What are the emerging state-of-the-art HTA methods that are relevant to the harmonisation of HTA across jurisdictions?

Poster No. HTA269

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Background

- Whilst the remit of Health Technology Assessment (HTA) bodies has evolved, the development of innovative therapies has revealed new methodological challenges. Despite previous reviews on best-practice in HTA methods[1] recent developments, including the new EU HTA Regulation, reinforce the need to assess emerging methods for harmonisation.
- Alignment on methods for evidence generation and synthesis is essential for harmonising HTA methods between stakeholders with potentially diverse evidence needs. This also provides certainty to health technology developers and improves inter-trial comparability. Several supra-national initiatives aimed at standardising outcome selection are ongoing.[2,3]
- Evidence generation for ATMPs, oncology, and orphan drugs is often associated with small patient populations, clinical comparator ambiguity, and high unmet need. This often leads to increased uncertainty as decision makers rely on non-randomised evidence, indirect comparisons, surrogate outcomes, and extrapolation of treatment benefit, requiring trade-offs between lower-quality evidence and patient access.

Objectives

1. Identify state-of-the-art methods relevant to evidence generation and HTA decision making which may influence HTA harmonisation efforts.
2. Provide a high-level review of their methodological challenges, and discuss potential barriers to the implementation in HTA of these identified methods.

Methods

- We defined state-of-the-art methods as the most recent stage of technological development for an area of evidence development, which may or may not be used for HTA decision making.
- We defined two areas with potential needs to improve appraisals of innovative therapies:
  - Comparators, including external control arms and indirect comparisons;
  - Outcomes, including surrogates, long-term extrapolation, and outcome measure selection.
- For each, we conducted a pragmatic literature review on PubMed for articles published in the last 5 years in the English language, search terms included 'HTA methods', 'outcomes', 'endpoints', 'comparators, and 'comparisons'.
- We also reviewed HTA websites, HTAi and ISPOR conferences, and HTA methods guides to understand the implementation status of different state-of-the-art methods.

Results

Literature search results

- The pragmatic search retrieved 674 hits, with 31 hits for digital outcomes, 6 for core outcome sets (COS), 6 for external control arms (ECA), and 26 for indirect treatment comparisons (ITC).
- Additional searches were conducted to identify ongoing initiatives in methodological development, and HTA methods from EUnetHTA, HAS, IQWiG and NICE, were also reviewed.

Topic selection

- For comparators, we identified emerging state-of-the-art methods on the use of external control arms and indirect comparisons and noted variability in implementation of newer methods, use of non-randomised evidence and population adjustments.
- For outcomes, selecting appropriate outcome measures was identified as an evidence need. We identified digital outcomes and use of COS as relevant state-of-the-art methods. The use of estimands for regulatory assessments was also identified as an emerging issue for HTA.

State of the art methods

- Digital outcomes are collected using connected digital health technologies, enabling the automated data collection outside of study visits. They also enable data collection that would otherwise be unfeasible and may reduce the burden of study visits and trial participation.
- A (COS) is a standardised set of outcomes agreed upon by multiple stakeholders as the minimum outcomes measured and reported in trials for a specific therapy area. COS may improve inter-trial comparisons and evaluations of relative effectiveness.
- ITC and ECA may be used to provide evidence of relative effectiveness where a randomised trial is not feasible. This may be because randomisation to a control arm is unfeasible or unethical, or there are multiple comparators making it unfeasible to collect direct comparative evidence.

Description of key findings

Digital outcomes

- Despite growing public familiarity with these digital health technologies and their potential applications for data collection in clinical research, there was limited recognition of digital outcomes for HTA submissions and decision making.
- HTA guidance was limited to the EUnetHTA draft guideline on Outcomes, which discussed their advantages and disadvantages, but did not their use in HTA submissions or decisions.[4]
- We identified several initiatives supporting best-practice in the implementation of digital outcomes, Mobilise-D and the Digital Medicine Society (DiMe), the latter recording a ~50% increase in the number of digital endpoints between 2021 and 2022.[5,6]

Core outcome sets

- There is a widespread recognition of COS by HTA bodies, common themes identified to support their use included improved inter-trial comparisons and evaluations of relative effectiveness, due to their potential for improving the quality of evidence available to decision makers by reducing heterogeneity and outcome reporting bias and enhancing transparency.
- Despite being widely referenced in HTA methodological guidelines, their uptake in evidence generation and synthesis is variable.[4,7-9] This was attributed to variation in the availability of validated measures, stakeholder consensus, and use in evidence generation and synthesis.
- To ensure COS can be appropriately used, guidance from the literature states these should be applicable in all appropriate settings, different countries, and to include detail on how to measure the outcomes once consensus is reached during the development process.[10]

Results

External control arms

- Our review found there was limited guidance on synthetic control arms for HTA submissions.[7] This may explain variation in HTA critique the role of this evidence for decision making, and the limited use of external controls for HTA appraisals based on single-arm trials.[11,12]
- There was no guidance from HTA bodies on the role of synthetic control arms to supplement a randomized control group. In the literature, this was described as a potential application of this method to improve the efficiency of RCTs.[13]

Indirect treatment comparisons

- Guidance from HTA bodies supports the use of ITC to compare the effectiveness of treatments of interest in situations where RCTs are unfeasible.[9,14] Several HTA bodies have stated that network meta-analyses (NMA) are the preferred method for ITCs, whilst HAS indicates a preference for Bayesian NMA due to its flexibility.[7-9,14]
- HTA bodies associate ITCs with greater uncertainty than direct comparisons. Evidence from ITCs may not be accepted some circumstances, such as networks with a small number of trials and non-randomised data.[7,8,14]

Table 2. Summary of methodological guidance and HTA positions

	Practical guideline available?	HTA position			
		HAS	IQWiG	NICE	EUnetHTA
External control arms	✓	Accepted in limited circumstances	Accepted with multiple restrictions	Accepted with justification	Acknowledged with negative perception
Indirect comparisons	✓	Accepted if justified in limited circumstances	Accepted in very limited circumstances	Accepted if direct comparison unfeasible	Acknowledged with negative perception
Digital outcomes	✗	Not acknowledged or recommended	Not acknowledged or recommended	Not acknowledged or recommended	Acknowledged, no recommendations
Core outcome sets	✓	Recommended	Recommended	Recommended	Recommended

HAS Transparency Commission Doctrine 2020, IQWiG General Methods v.6.1 2022, NICE health technology evaluations: the manual 2022, EUnetHTA methodological guidelines: Direct and Indirect Comparisons and Outcomes (endpoints) 2022

Perception by HTA: *Negative* ● ● ● ● *Positive*

Discussion

Digital outcomes

- The lack of guidance on digital outcomes for HTA submissions may be attributed to the infancy of this method and understanding of best practice applicable to HTA decision making.
- Whilst HTA guidance may be developed as this method matures, collaborative development of HTA guidance on this methodology has the potential to support its early implementation and ensure this method is used appropriately in future HTA submissions.

Core outcome sets

- Given the widespread recognition of COS by HTA bodies, this may be a topic where there is a high potential for harmonisation. However, it appears the uptake of COS is limited by their availability and the acceptance of outcomes for evidence generation.
- To ensure COS are appropriately integrated into HTA, collaboration and agreement from key stakeholders is needed on the evidence requirements and definitions of COS by therapy area.

External control arms

- Improved guidance for HTA submissions is may increase the availability of comparative effectiveness data for single-arm trials, improving HTA decision making and patient access.
- Practical guidance from HTA bodies is currently limited, as evidenced by varied use and interpretation of this method varies between assessments by different HTA bodies.

Indirect treatment comparisons

- Whilst ITCs are widely recognised by HTA bodies, the perception of novel methods for population-adjustment varied, for example, EUnetHTA guidelines were conservative in their acceptance of population-adjusted methods. Other HTA bodies, namely HAS and IQWiG only consider these acceptable in limited circumstances posing a barrier to their use.

Conclusions

- The varied implementation and acceptance of state-of-the-art methods may present a barrier to their use in HTA submissions and decision making, posing a barrier to harmonisation efforts in Europe.
- Consistent HTA guidance may improve the quality of evidence in HTA submissions and improve decision making, especially where evidence generation is challenging
- To ensure optimal and harmonised patient access to innovative treatments, implementation of state-of-the-art methods may be facilitated though multi-stakeholder engagement and collaborations on methods development.

References

1. EFPIA review of HTA methods in 2018/19
2. SISAQOL-IMI
3. COMET initiative
4. EUnetHTA methodological guideline – D4.4 Outcomes https://www.eunethta.eu/d4-4/
5. MobiliseD Consortium - https://www.mobilise-d.eu/
6. Digital Medicine Society - https://www.dimesociety.org/get-involved/library-of-digital-endpoints/
7. HAS Transparency Commission Doctrine 2020,
8. IQWiG General Methods v.6.1 2022,
9. NICE health technology evaluations: the manual 2022
10. Matvienko-Sikar K, et al., Use of core outcome sets was low in clinical trials published in major medical journals, J Clin Epidemiol, 2022
11. Ashley, J. et al., A Comparison of Seven Oncology External Control Arm Case Studies: Critiques From Regulatory and Health Technology Assessment Agencies, Value in Health, 2022
12. Patel, D. et al., Use of External Comparators for Health Technology Assessment Submissions Based on Single-Arm Trials, Value in Health, 2021
13. Dron L, et al., Minimizing control group allocation in randomized trials using dynamic borrowing of external control data - An application to second line therapy for non-small cell lung cancer. Contemp Clin Trials Commun. 2019
14. EUnetHTA methodological guideline – D4.3.2 Comparators and Comparisons https://www.eunethta.eu/d4-3/

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