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Mapping Patient-Reported Outcomes evidence requirements across global markets

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BACKGROUND & OBJECTIVES

- Regulatory and health technology assessment (HTA) bodies increasingly recognize the importance of incorporating patient perspectives in clinical trials, via capturing patient-reported outcomes (PRO) data. However, requirements relating to the inclusion of PRO data and how data is evaluated in regulatory or reimbursement decisions vary by markets and stakeholders. Where requirements exist, these are outlined in guidance documents, which often include information on how PRO measures should be selected and how their data should be collected, reported, and analysed
- This project aimed to identify guidance documents relating to the implementation and submission of PRO data from 10 regulatory agencies and 16 HTAs around the world

METHODS

- A targeted literature review was conducted in three stages:

1. HTA and regulatory websites hand searches
2. OVID database search
3. Google Scholar and Google hand searches (first five pages)

- Internal affiliates from Daiichi Sankyo were also asked to share any guidance documents which they used in their role that were relevant to their local market that had not already been identified from the above sources
- Eligibility criteria were applied to documents in the literature research: general (no specific population or intervention), any document that included PRO guidance or position documents – no specific study design, focus on PRO requirements, no specific outcomes, no date or language restrictions. Reports of clinical trials, interventional studies and observational studies were excluded
- Experts in clinical outcome assessments (COA) reviewed and extracted the data by hand. Where documents were only in local language, language experts at Clarivate reviewed and extracted any relevant information. Information was extracted into a bespoke Excel data table, organized by key topics relating to whether the documents included requirements relating to: PRO measure content validity, psychometric measurement properties, meaningful change thresholds, PRO data inclusion in product labelling, clinical trial data statistical analysis considerations, clinical trial design and conduct considerations, preferences for communication or submission of PRO data, and recommendations for using specific PRO measures

RESULTS

- A total of 65 guidance documents were included for extraction across the following markets **(Figure 1)**

Figure 1. Guidance document identification process – PRISMA

Number of guidance documents identified through each source: N=71

- Hand search of regulatory & HTA websites, n=53
- Hand search of reference lists & google scholar, n=2
- Electronic database search, n=12
- Daiichi Sankyo affiliates, n=4

Excluded due to being indication specific: N=6*

Included guidance documents per market: N=65

- Canada, n=5
- United States, n=7
- France, n=5
- United Kingdom (England & Scotland), n=11
- Germany, n=4
- Spain, n=3
- Italy, n=4
- EU4/EMA, n=9
- Australia, n=2
- Japan, n=2
- South Korea, n=2
- Taiwan, n=2
- Brazil, n=5
- China, n=4

* Four other oncology specific guidance documents (one from the EMA in Europe, one from ANVISA in Brazil, two from Taiwan CDE) were retained for extraction at the request of Daiichi Sankyo.

PRESENCE OF GUIDANCE DOCUMENTS ACROSS MARKETS

- The number and detail of guidance documents varied significantly by market **(Figure 2)**. PRO guidance and requirements were identified from five regulatory bodies (FDA, EMA, PMDA, ANVISA and NMPA) and 11 HTA bodies (CDA, ICER, NICE, SMC, HAS, G-BA, IQWiG, AIFA, PBAC, MHLC Chu-I-Kyo). Additional guidance and requirements were identified from six other bodies across various markets (OHID, CAEIP, EUnetHTA, HIRA and REBRATS), these were not initially noted as bodies of interest but appeared to have varying roles such as advisories to regulatory bodies or governments or collaborative organizations
- The identified guidance suggests most regulatory and HTA bodies recommend incorporating PRO measures into drug development and recognized their value in capturing patient experiences
- The guidance across bodies was aligned in emphasizing that sponsors should establish content validity, psychometric performance and ability to detect change for PRO measures that are planned to be implemented to support key endpoints in clinical trials
- Most regulatory bodies require PRO-based endpoints to be integrated early into trial protocols and statistical analysis plans. Trial protocols should include justification for the endpoint selection, specify the assessment frequency and statistical analysis considerations e.g. how missing data will be handled and pre-specifying meaningful change thresholds
- Establishing meaningful change thresholds associated with PRO measures should be evaluated prior to using the PRO measures within endpoints of confirmatory clinical trials. Terminology associated with meaningful change varied in the identified guidance, e.g. meaningful score differences/regions, minimal clinically important difference (MCID) or minimal important difference (MID). Most bodies required meaningful change thresholds to be established using anchor-based methods, which could be supported by distribution-based analyses

VARIABILITY IDENTIFIED WITHIN THE GUIDANCE ACROSS MARKETS

- The identified guidance and associated requirements often reflected each organisations priorities for using the data (e.g. regulatory or reimbursement)
- Generic preference-based measures like EQ-5D (3L or 5L) and SF-6D were widely recommended by HTA agencies in various markets for generating health state utility values. NICE, HAS, IQWiG, AIFA, PBAC, CADTH, REBRATS and the Spanish Ministry of Health explicitly reported the EQ-5D as the preferred instrument for sponsors to use. Country-specific value sets are often required by HTA bodies to reflect local population preferences. For example, NICE mandates UK-specific EQ-5D value sets, and similar requirements exist in other markets
- Some markets had more specific requirements, e.g. in Germany for responder analyses (patients classified as “responders” based on improvement), IQWiG requires that the response threshold equals at least 15% of the total PRO scale range. This differed to FDAs preference for deriving meaningful score differences for each specific PRO measure within each context of use
- Some bodies appeared to be open to PRO measures being used within primary or co-primary endpoints e.g EMA, FDA, MHLW, NMPA but other bodies appeared to state that PRO measures would likely only be accepted within secondary or exploratory endpoints e.g. ANVISA (guidance stated the body felt PRO measures were subject to limitations in interpretation and should be integrated with other data, specifically in oncology indications)

Figure 2. PRO Guidance Overview – Per market

Market	Regulatory	HTA	Other body found during search
Canada	Health Canada	Canada’s Drug Agency (CDA) formerly Canada’s Drug and Health Technology Agency (CDATH)	-
United States	Food and Drug Administration (FDA)	The Institute for Clinical and Economic Review (ICER)	-
United Kingdom (England & Scotland)	Medicines and Healthcare products Regulatory Agency (MHRA)	National Institute for Health and Care Excellence (NICE) Scottish Medicines Consortium (SMC)	Office for Health Improvement & Disparities, England (OHID)
France	European Medicines Agency (EMA)	Haute Authrité de Santé (HAS)	-
Germany		Gemeinsamer Bundesauss-chuss (G-BA) and Institute for Quality and Efficiency in Healthcare (IQWiG)	-
Spain		Agencia Espanola de medicamentos y productos sanitarios (AEMPS)	Spanish Ministry of Health and Comissió d’Avaluació Econòmica i d’Impacte Pressupostari (CAEIP)
Italy		Italian Medicines Agency (AIFA)	-
EU4 (France, Germany, Spain and Italy)		-	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) European Network for Health Technology Assessment (EUnetHTA)
Australia	The Therapeutic Goods Administration (TGA)	Pharmaceutical Benefits Advisory Committee (PBAC)	-
Japan	Pharmaceuticals and Medical Devices Agency (PMDA)	Ministry of Health, Labour, and Welfare’s (MHLW) Central Social Insurance Medical Council (Chu-I-Kyo)	-
South Korea	Ministry of Food and Drug safety/Ministry of Health and Welfare	National Evidence-based Healthcare Collaborating Agency (NECA)	Health Insurance Review & Assessment Service (HIRA)
Taiwan	Taiwan Food and Drug Administration (TFDA)	Center for Drug Evaluation (CDE)	-
Brazil	Agência Nacional de Vigilância Sanitária (ANVISA)	ANS (Agência Nacional de Saúde Suplementar) and CONITEC	Rede Brasileira de Avaliação de Tecnologias em Saúde (REBRATS)
China	National Medical Products Administration (NMPA)	China National Health Development Research Center (CNHDRC)	-

Key: Green = PRO guidance & requirements identified, Red = No PRO guidance & requirements identified

CONCLUSION

- The heterogeneity in the amount and detail of PRO guidance from stakeholders makes it challenging for sponsors to plan effective global PRO strategies
- Greater alignment on PRO data requirements across regulatory and HTA bodies would be beneficial for sponsors in providing robust PRO results for evaluation in regulatory or reimbursement submissions
- It will be interesting to follow whether initiatives like Joint Clinical Assessment (JCA) in Europe will lead to clearer and more aligned PRO evidence requirements for sponsors submitting the data within health technology assessments in the future

DISCLOSURES

Stephanie Fairhurst and Sarah Knight are employees and stockholders of Clarivate, a life sciences and healthcare company that consults with various pharmaceutical companies including Daiichi Sankyo who funded Clarivate to support this study. Francesco Cottone is an employee and stockholder of Daiichi Sankyo, pharma company.