IMPACT OF PATIENT REPORTED OUTCOME MEASURES ON HTA DECISIONS FOR RARE DISEASES

Shivani Shah
Senior HTA Analyst, EVERSANA

EVERSANA™

eversana.com

Rare Disease Day is observed globally on February 28th to raise awareness among the public and policymakers of rare diseases and how they impact patients' lives. In the United States, the Orphan Drug Act defines a rare disease as a disease or condition that affects fewer than 200,000 people,[1] whereas in the European Union (EU), a rare disease is one that affects no more than one person in 2,000.[2]

Although "rare" suggests not many people are affected with a condition, in the EU between 6,000 and 8,000 different rare diseases affect an estimated 30 million people collectively,[2] while in United States over 7,000 rare diseases affect more than 30 million people.[1]

Rare diseases can significantly reduce the quality of life for patients and their families. Ensuring the patient's voice is central to clinical decision-making is one key to delivering, evaluating and understanding the efficacy of therapeutic interventions.

Use of patient-reported outcomes (PRO) in rare disease research and clinical practice offers the potential to improve patient care and outcomes.[3] PRO measures are used to capture patients' views about their health status and to facilitate an understanding of the impact of these diseases and their treatments on patients' quality of life and symptoms. Patient input throughout the development of PROs, including qualitative research, is essential to ensure that the outcomes that impact people living with a rare disease are appropriately captured.

Inclusion of PROs helps in critical decision-making, especially for orphan medicines. An example is the German Federal Joint Committee (G-BA) assessment of Vertex's triple-combination therapy Kaftrio® (ivacaftor/tezacaftor/elexacaftor) – marketed in the U.S. as Trikafta® – for cystic fibrosis (CF). Within four months of market launch, Kaftrio exceeded the EUR 50 million sales threshold, and its orphan drug status was repealed, ultimately leading to Kaftrio undergoing standard assessment.[4]

The G-BA granted it major benefit rating[5], which is the highest possible rating from the assessor and is rarely granted; only three other products[4] have been given this rating since the Pharmaceutical Market Restructuring Act (AMNOG) went into effect in 2011. This rating has positive implications for Vertex during price negotiations with the statutory health insurance (SHI) funds.

The Kaftrio triple combination therapy received this highly positive benefit rating because it demonstrated significant efficacy in a clinical study design, adhering to the G-BA comparator and patient-relevant endpoints. The study demonstrated that the treatment was more effective than best supportive care (BSC) at improving lung function. Specifically, the G-BA considered the study primary endpoint, pulmonary exacerbations, especially those leading to hospitalization, to represent a clinically relevant endpoint and was therefore regarded as patient-relevant. In addition, the pivotal study conformed to the G-BA's requirement of a 24-week randomized, controlled trial. Overall, the G-BA's assessment found statistically significant advantages in the morbidity endpoints of pulmonary exacerbations and in all the domains of the validated PRO instrument (Cystic Fibrosis Questionnaire-Revised, CFQ-R) with no difference in mortality or adverse effects.[5] Vertex demonstrated patient-relevant value in a way that matched G-BA requirements and was rewarded with the highest rating.

This article provides a brief overview as to how PROs are utilized in HTA decision-making within Australia, Canada, France, Germany, Netherlands and United Kingdom.

Australia:

PROs are recommended by the Pharmaceutical Benefits Advisory Committee (PBAC) guidelines to be included, as the details inform clinical health outcomes in models for economic evaluation, although they are not mentioned as relevant efficacy endpoints. Details justifying the use of PRO measures must be included in the submission, and there should be a reliable existing method of mapping the PRO data into utility weights or QALY changes for the model.[6,7] Australia lacks a standardized approach, like the use of EQ5D in the case of NICE; hence, a company has flexibility to choose any model of its preference.

Canada:

PROs and minimal clinically important differences (MCIDs) are included in Canada's Common Drug Review (CDR) and pan-Canadian Oncology Drug Review (pCODR) processes to evaluate new drugs. Often, the measures report on the health-related quality of life (HRQoL) but can also describe the symptoms, efficacy and harms important to patients. They can be generic or population/condition specific.[8]

France:

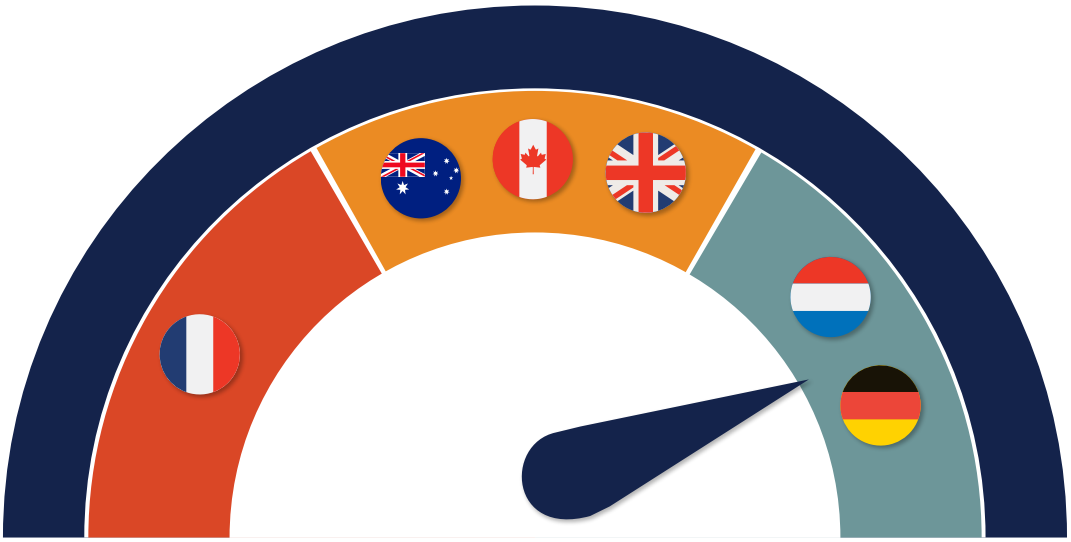
PRO measures have a minor role in overall HTA and market decision process in France – they are used as supplemental information in establishing incremental benefits. According to General Methods for Assessing Health Technologies of HAS,[9] the most important dimensions in France are the severity of the condition, efficacy, and safety, as well as other dimensions, such as unmet needs, mode of administration, mode of action, and Quality of Life (QOL). PROs are related to QOL. In the future, as QOL gains importance, PROs might also gain more relevance.[10]

Germany:

The importance of PROs in the HTA landscape is particularly emphasized in Germany. In the Act on the Reorganization of the Pharmaceutical Market (AMNOG) passed 11 November 2010, an added benefit of an intervention can be claimed only based on patient-relevant endpoints, which include mortality, morbidity, HRQoL and safety. PROs can cover the latter two dimensions, as they measure the health status (e.g., symptoms), functioning, and HRQoL directly from the patients' perspective. Most of all, the measurement of HRQoL based on PROs is crucial for the benefit assessment. For instance, the interpretation of the impact of adverse events (AE) should also be evaluated in terms of how patients perceive associated symptoms and HRQoL as measured by PRO.

In some therapeutic settings (e.g., palliative care), an advantage in overall survival (OS) alone might not be adequate to achieve an added benefit if downsides in AEs are observed. The G-BA, the organization responsible for determining reimbursement for pharmaceutical products, requires HRQoL data

Fig 1: Level of importance given to PRO data in HTA Decision-Making



to judge the overall impact of a new treatment. Neglecting to capture HRQoL data in a pivotal trial is regularly criticized by the G-BA and has a negative impact on the outcome of the benefit assessment.[11]

In May 2020, IQWiG adopted guidelines to develop a patient registry for data collection for rare diseases, when evidence available at the time of market access is insufficient for the early benefit assessment of drugs. Often, the studies of orphan medicines are too short, or no PRO data are collected. Also, the limited number of patients for a rare disease limits the number of datapoints. Thus, to close such evidence gaps in the future, routine practice data are to be included in early benefit assessments of drugs.[12]

Netherlands:

In Europe, the Netherlands prominently includes PROs in national registry collections as well as in clinical practice/hospitals.

Many parties in the Netherlands measure PROs, with large variations in their application. In the parliamentary letter of 12 February 2017, the Ministry of Public Health wrote that the government is going to work on making outcomes available for joint decision-making. The programme "Outcome Information for Joint Decision-Making" was set up for this purpose. The essence of the programme is to work on different registration and processing data, which will allow patients to share their outcomes with professionals and enable physicians and patients to jointly use the data from national quality records. Thus, joint decision-making implies the integration of the purposes of PROMs at an individual and group level.

The recent emphasis on value-based healthcare (VBHC) in health policy is thought to provide new opportunities for shared decision-making (SDM), especially by using information based on patient-reported outcome measures (PROMs) in routine medical encounters.[13]

In general, there is more evidence about the effectiveness of PROMs on the care process than on health outcomes. Several studies show positive effects of PROMs on doctor/patient communications, goal setting, joint decision-making and detection of problems that would otherwise not have been identified. Effects on heath outcomes are less often measured and show mixed results: Sometimes the use of PROMs has a positive effect on aspects of health, and sometimes it does not.[14]

United Kingdom:

PROs are not mentioned, with respect to their utilization and/or considered, within the National Institute for Health and Care Excellence (NICE) Guide to the Processes of Technology Appraisal. They are used as a tool to capture Quality-Adjusted Life-Years (QALY) in terms of utility measurements. EQ-5D has been used as a measure of health gain by NICE, and it has been given very strong preference.

PRO data are used as a surrogate endpoint for other parts of evaluations (e.g., within a cost-effectiveness calculation), to capture symptom or disease-specific measures to confirm and support evidence and direction of measures of utility.[15]

Conclusion:

A better understanding of the potential advantages, challenges and solutions when using PROs for rare disease therapies can help improve their uptake in HTA evaluations.

While the inclusion of PROs and/or patient voice within an HTA evaluation can have a positive influence on recommendations, inconsistencies in terms of how this information is collected across HTA agencies and across different assessments within the same HTA agency create challenges for manufacturers. Developing and administering PRO instruments for rare diseases creates unique challenges for manufacturers because of the small patient

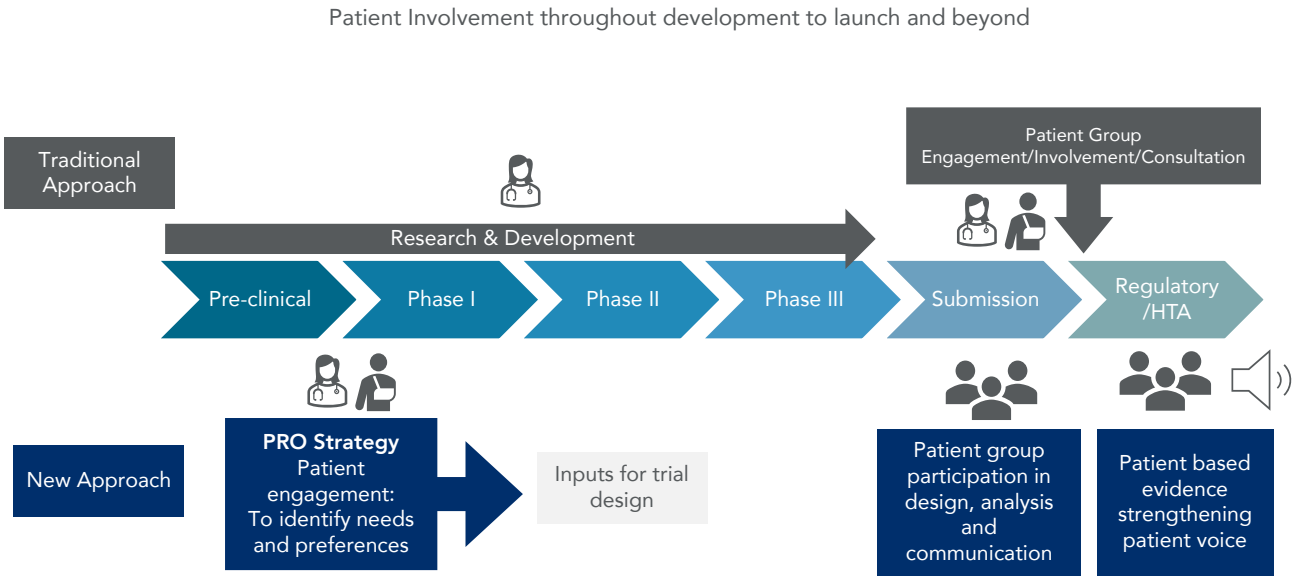
populations, disease heterogeneity, lack of natural history knowledge and short-term studies.[16]

There is a pressing need for HTA stakeholders to acknowledge these limitations and discuss innovative approaches and non-standard solutions, given the potential of PROs.

There is a growing recognition in the HTA community that the patient perspective is an important component of the assessment of benefits and harms, as well as identifying the economic, social and ethical implications of the approval and use of a treatment. Over the past two decades, greater recognition of patients' point of views has been facilitated by PROs.

Working with HTA consultants—such as EVERSANA's NAVLIN HTA Consulting Team—early in clinical development can help to ensure appropriate PRO strategy to meet the evidence requirements of HTA agencies and to develop a robust evidence generation plan. The earlier these activities are planned, designed and executed, the better it provides a manufacturer with the best chance of commercial success for its new drug at the time of launch.

Fig 2: Use of PROs in early patient development and launch



REFERENCES

1. FDA: Rare Diseases at FDA. Available at: https://www.fda.gov/patients/rare-diseases-fda#:~:text=The%20Orphan%20Drug%20Act%20defines,people%20in%20the%20United%20States. Accessed: February 16, 2022
2. European Commission: EU research on rare diseases, Available at: https://ec.europa.eu/info/research-and-innovation/research-area/health-research-and-innovation/rare-diseases_en. Accessed: February 16, 2022
3. Orphanet Journal of Rare Diseases. Patient reported outcome measures in rare diseases: a narrative review. [Online] 2018. Available at: https://ojrd.biomedcentral.com/articles/10.1186/s13023-018-0810-x. Accessed: February 16, 2022
4. Pricentric® by EVERSANA's Newsletter: Vertex's Kaftrio Plus Kalydeco Offers Considerable Added Benefit, Finds G-BA. Available at https://www.eversana.com/2021/02/19/vertexs-kaftrio-plus-kalydeco-offers-considerable-added-benefit-finds-g-ba/#:~:text=Vertex%20submitted%20a%20complete%20dossier,was%20subject%20to%20standard%20assessment. Accessed: February 16, 2022
5. Federal Joint Committee (G-BA): Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Ivacaftor/Tezacaftor/Elexacaftor (Exceeding the € 50 Million Limit, Cystic Fibrosis, Combination Treatment with Ivacaftor in Patients 12 Years and Older (Heterozygous for F508del and MF Mutation) of 18 February 2021. Available at https://www.g-ba.de/downloads/40-1465-7316/2021-02-18_AM-RL-XII_Ivacaftor-Tezacaftor-Elexacaftor_D-584_TrG_EN.pdf. Accessed: February 16, 2022
6. PBAC Guidelines on trial characteristics. [Online] Available at https://pbac.pbs.gov.au/section-2/2-4-trial-characteristics.html. Accessed: February 16, 2022
7. PBAC Guidelines on trial characteristics. [Online] Available at https://pbac.pbs.gov.au/section-3a/3a-5-health-outcomes.html. Accessed: February 16, 2022
8. Soprovich et al. The frequency and availability of population-specific patient reported outcome measures and minimal clinically important differences among approved drugs in Canada. [Online] Available at https://hqlo.biomedcentral.com/track/pdf/10.1186/s12955-018-1070-0.pdf. Accessed: February 16, 2022
9. HAS: General Method for Assessing Health Technologies. Available at https://www.has-sante.fr/upload/docs/application/pdf/general_method_eval_techno.pdf. Accessed: February 16, 2022
10. KCE guidelines on Use of Patient-reported Outcome and Experience Measures in Patient Care and Policy. Report 303 [Online] Available at https://www.nivel.nl/sites/default/files/bestanden/KCE_use_of_PROM_PREM.pdf. Accessed: February 16, 2022

11. Babac A. Patient-reported data informing early benefit assessment of rare diseases in Germany: A systematic review. [Online] Available at https://healtheconomicsreview.biomedcentral.com/articles/10.1186/s13561-019-0251-9 Accessed: February 16, 2022

12. IQWiG press release and report on Registry-data – of sufficient quality – are suitable for the extended benefit assessment of drugs. [Online] Available at https://www.iqwig.de/en/presse/press-releases/press-releases-detailpage_9982.html. Accessed: February 16, 2022

13. National Library of Medicine: The use of PROMs and shared decision-making in medical encounters with patients: An opportunity to deliver value-based health care to patients. Available at https://pubmed.ncbi.nlm.nih.gov/31840346/. Accessed: February 16, 2022

14. ZiN: Literature review on the use of PROMs, current knowledge and scientific evidence for the use of Patient-Reported Outcome Measures. Available at https://www.zorginzicht.nl/binaries/content/assets/zorginzicht/algemeen-ondersteuning/literature-review-on-the-use-of-proms.pdf, Accessed: February 16, 2022

15. NICE Technology appraisal guidance. [Online] Available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/process. Accessed: February 16, 2022

16. Whittal A, Meregaglia M, Nicod E. The Use of Patient-Reported Outcome Measures in Rare Disease and Implications for Health Technology Assessment. [Online] Available at https://link.springer.com/content/pdf/10.1007/s40271-020-00493-w.pdf. Accessed: February 16, 2022