Call in the PROs: Giving Credence to the Patient's Perspective in Healthcare Decision Making

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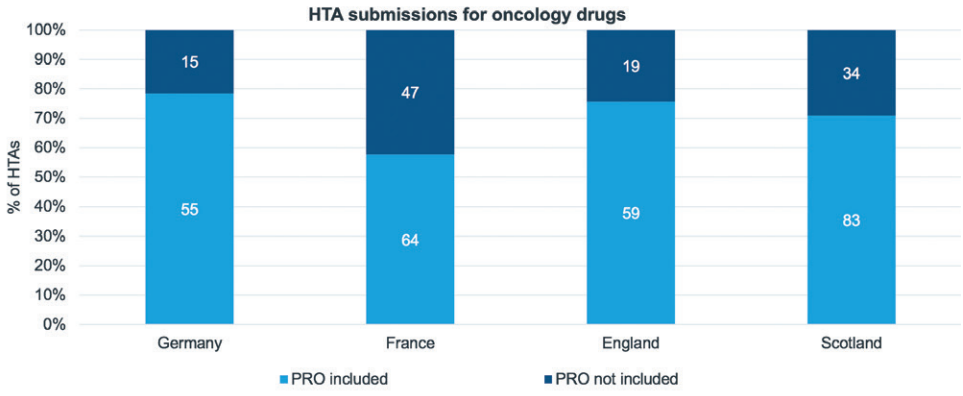
Guidance from HTA bodies should be clearer and more consistent, and to harness the opportunities of PRO data, careful planning and proper execution are needed.

There is a growing movement to incorporate how patients experience treatment into healthcare decision making. In a clinical trial setting, patient experience is measured through clinical outcome assessments (COAs) and in particular, through patient-reported outcomes (PROs), which are a specific type of COA where the report comes directly from the patient.[1] PROs measure the patient experience by asking patients how they feel and function in the context of their disease or condition, and in the context of their treatment.

Regulator interest in PROs goes back a long way, with both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) issuing their first guidance in 2004-2005.[2] The field has matured since then. For example, the EMA has specific guidance on the use of PRO measures in oncology studies,[3] and the FDA recently introduced the "Patient Experience Data" section in their drug review.[4] Consequently, the past decade has shown a marked increase in PRO data included in PRO label claims, particularly in Europe. In a recent survey of health technology assessment (HTA) institutions in the European Union (EU) and Norway, 36 institutions of 48 organizations (75%) reported that they use PRO when estimating effectiveness or safety in their assessments.[5] No distinction was made between disease-specific and generic PRO measures for symptoms, functioning, or health-related quality of life (HRQoL).

PROs have always been important in disease areas where the patient experience is central to the disease definition (eg, pain, autoimmune diseases), but in other therapeutic areas, PROs are less well established. For example, IQVIA analysis of reports by HTA bodies from France, Germany, and the United Kingdom (*Haute Autorité de Santé* [HAS], *Gemeinsamer Bundesausschuss* [G-BA], The National Institute for Health and Care Excellence [NICE], and Scottish Medicines Consortium [SMC] respectively) showed that only 27% of HTA reports in diabetes mentioned PRO data compared to 70% in oncology.[6] Oncology is an interesting case example, as this is a very dynamic field where we see PRO data increasingly being demanded and submitted as part of the evidence package to HTA bodies, yet the response and impact varies greatly from one body to another. Other therapeutic areas

Figure 1. Inclusion of PRO data in HTA submission per country.



Source: IQVIA HTA Accelerator. Scope: Single drug assessments (original, extension of indication, resubmissions) for oncology with a recommendation from Jan 2011 to Dec 2016 from 4 HTA bodies (G-BA, HAS, NICE, SMC).

such as heart failure will likely follow a similar journey, and lessons learned from oncology provide valuable insights in the challenges and opportunities in building a sound PRO strategy.

As mentioned previously, PRO evidence in oncology HTA reports varies across European HTA bodies (Figure 1). Our analysis showed that HAS reports in France mention PRO data less frequently than HTA reports from the independent Institute for Quality and Efficiency in Health Care, (IQWiG), NICE, and SMC in Germany, England, and Scotland, respectively. This is in line with feedback from French payers who consider PRO data as "nice-to-have," albeit figures might be slightly understated due to the fact that HAS assessment reports are less extensive than the publications by G-BA and NICE, which include the manufacturer submission. The impact of PROs on the overall recommendation seems limited: comparing HTA reports that included PRO data versus those that didn't show that drugs with PRO data do not necessarily receive a more favorable recommendation. Only in Germany did we observe higher benefit ratings in HTA reports containing PRO data. When looking specifically into those assessments where PRO data were included, we also saw that in Germany, PRO evidence was mentioned by the payer as being a decision driver far more often than in the other countries (Figure 2). Germany is the only country that explicitly looks at PROs, while other countries will look at PROs as part of the clinical benefit or cost-effectiveness assessment (Table 1).

The German perspective on PROs

New drugs entering the German market are appraised by the G-BA, which generally commissions the IQWiG with the scientific assessment.[7-12] These 2 HTA bodies assess the added benefit of a drug versus the appropriate comparator therapy based on patient-relevant endpoints. The patient-relevant endpoints are categorized in 3 outcome categories: mortality, morbidity, and HRQoL. PROs may offer support for an added benefit against the appropriate comparator in several of these outcome categories, especially in the morbidity area, where symptoms, complications, and adverse events are taken into account.

To determine the added benefit, IQWiG/G-BA look at 2 dimensions: "probability" and "extent of benefit demonstrated" (Table 1).[13] "Probability" indicates the degree of certainty that the results deliver an added benefit with 3 categories: proof, indication, or hint. "Extent of benefit demonstrated" is mainly based on the statistical effect size concerned; ie, explicit inferential statistical thresholds for each benefit category, and the outcome category, eg, all-cause mortality, serious/severe symptoms/adverse events (AEs) and HRQoL, and nonserious/nonsevere symptoms/AEs. HRQoL is grouped with the severe symptoms/AEs category, indicating its importance.

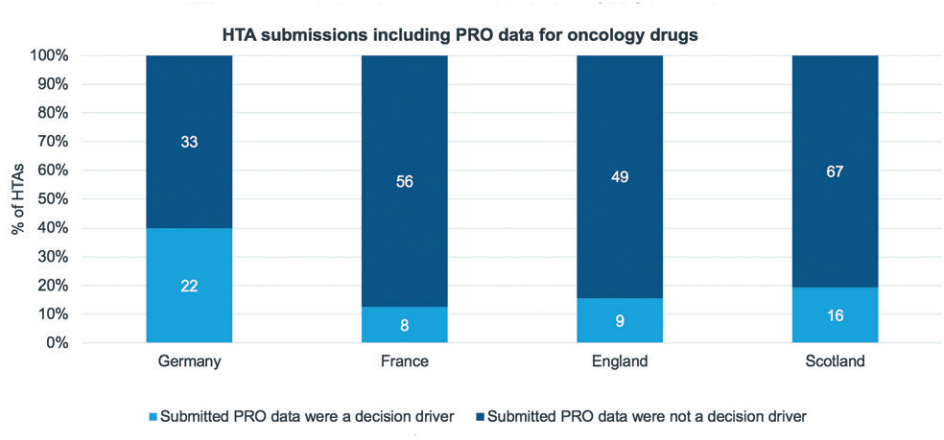
The "extent of benefit demonstrated" can be qualified as major, considerable, minor, nonquantifiable, no added benefit, or less benefit than the appropriate comparator therapy. To obtain an added benefit rating with a PRO (or COA), it is important to use a validated or established instrument, as well as a validated response criterion (minimal important difference [MID]).[14] In case a MID is not available, IQWiG uses the standardized mean difference (expressed as Hedges' g) with an irrelevance threshold of 0.2.[15] This can have serious implications on the IQWiG benefit rating as can be seen in the abiraterone example.

The industry perspective on PROs

While it is generally accepted that PROs are important in oncology, HTA guidance on the handling of PROs in assessments is not detailed and consistent enough for the industry to be able to implement it with a common global approach and strategy. Although Germany applies very specific criteria to assess PRO evidence, not all HTA bodies provide guidance or consistently assess PROs. For example, NICE has detailed guidance for generating health state utilities for cost-effectiveness analysis,[16] but does not cover PROs in relation to measuring patient's HRQoL and functioning.

The varying views of the HTA bodies were also seen in the case study of enzalutamide in men with metastatic castration-resistant prostate cancer not yet indicated for chemotherapy. Enzalutamide's pivotal trial included multiple PRO instruments and the PRO results were generally positive.[17] However, the PRO evidence packages submitted to HTA bodies differed, due to different requirements from the HTA bodies and different experiences of the manufacturer's local teams working on the submissions. This resulted in mixed critique of the submitted PRO data. In Germany, the Brief Pain Inventory (BPI) data were not accepted, as data collection was not consistent between treatment arms; (the difference in available Brief Pain Inventory data was more than 15% between the 2 treatments arms). G-BA did recognize an added benefit based on the median time to deterioration in Functional Assessment of Cancer Therapy-Prostate (FACT-P) total score.[18]

Figure 2. PRO data as a decision driver in oncology HTAs.



Source: IQVIA HTA Accelerator. Scope: Single drug assessments (original, extension of indication, resubmissions) for oncology with a recommendation from Jan 2011 to Dec 2016 from 4 HTA bodies (G-BA, HAS, NICE, SMC).

On the other hand, HAS concluded that the available data were inconclusive as to the effectiveness t of the treatment.[19] Lack of guidance from HTA bodies on PROs leads to several challenges for the industry. IQVIA research showed that the key challenges for collecting PROs lie with choosing the right endpoint and validation of the instrument (Figure 3).

Generating impact with a sound PRO strategy

A sound PRO strategy is needed to generate PRO evidence with impact. Currently, PROs are not consistently included as endpoints in clinical trials, or data are not adequately collected, or presented in an insightful way.

To aid the industry in developing a better PRO strategy, guidance from HTA bodies should be clearer and more consistent. On a European level, there are initiatives for providing better guidance. HRQoL is one of the main categories of endpoints in the EUnetHTA Guidelines for Clinical Endpoints.[20] EUnetHTA guidelines also touch upon the need for HRQoL measures in cost-effectiveness analyses that may also be of value in themselves as clinical assessments.[21] The majority of recent EUnetHTA assessments included PRO data, and in cases where it wasn't included, the lack of PRO data was criticized by EUnetHTA.

A new EU joint HTA structure may provide an opportunity for more consistency and more guidance for collecting PRO data and inclusion of PROs in HTA submissions—but individual HTA bodies should also provide guidance for the assessment of PRO evidence.

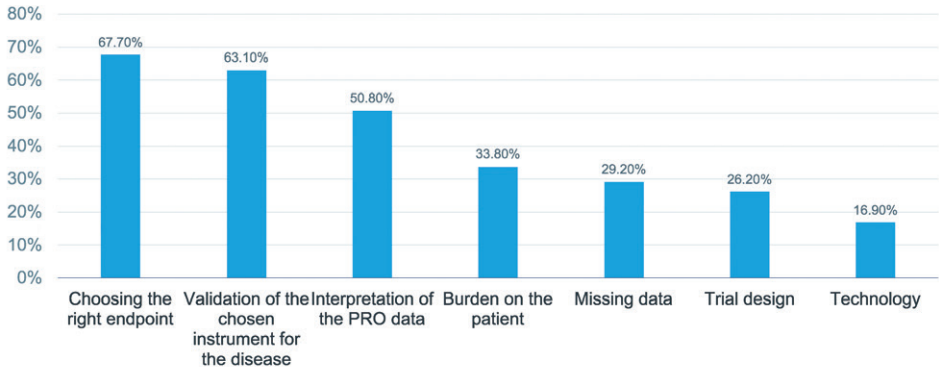
Adding benefit through PROs: a German case study example

The recent assessment of abiraterone for the treatment of metastatic hormone-sensitive prostate cancer is a rich case example that provides both positive and negative learnings in terms of how you should plan for PRO analysis, conduct the study, and analyze the data [IQWiG, March 2018[22-23]]. The study collected multiple PROs, including the Functional Assessment of Cancer Therapy-Prostate (FACT-P), Brief Pain Inventory (Short Form) (BPI-SF), Brief Fatigue Inventory, and EuroQol-5D (EQ-5D). IQWIG accepted the response criteria (ie, MID) of the EQ-5D VAS, FACT-P, and one of the BPI-SF items, but the response criteria of Brief Fatigue Inventory and all other BPI-

Table 1. Overview of remit and use of PROs by HTA bodies in scope

COUNTRY	GERMANY	FRANCE	UK
Agency	G-BA, IQWiG	HAS	NICE, SMC
Possible HTA outcomes	Two outcomes are provided: • Benefit ratings indicate the "extent of benefit demonstrated" compared to the appropriate comparator therapy): - Major - Considerable - Minor - Nonquantifiable - No added benefit - Less benefit • Probability indicates the degree of certainty that the results deliver an added benefit: - Proof - Indication - Hint	Ratings for 2 areas are provided: • Service médical rendu (SMR): actual (clinical) benefit - Important/High (65% reimbursement rate) - Moderate (30%) - Mild/Low (15%) - Insufficient (not included on the positive list) • Amélioration du service médical rendu (ASMR): improvement of actual benefit: - Major (ASMR I) - Important (ASMR II) - Moderate (ASMR III) - Minor (ASMR IV) - No clinical improvement (ASMR V)	NICE: • Recommended • Recommended with restrictions (optimized) • Recommended for use in Cancer Drug Fund • Not recommended SMC: • Recommended • Recommended with restrictions • Not recommended
Impact of HTA outcomes on pricing and reimbursement	Drugs are automatically reimbursed once marketing authorization has been approved. The G-BA benefit ratings influence price negotiations with the National Association of Health Insurance Funds	The SMR determines a new drug's reimbursement rate and the ASMR rating influences the pricing negotiation with the Pricing Committee (Comité économique des produits de santé, CEPS)	• In England, all NICE-approved drugs need to be funded • In Scotland, health boards are required to fund any drug recommended by SMC
Assessment of PROs in HTAs	Submitted PROs are reviewed in patient-relevant morbidity and HRQoL outcomes	Submitted PROs are reviewed as part of clinical benefit	NICE and SMC decisions are primarily based on cost-effectiveness considerations. Submitted PROs are reviewed as part of clinical benefit or used as utility input for cost-effectiveness analyses
PRO guidance for HTA submissions	German HTA bodies apply very specific criteria to assess PRO evidence[12]	No explicit HAS guidance for PROs	NICE and SMC have guidance for generating health state utilities for cost-effectiveness analysis[16,24]

Figure 3. Key challenges for collecting PRO data.
Question: What do you currently see as the top 3 challenges of collecting PRO data? N=62



Source: IQVIA webinar "PROving its worth: How to develop a PRO strategy to distinguish your product with regulators and payers".

SF items were initially not accepted, and because the 95% CI of the standardized mean difference (Hedges' g) was not fully beyond the irrelevance threshold, IQWIG concluded there was no added benefit associated with these endpoints. In response, the manufacturer subsequently submitted many staggered response criteria sensitivity analyses. On one of the Brief Fatigue Inventory items (item 3: measuring worst fatigue), they showed robust effects, which led IQWiG to accept the BFI item 3 response criteria, resulting in a change in IQWiG's rating. This example illustrates that the PRO data had positive effects on the added benefit rating, although it should be noted that overall survival data were available and convincing (ie, significant improvement), which was the key driver in the overall added benefit rating.

Building a convincing case for PROs

A sound PRO strategy starts with a robust understanding of the patient experience within a given disease area and what the patient reports as meaningful benefits. This understanding of the concepts to measure can be developed from a literature review but if high-quality qualitative research has not been published, then researchers should invest early in patient interviews. Robust qualitative evidence supports the PRO strategy with regulatory agencies and argumentation on the severity of measured symptoms/concepts for payers. The target product profile of the drug should include hypotheses for PRO claims and endpoints that address the patient experience, and should be considered early in development to be matured as data becomes available.

PRO instrument selection to measure the concept must be done thoughtfully. Too often these decisions are left late (just before protocol finalization) and the temptation is to adopt an existing instrument or to copy competitors. Researchers selecting instruments that are not appropriate for their context of use, or with designs that are unsuitable for clinical endpoints may be insensitive or see their evidence being rejected by regulatory agencies and payers. Selected instruments should have evidence for their content validity and psychometric properties, or researchers should plan to develop this evidence themselves. Evidence supporting the threshold for clinically meaningful change on the instrument is necessary for endpoints that require a responder definition and to put a statistically significant mean change on the PRO scales into context. Furthermore, endpoints should be pre-specified and alpha-controlled for the best chance of acceptance by regulatory agencies and HTA bodies.

To harness the opportunities of PRO data, careful planning and proper execution are needed. Once a strategy is in place, researchers must ensure they follow through consistently, as poor execution of a PRO strategy in trial operations could result in missing or poor-quality data and suboptimal demonstration of patient benefit. Poor execution of the PRO strategy can lead to payers and regulators dismissing the PRO data or even degrading their rating.

Researchers should further include PRO questions in early scientific advice consultations offered by EMA and EUnetHTA since July 2017. Past HTA advice can prove significant for companies looking for successful strategies and data presentations. For example, in Germany, we can see the need to provide evidence on severity of measured symptoms/concepts. In addition, researchers need to re-think how data are presented to ensure results are understandable and meaningful to all stakeholders. As the importance of PRO data is increasing, this is a great opportunity to prove it with PROs!

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