Evaluating the Role of Disease-Specific Patient-Reported Outcomes in HTA Submissions for Rare Conditions: A Comparative Case Study of Narcolepsy and Phenylketonuria

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Introduction

- In rare diseases, disease-specific (or condition-specific) patient-reported outcome (dsPRO) measures are often essential to capture symptoms, severity and functional limitations unique to the condition,[1-2] elements that generic tools such as the EQ-5D can miss **(Figure 1).**[3-4]
- While dsPROs offer greater clinical relevance and sensitivity within a disease, their lack of cross-condition comparability may limit their influence on reimbursement decisions.

Objective: This study examined narcolepsy and phenylketonuria (PKU), two conditions where key symptoms can be overlooked by generic tools, to explore the influence of dsPROs on HTA decisions.

Figure 1. Examples of symptoms and impacts captured by dsPRO that generic tools can miss

	Symptoms and impacts captured by dsPROs	Assessment gap by generic tools
Narcolepsy	• Excessive daytime sleepiness • Cataplexy • Sleep paralysis • Disrupted nighttime sleep	EQ-5D does not include a sleep dimension and may fail to capture the impact of fatigue and vigilance loss.
PKU	• Cognitive impairment • Attention and memory difficulties • Executive dysfunction • Mood instability • Fatigue	EQ-5D lacks sensitivity to capture meaningful neurocognitive or psychosocial changes that define treatment benefit.

Abbreviations: dsPRO, disease-specific patient-reported outcome; EQ-5D, EuroQol 5-Dimension health-related quality-of-life questionnaire; PKU, phenylketonuria.

Methods

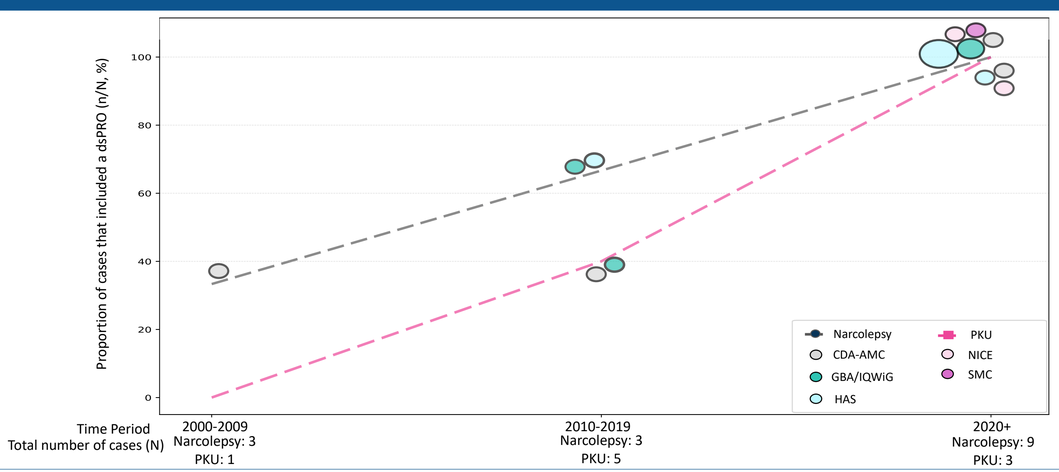
- Public HTA dossiers for narcolepsy and PKU from NICE, SMC, CDA-AMC, HAS, PBAC, IQWiG/G-BA and INAHTA (inception–May 2025) were reviewed. Submissions for the same intervention and indication (including resubmissions) were grouped as one case.
- The influence of dsPRO evidence was qualitatively rated as low, moderate, or high based on integration, relevant HTA comment, and the extent to which dsPROs shaped the decision (positively/negatively).
- Two reviewers rated independently and resolved discrepancies by consensus.

Results

Overview

- 24 cases were identified, covering five narcolepsy and two PKU treatments assessed by six agencies between 2008 and 2023 **(Table 1).**
- dsPRO use increased over time in both diseases, with inclusion in submissions to a wider range of agencies. All submissions to NICE and G-BA/IQWiG included dsPROs for both diseases, whereas none of the submissions to PBAC did **(Figure 2** and **Table 1).** In two cases, sponsors included dsPRO in the resubmissions to strengthen the patient-centred framing of evidence packages.
- dsPROs were more frequently used in narcolepsy (12/15) than PKU (5/9), and their influence on decisions was mostly rated as moderate (14/24), high in three narcolepsy cases when they contributed to both clinical evidence and economic evaluation, and low in seven cases where they were completely omitted **(Table 1)**.

Figure 2. Trends in the inclusion of dsPROs in HTA cases (2000–2023)



Note: *Size of bubble represents the number of cases that included a dsPRO for each agency.*
Abbreviations: dsPRO, disease-specific patient-reported outcome; HTA, health technology assessment; PKU, phenylketonuria.

Insights from narcolepsy: mature tools, translation challenge

- In narcolepsy, dsPROs such as the Epworth Sleepiness Scale (ESS) and the Functional Outcomes of Sleep Questionnaire (FOSQ) were commonly used as primary or secondary endpoints and, in three cases, incorporated in the economic evaluation.
- Across the three cases, sponsors took differing approaches to incorporating dsPROs into economic evaluations: in two cases, the inclusion was sponsor-initiated (one accepted and one rejected), while in the third, the committee incorporated the dsPRO in its own reanalysis **(Figure 3).**
- Overall, narcolepsy cases benefited from having established dsPROs recognised as clinically relevant and sensitive, and allowed sponsors to link patient-reported changes directly to cost-effectiveness estimates. HTA critique increasingly focused on interpretation, particularly how changes in dsPRO scores should be translated into economic value and overall quality-of-life gain **(Figures 3, Figure 4** and **Table 1).**

Table 1. Summary of dsPROs use and influence in the HTA cases*

Intervention	HTA body	Year†	Recommended by HTA body?	dsPRO reported in clinical section	dsPRO used in economic evaluation	Assessed influence of dsPRO‡
Narcolepsy						
Sodium Oxybate	SMC	2007	✗	✗	✗	🔴
Sodium Oxybate	CDA-AMC	2009	✗	✓	✓	🟢
Sodium Oxybate	HAS	2017	✓	✓§	N/A	🔴
Sodium Oxybate (children)	HAS	2021	✓	✓	N/A	🟡
Modafinil	PBAC	2008	✓	✗	✗	🔴
Armodafinil	PBAC	2016	✓	✗	✗	🔴
Pitolisant	GBA/IQWiG	2016	✓	✓	✗	🟡
Pitolisant (children)	GBA/IQWiG	2023	✓	✓	✗	🟡
Pitolisant	HAS	2023	✓	✓	N/A	🟡
Pitolisant (children)	HAS	2023	✓	✓	N/A	🟡
Pitolisant	CDA-AMC	2023	✗	✓	✓	🟢
Solriamfetol	GBA/IQWiG	2020	✗	✓	✗	🟡
Solriamfetol	HAS	2020	✓	✓	N/A	🟡
Solriamfetol	SMC	2022	✓	✓	✗	🟡
Solriamfetol	NICE	2022	✓	✓	✓	🟢
PKU						
Sapropterin	HAS	2009	✓	✗	N/A	🔴
Sapropterin (children)	HAS	2016	✓	✗	N/A	🔴
Sapropterin	PBAC	2011	✗	✗	✗	🔴
Sapropterin	CDA-AMC	2016	✓	✓§	✗	🟡
Sapropterin	SMC	2018	✗	✗	✗	🟡
Sapropterin	NICE	2021	✓	✓	✗	🟡
Pegvalise	GBA/IQWiG	2019	✓	✓	✗	🟡
Pegvalise	HAS	2020	✓	✓	N/A	🟡
Pegvalise	CDA-AMC	2022	✓	✓	✗	🟡

*Submissions for the same intervention and indication (including resubmissions) were grouped as one case; distinct indications or different agencies were treated as separate cases.
†Refers to the publication date of the HTA submission; where a resubmission occurred, the year of the resubmission has been prioritised.
‡Influence of dsPRO on final recommendation: low 🔴; medium 🟡; high 🟢
§dsPRO included in resubmission.
Abbreviations: dsPRO, disease-specific patient-reported outcome; HTA, health technology assessment; N/A, not applicable.

Figure 3. How dsPROs were incorporated and challenged in narcolepsy cases

Sodium oxybate — CDA-AMC — SR0141-000, 2009

Outcome strategy:
FOSQ was used in trials to assess quality of life.

Utility derivation:
Sponsor did not include FOSQ in economic evaluation.

Committee view:
The sponsor did not account for quality-of-life benefits observed in the FOSQ scores for the no-treatment group.

Decision and impact
✗ Rejected: The committee reanalysed* the cost-utility model including FOSQ improvements, cost-effectiveness was not demonstrated.

Solriamfetol — NICE — TA758, 2022

Outcome strategy:
ESS was used to define treatment response.

Utility derivation:
Sponsor cited insensitivity of EQ-5D to narcolepsy impacts; utility values derived by mapping ESS scores to EQ-5D.

Committee view:
Accepted mapping with caution (EQ-5D-5L collected but unused). Noted the approach might not fully capture quality-of-life change.

Decision and impact
✓ Committee accepted the mapping approach and sponsor's justification.

Pitolisant — CDA-AMC — SR0715-000, 2023

Outcome strategy:
Sponsor used ESS-based responder/non-responder structure and mapped to utilities.

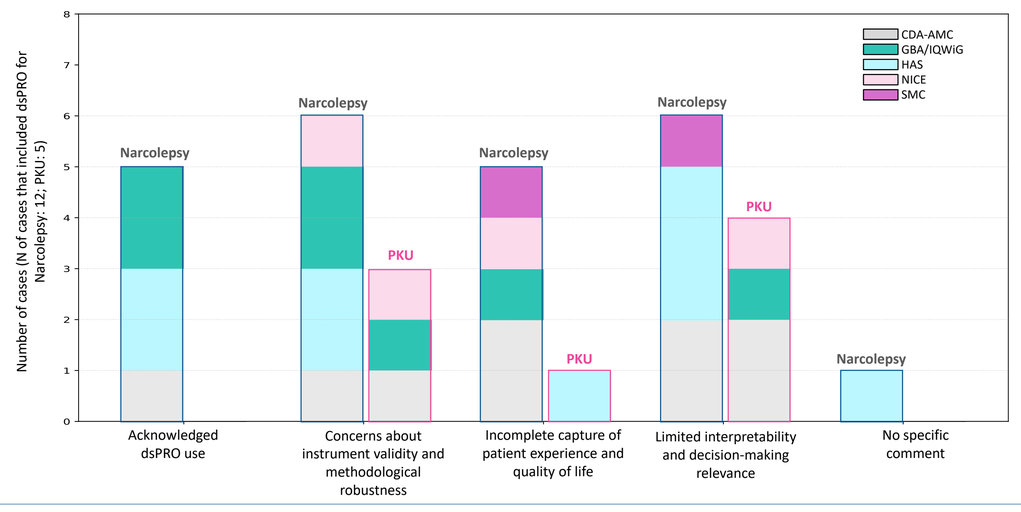
Utility derivation:
- Responders: same utility as general population.
- Non-responders: mapping SF-36 (published data for narcolepsy patient) to EQ-5D.

Committee view:
Committee judged utility assumptions as inadequate, including omission of partial responders.

Decision and impact
✗ Cost-utility analysis rejected → committee opted for cost comparison instead.

** Further details on how FOSQ was incorporated into the reanalysis were not available in the public report.*
Abbreviations: EQ-5D, EuroQol 5-Dimension health-related quality-of-life questionnaire; EQ-5D-5L, EuroQol 5-Dimension, 5-Level version; ESS, Epworth Sleepiness Scale; FOSQ, Functional Outcomes of Sleep Questionnaire; PKU, phenylketonuria; SF-36, Short Form Health Survey with 36 items.

Figure 4. Committee commentary on dsPRO among cases that included dsPROs



Abbreviations: dsPRO, disease-specific patient-reported outcome; PKU, phenylketonuria.

Insights from PKU: gaps in tools, reliance on indirect evidence

- In contrast, PKU cases revealed a more fundamental gap: the very limited numbers of validated, fit-for-purpose dsPROs. Instruments such as the PKU-QoL and PKU-POMS were submitted in some cases but were often early in development, poorly validated, or lacked established minimal clinically important differences (MCIDs). Some tools were adapted from other populations (e.g. ADHD questionnaires) or developed within the same trials they were used to evaluate, raising concerns about internal validity **(Figure 4, Table 1).**
- As a result, dsPROs were rarely included in economic models for PKU and were often excluded from benefit assessments. Instead, utilities were typically inferred from biochemical surrogates (e.g. phenylalanine levels), a practice frequently questioned by HTA bodies due to the lack of direct evidence linking surrogate changes to quality-of-life improvements.

Generic measures reported across all cases

Only seven cases included generic measures (EQ-5D: 2 cases; EQ-5D and SF-36: 3 cases; SF-36: 2 cases); and two cases explicitly justified the limitations of generic tools.

- Solriamfetol (NICE 2022, TA758): EQ-5D-5L data were collected but not used as the sponsor argued that the tool lacked a sleep-related dimension, showed ceiling effects, and demonstrated minimal change in trials. This was supported by published literature and by precedent use of ESS–EQ-5D mapping in similar diseases' submission.
- Sapropterin (NICE 2021, TA729): Sponsors cited that impaired executive functioning in PKU hinders reliable self-reporting, making both generic instruments (e.g. EQ-5D, SF-36) and self-completed disease-specific tools difficult to interpret. Consequently, most evidence relied on biochemical surrogates such as phenylalanine reduction as a proxy for patient benefit.

General HTA agency responses to dsPRO evidence

HTA bodies generally acknowledged the relevance of dsPROs, particularly where generic tools were considered insensitive. However, no agency explicitly endorsed any dsPRO as a preferred measure. In practice, such measures were often downgraded or excluded due to concerns over three recurring themes: methodological robustness, incomplete patient experience and HRQoL capture, and limited interpretability or decision-making relevance **(Figure 4).**

- CDA-AMC and IQWiG applied stricter standards, often excluding dsPROs from benefit assessments due to methodological concerns. G-BA noted that future submissions could benefit from validated, purpose-built instruments to better capture patient-relevant outcomes.
- NICE occasionally accepted mapped dsPROs but questioned their validity in capturing full impact on quality-of-life change, particularly when generic preference-based measures (e.g. EQ-5D) were collected but not used.
- In the HAS cases we reviewed, dsPROs were generally accepted as supportive clinical evidence when better-validated tools or endpoints were unavailable.

Conclusions and implications

- Our findings highlight a persistent tension in rare disease HTA. Generic measures often fail to capture condition-specific impacts, especially in neurocognitive or episodic disorders, while dsPROs rarely meet HTA standards for methodological robustness or integration into cost-effectiveness frameworks. The two cases illustrate a two-fold challenge: in narcolepsy, mature instruments face scrutiny over interpretation and linkage to quality of life and economic value; in conditions like PKU, cognitive variability can undermine self-report reliability, complicating dsPRO development and limiting their uptake.
- To ensure dsPROs have greater impact, sponsors should engage early with HTA bodies to align on outcome selection and interpretation, identify fit-for-purpose instruments, and establish clear pathways to translate patient experience into credible utility inputs and decision-relevant analyses.
- As this review was limited to two rare-disease cases with subjectively rated influence, findings should be interpreted with caution.

Key message: Including dsPROs can strengthen the completeness of evidence, but consideration should be given to their intended purpose and the specific expectations of the target HTA agency.

References: *(1) Cochrane Handbook 2nd Edition. Chichester (UK): John Wiley Sons, 2019; (2) Whittal A, et al. Patient. 2021; (3) Maissen-Abgottspon, S, et al. Orphanet J Rare. 2023; (4) Woods TJ, et al. Qual Life Res. 2024.*
Declaration of funding: *This project has been funded in full by Symmetron Limited.*