Evaluating the acceptability of vignette studies in eliciting utility values for rare diseases: perspectives from European HTA agencies

Dodd O[1], Bridge D[1], Chassat C[1], Heron L[1]
[1]Adelphi Values PROVE™, Bollington, Cheshire SK10 5JB, United Kingdom

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Introduction

While access challenges for rare disease treatments can be influenced by various factors, a key contributing issue relates to the complexities of establishing cost-effectiveness in health technology assessments (HTAs).[1,2] HTA agencies typically prefer utility values from generic measures, but this can be challenging for rare diseases due to small, heterogenous populations, and measures which may not sufficiently capture impact on health-related quality of life (HRQoL). Where utility values from clinical trials are unavailable or generic measures are insufficiently sensitive or appropriate for HRQoL assessment, vignette-based studies can be employed.[3,4] In these studies, detailed descriptions of disease or treatment health states are developed and valued using preference-elicitation methods such as time trade-off (TTO), standard gamble (SG), or the EQ-5D. Valuations may be obtained from members of the general population, clinical expert proxies, or, where feasible, patients or caregivers themselves.[4,5] This approach provides utility estimates when direct measurement is not possible, although HTA agencies acknowledge the greater uncertainty inherent in vignette-based valuations.[4,5]

We sought to investigate the acceptability of vignette studies to elicit utility values in rare diseases to inform HTA submissions and any associated methodological considerations given the criticality of utility data in HTA submissions.

Methods

A targeted review of HTA guidance documents was conducted across eight European countries for perspectives and commentary on the use of vignette-based methodologies for the elicitation of utility values in rare disease (Figure 1). Table 1 outlines the countries and HTA agencies included within the review. Countries were then ranked by level of acceptability based on the evidence available. A lack of available guidance was considered within the ranking.

Figure 1. Overview of methodology

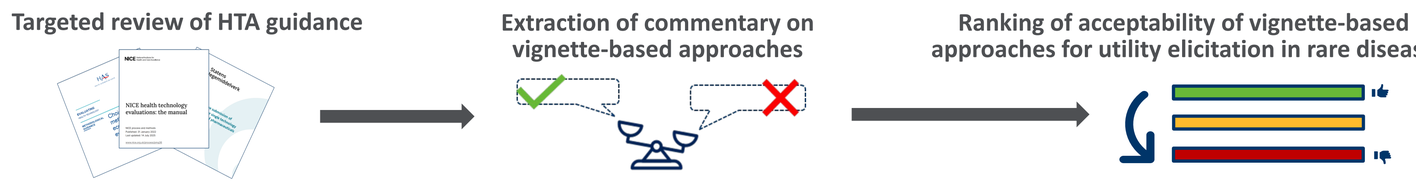


Table 1. HTA agencies included within review

Country	HTA agency (abbreviation)
UK	National Institute of Health and Care Excellence (NICE)
Denmark	Medicinrådet
France	Haute Autorité de santé (HAS)
Germany	Institute for Quality and Efficiency in Health Care (IQWiG) / Germeinsamer Bundesausschuss (G-BA)
Italy	Agenzia italiana del Farmaco (AIFA)
Norway	Norwegian Medical Products Agency (NoMA)
Spain	Ministerio de Sanidad
Sweden	Tandvårds- och läkemedelsförmånsverket (TLV)

Results

Across European countries, HTA agencies broadly prefer direct patient-reported utilities (especially EQ-5D) but may consider vignette-based approaches when direct measurement is infeasible, most often in ultra-rare or paediatric settings (Figure 2).

UK

In the UK, NICE prefers patient-reported EQ-5D utilities in the reference case; however, alternative approaches, including vignette approaches, can be considered when direct data are justified as unavailable or infeasible especially in rare and ultra-rare settings.[3,6]
NICE guidance suggests that if the EQ-5D is justified as unavailable or infeasible in the disease context, alternative suggested methods include:[3,6]

1) Vignette-based approaches including valuation with the EQ-5D (with clinical experts, patients, or the general population), TTO with the general population, and elicitation with clinical experts (e.g. using Delphi panels or TTO).
2) "Proxy condition" utility values involving the use of utility values from another disease as a proxy for the disease in question.

Sweden

The TLV bases assessments on QALYs and notes that weights can be derived using methods such as TTO or SG. Although TLV does not explicitly instruct on vignettes, the framework allows indirect utility estimation when well-documented.[10]

Denmark and Norway

HTA agencies that reference international standards, such as NICE, (Denmark and Norway) acknowledge that direct patient elicitation is preferred (e.g. through generic utility measures); however, where data are unavailable or infeasible, vignette-based approaches are acceptable if rigorously conducted.[7,8] Denmark's Medicinrådet moved formally to quality-adjusted life years (QALY)-based evaluations in 2020 and, while sharing no specific guidance for vignette-based approaches, the method handbook emphasises transparent economic evidence and references NICE. As of September 2025, the guidelines for submitting a single technology appraisal to NoMA state that EQ-5D-5L data are preferred for documenting HRQoL.[9] However, the guidance states a hierarchy of evidence which recognizes that if empirical evidence shows that the EQ-5D is unsuitable, and values from another generic instrument are also unsuitable, values from vignette-based approaches can be accepted.[9]

Spain

The Ministerio de Sanidad does not offer specific guidance on vignette-based approaches. However, the available documentation explicitly recommends the use of EQ-5D or SF-6D with the Spanish general population to generate QALYs to inform subsequent economic evaluations. Direct valuation of vignettes is hence acceptable only with strong justification, full transparency, and robust sensitivity analysis.[13]

Italy

The AIFA requires economic evaluations to describe and justify HRQoL sources but offers no specific guidance on vignette-based approaches. This results in pragmatic, case-by-case appraisals when EQ-5D collection is infeasible.[12]

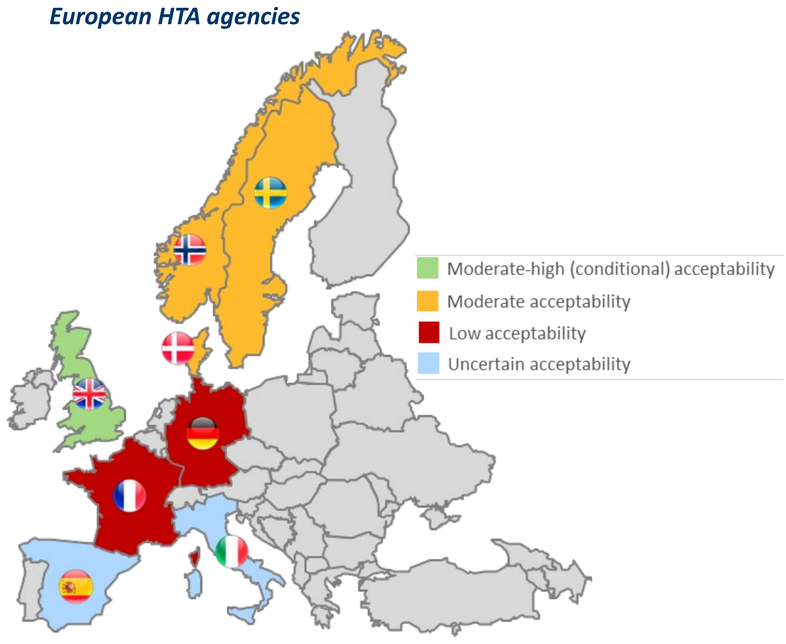
France

The HAS in France requires validated instruments (EQ-5D) and full methodological transparency in economic evaluations. Approaches based on hypothetical health states, such as vignettes, are not recommended for primary analyses or sensitivity analyses.[11]

Germany

IQWiG placed the greatest weight on empirically observed patient data and standardised instruments. Specifically, expert-valued vignette utilities face high scepticism and would be accepted only in exceptional circumstances with extensive transparency.[14]

Figure 2. Acceptability of vignette-based approaches across European HTA agencies



Moderate-high (conditional) acceptability: HTA agency prefers direct patient-reported utilities (e.g. EQ-5D or similar). Specific guidance on use of vignette-based approaches is publicly available, and use of vignette-based approaches has been accepted and specifically discussed in previous HTA appraisals.
Moderate acceptability: HTA agency prefers direct patient-reported utilities (e.g. EQ-5D or similar) but permits vignette-based approaches as exceptions if direct measurement is unavailable or inappropriate. Vignette-based approaches may be accepted when direct measures are unavailable or inappropriate, but guidance is less explicit, not comprehensive, or only references international/other agencies' standards. There is limited or no discussion of the use of vignette-based approaches in previous appraisals.
Low acceptability: HTA agency expresses a strong preference for patient-reported or directly measured utilities and only considers vignettes in exceptional cases. If permitted, requirements for transparency and justification are very stringent, and vignette-based data is viewed skeptically.
Uncertain acceptability: HTA agency provides no specific guidance on vignette-based approaches, and there are no clear precedents or published examples of acceptance or rejection. The acceptability is unclear and may depend on case-by-case negotiation or future decisions.

Case study - Cerliponase alfa (Brineura®)

Cerliponase alfa (Brineura®) is an enzyme replacement therapy (ERT) for neuronal ceroid lipofuscinosis type 2 (CLN2), an ultra-rare paediatric neurodegenerative condition leading to progressive motor and cognitive decline, blindness, and premature death.[15] The health technology developer submitted evidence for review by NICE in the UK via the highly specialised technologies (HST) route in 2019.[15] Utility values elicited during clinical trials were not available for all health states within the model, and no utility values were available for patients receiving standard care.[15] Therefore, the health technology developer submitted a vignette-based utility study in which clinical experts acted as proxies to elicit utility values via the EQ-5D for relevant disease states, to subsequently inform the cost-effectiveness model.[15] The utility values were mapped to the EQ-5D-3L before being applied in the model.[15] The Evidence Review Group (ERG) committee was concerned about the robustness of the vignettes used to elicit these utility values and noted that it would generally be preferred to include values directly collected in trials.[15] However, it was acknowledged that the Pediatric Quality of Life Inventory (PedsQL) measure (clinical trial patient-reported outcome measure (PROM) excludes the possibility of negative values, so may not be realistic given the severity of disability with CLN2.[15] It was therefore recognised that, in the absence of further evidence, the committee would consider analyses based on EQ-5D-3L values estimated from the utility study using vignettes, in line with guidance documents.[3,6,15] This demonstrates conditional acceptability, but a requirement for transparency, justification, and sensitivity analysis.

> *"However, it [the NICE review committee] concluded that, in the absence of further evidence, it would consider analyses based on EQ-5D-3L values estimated from the utility study using vignettes."*
> ***NICE, 2019 [HST12]***

Across Europe, decision-making reflects a pragmatic but cautious approach. The UK (NICE) set a precedent for conditional use of vignette utilities in CLN2, granting a positive Managed Access Agreement for Brineura®.[15] France (HAS), Germany (IQWiG / Germeinsamer Bundesausschuss), Italy (AIFA) and Spain (Ministerio de Sanidad) issued positive or favourable positions that enable access.[16-19] However, no HTA agency other than NICE provided explicit methodological commentary on the use of vignette-derived utilities in their assessment of Brineura®, suggesting that acceptance was largely assessed on a case-by-case basis rather than formally endorsed, and it is unclear whether the same data were submitted across all HTAs.[15-19] In contrast, Norway's NoMA did not introduce Brineura® nationally,[20] in Sweden, TLV has not included Brineura® in the national pharmaceutical benefits scheme,[21] and no positive national decisions were identified from Denmark's Medicinrådet. Overall, the Brineura® case indicates that vignette studies can be considered acceptable when rigorously developed, transparently documented, and contextually justified, but clear cross-agency guidance on their methodological application remains lacking.

Conclusions

European HTA agencies generally prioritise direct patient-reported utilities (typically EQ-5D with country-specific general population valuation) but will accept vignette-based utilities in rare or paediatric diseases when direct measurement is justified as infeasible and methods are rigorous. In practice, acceptance generally hinges on a systematic vignette development process (published literature, clinician and, where possible, caregiver/patient input), transparent health-state definitions aligned to validated clinical scales and the economic model and appropriate valuation (e.g., TTO or SG with a representative general-population sample or clearly justified expert panels). This is important as generic measures can be insensitive in ultra-rare conditions, and utility inputs often drive the incremental cost-effectiveness ratio (ICER). A practical strategy is to draw on several types of evidence, use any available trial or EQ-5D values (where appropriate), map disease-specific measures where valid, and augment gaps with vignettes, while fully documenting assumptions, sample characteristics, and validation steps. Cross-country comparison indicates some conditional openness, reinforcing that methodological transparency, justification, and sensitivity testing are essential to optimise the credibility of cost-effectiveness results and, ultimately, patient access to new therapies.

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