, disagreements were reached in 61%, 23% and 16% of responses
- Several compromises in product development have been noted
- Tafuri and colleagues found that developers implemented comparators to address needs of HTA and regulators in 60% (12/21) studies
- Developers more inclined to satisfy regulatory advice
- No mechanism for addressing divergence

Parallel submission

Region/country	Stakeholders	Name of program
Australia	TGA (Regulator) PBAC (HTA/payer)	Parallel submission/review
Canada	Health Canada (Regulator) CADTH (HTA/payer)	Parallel submission/review
Netherlands	MEB (regulator) ZIN (HTA/payer)	Parallel submission/review (Pilot)
US	FDA (regulator) CMS (HTA/payer)	Parallel submission/review

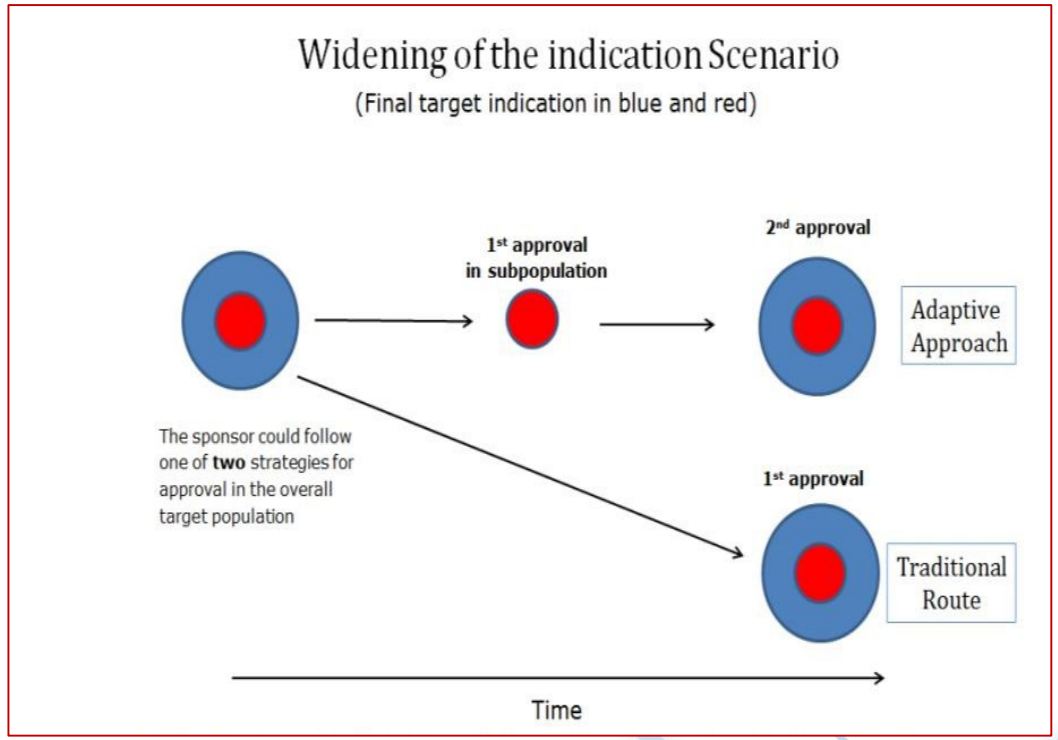
Could parallel submission explain the shorter time between regulatory approval to HTA decision in certain countries?

- Australia (n=46; median=44 days) compared to Canada (n=38; median=269 days), France (n=57; median=230 days), England (n=27; median=314 days), Germany (n=51; median=139 days), Poland (n=32; median=444 days), Scotland (n=47; median=260 days), and Sweden (n=48; median=184 days)[1]

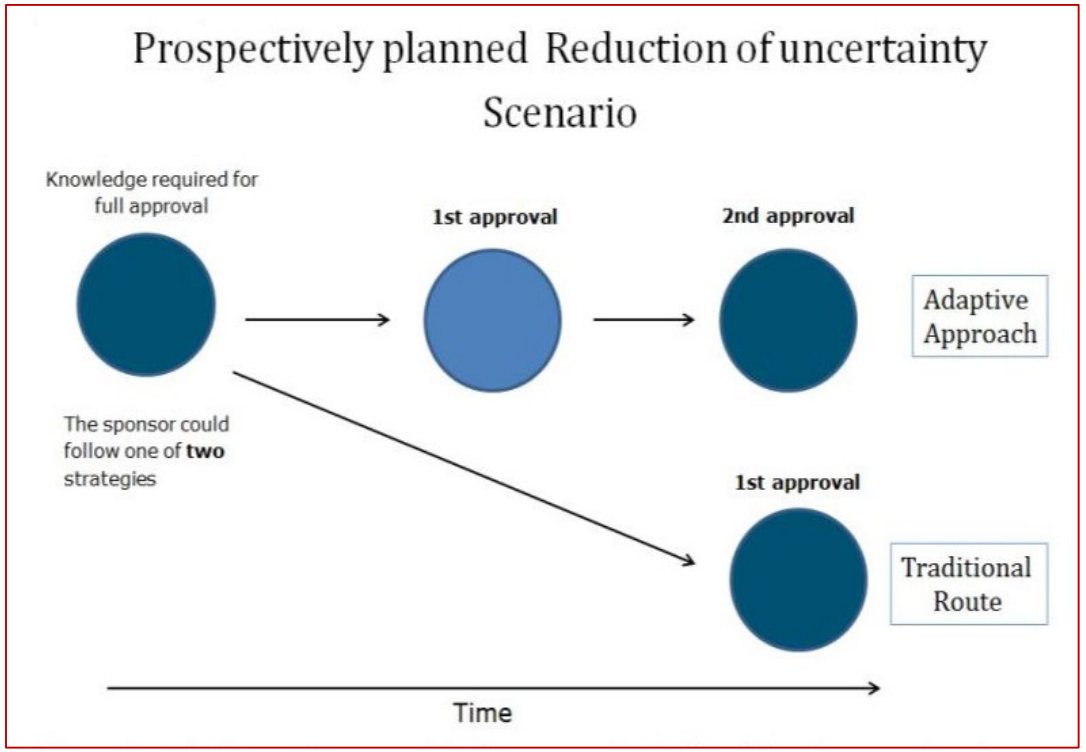
[1]Centre for Innovation in Regulatory Science (CIRS). *Review of HTA outcomes and timelines in Australia, Canada and Europe 2014-2015.* London: CRIS; 2017.

Adaptive licensing pathways

A



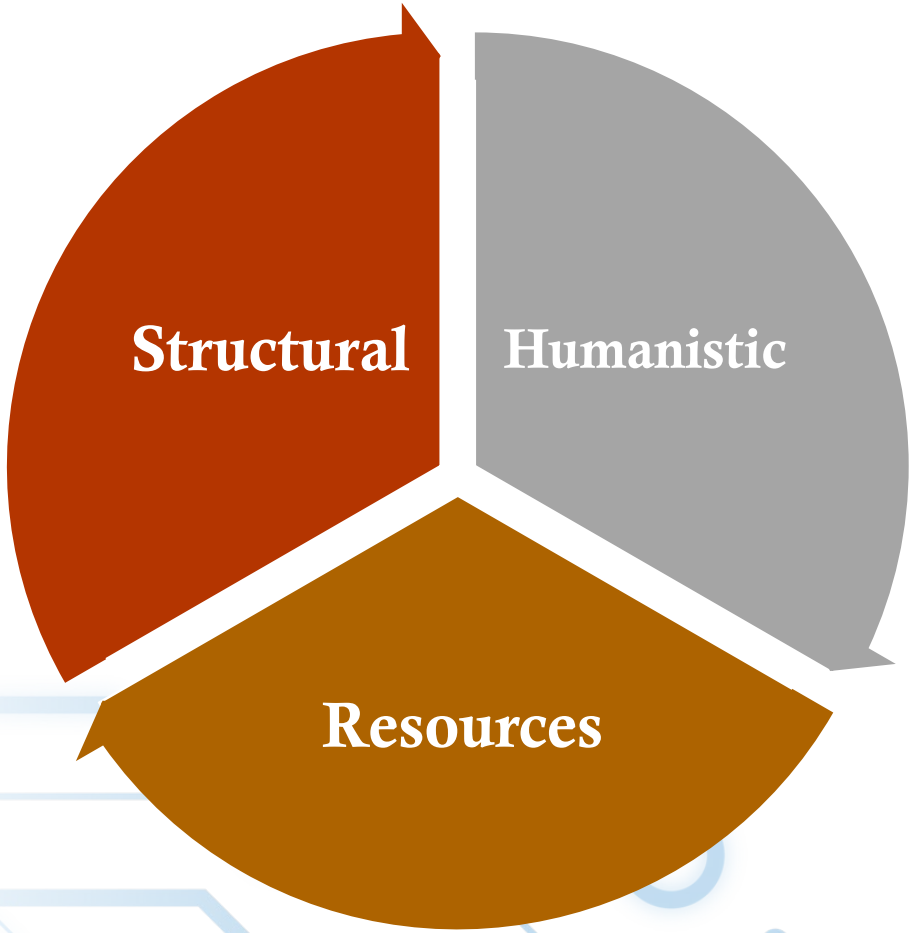
B



Post-authorisation data generation

- Post-authorisation efficacy studies
- Post-authorisation safety studies
- Development of methodological guidance
- Use of real-world data
  - ✓ *Establishment of patient registries*

Barriers and challenges



Key limitations

- Survey experience limited to Europe
- Most PSA dialogues are confidential, so document review may not fully capture processes
- Further dialogue planned for October 2020

Conclusions

- Overall, we found that while there are areas of divergence, there has been progress over time in narrowing the gap in evidentiary requirements for HTA and regulatory agencies

- Several mechanisms such as early tripartite dialogues, parallel submissions (reviews), adaptive licensing pathways, and post-authorisation data generation have been explored as avenues for improving collaboration.

- Several pilot initiatives have shown positive effects of these models to reduce the time between regulatory and HTA decisions

- Data on long-term impacts are limited.

- Several barriers including legal, organizational, and resource-related factors were also evident

Thank you!