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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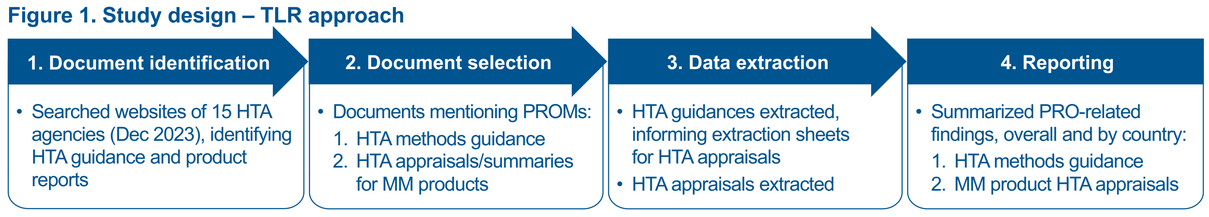
Background

- 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



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

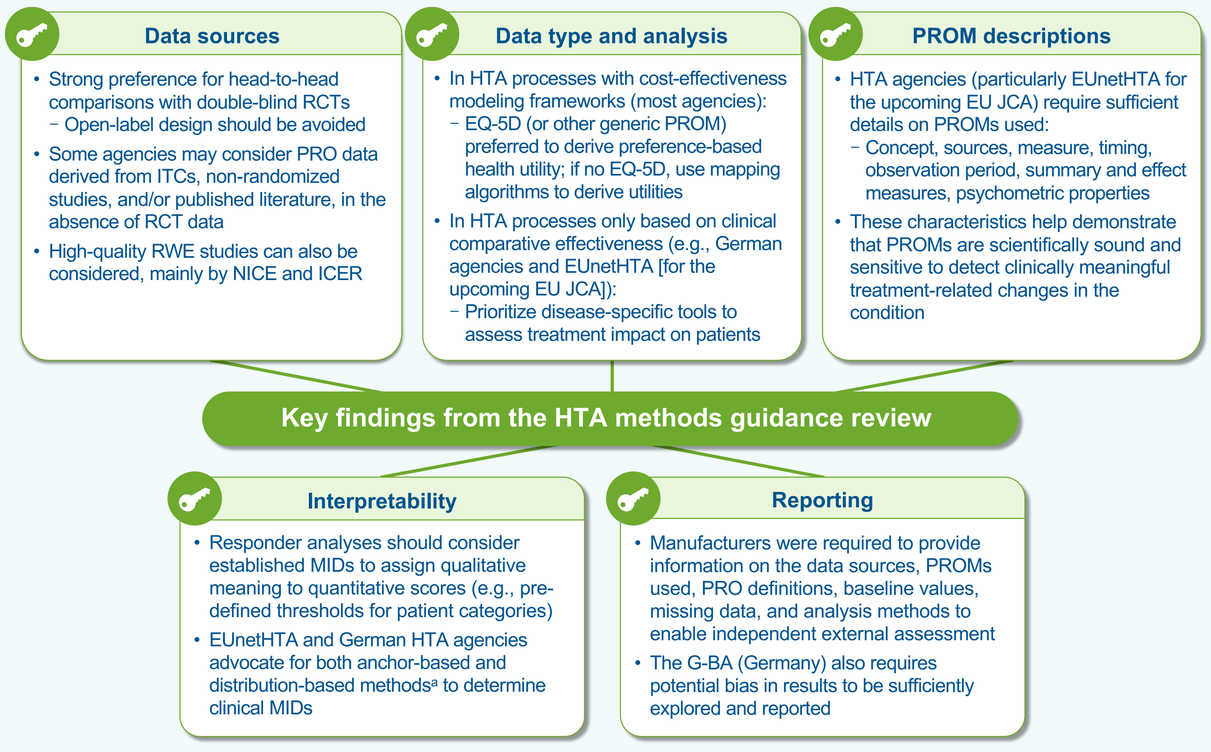
	Australia PBAC	Brazil CONITEC[b]	Canada CDA-AMC	China CNHDRC[c]	England NICE	EU EUnetHTA	France HAS	Germany G-BA; IQWiG	Italy Agenas; AIFA	Japan C2H	Scotland SMC	Spain AETS	US ICER[d]
HTA Guidance Documents	1	0	1	0	3	3	2	2	1	1	4	2	2
HTA Appraisals in MM	4	6	16	0	12	0	12	48	0	1	15	0	2

Note: Most documents were from German (G-BA and IQWiG; n = 50), Canadian (CDA-AMC; n = 17), and Scottish (SMC; n = 19) HTA agencies.
[a]Some guidance documents included multiple files (e.g., dossier template, instructions for manufacturers). [b]Although Brazilian HTA agencies have not published guidance on PRO data, the Ministry of Health has released guidance on utility measures for economic analyses.[12] [c]The CNHDRC did not provide publicly available information.
[d]ICER 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)



[a]Anchor-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)

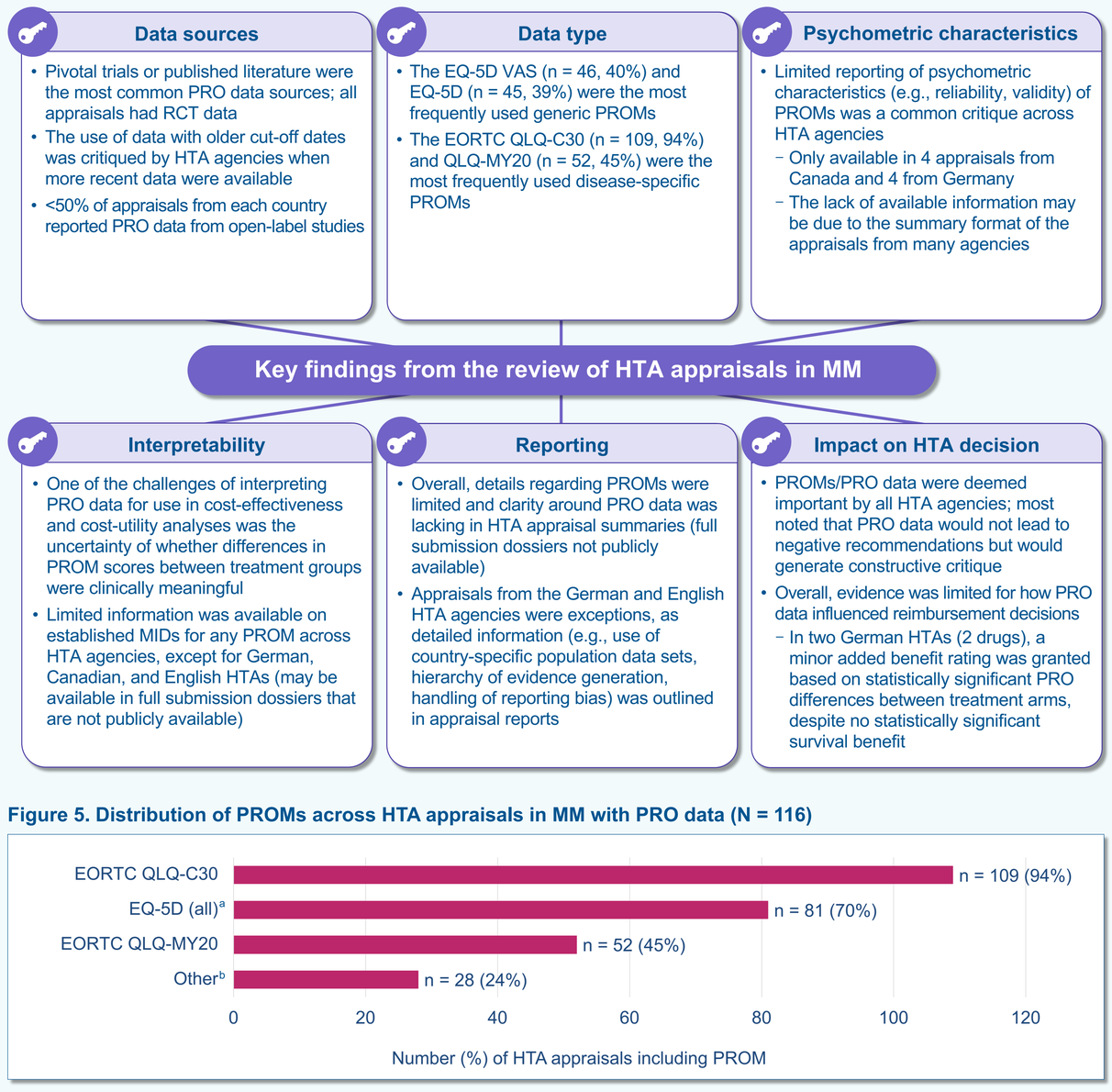


Figure 5. Distribution of PROMs across HTA appraisals in MM with PRO data (N = 116)

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

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 HTA[13] 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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Disclosures

Dasha Cherepanov, Mary Lynn Cala, Thomas Duterte, and Luis Hernandez are employees of Takeda. Grammati Sarri, Andreas Freitag, Laura Gurskyte, and Rachel Van Dusen were employees of Cytel at the time of this research, which received research funding from Takeda. This study was sponsored by Takeda Development Center Americas, Inc.

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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