Spain Levelling Up: A Comparison of Spain's New National Health Economic Evaluation Guidelines With Those of England, France, Germany, Italy, Portugal, Sweden, Ireland, Canada, Australia and Japan

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Inizio Advisory

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Background and objectives

- In March 2024, the Spanish Ministry of Health published its first national health economic evaluation (HEE) guideline as part of broader pharmaceutical policy reforms.
- This study compares Spain's new HEE guideline with those from ten countries.

Objective and methods

- Guidelines were compared for population/comparator selection, perspective, analytical approach, utility measurement, discounting, uncertainty analysis and equity considerations.
- Based on Nomoto et al[1], this study has been updated through a targeted literature review and extended through the addition of countries.

Results

- Similarities in HEE parameters between Spain and other countries are presented in the Table below, highlighted through shaded boxes.
- Since 2023, several guidelines have been updated, and the table reflects these updates.
- Spain's guidelines are similar to other HTA countries, with an emphasis on cost utility analysis.
- A unique methodological difference seen in Spain is to mandate HEE model validation by a researcher external to model design and development.
- A formal willingness to pay (WTP) and the exact role of CUA in decision-making in the HTA framework has not yet been formalized.

Item	Spain: MoH[2,3]	England and Wales: NICE[4]	France: HAS[5]	Germany: IQWiG/G-BA[6]	Italy: AIFA[7]	Portugal: INFARMED[8]	Sweden: TLV[9,10]	Ireland: NCPE[11]	Canada: CADTH[12,13]	Australia: PBAC[14]	Japan: C2H[15]
HEE mandatory for HTA	**[Expected] Mandatory** with full EE for medicines providing a substantial additional clinical benefit	**Mandatory**, used to determine entry to national reimbursed drug list	**Mandatory** for ASMR 1-3 and €20million of sales in second full year of marketing across all indications	**Not mandatory** Used to inform price negotiations if standard process has failed (rare cases)	**Mandatory** for TN1 negotiations	**Mandatory,** used to determine entry to national reimbursed drug list and pricing	**Mandatory**, used to determine entry to national reimbursed drug list and pricing	**Mandatory**, if a full EE required used to determine entry to national reimbursed drug list	**Mandatory**, used to provide reimbursement recommendations and review reports participants of the CDA-AMC	**Mandatory**, used to determine entry to national reimbursed drug list	**Mandatory**, used to adjust the price premium after entry to national reimbursed drug list
Population	Licensed indication and population eligible	Licensed indication, defined during scoping phase	All individuals whose health is directly or indirectly affected by the intervention	Licensed indication and population eligible	Population for which reimbursement is requested	Licensed indication, aligned during scoping phase	Population for which reimbursement is requested	Licensed indication and reimbursable population in Ireland, defined at scoping	Licensed indication and eligible population	Population for which reimbursement is requested	Licensed indication
Subgroups considered	Yes – where heterogeneity observed	Yes	Yes – where heterogeneity observed (justification needed)	Yes – determined by the commission	Yes – sensitivity analysis to explore heterogeneity	Yes – where heterogeneity is observed	No specific statement	Yes – prespecified subgroups where heterogeneity is observed	Yes – in scenario analysis	Yes – must be justified	Yes – for differences in outcome, doses, administration methods, comparators
Economic comparator	Standard practice Concurrently, the most efficacious/ effective alternative, the most cost-effective and the lowest-priced alternatives	All clinically relevant comparators defined during the scoping phase	All clinically relevant comparators	Clinically relevant comparator used in the preceding benefit assessment specified by the G-BA	Standard of care in Italy	All clinically relevant technologies; unless most efficient alternative is clearly established most efficient	Most cost-effective of the clinically relevant comparators	Routine care technologies most widely used in clinical practice in Ireland for the target population	Current care in Canada reflecting target population of interest and jurisdiction for decision	Main comparator – therapy or therapies most likely to be replaced	Most commonly used or standard therapy reimbursed by public healthcare insurance, needs to agree with C2H
Accepted analytical techniques[a]	CUA CEA only if CUA not feasible[b]	CUA or CCA	CUA and/or CEA CEA using LY preferably	CEA or CUA	CUA, CEA[b]	CUA preferred, CEA	CUA[b]	CUA preferred CEA as alternative or supplementary	CUA[b]	CUA, CEA[b] Supplementary – CCA or CBA	CEA or CUA[b]
Preferred method to derive utility	EQ-5D and SF-6D with utilities derived from general population	Preference for EQ-5D-5L, but preferred value set is for EQ-5D-3L	EQ-5D and HUI3[c]	TTO, SG, EQ-5D VAS, SF-12, SF-36, HUI2 or HUI3[c] preference for utilities derived by valuations by patients	No specific statement however method of obtaining utilities must be explained in detail[c]	EQ-5D-5L, if not available EQ-5D-3L Other generic preference-based measures require justification	TTO, SG, VAS, EQ-5D Direct valuation preferred over population (e.g., EQ-5D social tariff)	EQ-5D or SF-6D[c]	EQ-5D, HUI, SF-6D	Indirect methods e.g., HUI2 or HUI3, EQ-5D, SF-6D, AQoL and CHU9D for children and adolescents	EQ-5D-5L[c] General population derived utilities using health scenarios and SG, TTO and DCE are acceptable
Perspective	Healthcare system	Healthcare system	Collective perspective	SHI insured community	Healthcare system	Healthcare system	Societal	Healthcare system	Payer (public)	Healthcare system	Payer (public)
Costs to be included	Direct medical and non-medical	Direct medical	Direct medical and non-medical	Direct (medical, non-medical) reimbursable and non-reimbursable	Direct healthcare	Direct medical	Direct, indirect medical and non-medical	Direct medical and social care (HSE only)	Direct medical	Direct medical	Direct medical
WTP	**To be seen**	Formal WTP – Standard: £20,000 – £30,000 per QALY gained Highly HST: £100,000 – £300,000 per QALY gained[g]	No formal WTP	No formal WTP	No formal WTP	No formal WTP	No formal WTP	No formal WTP	No formal WTP	No formal WTP	Formal WTP – Standard products: ¥5 million or less per QALY gained, special consideration: ¥7.5 million or less per QALY gained
Discount rate	After 1 year: 3%	3.5%[d]	2.5%[e]	3%	3%	4%	3%[f]	4%	1.5%[f]	5%[f]	2%[f]
Validation of decision model	Internal and external validity, relevant to Spanish context **External model validation is recommended.**	Internal and external validity	Internal, external, face and cross-validity	External, face, technical and predictive validity	ISPOR best practices recommended and comparison to Italian data	Internal, external and adaptive validity	Internal and external validity	Internal and external validity	Internal, external and face validity	Face validity, computerisation and external validity, other validation techniques encouraged	Internal and external validity
Sensitivity analyses	Univariate and multivariate DSA and PSA	PSA and DSA Scenario analyses	PSA and DSA Scenario analyses	Univariate and multivariate DSA and PSA Scenario analyses	Univariate DSA, PSA Scenario analyses	PSA, EVPI Scenario analyses	Required but not prescribed	Univariate and multivariate PSA Scenario analyses	PSA Scenario analyses	Univariate and multivariate DSA and PSA	PSA when possible Scenario analyses
Equity considerations	In report	QALY weights possible and DCEA considered	None specified	None specified	None specified	None specified	Productivity losses avoided	In report	Report on equity related subgroup variation	None specified	None specified, weighted ICER by subgroup

Discussion and conclusion

- Spain's guideline broadly aligns with international standards and marks a significant step in formally integrating HEE into pharmaceutical decision-making.
- While it remains to be seen whether its publication signals a shift toward greater importance of HEE, it signals a shift toward a more rigorous, value-based environment, challenging therapies with marginal benefit.

Abbreviations

AIFA: Italian Medicines Agency; ASMR: added clinical benefit; CADTH: Canadian Agency for Drugs and Technologies in Health; CBA: Cost Benefit Analysis; CCA: Cost Consequence Analysis; CDA-AMC: Canada's Drug Agency, CEA: Cost-Effectiveness Analysis; CHU9D: Child Health Utility 9 Dimensions; CMA: Cost Minimisation Analysis; CUA: Cost-Utility Analysis; C2H: Core 2 Health, Centre for Outcomes Research; DCE: Discrete Choice Experiment; DCEA: Distributional Cost-Effectiveness Analysis; DSA: Deterministic Sensitivity Analysis; EVPI: Expected Value of Perfect Information EQ-5D: EuroQol 5 Dimensions; EQ-5D-5L: EuroQol 5 Dimensions, 5 Level version; G-BA: Federal Joint Committee, Germany; HAS: French National Authority for Health; HSE: Health Service Executive; HST: Highly Specialised Technologies; HTA: Health Technology Assessment; HUI2: Health Utilities Index Mark 2; HUI3: Health Utilities Index Mark 3; INFARMED: National Authority for Medicines and Health Products; IQWiG: Institute for Quality and Efficiency in Health (Germany); ISPOR: International Society for Pharmacoeconomics and Outcomes Research; LY: Life Years; MoH: Ministry of Health; NCPE: National Centre for Pharmacoeconomics (Ireland); NICE: National Institute for Health and Care Excellence (UK); PBAC: Pharmaceutical Benefits Advisory Committee (Australia); PSA: Probabilistic Sensitivity Analysis; QALY: Quality Adjusted Life Years; SBU: Swedish Agency for Health Technology Assessment and Assessment of Social Services; SG: Standard Gamble; SHI: Social Health Insured; SF-6D: Short Form 6 Dimensions; TLV: Swedish Dental and Pharmaceutical Benefits Agency; TN1: Italian procedure for new medicines; TTO: Time Trade-Off; VAS: Visual Analogue Scale; WTP: Willingness to Pay

Notes

[a] CUA, cost utility analysis measured as Δcosts/ΔQALYs where QALYs derived using HRQoL, CEA, cost effectiveness analysis measured as Δcosts/Δdifference in health outcome, shading represents preference for CUA, [b] CMA accepted in certain situations, [c] Preference for local data, [d] Rate is 2.5% for time horizons less than 30 years, after 30 years it reduces to 1.5%, [e]Alternative rate of 1.5 % for specific circumstance; technology for people who would otherwise die or have a very severely impaired life, it is likely to restore them to full or near-full health, benefits are likely to be sustained over a very long period, [f] sensitivity analysis requested, [g] effective threshold based on QALY weighting

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