The Landscape of Current Policy and Health Authority Positions on Intermediate End Points for Clinical Outcomes in Oncology

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Conflict of Interest Statement

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Guidance on IE Validation and Usage Is Often Lacking

- Increasing numbers of new drugs and biologics have been approved by the FDA and the EMA based on intermediate end points (IEs), or surrogate end points
  - IEs, such as progression-free survival, metastasis-free survival, and event-free survival, enable earlier assessment of treatment benefits than clinical end points, such as overall survival
- IEs can reduce required sample sizes, trial duration, and costs, and can enable early decision-making; however, regulatory bodies and HTA agencies are often cautious when evaluating IEs, and guidance is often unclear or nonspecific
- Objective: In this analysis, we reviewed documents from regulatory bodies, HTA agencies, payers, and other policy-makers for IEs in oncology to assess the current landscape of guidance for IE validation

EMA, European Medicines Agency; FDA, US Food and Drug Administration; HTA, health technology assessment; IE, intermediate end point.

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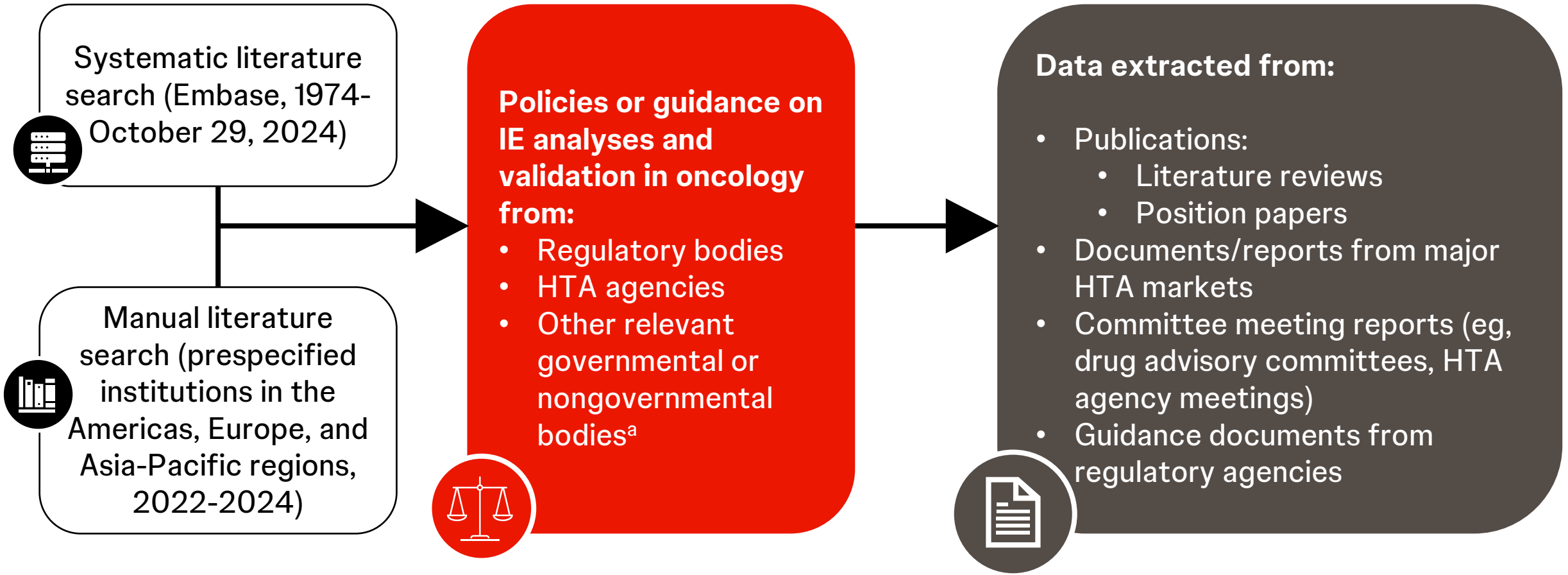
Methods



- Relevant documents related to any cancer type were included

[a]Includes research and funding agencies and organizations that provide recommendations and determine policy for multiple countries.
Due to variation in the use of terms such as "surrogate end points/outcomes/markers" and "intermediate outcomes/end points," we have used the term "intermediate end point" throughout our analysis where possible to maintain consistency.

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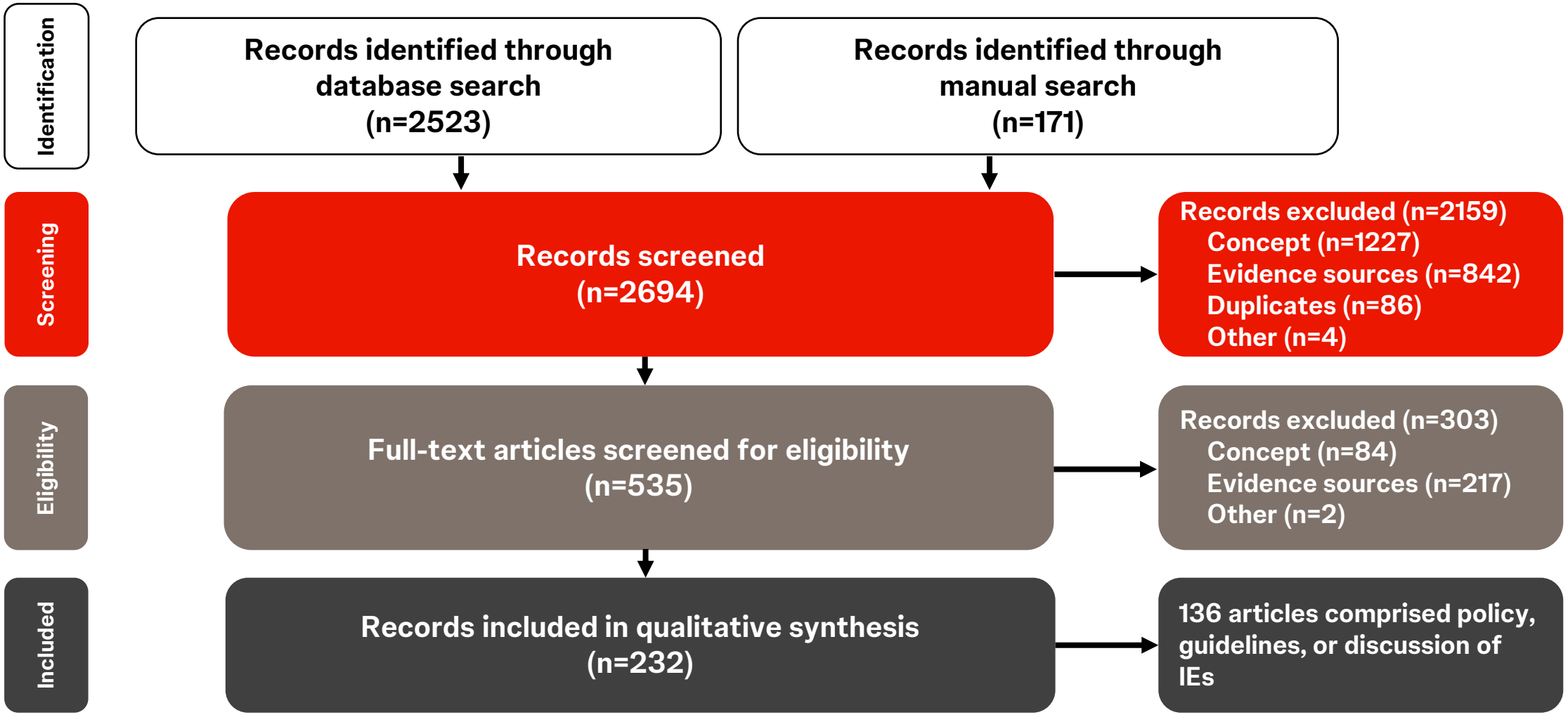
A Total of 136 Records From 44 Institutions Were Included in the Analysis



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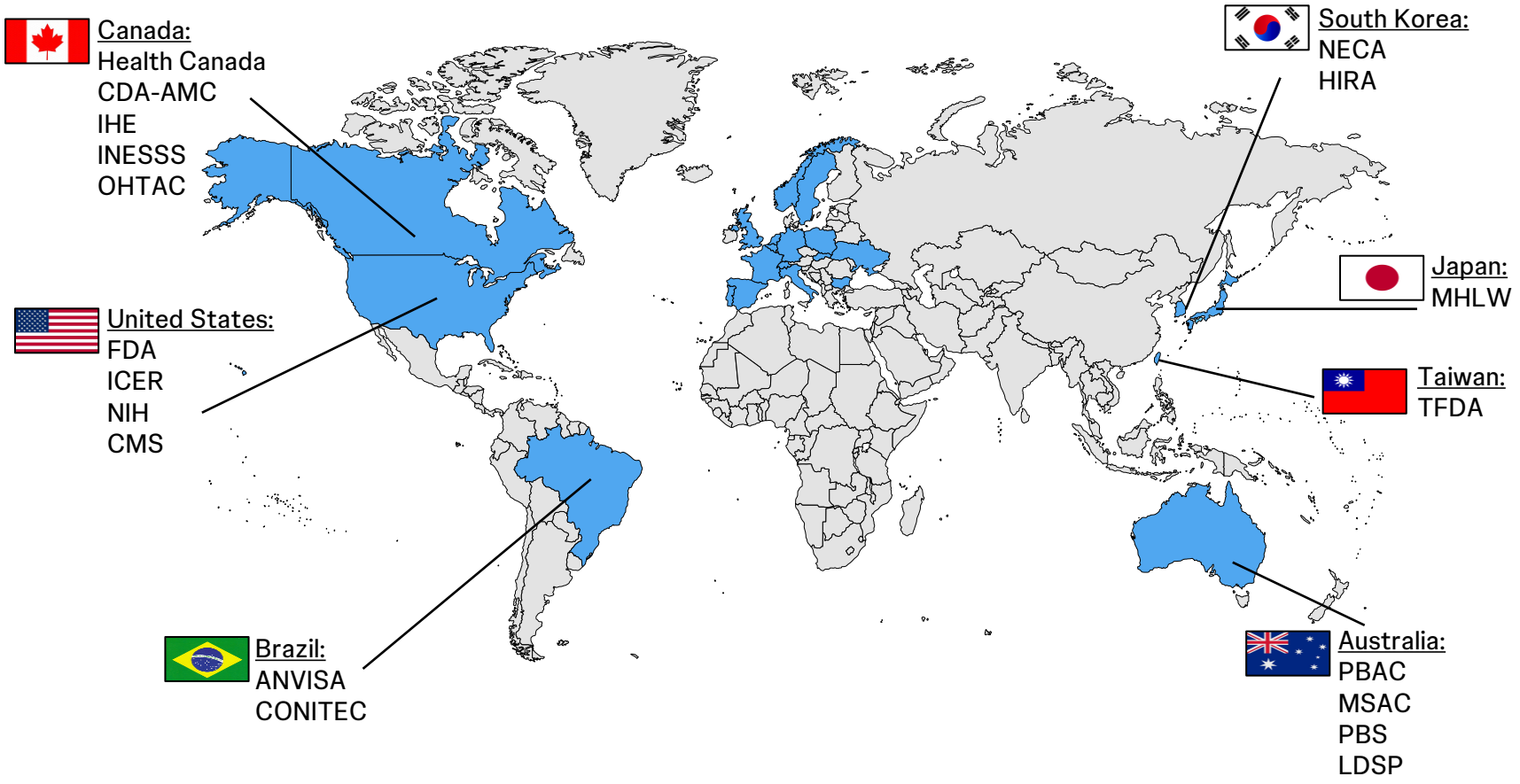
Guidance Documents That Refer to the Use of IEs Were Identified From 44 Institutions, Comprising 22 Countries/Regions



Europe:
EMA
European Commission
EUnetHTA

Austria:
AIHTA

Belgium:
KCE

Bulgaria:
NCPHA

France:
HAS

Germany:
IQWiG
BfArM

Italy:
AIFA

Norway:
NIPH-FHI

Poland:
AOTMiT

Portugal:
INFARMED

Slovak Republic:
MZSR

Spain:
AETS
AETSA
AVALIA-T
IACS

Sweden:
SBU
TLV

The Netherlands:
ZIN

UK:
MHRA
NICE
SMC
AWTTC

EMA and the European Commission include all countries in the EU. EUnetHTA includes all countries in the EU and Norway, Switzerland, Ukraine, and the UK.
AETS, Health Technology Assessment Agency; AETSA, Andalusian Agency for Health Technology Assessment; AIFA, Italian Medicines Agency; AIHTA, Austrian Institute for Health Technology Assessment; ANVISA, Brazilian Health Regulatory Agency; AOTMiT, Agency for Health Technology Assessment and Tariff System; AVALIA-T, Galician Health Technology Assessment Agency; AWTTC, All Wales Therapeutics and Toxicology Centre; BfArM, Federal Institute for Drugs and Medical Devices; CDA-AMC, Canada's Drug Agency; CMS, Centers for Medicare and Medicaid Services; CONITEC, National Committee for Health Technology Incorporation; EUnetHTA, European Network for Health Technology Assessment; HAS, French Health Authority; HIRA, Health Insurance Review and Assessment Service; IACS, Aragon Health Sciences Institute; ICER, Institute for Clinical and Economic Review; IHE, Institute of Health Economics; INESSS, Institut National d'Excellence en Santé et en Services Sociaux; INFARMED, National Authority of Medicines and Health Products; IQWiG, Institute for Quality and Efficiency in Health Care; KCE, Belgian Federal Health Care Knowledge Centre; LSDP, Life Saving Drugs Program; MHLW, Ministry of Health, Labour and Welfare of Japan; MHRA, Medicines and Healthcare Products Regulatory Agency; MZSR, Ministry of Health of the Slovak Republic; MSAC, Medical Services Advisory Committee; NCPHA, National Centre of Public Health Protection; NECA, National Evidence-based healthcare Collaborating Agency; NICE, National Institute for Health Care and Excellence; NIH, National Institutes of Health; NIPH-FHI, The Norwegian Institute of Public Health; OHTAC, Ontario Health Technology Advisory Committee; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme; SBU, Swedish Agency for Health Technology Assessment and Assessment of Social Services; SMC, Scottish Medicines Consortium; TFDA, Taiwan Food and Drug Administration; TLV, Dental and Pharmaceutical Benefits Agency; ZIN, National Health Care Institute.

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Regulatory Bodies: Lack of Detailed Guidance on Preferred Methods for IE Validation

Brazil
ANVISA

Cancer (unspecified)

4-level hierarchy of clinical evidence:

1. Direct measure of benefit indicated by a non-IE
2. Validated IE
3. IE not validated but "reasonably capable" of indicating clinical benefit
4. Correlation only measures biological activity

IE validation using meta-analysis requires demonstration of correlation with expected clinical benefit

Canada
Health Canada

Serious/life-threatening diseases

IEs "reasonably likely" to predict drug effect on recognized outcomes like morbidity and mortality, judged on well-controlled and conducted clinical trials

Europe
EMA

Cancer (unspecified)

- IEs considered "less convincing" unless delays in progression are likely to favorably affect OS or QOL
- If IEs are used as primary end points, OS should be a secondary end point and no negative OS effect observed

Japan
MHLW

Cancer (unspecified)

- No specific guidance
- IEs may be accepted in conditional approval

Taiwan
TFDA

Serious/life-threatening diseases

Demonstrated effect on IE should be "reasonably likely" to predict clinical benefit

UK
MHRA

Disease type unspecified

- No specific guidance
- IE identification and validation are key priorities

US
FDA

Disease type unspecified

IE validation requires clear mechanistic rationale and clinical data with "strong" evidence that IE predicts clinical benefit

OS, overall survival; QOL, quality of life.

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HTA Agencies: Two Provide Detailed Validation Methodology and Correlation Thresholds

Germany
IQWiG

Cancer (unspecified)

- IE validity is determined by both level of reliability of the validation study and defined thresholds of R values; high correlation, lower limit of 95% CI ≥0.85; low correlation, upper limit of 95% CI ≤0.75
- Provides algorithms accounting for surrogate threshold effect in cases of high, moderate, and limited reliability of validation study. Both IE and clinical end point must have been analyzed in the validation studies used to establish surrogacy

Portugal
INFARMED

Disease type unspecified

3-level IE validation framework:

1. Relationship between treatment effect on IE and clinical outcome, preferably via randomized clinical study
2. Strong correlation between IE and clinical outcome at individual patient level
3. Biological plausibility between IE and clinical outcome

Cites IQWiG correlation thresholds and adapts IQWiG validation methodology. Provides algorithms for determining IE validity in cases of high and moderate quality

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HTA Agencies: NICE Endorses Multivariate Analysis Within a Bayesian Framework for Validation

UK
NICE

Disease type unspecified

- IE validity based on biologic plausibility and bivariate meta-analytic methods using a Bayesian approach. Prediction interval-based criterion: ≥95% of study's treatment effect for true outcome should fall within 95% prediction interval of model-predicted treatment effect
- Uncertainty of association between IE and final outcome to be assessed in probabilistic sensitivity analysis

Austria:
AIHTA

Australia:
PBAC
MSAC

Belgium:
KCE

Brazil:
CONITEC

Bulgaria:
NCPHA

Canada:
CDA-AMC
IHE
INESSS
OHTAC

France:
HAS

Italy:
AIFA

Norway:
NIPH-FHI

Poland:
AOTMiT

Slovak Republic:
MZSR

South Korea:
NECA

Spain:
AETS
AETSA
AVALIA-T
IACS

Sweden:
SBU
TLV

The Netherlands:
ZIN

UK:
SMC
AWTTC

United States:
ICER

[a]Among workshop participants.

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Payer Organizations: Differing Views on IE Use

Australia
LSDP

Rare and life-threatening diseases

Refers to PBAC guidelines for justification of IE use; where data are insufficient, biological plausibility should be addressed at minimum

Australia
PBS

Disease type unspecified

Refers to PBAC guidelines on IE justification to inform decisions on listing of drugs for subsidization

South Korea
HIRA

Disease type unspecified

Recommends use of “final intended outcomes” over IEs

US
CMS

Disease type unspecified

- IEs must be supported through validation studies published in peer-reviewed journals
- Validation studies should be longitudinal and demonstrate statistical association with outcome of interest

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Other Institutions: No Current "Gold Standard" for IE Validation

Europe
European Commission and EUnetHTA

Disease type unspecified

3 levels of evidence for surrogacy:

1. Clinical trial evidence (treatment effect on IE correlates with effect on patient-relevant outcome), meta-analysis of randomized clinical trials
2. Evidence from interventional, epidemiological, or observational studies showing association of IE with patient-relevant outcome
3. Biologically plausible relationship between IE and final outcome

Correlation threshold (European Commission): ≥0.85

Correlation threshold (EUnetHTA): 0.85-0.95

Germany
BfArM

Disease type unspecified

Criteria include:

- Biological plausibility
- Magnitude of association between IE and relevant end point
- Evidence from randomized clinical trials

Meta-analysis is preferable to single studies

US
NIH

Disease type unspecified

Preference for meta-analytic approaches for IE validation[a]

[a]Among workshop participants.

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Four Organizations Provide Specific Correlation Thresholds for IE Validation

Europe + Other Countries	**EUnetHTA** Other Institution	• Correlation ≥0.85, among other approaches
Europe	**European Commission** Other Institution	• Correlation between 0.85 and 0.95, although other approaches can be considered
Germany	**IQWiG** HTA Agency	• High correlation[a]: Lower limit of 95% CI for R value ≥0.85 • Unclear validity: 95% CI values overlap interval of 0.7-0.85[b] • Weak correlation: Upper limit of 95% CI for R value ≤0.7
Portugal	**INFARMED** HTA Agency	• High correlation[a]: Lower limit of 95% CI for R value ≥0.85 • Unclear validity: 95% CI values overlap interval of 0.7-0.85[b] • Weak correlation: Upper limit of 95% CI for R value ≤0.7

EUnetHTA and the European Commission indicate R ≥0.85 as thresholds for IE validation, while IQWiG and INFARMED indicate that the lower 95% CI value of R should be ≥0.85

The European Commission includes all countries in the EU. EUnetHTA includes all countries in the EU and Norway, Switzerland, Ukraine, and the UK.
[a]Valid if validation study has high reliability. [b]Or limited to moderate reliability and lower limit of 95% CI for R value ≥0.85.

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Conclusions

- Detailed guidance on IE validation is lacking across most regulatory bodies, HTA agencies, payers, and other institutions, and most guidance is not disease specific. A minority of HTA agencies provide more comprehensive validation frameworks
- Many organizations only provide limited validation criteria, and most do not provide correlation thresholds. When thresholds are provided, they are often stringent
- It is crucial to align on robust validation approaches, including correlation thresholds, that account for tumor type and disease context to enhance the decision-making processes of the organizations responsible for the approval of new treatments and improve clinical development processes

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