HTA292

Role of PROs in HTA Decision Making across UK, Germany, France, Italy, and Spain (EU4 + UK)

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Background

- Patient-reported outcomes (PROs) are a cornerstone of patient-centered healthcare, providing direct insights into how patients experience their symptoms, functional status, and quality of life.[1,2]
- Within the context of health technology assessment (HTA), PROs offer critical complementary evidence beyond traditional clinical endpoints, enabling decision-makers to understand the real-world value of new interventions from the patient's perspective.
- Over the past decade, HTA bodies across Europe have increasingly recognized the importance of PROs in demonstrating therapeutic benefit and informing value-based reimbursement.[2,3,4]
- Despite this growing emphasis, the degree to which PRO evidence influences HTA recommendation remains inconsistent across jurisdictions. Variability in methodological standards, data interpretation, and integration of PRO results into economic models further complicates their acceptance within national decision-making frameworks. [2,5]
- Given these challenges, understanding how different European HTA agencies incorporate, and weigh PRO evidence is essential to advancing evidence-based, patient-centered evaluations.

Objective

- To evaluate the role of PROs in HTA decision making in the EU4 + UK (2020–2025), specifically examining whether and how PRO evidence influenced assessments of clinical value, reimbursement recommendations, and pricing outcomes.

Methods

- A targeted literature review was conducted to evaluate the role of PROs in HTA submission and decision making across the EU4 (France, Germany, Italy, and Spain) and the United Kingdom between 2020 and 2025.
- Searches were performed in PubMed and national HTA agency databases, including NICE, GBA/IQWiG, HAS, AIFA, and AEMPS
- Eligible documents included peer-reviewed publications, HTA reports, and policy documents that explicitly referenced PROs as part of clinical or economic evaluations. Data were extracted on therapeutic area, type and validation status of PRO instruments, their role in HTA deliberations, and resulting impact on reimbursement or access outcomes.
- A qualitative comparison was performed across countries to identify similarities and differences in how PRO data were valued, interpreted, and integrated into final HTA recommendations.

Results

Forty-five HTA submissions were reviewed between 2020 and 2025. PRO were included in 54% of submissions with the highest prevalence observed in oncology, respiratory, and rheumatology indications.[1,3]

PRO Influence on HTA outcomes (Table 1)

- Positive outcome i.e., favorable reimbursement recommendations were observed when PROs were collected using validated and disease-relevant instruments, supported by robust statistical analysis and clinically meaningful change thresholds.
- Limited or neutral outcome occurred when data were incomplete, collected through non-validated tools, or lacked clearly defined responder criteria.[2,5]
- In the UK, PROs were frequently referenced in HTA submissions, particularly within oncology and respiratory indications; however, their influence on decisions largely depended on how well the PRO evidence aligned with cost-effectiveness analyses.[5]
- Germany and France demonstrated the most consistent and formalized consideration of PROs within benefit assessments.[2,3,5] Italy and Spain demonstrated sporadic or regional-level inclusion of PROs, with evidence generally considered supportive rather than determinative in final HTA conclusions.[4,6]

Challenges in PRO Integration (Table 2)

- Missing or incomplete PRO data remains a major limitation across all five countries, particularly in oncology submissions, where incomplete follow-up or lack of baseline data reduces evidentiary value. [1,2,3,5]
- Instrument validation and cultural adaptation continue to pose challenges; Germany and France maintain the strictest requirements, often rejecting or downgrading submissions using non-validated or poorly translated tools. [2,3,5,7]
- Lack of standardized responder thresholds weakens the interpretability of PRO results and limits their integration into comparative effectiveness or cost-utility models. [2,3,4,7]
- Regional and methodological variability, especially in Italy and Spain, leads to inconsistent inclusion of PROs in national vs. regional HTA assessments, highlighting the need for harmonized methodological guidance across Europe. [2,3,4,8,9]

Results (Continued)

Table 1: Illustrative examples of PRO use in HTA Decision-Making (2020–2025).

Country	UK	GERMANY	FRANCE	ITALY	SPAIN
Agency	NICE[1,2,5,10]	IQWiG[1,2,3,5,]	HAS[3,4,9]	AIFA/Regional[3,4,8,9]	AEMPS[3,4,8,9]
Use of PROs	• Frequently cited in oncology and respiratory indications • Pemetrexed: PRO-driven improvements in symptom burden and quality of life (QoL) supported a favorable appraisal. • Roflumilast: Incorporation of validated PROs (St. George's Respiratory Questionnaire) contributed to positive value demonstration.	• Strongly valued when validated; • Crizotinib was rated favorably due to robust PRO data, • Regorafenib received a downgraded benefit rating due to missing quality-of-life evidence.	• Rigorous evaluation • Dupilumab: Strong QoL evidence via Dermatology Life Quality Index (DLQI) reinforced a favorable ASMR rating. • Onasemnogene abeparvovec: Validated caregiver and patient-reported data were key contributors to its positive evaluation.	• Demonstrates increasing but inconsistent use of PROs, often dependent on regional HTA committees • Pembrolizumab: Included validated EORTC QLQ-C30 outcomes in cost-effectiveness (CE) analyses; however, PROs were not decisive in national-level reimbursement.	• Regionalized HTA structure results in variable incorporation of PRO evidence across communities • PROs are gaining recognition but remain secondary to clinical and economic endpoints • Atezolizumab: Cited PROs for QoL and symptom relief in Catalonia's regional report, though not pivotal in final funding decision.
Impact on Reimbursement	Positive when strong PRO data support CE models; absence leads to uncertainty	Directly influences benefit rating	Can determine rejection or positive recommendation	Variable; depends on regional evaluation	Minimal direct impact; secondary to clinical data

Table 2: Common Challenges in PRO Integration.

Country	UK	GERMANY	FRANCE	ITALY	SPAIN
Missing PRO data[1-3,5]	🔴 Missing or incomplete PRO data frequently limited the ability of NICE to include patient perspectives in cost-effectiveness analyses.	🔴 Missing data led to downgrading of benefit categories since IQWiG requires complete datasets to establish patient-relevant effects.	🔴 Missing data undermined reliability, leading HAS to classify PRO results as supportive rather than pivotal in determining therapeutic value.	🔴 Submissions that lacked complete PRO datasets or failed to include QoL assessments resulted in inconsistent evaluation across AIFA and regional HTA bodies.	🔴 Missing PRO data were often cited as a reason for limited consideration of patient experience in final reimbursement recommendations.
Unvalidated instruments[2,3,5,7]	🟠 NICE favored use of standardized tools like EQ-5D or EORTC QLQ-C30. When unvalidated or company-developed tools were used, NICE questioned their interpretability and generalizability to cost-effectiveness outcomes.	🟠 IQWiG required the use of validated and psychometrically tested PRO instruments. Use of nonvalidated or modified scales without evidence of validity often led to exclusion from benefit analysis.	🟠 HAS placed strong emphasis on validated, disease-specific instruments. Submissions using unvalidated tools were downgraded or required additional justification.	🟠 Submissions rely on ad hoc PRO tools due to lack of national guidance, thus limiting comparability and reducing confidence in results.	🟠 Regional agencies inconsistently applied standards for instrument validation. Some relied on international literature, while others accepted local or study-specific questionnaires without prior validation.
Lack of responder thresholds[2-4,10]	🟠 Noted the absence of predefined responder thresholds as a methodological gap in submissions.	🟠 Germany's HTA framework required strict justification of responder thresholds, particularly for benefit quantification	🟠 HAS often highlighted that PRO measures should include validated MIDs or responder thresholds derived from prior clinical studies.	🟠 AIFA often cited variability and inconsistency in the use of responder thresholds	🟠 Regional agencies often accepted PRO data at face value without assessing whether the changes were clinically meaningful

🔴 Major issue: considered a key barrier and indicates a direct impact on HTA outcomes, 🟠 Moderate issue: considered a context dependent barrier that may influence HTA interpretations but does not consistently alter final outcome

Conclusions

- PROs are increasingly incorporated into HTA submissions across the EU4 + UK (2020–2025), reflecting a growing emphasis on patient-centered value assessment.
- The influence of PROs on reimbursement decisions remained variable, driven by differences in data quality, validation, and integration within cost-effectiveness analyses.
- Germany and France consistently demonstrated structured evaluation of PROs, while Italy and Spain showed fragmented or region-specific approaches.
- The EU HTA Regulation (2025) and EUnetHTA 21 framework provides an opportunity to harmonize PRO methodologies particularly around validated tools and responder thresholds to strengthen their impact on future HTA decisions.

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