HTA80

To what extent do the EUnetHTA 21 D4.4 guidelines on endpoints recognise non-OS endpoints and patient-reported outcomes, and what opportunities exist in the Joint Clinical Assessment to reflect their value?

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Background

- The EU Health Technology Assessment (HTA) regulation 2021 aimed to harmonise the HTA procedure across the EU and makes the Joint Clinical Assessment (JCA) mandatory for oncology drugs in 2025
- The mandate of EUnetHTA 21 ended on 16 September 2023, and its deliverables are handed over for consideration, review and modifications to the Coordination Group and the European Commission
- The EUnetHTA 21 joint consortium developed guidelines to support the JCA, including the D4.4 guideline on endpoints, which provides guidance on the selection and evaluation of outcomes in JCAs
- In oncology, overall survival (OS) is traditionally the preferred outcome for HTA bodies / payers, but it has limitations such as long follow-up time, confounding factors and failure to capture other outcomes beyond survival of value to patients and clinicians, e.g., HRQoL* outcomes
- Non-OS endpoints and patient-reported outcomes (PROs) have value as surrogates for survival-related outcomes (e.g., OS, DFS, EFS*, etc.) as well as standalone value in measuring outcomes beyond survival that are important to patients and clinicians (e.g., avoidance of surgery, HRQoL*)

Aims

This research aims to assess the extent to which the EUnetHTA 21 D4.4 guideline on endpoints recognises non-OS endpoints and PROs in oncology, and what opportunities exist in the JCA to reflect their value. The goal is to:

1. Understand the guideline's position on the identification of fit-for-purpose endpoints per treatment setting
2. Assess the guideline's position on the acceptability of specific non-OS endpoints / PROs as surrogate endpoints
3. Assess the extent to which standalone value of non-OS endpoints and PROs is recognised in the guidelines
4. Ensure future EUHTA result in the best outcomes for patients

Methods

LITERATURE REVIEW OF NON-OS ENDPOINTS AND PROs, EUNETHTA 21 GUIDELINES

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INTERVIEWS WITH EX-PAYERS FROM ITALY, UK, BELGIUM AND DENMARK

Results

1. Identification of fit-for-purpose endpoints per treatment setting

- The guideline recognises the need to tailor outcomes per treatment setting by using core outcome sets (COS) that involve multiple stakeholders, such as patients, clinicians and industry
- The guideline provides guidance on the definitions and use of PROs in JCAs, including the validity, reliability and interpretability of outcome instruments
- It also allows for other outcomes deemed relevant by key stakeholders to complement the use of COS in the scoping process

> *"By **involving a wide range of stakeholders**, such as patients, caregivers and healthcare professionals and health technology developers, it is **more likely that patient-centred outcomes will be identified**. By contributing to less heterogeneity in clinical outcome assessments in original clinical studies, COS use may facilitate the conduct of evidence synthesis"*
>
> *EUnetHTA D4.4 guideline*

2.. Need for greater clarity on the acceptability of specific non-OS endpoints / PROs as surrogate endpoints

- The guideline favours long-term outcomes like OS, but could provide clearer guidance on the acceptability of non-OS endpoints and PROs as surrogates.

The guideline recommends the use of long-term or final outcomes, such as OS, and states that surrogate endpoints should only be used if it is not feasible to measure a final outcome

The guideline provides evidence requirements for the validity of surrogate endpoints to OS in JCAs, but does not specify the acceptability of particular non-OS endpoints / PROs as surrogates

The guideline could benefit from a more comprehensive list of acceptable outcomes in oncology, more detailed use cases and clearer conclusions on the validity of specific non-OS endpoints as surrogates

Results (*cont.*)

3. Recognising the standalone value of non-OS endpoints and PROs

Recommendations

The guideline should recognise the stand-alone value of non-OS endpoints and PROs in capturing outcomes important to patients and clinicians (e.g., PFS, HRQoL) and in guiding treatment decisions	The guideline should recognise the importance of considering a combination of endpoints, rather than just relying on a single primary endpoint, such as OS, in HTA body / payer decision-making

- In the EUnetHTA Joint Assessment 2 guideline on surrogate endpoints used in relative effectiveness assessments, published in 2015, PFS was recognised as an outcome with standalone value, acceptable in HTA body / payer decision-making in the adjuvant setting
- However, in the EUnetHTA D4.4 guideline, conclusions on the acceptability of PFS in the JCA process are unclear and the standalone value is not explicitly recognised
- Explicitly **recognising the standalone value of non-OS endpoints and PROs beyond OS** in oncology is critical in order to expedite access to medicines which provide benefits of high importance to patients beyond survival (e.g., quality of life) and to optimise patient outcomes

> *"It is **important to look at a variety of endpoints** when deciding treatment for the patient. It's not only just about the tumour size but also the **patient's quality of life**, which they can report via PROs"*
>
> *Clinician, United Kingdom*

4. The value of non-OS endpoints and PROs

- Non-OS endpoints and PROs provide the opportunity to reflect broader patient health priorities beyond survival

	Patient reported outcomes (PROs)	Delay to progression / recurrence (PFS, DFS)	Better tumour response (pCR, MRD)
	Patient reported outcomes directly capture outcomes relating to the patients' quality of survival	Disease progression can be associated with an increase in patient symptoms and may reflect morbidity and QoL; it will also trigger subsequent therapies	Achieving a better response can be prognostic of a delay in progression and can have ongoing implications on a patient's treatment journey
Value beyond survival	Reduced symptoms	Reduced symptoms	Reduced symptoms
	Improved QoL	Improved QoL	Improved QoL
	Improved function	Improved function	Improved function
	Reduced side effects	Benefit from future innovation	Benefit from future innovation
		Avoid/delay future treatment burden	Avoid/delay future treatment burden

Source: Fameli et al.(2023); Delgado et al. (2021); Harbeck et al. (2021); Gulla et al. (2020)

Direct measure
Indirect measure

Conclusions

More guidance on the use of non-OS endpoints and PROs as surrogates is needed, including more detailed use cases and clearer conclusions on the validity of specific endpoints. Further, the guideline does not explicitly recognise the standalone value of non-OS endpoints and PROs.

One size may not fit all, and new approaches may be needed to ensure patients get access to life-extending or life-improving drugs in a timely way.

Member States (MS) can specify outcomes beyond OS in the JCA through the PICO (Population, Intervention, Comparison, Outcomes) process, capturing the comprehensive value of novel therapies and ensuring optimal patient outcomes.

As MS have the ultimate responsibility for choosing relevant endpoints per treatment setting, there is potential for greater recognition of non-OS endpoints at both the JCA level (through PICO) and in final HTA decision-making at the national level.

Find out more on surrogate endpoints from our ISPOR supplement article

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Prepared for the ISPOR Europe Conference 2023

**Overall survival (OS), Disease-free survival (DFS), Event-free survival (EFS), Health-related quality of life (HRQoL), Patient-reported outcome (PRO), Patient reported outcome measure (PROM), Progression-free survival (PFS), Population, Intervention, Comparison, Outcomes (PICO)*