Patient Experience in Health Technology Assessment: Landscape Assessment and Comparison of Health Technology Assessment Guidance on Patient-reported Outcome Measures, with a Review of HTA Appraisals in Multiple Myeloma

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Background

- Data regarding patients' treatment experience, patient-reported health status and symptoms are necessary during drug development and medical decision-making. 1-3
- PROMs are questionnaires designed to collect health outcomes data directly from patients.^{1,4-7}
- Generic PROMs capture data for non-disease-specific health aspects (e.g., HRQoL, functioning), whereas disease-specific PROMs capture patients' experience with a specific condition and disease-specific symptoms. 1,7
- Regulatory bodies provide guidance regarding the inclusion of PROMs in clinical trials,^{5,6,8,9} yet guidance from HTA agencies on their use in the context of reimbursement assessments is lacking and inconsistent.
- This landscape assessment summarizes guidance on PROMs across HTA agencies globally, and describes observed practical acceptability, use, and impact of PROMs in HTA appraisals for MM as a case study.

Methods

• A comprehensive TLR (Figures 1 and 2) was conducted per PRISMA and Cochrane Reviews standards, 10,11 as applicable.

Figure 1. Study design – TLR approach

1. Document identification

Searched websites of 15 HTA agencies (Dec 2023), identifying HTA guidance and product reports

2. Document selection

Documents mentioning PROMs: 1. HTA methods guidance 2. HTA appraisals/summaries

for MM products

HTA guidances extracted. informing extraction sheets for HTA appraisals

3. Data extraction

HTA appraisals extracted

Summarized PRO-related findings, overall and by country:

1. HTA methods guidance 2. MM product HTA appraisals

4. Reporting

Results

Overview of included evidence

• The search identified 1,689 HTA methods guidance and 1,945 MM HTA appraisal records; of these, 22 HTA guidance documents (12 organizations) and 116 MM product HTA appraisals (10 organizations) mentioned PROMs (Figure 2).

Figure 2. HTA guidances^a and appraisals by country/region

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	Australia PBAC	Brazil CONITEC ^b	Canada CDA-AMC	China CNHDRC°	England NICE	EU EUnetHTA	France HAS	Germany G-BA; IQWiG	Italy Agenas; AIFA	Japan C2H	Scotland SMC	Spain AETS	US ICER ^d
HTA Guidance Documents	1	0	1	0	3	3	2	2	1	1	4	2	2
HTA Appraisals in MM	4	6	16	0	12	0	12	48	0	1	15	0	2

Note: Most documents were from German (G-BA and IQWiG; n = 50), Canadian (CDA-AMC; n = 17), and Scottish (SMC; n = 19) HTA agencies. ^aSome guidance documents included multiple files (e.g., dossier template, instructions for manufacturers). ^bAlthough Brazilian HTA agencies have not published guidance on PRO data, the Ministry of Health has released guidance on utility measures for economic analyses. The CNHDRC did not provide publicly available information.

dICER is a non-profit organization but is referred to hereafter as an HTA agency for ease of reporting, with ICER reports referred to as "assessments".

Review of HTA methods guidance documents

• Most agencies emphasized the importance of using validated PROMs, but guidance on the collection and use of PRO data in HTA submissions varied (Figure 3).

Figure 3. Key findings from the review of HTA methods guidance documents (12 HTA agencies, 10 countries/regions)

Data sources Strong preference for head-to-head comparisons with double-blind RCTs

- Open-label design should be avoided Some agencies may consider PRO data derived from ITCs, non-randomized studies, and/or published literature, in the absence of RCT data
- High-quality RWE studies can also be considered, mainly by NICE and ICER

Data type and analysis

- In HTA processes with cost-effectiveness modeling frameworks (most agencies):
- EQ-5D (or other generic PROM) preferred to derive preference-based health utility; if no EQ-5D, use mapping algorithms to derive utilities

In HTA processes only based on clinical

- comparative effectiveness (e.g., German agencies and EUnetHTA [for the upcoming EU JCA]): - Prioritize disease-specific tools to
- assess treatment impact on patients

PROM descriptions

- HTA agencies (particularly EUnetHTA for the upcoming EU JCA) require sufficient details on PROMs used:
- Concept, sources, measure, timing, observation period, summary and effect measures, psychometric properties
- These characteristics help demonstrate that PROMs are scientifically sound and sensitive to detect clinically meaningful treatment-related changes in the condition

Key findings from the HTA methods guidance review

Interpretability Responder analyses should consider established MIDs to assign qualitative meaning to quantitative scores (e.g., pre-

defined thresholds for patient categories) EUnetHTA and German HTA agencies advocate for both anchor-based and distribution-based methodsa to determine clinical MIDs

Reporting

- Manufacturers were required to provide information on the data sources, PROMs used, PRO definitions, baseline values missing data, and analysis methods to enable independent external assessment
- The G-BA (Germany) also requires potential bias in results to be sufficiently explored and reported

^aAnchor-based methods relate PROM changes to an external criterion, whereas distribution-based methods consider the statistical properties (e.g., standard deviation, standard error).

Review of HTA appraisals in MM

- HTA agencies differed in the way they assessed and interpreted the submitted PRO data for decision making (Figure 4). Limited information in the published HTA appraisal documents precluded any direct conclusion about the isolated impact of PRO data on final reimbursement decisions.
- Disease-specific PROMs were the most used PROMs across HTA submissions, followed by the generic EQ-5D (Figure 5).
- Examples of country-specific findings from the review of MM HTA appraisals in France and Germany indicated that disease-specific PROMs were the most common and suboptimal study design and data collection methods contributed to uncertainty/inconclusiveness of results. Although PRO data was found to impact decision-making, the extent of the impact was unclear (Figure 6).

Figure 4. Key findings from the review of HTA appraisals in MM (116 appraisals, 10 HTA agencies)

Data sources

- Pivotal trials or published literature were the most common PRO data sources; all appraisals had RCT data
- · The use of data with older cut-off dates was critiqued by HTA agencies when more recent data were available
- <50% of appraisals from each country reported PRO data from open-label studies

Data type

- The EQ-5D VAS (n = 46, 40%) and EQ-5D (n = 45, 39%) were the most frequently used generic PROMs
- The EORTC QLQ-C30 (n = 109, 94%) and QLQ-MY20 (n = 52, 45%) were the most frequently used disease-specific **PROMs**

Psychometric characteristics

- Limited reporting of psychometric characteristics (e.g., reliability, validity) of PROMs was a common critique across HTA agencies
 - Only available in 4 appraisals from
 - Canada and 4 from Germany - The lack of available information may be due to the summary format of the appraisals from many agencies

Key findings from the review of HTA appraisals in MM

Interpretability

- One of the challenges of interpreting PRO data for use in cost-effectiveness and cost-utility analyses was the uncertainty of whether differences in PROM scores between treatment groups were clinically meaningful
- Limited information was available on established MIDs for any PROM across HTA agencies, except for German, Canadian, and English HTAs (may be available in full submission dossiers that are not publicly available)

Reporting

- Overall, details regarding PROMs were limited and clarity around PRO data was lacking in HTA appraisal summaries (full submission dossiers not publicly available)
- Appraisals from the German and English HTA agencies were exceptions, as detailed information (e.g., use of country-specific population data sets, hierarchy of evidence generation, handling of reporting bias) was outlined in appraisal reports

Impact on HTA decision

PROMs/PRO data were deemed

- important by all HTA agencies; most noted that PRO data would not lead to negative recommendations but would generate constructive critique
- Overall, evidence was limited for how PRO data influenced reimbursement decisions - In two German HTAs (2 drugs), a minor added benefit rating was granted based on statistically significant PRO differences between treatment arms despite no statistically significant survival benefit

EMA. Appendix 2 to the Guideline on the Evaluation of Anticancer Medicinal Products

in Man: The Use of Patient-Reported Outcome Measures in Oncology Studies. 2016.

U.S. FDA. Core Patient-Reported Outcomes in Cancer Clinical Trials: Guidance for

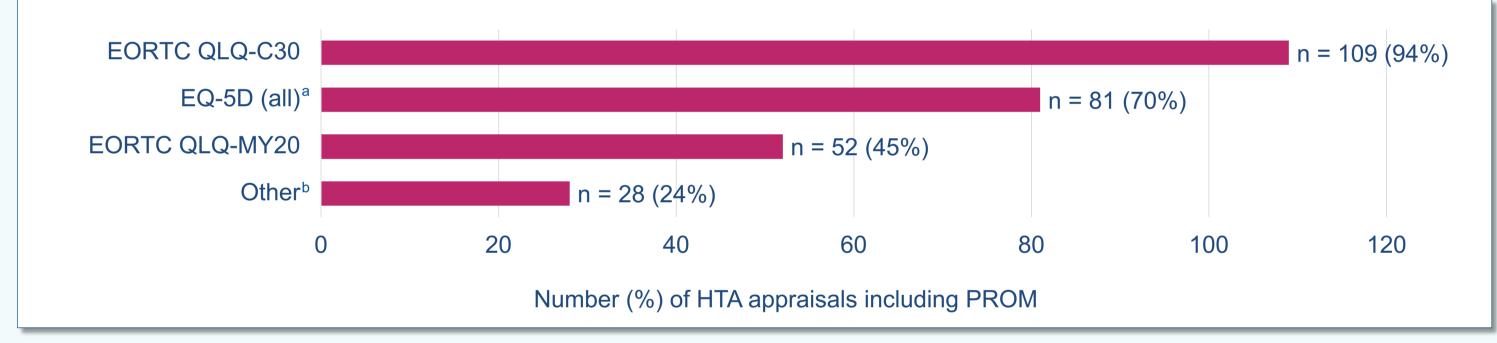
12. Brazilian Ministry of Health. Methodological guidelines: Economic evaluation guideline

11. Cochrane. Cochrane Handbook for Systematic Reviews of Interventions. 2023

13. EU Member State Coordination Group on HTA. Guidance on Outcomes for Joint

14. EUnetHTA. Endpoints Used for Relative Effectiveness Assessment: Health-related

Figure 5. Distribution of PROMs across HTA appraisals in MM with PRO data (N = 116)



^aEQ-5D (all) includes all encountered variations/versions (3L/5L/unspecified only [n = 35], VAS only [n = 36], or both [n = 10; 1 of which included HSUV]). ^bOther PROMs include: OSDI, CTSQ, PGIC, FACT (all subscales), PGIS, EORTC QLQ-CIPN20, MDASI-MM, BPI-SF, FACT/GOG-Ntx; the reported value is the total of each of these individual PROMs.

Figure 6. Summary of findings from the review of MM HTA appraisals in France and Germany

Summary of manufacturer Agency critiques Impact on decision-making submissions / appraisals Only appraisal summary documents · In many instances, HAS could not draw The absence of PRO data from were publicly available, limiting conclusions on HRQoL data because validated PROMs and adjusted to information on PROs the endpoint was exploratory in the the population of interest may have a **France** clinical trial, the data were obtained negative impact on drug evaluations, EORTC QLQ-C30 was mentioned in all (HAS) especially for chronic and/or disabling from a non-comparative study, or the but one appraisal N = 12illnesses or end-of-life situations study had an open-label design All submissions had detailed information Open-label study design, variable data In two G-BA appraisals, improved on PROMs/PRO data; this was unique collection across study arms, and high HRQoL led to a minor added treatment to Germany and a result of the detailed benefit and positively impacted the Germany missing data rates contributed to (G-BA/ guidance/framework uncertainty in the PRO results; decision despite no significant overall survival benefit; this was unique versus responder analyses based on MIDs **IQWiG**) EORTC QLQ-C30 and QLQ-MY20 were preferred over analyses of other G-BA submissions and other N = 48were the most frequently used PROMs HTA agencies mean/median differences with psychometric characteristics available in some cases Multiple submissions showed statistically significant differences in PROs between treatments, but their impact on the added benefit rating could not be consistently determined

Industry, 2021.

(second edition). 2009.

Clinical Assessments. 2024.

10. Page MJ, et al. *PLoS Med.* 2021;18(3):e1003583

Quality of Life and Utility Measures. 2015.

Limitations

- This TLR was limited to publicly available records, which were sometimes redacted or presented in summarized formats.
- HTA guidance documents may not be available from a centralized HTA agency in some jurisdictions, but rather from other government/non-governmental organizations or from decentralized regional/national agencies (e.g., in Italy and Spain).
- Future updates to this review are warranted as new information becomes available.

Discussion

Variation in approaches of HTA agencies

- Despite the recognized importance of PROs in HTAs and the substantial increase in their inclusion in MM HTA submissions over time, there remains considerable variability and lack of clarity in PROM methods guidance across HTA agencies.
- No oncology-specific HTA guidance on PROMs was identified.

Generic versus disease-specific PROMs

- Generic PROMs (e.g., EQ-5D) are preferred for health utility inputs in economic models, while disease-specific PROMs (e.g., EORTC QLQ-MY20) are vital for capturing specific PRO improvements in benefit-risk assessments in a given indication.
- The acceptability of PROMs is influenced by the evidence base provided to justify their selection, which is largely underreported in manufacturer submissions.

Impact on decision-making

• The impact of PRO data on decision-making varies among HTA agencies and is difficult to determine in isolation, as it is often overshadowed by mortality, morbidity, and cost-effectiveness data.

Need for harmonization and further research

- Efforts by the EU Member State Coordination Group on HTA¹³ and EUnetHTA^{7,14} have helped to clarify minimum reporting requirements for PROMs from the HTA perspective.
- Nonetheless, additional clarity and transparency are required to facilitate standardization and harmonization of PROM preferences and PRO data collection, analysis, and interpretation expectations across HTA agencies globally, with the goal of optimizing integration of the patient experience in HTA decision-making.

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Abbreviations

AETS, Agencia de Evaluación de Tecnologias; Agenas, Italian National Agency for Regional Healthcare Services; AIFA, Italian Medicines Agency; BPI-SF, brief pain inventory short form; C2H, Center For Outcomes Research and Economic Evaluation for Health; CDA-AMC, Canada's Drug Agency; CNHDRC, China National Health Development Research Center; CONITEC, National Committee for Health Technology Incorporation; CTSQ, Cancer Therapy Satisfaction Questionnaire; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D, EuroQol-5 dimension; EU, European Union; EUnetHTA, European Union Network for Health Technology Assessment; FACT, Functional Assessment of Cancer Therapy; G-BA, Federal Joint Committee; GOG-Ntx, Gynecologic Oncology Group-Neurotoxicity; HAS, Haute Autorité de Santé; HRQoL, health-related quality of life; HSUV, health state utility values; HTA, health technology assessment; ICER, Institute for Clinical and Economic Review; IQWiG, Institute for Quality and Efficiency in Health Care; ITC, indirect treatment comparison; JCA, joint clinical assessment; MDASI-MM, MD Anderson Symptom Inventory for multiple myeloma; MID, minimally important difference; MM, multiple myeloma; NICE, National Institute for Health and Care Excellence; OSDI, Ocular Surface Disease Index; PBAC, Pharmaceutical Benefits Advisory Committee; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PRO, patient-reported outcome; PROM, patient-reported outcome measure; QLQ-C30, Quality of Life questionnaire – Core 30; QLQ-CIPN20, Quality of Life questionnaire – chemotherapy-induced peripheral neuropathy, 20 items; QLQ-MY20, Quality of Life questionnaire – Multiple

Myeloma module; RCT, randomized controlled trial; RWE, real-world evidence; SMC, Scottish Medicines Consortium; TLR, targeted literature review; VAS, visual analog scale.

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