Caregiver Quality of Life in Orphan Drug Health Technology Assessment Submissions in Europe: A Comparative Analysis

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HTA65

01 BACKGROUND

- Patients with rare diseases frequently require the support of one or more caregivers, often family members.[1]
- These informal caregivers provide a crucial role in supporting patients, yet they often suffer substantial financial, physical, and psychological detriment as a consequence.[2]
- CQoL is increasingly being recognised by European Health Technology Assessment (HTA) committees as a relevant factor in decision making. Several HTA agencies have published guidance on the inclusion of CQoL data in their methodological guidelines (**see Table 1**).
- These guidelines generally refer to the indirect impact that diseases may have on caregivers and family members and recommend the inclusion of CQoL data where relevant.

02 OBJECTIVE

- This study aimed to analyse and compare how CQoL is incorporated into recent orphan drug HTA submissions across Europe.

03 METHODS

- A targeted literature review of orphan drug HTA submissions in **England**, **Germany**, **Norway**, **Republic of Ireland**, **Scotland** and **Spain** between January 2024 and May 2025 was conducted. Publicly available HTA documents, including technology appraisal guidance, committee papers, and assessment reports, were identified and reviewed.
- Analysis identified CQoL measurement tools, frequency of inclusion, evidence requirements, methodological approaches, barriers to integration and the impact of CQoL on decisions.

04 RESULTS

Analysis of CQoL incorporation into recent European orphan drug HTA submissions revealed varying approaches and acceptance rates. In each country (except Scotland) the majority (50-100%) of orphan drug HTA submissions were for paediatric or adolescent indications (**Table 2**). The distribution of CQoL inclusion, measurement tools, patient populations, and economic model integration are summarised in **Table 2**, and the therapeutic areas represented in the review are shown in **Figure 1**.

Figure 1. Therapeutic Areas Indicated in Orphan Drug HTA Submissions that Included CQoL, (n=63) January 2024 - May 2025

Country-Specific Findings

- England demonstrated a high CQoL incorporation rate of orphan drug HTA submissions, and the majority were for paediatric indications (**Table 2**).
- Health-related quality of life (HRQoL) estimates were derived using validated instruments (7/16 submissions) and disease specific HRQoL tools (1/16). In the remaining 9 submissions, CQoL was mentioned qualitatively with no quantitative data provided (**Table 2**).
- CQoL was incorporated into economic models using carer disutilities (5/16) or carer utility benefit (4/16), with limited rationale provided for the selection of the approach.
- Due to the lack of available primary data, proxy values for caregiver (dis)utilities were used in four orphan drug HTA submissions.
- The main criticisms regarding use of CQoL were a lack of CQoL derived from pivotal trials, use of proxy data and vignette studies from outside the scoped population to generate HRQoL and utilities for carers, and assumptions regarding (dis)utilities, particularly regarding the number of carers (**Figure 2**).

- In Germany, the majority of orphan drug HTA submission mentioning CQoL were for paediatric indications, as reflected in the QoL measurement tools used (**Table 2**).
- However, CQoL data were not used to support any economic model, as modelling is not a requirement in the German system.[3]
- Interestingly, the most recent IQWiG guidance (**Table 1**) states that the effect of the intervention on indirectly affected individuals, including caregivers, can be taken into account in the HTA assessment, but does not elaborate on specific methodological recommendations.[4]

- In the Republic of Ireland, the impact of CQoL was included in scenario analyses within the economic model in all five paediatric orphan drug HTA submissions. (**Table 2**).
- One orphan drug HTA submission (1/5; 20%) was rejected due to insufficient evidence. Following assessment, no drugs were initially recommended, but one (1/5; 20%) was subsequently recommended following a price negotiation.

- In Norway, all four cases of CQoL evidence in the economic model was rejected by the assessment committee due to inadequate standards regarding the quality of CQoL data, lack of CQoL data derived from pivotal studies and use of proxy data from other populations or conditions (**Figure 2**).
- It is important to note that CQoL was not considered in two orphan drug HTA submissions via the JNHB (Joint Nordic HTA bodies; a joint assessment route encompassing the five Nordic countries) due to differing guidelines and reference cases regarding economic modelling for the different Nordic countries.

- Scotland demonstrated the highest incorporation rate of CQoL in orphan drug HTA submissions, however, only one (7%) included CQoL in the economic analysis (**Table 2**).
- All CQoL input used proxy data and reported using a generic QoL measurement tool.
- In contrast to other countries, 70% (7/10) orphan drug HTA submissions were for drugs with an indication for adult patients (**Table 2**).
- In all cases, CQoL was discussed at a Patient and Clinician Engagement (PACE) meeting, with key themes raised regarding impacts on CQoL including the impact of patient side effects, medical emergencies, treatments, worry regarding future health and the unknown, behavioural issues in children, financial implications due to loss of earnings and travel away from home.

- The Spanish Agency of Medicines and Medical Devices (AEMPS) in Spain publish a final HTA report summary (Informe de Posicionamiento Terapéutico, IPT) but do not publish other documentation used by the CIPM (Interministerial Commission on Medicine Prices) to make approval decisions regarding orphan drugs.[5]
- HTA reports are only published if the drug receives a positive or conditional recommendation.
- In 55% (6/11) orphan drug HTA submissions it was inferred that CQoL was incorporated into an economic model, but no methodological details were provided in the published reports (**Table 2**).

Figure 2. Barriers to the Inclusion of CQoL in HTA Submissions

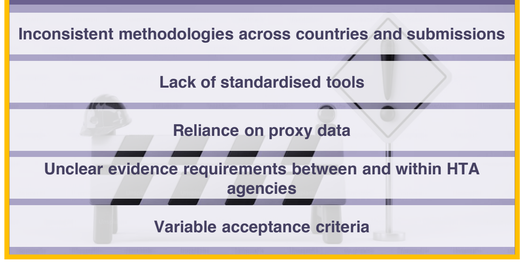

Table 1. Current Status of Inclusion of Caregiver QoL in HTA Guidance in Europe

Country (HTA Agency)	Guidance date	CQoL discussed in guidance	CQoL accepted in submissions	Recommendations on how CQoL can be used
England[6] (NICE)	2022 (2025 update)	✓	✓	Include detail on health effects for carers where relevant, with evidence of how the condition has a substantial effect on CQoL and how the technology may affect the carer.
Germany[4] (IQWiG)	Sept 2025	✓	✓	Effect of the intervention on indirectly affected individuals, including caregivers, can be taken into account (no further guidance).
Norway[7] (NoMA)	2018 (2024 update)	✓	✓	CQoL can be included in economic analyses quantified as QALYs with the same level of evidence as provided for patients including the effect of the condition and the impact of the intervention and comparator on CQoL.
Republic of Ireland[8] (HIQA)	2025	✓	✓	Health spillovers (impact on family and caregiver health) can be considered in economic evaluations.
Scotland[9,10] (SMC)	2019 (2025 update)	✓	✓	Separate sensitivity analyses including appropriate data on utilities/QALYs for carers can be provided as additional evidence separate from the primary QALY analysis. Clinical data on the impact of the intervention on CQoL (using QoL tools) and impact on cost-effectiveness (including carer disutilities) can be included in submissions for ultra-orphan drugs. CQoL can also be discussed in partnership with patient groups and in PACE meetings.
Spain[11] (CAPF)	February 2025	✓	✓	Guideline acknowledges CQoL conceptually but does not mandate its inclusion, positioning it within the optional social perspective rather than the base case healthcare payer perspective. It is stated that CQoL should be appropriately measured and valued. The guideline calls for CQoL inclusion in ethical and equity discussions given the broader implications of health technologies.

Table 2. Incorporation of Caregiver Quality of Life in Orphan Drug HTA in Europe

Country	Proportion of HTAs that included CQoL	Patient population of studies that mentioned CQoL	HRQoL measurement tools used	Proportion of drugs recommended	Economic model integration of CQoL
England[6]	59% (16/27)	Adult: 38% (6/16) Adolescent: 6% (1/16) Paediatric: 56% (9/16)	▪ EQ-5D ▪ CFQR-8D ▪ CarerQoL-7D ▪ DMD-QoL ▪ SF-12 ▪ HADS ▪ ZBI	56% (9/16)	56% (9/16)
Germany[4]	38% (13/34)	Adult: 31% (4/13) Paediatric: 69% (9/13)	▪ ITQoL ▪ QoLISSY	8% (1/13)	NR
Norway[7]	27% (8/30)	Adult: 50% (4/8) Paediatric: 50% (4/8)	▪ EQ-5D	25% (2/8)	50% (4/8)
Republic of Ireland[8]	17% (5/30)	Paediatric: 100% (5/5)	▪ VAS ▪ TTO	20% (1/5) recommended	NR
Scotland[9,10]	71% (10/14)	Adult: 70% (7/10) Paediatric: 30% (3/10)	▪ EQ-3D	80% (8/10) recommended 20% (2/10) accepted for restricted use	10% (1/10)
Spain[11]	13% (11/87)	Paediatric or paediatric & adult: 100% (11/11)	▪ CATCH questionnaire ▪ CGI-I ▪ CIS ▪ Paediatric Quality of Life Inventory (PedsQL) ▪ PedsQL Family Impact Module ▪ PROMIS-parent ▪ Sleep Disturbance Scores	91% (10/11) recommended* 9% (1/11) conditional authorisation*	55% (6/11) mentioned inclusion, but no details provided

*Unsuccessful HTA submissions not reported

05 DISCUSSION AND CONCLUSIONS

- CQoL was often included in European orphan drug HTA submissions using a variety of **qualitative, quantitative, and mixed methods of measurement**. However, the quality of CQoL data and the tools used to measure it were inconsistent both within and across different countries' submissions
- Due to a lack of quality CQoL data included in pivotal trials, **proxy data and vignette studies were often used to provide values, however this approach was often criticised or rejected by HTA committees**.
- CQoL was incorporated into economic evaluations in England, Norway, Republic of Ireland, Scotland and Spain, however the methods used were often not well defined or reported.
- When included in economic models, CQoL often impacted cost-effectiveness, however criticism regarding the approach used was common. In England common criticisms of CQoL in economic models included use of proxy data not matching the scoped population, while in Norway the main criticism was the CQoL data did not satisfy the requirements for consideration.
- In one case regarding sickle cell disease in England, **qualitative consideration of the impact of CQoL was used to offset uncertainty in an unacceptable economic model and clinical effectiveness evidence**.
- In conclusion, CQoL is applied in submissions for orphan drugs with varying success across European HTAs. Key barriers to acceptance of CQoL in submissions include lack of robust QoL measurement in pivotal trials, use of proxy data and lack of consistent guidance methods for incorporation of CQoL in economic models. **The potential consequence of failing to adequately capture the impact of caregiving in the treatment of orphan conditions in HTAs, are reimbursement decisions that underrepresent and fail to acknowledge the practical, financial, and social impacts on families and caregivers**

Abbreviations

CAPF, Advisory Committee on the Financing of Pharmaceuticals; CarerQoL-7D, Carer Quality of Life 7-Dimension; CATCH, Comprehensive Assessment Tool of Challenges in Hemophilia; CFQR-8D, Cystic Fibrosis Questionnaire-Revised 8-Dimension; CGI-I, Clinical Global Impression of Improvement; CIS, Caregiver Impression of Severity; CQoL, caregiver quality of life; DMD-QoL, Duchenne Muscular Dystrophy Quality of Life; EQ-3D, EuroQol 3-Dimension Questionnaire ; EQ-5D, EuroQol 5-Dimension Questionnaire; HADS, Hospital Anxiety and Depression Scale; HIQA, Health Information and Quality Authority; IQWiG, Health Information and Quality Authority; ITQoL, Infant Toddle Quality of Life questionnaire; NA, not applicable; NICE, National Institute for Health and Care Excellence; NoMA, Norwegian Medical Products Agency; NR, not reported; PedsQL, Pediatric Quality of Life Inventory); PROMIS-parent, Patient-Reported Outcomes Measurement Information System parent Proxy Profile; QALYs, quality adjusted life years; QoL, quality of life; QoLISSY, Quality of Life in Short Stature Youth – Children; PACE, patient and clinician engagement; SF-12, Short Form 12-item Health Survey; SMC, Scottish Medicines Consortium; TTO, time trade off; VAS, visual analogue scale; ZBI, Zarit burden interview.

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