Mendelian Randomization Identifies the Potential Causal Impact of Dietary Patterns on Circulating Blood Metabolites

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Consideration of quality of life in the health technology assessments of rare disease treatments

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Key words: patient-reported outcome, rare disease, orphan medicinal products, health-state utility value, health technology assessment, reimbursement

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ABSTRACT

Objectives: Challenges with patient-reported outcome (PRO) evidence and health state utility values (HSUVs) in rare diseases exist due to small, heterogeneous populations, lack of disease knowledge and early onset. To better incorporate quality of life (QoL) into Health Technology Assessment, a clearer understanding of these challenges is needed.

Methods: NICE appraisals of non-oncology treatments with an EMA orphan designation (n=24), and corresponding appraisals in the Netherlands, France, and Germany were included. Document analysis of appraisal reports investigated how PROs/HSUVs influenced decision-making and was representative of QoL impact of condition and treatment.

Results: PRO evidence was not included in 6/24 NICE appraisals. When included, it either failed to demonstrate change, capture domains important for patients, or was uncertain. In the other countries, little information was reported and evidence largely did not demonstrate change. In NICE appraisals, HSUVs were derived through the collection of EQ-5D data (7/24 cases), mapping (6/24), vignettes (5/24), and published literature or other techniques (6/24). The majority did not use data collected alongside clinical trials. Few measures demonstrated significant change due to lack of sensitivity or face validity, short-term data, or implausible health states. In 8/24 NICE appraisals, patient surveys or input during appraisal committee meetings supported the interpretation of uncertainty or provided evidence about QoL.

Conclusions: This study sheds light on the nature of PRO evidence in rare diseases and associated challenges. Results emphasise the need for improved development and use of PRO/HSUVs. Other forms of evidence and expert input are crucial to support better appraisal of uncertain or missing evidence.

Introduction

Rare diseases are conditions affecting a small number of patients (e.g. less than 1/2,000 people in Europe), which are life-threatening and/or chronically debilitating, frequently genetic and with an early onset [1, 2]. Quality of life (QoL) of patients living with a rare disease is often poor due to multiple aspects affecting functioning [3]. This is partly explained by issues around diagnostic delays, and/or a lack of knowledge about the disease, its treatment pathways or treatment options [3]. Given the severity of these conditions and paucity of curative treatments, understanding their impact on QoL is crucial, particularly when assessing the benefit of a new treatment.

Health Technology Assessment (HTA) aims to assess the value of a treatment to inform decisions on whether it should be provided routinely to the relevant patient population. The assessment generally relies on clinical and patient-reported outcome (PRO) endpoints, which provide evidence about health outcomes and impact on patients' wellbeing [4]. In the latter case, PRO evidence is collected directly from patients or proxies using patient-reported outcome measures (PROMs) [5]. PROMs are intended to capture aspects that matter most to patients about the impact of disease and treatment on symptoms, QoL or health status [6].

HTA relies on the critical assessment of added benefit or cost-effectiveness of a treatment. This is then appraised by a Committee, taking account of other relevant factors, who decide on reimbursement (and pricing in some cases). Added benefit is assessed by considering the magnitude and certainty of treatment benefit over existing therapies based on the clinical and PRO evidence presented. The level of benefit is then generally ranked into categories as, for example, in France, where the added benefit (ASMR) is ranked between I and V. In cost-effectiveness assessments, an economic evaluation is conducted that models the progression through health states along the care pathway, with and without the new treatment under review. In order to assist cost-effectiveness assessments, techniques have been developed to translate PRO evidence into numerical values called health state utility values (HSUVs). HSUVs represent individual preferences for given health states measured on a scale between 0, representing dead and 1, full health (with negative values implying states considered to be worse than dead). These are then merged with survival data (e.g., length of life) into a composite measure called quality-adjusted life-year (QALY). HSUVs represent the utility value associated with the different models' health states, for both treatment and comparator arms [7]. The most common way of deriving HSUVs is currently using indirect techniques, e.g. preference-based instruments such as EQ-5D that are accompanied by an algorithm (or a set of tariffs) providing HSUVs. Tariffs are pre-determined at individual country level by a sample of the general population that uses direct techniques (e.g. time trade-off) to express preferences for a subset of health states derived from the combination of instrument's dimensions and levels.

Challenges exist when developing and using PRO evidence and HSUVs for HTAs of rare diseases treatments due to the small and heterogeneous nature of the patient populations, and frequent lack of knowledge about the disease [8, 9]. Additionally, patients are often children or infants who cannot self-report and who may be cognitively impaired or unable to communicate. There may also be

distinct challenges around capturing meaningful outcomes, including: difficulty achieving concept validity through concept saturation, use of methods that may not capture aspects important for patients, or selecting the appropriate PROM when natural history is poorly understood. There are also few validated disease-specific PROMs for rare diseases, probably due to the amount of time and resources needed to develop these instruments, which are further complicated by the nature of these diseases [10].

Additional challenges frequently encountered when deriving and using HSUVs for rare diseases include the need for a large number of respondents to minimise random measurement errors (e.g. person-trade-off, development of mapping algorithms), identification of appropriate values corresponding to the model's health states from the existing literature, and QALYs being insufficiently sensitive to disease severity or changes that are important for patients [11–14].

Although these challenges in measuring QoL are common to all rare disease treatments, they are most important in treatments of non-oncological diseases, since in cancer the main value of treatment is often increased survival, and many rare disease treatments in cancer are for sub-populations of a more common cancer for which validated QoL measures may be available.

To better incorporate QoL evidence into HTA decision-making, a clearer understanding of the challenges encountered when using PRO evidence and HSUVs in rare diseases is needed. Hence this research explored how QoL evidence has been used in appraisal of non-oncology rare disease treatments in a selection of countries using different HTA approaches.

Methods

Study sample

For this EU Horizon2020 project, European countries were selected to represent those that make decisions based on added clinical benefit and those that focus on cost-effectiveness, and who have publicly available reports. Those selected were England (National Institute for Health and Care Excellence, NICE) and the Netherlands (National Health Care Institute, ZIN) as users of the cost-effectiveness approach, and France (Haute Autorité de Santé, HAS) and Germany (Federal Joint Committee, G-BA) as users of the added benefit approach. Considering the depth of the analysis conducted, the inclusion of four countries was considered sufficient to understand the nuances between one HTA approach and another, and the types of contrasts within one approach. As only the reports from NICE presented detailed information about the committee deliberations of the QoL evidence, the analysis focused on the NICE appraisals, and other countries' appraisals were used as a contrast to highlight any different approaches.

All treatments with a European Medicines Agency (EMA) orphan medicinal product designation and appraised by NICE within its Technology Appraisal (TA) or Highly Specialised Technologies (HST) programmes before 1 June 2020 were selected (n=50). Cancer treatments (26) were excluded

because added benefit often relies on survival gains, and many rare cancers are subsets of more common cancers for which a validated PRO often exists [4, 15]. This left 24 rare disease treatments (12 TA and 12 HST) for analysis [16, 17, 26–35, 18, 36–39, 19–25] In the results section, the information reported for the individual NICE sample was extracted from these reports.

Data collection and analysis

Information about QoL, PROs, HSUVs and other evidence from patients about their QoL (such as patient group submissions and patient expert input) was extracted from NICE's appraisal reports. These were sufficiently detailed to enable documentation of the source of the evidence, results, issues highlighted by the appraisal committee and the influence on the decision. If needed, supporting documentation such as manufacturer submissions and Evidence Review Group (ERG) reports were reviewed. A published framework was used to extract these key aspects of the appraisal in a structured way [40]. PRO evidence was categorised on the basis of the type of PROM used (generic, disease-group (developed for a range of conditions), disease-specific or symptom-specific). HSUVs were categorised on the basis of the technique used to derive them (e.g. collection using an instrument such as EQ-5D, or mapping from other PROMs).

Thematic analysis was undertaken to identify issues arising in appraisals and their influence on decision-making based on the researchers' interpretation of the discussion reported in the published documents. The identification of themes was done iteratively and was continuously refined while the researchers familiarised themselves with the data and grouped the data in a logical way to allow for a better understanding of the decision process [41]. Once the themes were identified and categorised, the researchers assessed the level of influence of PRO evidence or patient evidence on decisions. This was categorised as "influence" when the Committee explicitly recognised and accounted for a change in QoL in their decisions, "possible influence" when PRO evidence or patient evidence was explicitly reported but considered limited by the Committee and it was therefore unclear whether it influenced the decision, and "no influence" when PRO evidence or patient evidence was reported, but inconclusive or failed to demonstrate change and did not influence the Committee's decision. HSUVs were considered in all cases to have influence on the decision, since the Committee always took note of the incremental cost per QALY ratio. The interpretation of the HSUV evidence was distinguished as "accepted" when the Committee recognised the evidence presented was acceptable, "not commented" when no issues were raised with the HSUVs presented and therefore there was a high likelihood that it was accepted, and "uncertain" when a number of issues around the HSUV were highlighted, which rendered their interpretation challenging.

The second set of extracted information related to the burden of disease and treatment impact: infant/childhood onset; progressive; heterogeneous; multi-systemic; debilitating; life-threatening; supportive care; and regarding the impact of treatment on QoL: length of life improved, QoL improved from reduced symptoms, daily living, families/carers, compared to current treatment, administration

mode. The burden of disease and intended impact of the treatments reported in the HST and TA programmes, respectively, were extracted and compared.

The analysis aimed to understand how QoL was appraised, and the extent to which PRO evidence and/or HSUVs were considered appropriate. The possible influence of the nature of the rare diseases on PRO evidence and HSUV estimates was also explored to generate a better understanding of what was feasible in the different contexts. In the cross-country analysis, the information reported by the other countries was scarce. The focus was therefore on the PRO evidence and HSUVs considered and their influence on the decision.

Results

Impact of disease and treatment on quality of life

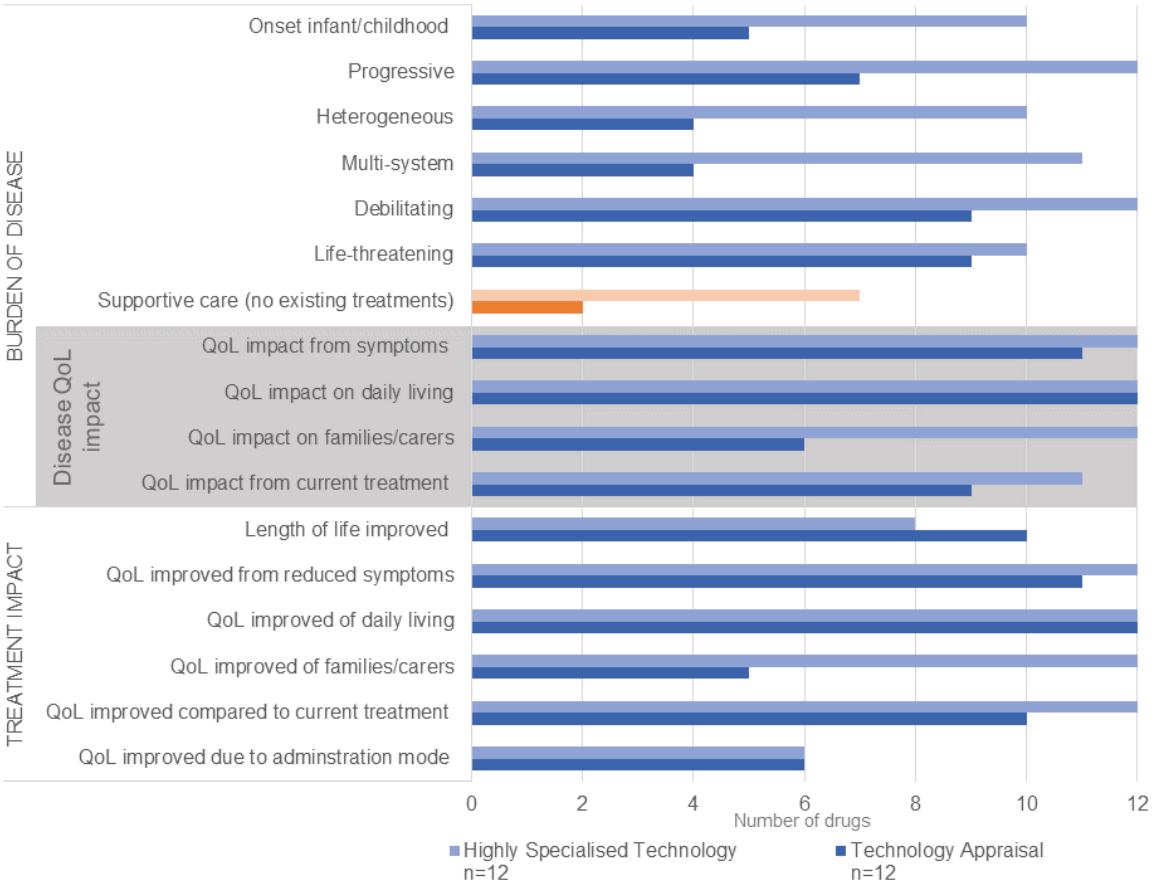
Most of the diseases undergoing the TA and HST processes were life-threatening and/or debilitating (Figure 1). The burden of disease, however, was greater in the diseases undergoing the HST programme compared with the TA in that these diseases affect children, have a heterogeneous and progressive nature, or affect multiple organs. With the exception of the prophylaxis treatment letermovir, the symptoms of all of the diseases analysed affect patients' daily living and QoL. No previous treatments were available for 58% (7/12) and 17% (2/12) of those undergoing the HST and TA processes, respectively.

In terms of the intended effects of treatment, 67% (8/12) of HST and 83% (10/12) of TA treatments aim to improve length of life, while all improve patients' daily living and QoL by reducing symptoms (with the exception of letermovir). Six of these aim solely to improve QoL. Furthermore, all of the HST and 83% (10/12) of the TA treatments aim to improve patients' daily living and QoL over standard of care. In 50% of all cases (12/24), QoL improvement is linked to a different administration mode.

All conditions appraised by HST and half of those by TA were considered to affect carer QoL. In all cases, with the exception of letermovir, the treatment intends to improve their QoL.

The estimated yearly number of patients to be treated in England ranged between 1-50 for 10 of the 12 HST treatments [1-7 patients for 3 treatments, 20-35 for 2 treatments, 50-100 for 3 treatments, and 140-150 for 2 treatments]. No details about patient numbers were provided in all other cases.

Figure 1. Proportion of appraisals for which various items of burden of disease and treatment impact are relevant in NICE Highly Specialised Technology and Technology Appraisal programmes (n=24)



Use and influence of PRO evidence in NICE appraisals

In NICE appraisals, PROMs can have an influence either through being considered directly and/or through their use in generating HSUVs. Across the 24 treatments appraised by NICE, 28 different PROMs were reported. This included 10 generic PROMs considered across 14 treatments, seven disease-group PROMs across seven treatments, three disease-specific PROMs across five treatments, and eight symptom-specific PROMs across seven treatments (Table 1). Several PROMs could considered for the same treatments. Examples of disease-group PROMs include the Paediatric Outcomes Data Collection Instrument (PDOCI) measuring functional outcomes in paediatric orthopedics [42], and the St George's Respiratory Questionnaire (SGRQ) measuring overall health, daily life, and perceived well-being in patients with obstructive airways disease [43]. The three disease-specific PROMs considered were for cystic fibrosis (Cystic Fibrosis Questionnaire Revised questionnaire, CFQ-R), recurrent angioedema (Angioedema Quality of Life questionnaire, AE-QoL), and neuronal ceroid lipofuscinosis type 2 (Neuronal Ceroid Lipofuscinosis Type 2 Quality of Life Instrument, CLN2-QoL). The seven symptom-specific PROMs related to pain, gastro-intestinal symptoms, diabetic neuropathy, fatigue, asthma, and anxiety and depression (Table 2).

Forty-two percent (10/24) of submissions did not include any generic PRO, and 25% (6/24) no PRO evidence at all. Reasons for the latter included PRO evidence not collected in trials (elosulfase alfa, obetocholic acid, holoclar), collected but limited (strimvelis), being collected and not reported (burosumab), or not presented given it was a re-assessment based on new clinical evidence (pirfenidone). In two of the cases without PRO evidence, other QoL evidence was considered, such as observational studies and cross-sectional surveys involving patients and families (elosulfase alfa), and visual acuity data from the literature used to derive HSUVs (holoclar) (Table 1). QoL evidence for the remaining drugs without PRO data was based on HSUVs derived from vignettes or published evidence (Table 3, discussed in the next section on HSUVs).

Table 1. Types and influence of PRO evidence considered in NICE TA and HST appraisals of non-oncology rare disease treatments (n=24)

		PRO data considered in NICE appraisals by PROM type and level of influence				**Patient evidence**
		Generic	**Disease-group**	**Disease-specific**	**Symptom-specific**	
NICE Highly Specialised Technology	Asfotase alfa	++	NR			
	Eculizumab	HSUV				+++
	Patisiran	HSUV			+++	+++
	Voretigene		NR			
	Cerliponase	++		++		
	Elosulfase alfa*					+++
	Ataluren	++	++			
	Migalastat	≈			≈	+++
	Eliglustat	HSUV			++	+++
	Strimvelis**					
	Burosumab**					
NICE Technology Appraisal	Inotersen				≈	
	Mannitol	HSUV		++		
	Colistimethate sodium and tobramycin dry powders for inhalation (DPI) [=antibiotics]			HSUV		+++
	Nintedanib	HSUV	NR		NR	++

	Lumacaftor–ivacaftor	HSUV		++		
	Mepolizumab	HSUV	HSUV		NR	
	Obeticholic acid**					
	Holoclar *					
	Pirfenidone***					
	Darvadstrocel		NR			
	Nusinersen	HSUV				
	Letermovir	≈	≈			+++
	Lanadelumab	≈		≈	NR	

Legend: HSUV: Health State Utility Value; NICE: National Institute for Health and Care Excellent; PRO: Patient Reported Outcome; PROM: Patient Reported Outcome Measure

*No PRO data was provided, but patient based evidence or PRO data from the literature was used instead

** No PRO data was provided, QoL evidence was derived from HSUVs from vignettes or published literature

*** No PRO data was included in the appraisal report as this is a re-assessment and no new QoL evidence was presented

+++	**Influence** – PRO results / patient evidence were influential in the final decision
++	**Possible influence** - PRO results / patient evidence were reported and suggested some type of benefit, but no discussion about these results was reported
≈	**No influence** - PRO results were reported, but did not show any benefit and no discussion about these results was reported
NR	**Not reported / no influence** - PRO results not reported, but the report listed the PROM as having been collected
HSUV	**Used to derive HSUVs** – PRO results was used to derive HSUVs (further discussed in Table X)

Table 2. Use and influence of PRO evidence in NICE TA and HST appraisals of non-oncology rare disease treatments (n=24)

MEDICINE Generic name - indication	PROM (by type) Instrument (source)	PRO EVIDENCE Description of results	APPRAISAL Influence of PRO evidence on decision
Asfotase alfa Paediatric-onset hypophosphatasia	**G** - EQ-5D (EU patient survey) **G** - CHAQ, LEFS (small trials)	EQ-5D - children 0.76 treatment arms 0.43 no treatment - adults 0.39 no treatment - scores varied depending on walking ability [-0.24 to 0.73 in children, -0.01 to 0.51 in adults] Other trial PRO data in academic confidence	EQ-5D results not used to derive HSUVs but may have been considered by clinicians when developing the vignette's health states based on 6MWT severity levels. Specifically, mental health and pain domains
Eculizumab Atypical haemolytic uraemic syndrome (aHUS)	**G** - EQ-5D (2 phase II prospective, open-label, non-randomised, single arm trials, n=37) **P** - Survey (patient submission, n=37)	EQ-5D: mean improvement = 0.208 Survey: burden of disease and of current treatment on patients, carers/families	EQ-5D used to derive HSUVs. Survey shows greatly impaired QoL of patients and carers from living with aHUS
Patisiran Hereditary transthyretin amyloidosis	**G -** EQ-5D-5L (RCT, n=255) **D -** NIS, Norfolk-DN (RCT, n=255) **P -** Patient and clinical input	All PRO evidence significantly improved. NIS was trial's primary endpoint Patient input: factors not captured in model important for patients, e.g. ability to walk	EQ-5D-5L used to derive HSUVs. Effective based on significantly improved outcomes. PRO evidence captures most relevant treatment impacts, except for ability to return to work, daily activities, social life, impact on carers and families. Higher ICER accepted given effect size and aspects not captured.

MEDICINE Generic name - indication	PROM (by type) Instrument (source)	PRO EVIDENCE Description of results	APPRAISAL Influence of PRO evidence on decision
Voretigene Inherited retinal dystrophies	**D -** VFQ (patient survey)	Results not reported as confidential	The committee highlighted preference for QoL collected from trials
Cerliponase Nuronal ceroid lipofuscinosis type 2	**G -** EQ-5D 5L, PedsQL, PedsQL-FM (pivotal trial, single-arm, open-label, n=23, children 3-16 years) **D -** CLN2-QoL (pivotal trial)	QoL evidence: improvement in initial treatment phase (only short term data)	Recognition of limited QoL evidence due to short term data. Unclear if PRO data influenced committee discussions
Elosulfase alfa Mucopolysaccharidosis type IVa	**P** - Cross-sectional survey from patient and family, company submission, 63 patients + 56 families **O -** Observational study on natural history (n = 325 people, up to 10 years)	No PROMs collected in trials Survey: QoL impact related to reliance on wheelchair, endurance, pulmonary function and height. Impact on carers up to 15 hours/day Observational study: decline in endurance, restricted growth, limitations in daily living	Survey used to derive HSUVs Observational study: supported interpretation of impact on QoL and HSUVs, including aspects not captured in HSUV

MEDICINE Generic name - indication	PROM (by type) Instrument (source)	PRO EVIDENCE Description of results	APPRAISAL Influence of PRO evidence on decision
Ataluren Duchenne muscular dystrophy	**G -** PedsQL (phase IIb) **G -** PODCI, ADLQ (RCT, confirmatory trial) **P** - Survey of carers (company submission)	PRO results not reported. PODCI, ADLQ confidential Survey: impact on multiple aspects of life, e.g. emotional wellbeing, mental health, personal care, ability to maintain relationships. Caregivers felt tired, depressed, anxious. In many cases, at least another family member in addition to both parents were involved in giving care (for example, siblings and grandparents)	QoL data (all): underestimate due to short trial duration (48 weeks too short to capture impact on ability to walk) PedsQL: results not aligned with patient statements on meaningful stabilisation or improvement in walking, or ability to conduct daily activities Survey: unclear influence , possibly considered in estimating extent of impact on caregivers, but not reported
Migalastat Fabry disease	**G** - SF-36 physical and mental health components (open-label, non-inferiority RCT (ATTRACT) and RCT (FACETS)) **D** - BPI, GSRS (ATTRACT, FACETS) **P -** Patient and clinical input (oral administration)	QoL data: inconclusive (no change), except for change in GSRS Input: benefits of oral administration	Patient input confirmed benefit of oral administration over infusion PRO data not discussed in report, nor used to derive HSUVs

MEDICINE Generic name - indication	PROM (by type) Instrument (source)	PRO EVIDENCE Description of results	APPRAISAL Influence of PRO evidence on decision
Eliglustat Gaucher disease	**G -** SF-36 general health, physical and mental components (open-label trial (ENCORE) and RCT (ENGAGE)) **D -** FSS, BPI (ENCORE and ENGAGE) **P -** Patient survey and patient submission (oral administration)	QoL: maintained with treatment FSS: fatigue > placebo (not statistically significant) SF-36, BPI: no change Patient input: preference for oral administration	SF-36 used to derive HSUV Unclear influence of PRO evidence. Adverse event HSUVs included, not clear if influenced by FSS or BPI Advantage of oral administration as key driver for decision (patient survey)
Strimvelis Adenosine deaminase deficiency–severe combined immunodeficiency	None	No QoL evidence presented. Data being collected within trial (not reported)	Not reported
Burosumab for X-linked hypophosphataemia	None	No QoL evidence presented. Data being collected within trial (not reported)	Not reported
Inotersen Hereditary transthyretin amyloidosis	**D** – Norfolk QoL-DN (RCT)	Norfolk QoL-DN: no change in treatment arm, decrease in placebo arm	Not reported

MEDICINE Generic name - indication	PROM (by type) Instrument (source)	PRO EVIDENCE Description of results	APPRAISAL Influence of PRO evidence on decision
Mannitol for cystic fibrosis	**G** - HUI2 (RCT, trial 301) **D -** CFQ-R (RCT, trial 302)	HUI2: no significant change CFQ-R: no significant change, improvement in respiratory, physical and vitality domains, but not significant	HUI2 used to derive HSUVs. No ideal measures to capture the QoL impact, including adverse events from current treatments, e.g. unpleasant taste or sensations, as reported by patients
Colistimethate sodium and tobramycin dry powders for inhalation (DPI) [=antibiotics] Pseudomas lung infection in cystic fibrosis	**D** - CFQ-R (open-label RCT) **P -** Treatment satisfaction questionnaire: administration mode, manufacturer submission **P -** Patient input	**Colistimethate sodium DPI** CFQ-R from non-inferiority trial **Tobramycin DPI** No QoL data collected in trial, relied on treatment satisfaction questionnaire and patient input	**Colistimethate sodium DPI** CFQ-R: no improvement since non-inferiority trial **Tobramycin DPI** Questionnaire: higher values for DPI over nebuliser Limited influence of QoL data on decision and interpretation of economic model. Recognition of improved speed and adherence with DPI based on patient input and questionnaire
Nintedanib Idiopathic pulmonary fibrosis	**G -** EQ-5D, PGI-C (RCT) **D -** SQRQ, SOBQ, CASA-Q **P -** Patient input (tolerability)	PRO data: not reported Patient input: better tolerability profile impacting QoL, ability to go outdoors due to less photo sensibility	EQ-5D used to derive HSUVs

MEDICINE Generic name - indication	PROM (by type) Instrument (source)	PRO EVIDENCE Description of results	APPRAISAL Influence of PRO evidence on decision
Lumacaftor–ivacaftor Cystic fibrosis	**G** - EQ-5D (RCTs TRAFFIC and TRANSPORT) **D -** CFQ-R (TRAFFIC and TRANSPORT)	EQ-5D: high baseline values due to patients perception of life as "normal", difficult to capture improved QoL (ceiling effect, common in cystic fibrosis). No significant difference [mean difference 0.0095 (TRAFFIC) and -0.0009 (TRANSPORT)] CFQ-R: mean difference of 2.2 < 4 MID	CFQ-R: other studies with similar severity levels showed greater changes compared to trial results EQ-5D: no evidence on reasons for being inappropriate. EQ-5D usually captures most important aspects in cystic fibrosis based on expert input
Mepolizumab Severe refractory eosinophilic asthma	**G -** EQ-5D (RCT DREAM) **D** - SGRQ, ASQ (RCTs MENA and SIRIUS)	SGRQ: QoL increase due to fewer exacerbations AND improved symptom control and lung function	EQ-5D used to derive HSUVs SGRQ: possible confounding (exacerbation reduction ~ fewer symptoms). Improved symptoms recognised (beyond those from fewer exacerbations). SGRQ also mapped to derive HSUVs
Obeticholic acid for primary biliary cholangitis	None	No PRO data collected in trial	
Holoclar for limbal stem cell deficiency after eye burns	None	No PRO data collected in trial	HSUVs derived from impact on visual acuity

MEDICINE Generic name - indication	PROM (by type) Instrument (source)	PRO EVIDENCE Description of results	APPRAISAL Influence of PRO evidence on decision
Pirfenidone Idiopathic pulmonary fibrosis	None	Re-submission to extend indication to patients >80% FVC. Quality of life data not discussed (as did not change from initial submission, for which the report was no longer available)	No PROMs reported, no impact on decision (apart from QoL data captured in model).
Darvadstrocel Crohn's disease	**D -** PDAI (RCT ADMIRE)	PDAI results not reported	PDAI does not capture QoL impact (only symptoms) => preference for EQ-5D trial data
Nusinersen Spinal muscular atrophy	**G -** PedsQL (RCT CHERISH)	PedsQL results not reported in appraisal report, only in committee papers. Data kept confidential, likely due to the challenges to collect data from babies and children for SMA	PedsQL mapped to EQ-5D
Letermovir Cytomegalovirus	**G** - EQ-5D (RCT PN001) **D** - FACT-BMT (PN001) **P** – Patient and clinical input (on QoL from preventing CMV)	PN001 trial: not powered to show changes QoL, no improvements Results confounded by mix of patients who have had CMV reactivation and started pre-emptive therapy and those who have not	Trial limitations and challenges to capture change recognized Patient and clinical experts input on QoL impact from preventing CMV accounted for in decision (ICER likely to be lower due to this, which lead to a positive decision)
Lanadelumab for hereditary angioedema	**G -** EQ-5D-5L, SF12, WPAI:GH (RCT HELP-03, open-extension HELP-04)	EQ-5D-5L: no change due to lack of sensitivity in condition (timing of response - only two responses during attacks captured) AE-QoL: statistically improved	EQ-5D-5L data used to derive HSUVs Other results not commented

MEDICINE Generic name - indication	PROM (by type) Instrument (source)	PRO EVIDENCE Description of results	APPRAISAL Influence of PRO evidence on decision
	D - AE-QoL, HADS (HELP-03 + 04)	Other PROMs not reported in appraisal report or committee papers	

Legend: G: generic patient reported outcome measure; D: disease, disease-group or symptom-specific patient reported outcome measure; P: patient evidence; NA: no report available; MID: minimal important difference; CHAQ: childhood health assessment questionnaire; LEFS: lower extremity functional scale; NIS: neuropathy impairment score; Norfolk-DN: Norfolk quality of life-diabetic neuropathy; VFQ: visual function questionnaire; PedsQL: Paediatric Quality of Life Inventory - Parent Report for Toddlers; PedsQL-FM: PedsQL family impact module; CLN2-Qol: CLN2 quality of life instrument; PODCI: paediatric outcomes data collection instrument; ADLQ: activities of daily living questionnaire; FSS: fatigue severity scale; BPI: brief pain inventory; CFQ-R: cystic fibrosis questionnaire revised; HUI2: Health Utility Index Mark 2; SGRQ: St George Respiratory Questionnaire; SOBQ: University of California San Diego shortness of breath questionnaire; CASA-Q: cough and sputum assessment questionnaire; PGI-C: patient global impression of change; ASQ: asthma control questionnaire; PDAI: perianal disease activity index; FACT-BMT: functional assessment of cancer therapy; AE-QoL: angioedema quality of life questionnaire; WPAI:GH: work productivity and activity impairment questionnaire - general health; HADS: hospital anxiety and depression scale; EQ-5D-5L: EuroQol-5 Dimension-5 Level

Sources: [16-39]

Further exploration of the influence of PRO evidence on NICE decisions suggested that beyond those used to derive HSUVs, few of them had any influence on the decisions (Tables 1 and 2).

Of the 14 appraisals considering generic PRO evidence, eight were used to derive HSUVs and the remaining six had unclear or no influence on the decisions. For asfotase alpha, the EQ-5D data collected in a patient survey may have been considered by clinicians when developing the vignette's health states, but it is not discussed in the report. For cerliponase, it was inconclusive due to the lack of correspondence between EQ-5D and the model's health states, and short trial duration for the Pediatric Quality of Life Inventory (PedsQL). For ataluren, no significant improvements in the PedsQL were shown, despite the positive trend in the functioning subscale. For the remaining treatments (migalastat, letermovir, lanadelumab), the SF36 and EQ-5D collected did not show any significant improvements and were not considered.

With the exception of one disease-group PROM used to derive the economic model's HSUVs, their inclusion had limited influence. This was the case for mepolizumab, where SGRQ data, suggesting improved QoL due to fewer exacerbations and improved symptom control and lung function, was mapped to EQ-5D to obtain HSUVs. In the other cases, the PODCI data collected for ataluren showed improvements on two dimensions, but was considered uncertain due to the short trial duration. In all other cases (letermovir, asfotase alfa, voretigene, darvadstrocel and nintedanib), the disease-group PROMs, Functional Assessment of Cancer Therapy - Bone Marrow Transplantation (FACT-BMT), PODCI, Visual Function Questionnaire (VFQ), perianal disease activity index (PDAI), SGRQ or Shortness of Breath Questionnaire (SOBQ) either did not show a significant improvement or were not reported.

A similar situation was seen for the disease-specific PROMs. For only one case, colistimethate sodium and tobramycin DPI, the CFQ-R was mapped to HSUVs and used for the decision. However, it did not show any improvement in QoL relating to administration mode (dry powders for inhalation versus nebuliser) given a non-inferiority trial design was adopted. For three treatments, the PRO evidence was uncertain and thus the influence on the decision was unclear. The data collection period of CLN2-QoL for cerliponase was considered too short, and the CFQ-R data collected for mannitol dry and lumacaftor-ivacaftor did not show a statistically significant improvement. Results from the AE-QoL data collected for lanadelumab were not commented on in the appraisal report.

Of the six treatments that considered symptom-specific PROMs, one of them influenced and another possibly influenced the decision. For patisiran, the Neuropathy Impairment Score (NIS) and Norfolk Quality of Life Questionnaire - Diabetic Neuropathy (Norfolk QoL-DN) data collected was statistically improved and contributed to recognising treatment effectiveness. For eliglustat, no significant improvements were demonstrated for the Fatigue Severity Scale (FSS) and Brief Pain Inventory (BPI), and it was unclear whether they were used to determine the HSUV estimated to measure the impact of adverse events on QoL included in the submission. In the remaining cases, there was either no demonstration of change with BPI and Gastrointestinal Symptoms Rating Scale (GSRS) for migalastat and with Norfolk QoL-DN for inotersen, or results were not reported (Cough and Sputum

Assessment Questionnaire, CASA-Q for nintedanib, Asthma Control Questionnaire, ASQ for mepolizumab and Hospital Anxiety Depression Scale, HADS for lanadelumab).

For eight of these drugs, determination of QoL impact was influenced by patient evidence (Table 2). First, patient surveys provided information about impact of QoL on patients and carers (eculizumab, ataluren), preferences for administration mode (eliglustat, colistimethate sodium and tobramycin DPI), or whether it was used to derive HSUVs (elosulfase alfa). Respondents were patients and in one case also family members, three formed part of the company submissions and the other two, patient submissions. Second, patients and clinicians provided input about the dimensions not captured in the model (patisiran), about impact on QoL (letermovir), effect on tolerability (nintedanib), and administration mode (migalastat, eliglustat, colistimethate sodium and tobramycin DPI).

Use and influence of HSUV estimates in NICE appraisals

The most frequently used technique to derive HSUVs in NICE appraisals was through EQ-5D data (7/23) collected within a trial (4/7) or from a registry or cohort study (3/7), followed by mapping (6/23), vignettes (5/23), published literature (3/23), Health Utility Index Mark 2 (HUI2) (1/23) and other (1/23) (Table 3). No HSUVs were reported for one treatment (pirfenidone) given it was a re-assessment; therefore, it was excluded from this analysis, which focused on the 23 remaining treatments. The mapping technique was more frequently used in the TA, and vignettes in the HST process. Additional HSUVs were derived to measure the impact on QoL of adverse events (9/23), of the administration mode (4/23), of carer burden (7/23) or other (7/23) and considered alongside the HSUV derived.

Table 3. Techniques used to derive HSUVs in NICE TA and HST appraisals of non-oncology rare disease treatments (n=23)

		Techniques to derive HSUVs considered in NICE appraisals by HSUV technique and level of influence					**Patient evidence**
		Generic PROMs	Mapping	Vignettes	Published literature	Various	
NICE Highly Specialised Technology	Asfotase alfa			≈			
	Eculizumab	≈					+++
	Patisiran	≈					+++
	Voretigene			≈			
	Cerliponase			≈			
	Elosulfase alfa					+++	+++
	Ataluren				++		
	Migalastat	≈					+++

	Eliglustat		++				+++
	Strimvelis				++		
	Burosumab			≈			
NICE Technology Appraisal	Inotersen	≈					
	Mannitol	+++					
	Colistimethate sodium and tobramycin dry powders for inhalation (DPI) [=antibiotics]		≈				+++
	Nintedanib	≈					++
	Lumacaftor–ivacaftor		≈				
	Mepolizumab		+++				
	Obeticholic acid				++		
	Holoclar		++				
	Pirfenidone*						
	Darvadstrocel			≈			
	Nusinersen		≈				
	Letermovir	≈					+++
	Lanadelumab	+++					

Legend: HSUV: Health State Utility Value; NICE: National Institute for Health and Care Excellent; PRO: Patient Reported Outcome; PROM: Patient Reported Outcome Measure

*No HSUV results were considered as this is a re-assessment and no new QoL evidence was provided

+++	**Accepted** – HSUV results / patient evidence were influential in the final decision
++	**Not commented** - HSUV results / patient evidence were reported and suggested some type of benefit, but no discussion about these results was reported – assumption is that they are likely to have influenced the decision
≈	**Uncertain** - HSUV results were reported, but were considered uncertain

The detail and summary of the individual appraisals are summarised in Table 4. Seven treatments used EQ-5D, two of which collected EQ-5D 3L in trials and the remaining collected EQ-5D 5L (mapped to 3L) or foreign EQ-5D datasets converted using the UK tariff. In one case, the HSUVs included in the model were considered acceptable by the TA Committee (lanadelumab). For mannitol,

the generic Health Utility Index Mark 2 (HUI2) was used to derive HSUV estimates. Even if EQ-5D would have been preferred, the HUI2 was accepted by the relevant committee. For all remaining cases, a number of issues were raised by the relevant committees, which included benefits (eculizumab, migalastat) or long-term effects not captured (letermovir), measure insensitive to change (nintedanib), uncertain duration (patisiran), or possible implausible health states (inotersen).

Mapping was used in six cases, in one of which (lumacaftor-ivacaftor) the applicant developed a new algorithm, while in the others published functions were used. Source measures included lung function and pulmonary exacerbation (lumacaftor–ivacaftor), SF36 (eliglustat), PedsQL (nursinersen), CFQ-R (colistimethate sodium and tobramycin DPI), SGRQ (mepolizumab) and visual acuity (holoclar); all were converted to EQ-5D-3L. The results were considered acceptable in only one case (mepolizumab), or not commented on (likely acceptable) in two cases (eliglustat, holoclar). The issues raised regarding the remaining cases included: ceiling effects and little change captured even though it was collected in the largest existing cystic fibrosis trial (lumacaftor-ivacaftor), limited face validity resulting in expert elicitation being used to estimate the HSUVs (nusinersen), or limited methodological approach (colistimethate sodium and tobramycin DPI).

Vignettes were used in five cases. Reasons for their use over more conventional approaches included a lack of correspondence between QoL data collected in the clinical trial and model health states (cerliponase), lack of negative values when deriving the PedsQL being considered unrealistic considering the condition's severity (cerliponase), or QoL data not collected in trial (darvadstrocel, burosumab, voretigene). The health states were developed by patient and clinical experts (voretigene), or only clinicians (cerliponase, asfotase alpha, burosumab). Respondents included clinicians (voretigene, cerliponase, asfotase alpha, burosumab), or patients and public (darvadstrocel). The QoL measure included was EQ-5D-5L (cerliponase, asfotase alpha, burosumab), and HUI2 and EQ-5D (voretigene).

Table 4. Use and influence of HSUVs in NICE TA and HST appraisals of non-oncology rare disease treatments (n=23)

MEDICINE Generic name, indication	**HSUV** Technique, appraisal	DECISION ICER, reasons
Eculizumab Atypical haemolytic uraemic syndrome	**EQ-5D** - all benefits not captured due to lack of data - ERG's HSUV lower than manufacturers (10 versus 25 QALYs) => in both cases, substantial increase in QoL recognised	**Restrict - monitoring and stopping rules** Cost-consequence model ~10-25 QALYs => QoL underestimated due to lack of data => magnitude of benefit substantial despite uncertainty
Patisiran Hereditary transthyretin amyloidosis	**EQ-5D: 5L mapped to 3L** => uncertain assumptions around HSUV, duration of treatment benefit **HSUV after stopping treatment** **-** uncertain evolution after stopping => little effect on ICER **HSUV carer** - estimates revised to align with inotersen => considered acceptable **HSUV adverse events (gastro-intestinal, GI)** - possible overlap with impact captured in EQ-5D => value between manufacturer's estimate and no disutility => scenario analysis using pessimistic GI disutilities ~£125k/QALY **Benefits not captured**: ability to work, carry out daily activities, more active family and social life, maintain independence and dignity	**List - commercial agreement** ~£80-125k/QALY => no QALY weighing (~9.16 QALYs) => ICER acceptable due to additional factors (severity, rarity, size of health benefits, benefits not captured, innovativeness, impact on carers)

MEDICINE Generic name, indication	**HSUV** Technique, appraisal	DECISION ICER, reasons
Voretigene Inherited retinal dystrophies (caused by RPE65-mediated IRD)	**Vignettes** - implausible lowest health state [worse than death (-0.04)] given patients confirmed adapting to disease - few clinicians involved in development - focus of clinicians focus on vision loss rather than QoL => possible underestimation of QoL => EQ-5D more appropriate due to focus on QoL (and not vision loss) **TTO (published literature)** - not robust, good complement to vignettes => HSUV to fall between vignettes (company) and TTO (ERG) **HSUV adverse events** => suitable, small effect on ICER **HSUVs carers (published literature)** => only children included (adults excluded)	**List - commercial agreement** ICER range £114,956 (company)-£155,750 (ERG) => 1.2 QALY weight (QALY gains 12.1-17.7)
Cerliponase Nuronal ceroid lipofuscinosis type 2	**PedsQL** - Trial QoL data not used as HSUVs unavailable for all model health states => preference for trial data, but recognition that possibility of negative values excluded, unrealistic given the severity of disability **Vignettes/EQ-5D (5L mapped to 3L)** - validation of vignettes and completion of EQ-5D 5L by clinical experts. 5L mapped to 3L - issues with robustness: additional elements such as pain and frequency of seizures included, but their association to motor and language scales defining health states unclear	**List - Managed Access Agreement** ICER not specified, 3.0 QALY weight

MEDICINE Generic name, indication	**HSUV** Technique, appraisal	DECISION ICER, reasons
	=> neither source of data sufficiently robust, suggesting lack of correspondence between vignette and model health states => EQ-5D 3L mapped to HSUVs using vignettes considered, given no alternative data **HSUV carers/siblings** => disutilities included, but 30 years considered to better reflect real life compared to life long	
Elosulfase alfa Mucopolysaccharidosis type IVa	**Various approaches and sources** Issues around capturing QoL: - QOL rarely collected in trials, as challenging particularly for children (e.g. recollection of how they felt before treatment) - potential issue around questions: it's not about the activities they can do post-treatment, but about how they feel => EQ-5D not collected in trial, limited evidence on QOL => lack of developed/validated methods => impact of adverse effects on QoL not included => treatment improves QOL and HSUV increment considered appropriate => uncertainty remains in HSUV modelled	**List - Managed Access Agreement + commercial agreement** Cost-consequence model: limited impact on incremental QALYs QoL not appropriately captured due to challenges in measuring relevant effects and collecting data from children. No QoL measures collected in trials
Ataluren Duchenne muscular dystrophy	**HSUV scoliosis and carers (published literature)** - uncertainty around scoliosis not occurring after puberty (model assumption), or applying different HSUVs after loss of walking. Company's assumption: QOL linked to ability to walk greater since loss of walking would occur later. Clinical experts commented plausibility if loss is in upper limb muscle strength when ability to walk is lost, for which no evidence was presented => unreasonable to assume different HSUVs across treatment group once ability to walk is lost given no evidence	**List - Managed Access Agreement** Managed Access Agreement to capture carer HSUV using EQ-5D and Child Health Utility 9D Cost-consequence model ~2.389-8.562 QALY gains Wider benefits: indirect costs/benefits (ability to work of carers, decrease in out-of-pocket costs)

MEDICINE Generic name, indication	**HSUV** Technique, appraisal	DECISION ICER, reasons
Migalastat Fabry disease	**EQ-5D (questionnaire, Dutch cohort study with UK tariff) - enzyme replacement therapy and complications (comparator)** - to measure disutility of patients undergoing enzyme replacement therapy - similar HSUV as for end-stage renal disease, stroke, heart complications - patients/clinicians emphasised major impact on QoL => uncertain disutility values **HSUV infusion (DCE)** - 506 people from UK general population - HSUV infusion > HSUV complications => not comparable since different methods used (uncertain face validity) => patient input: recognition of added benefit of migalastat over ERT infusion (convenience from oral administration) => decreasing infusion-disutility by 50% decreased QALY gains (from 0.98 to 0.34 incremental QALYs)	**Restrict - if ERT + patient access scheme** Confidential cost-consequence model Miglastat considered to have similar benefits compared to ERT, with the main advantage of oral administration (patient input). Main concern about adherence with oral administration. Main driver of model infusion disutility
Eliglustat **Gaucher disease**	**SF36 mapped to EQ-5D (published algorithm)** **HSUV adverse events** - HSUV decrements applied **HSUV oral administration** - HSUV increment (0.12) based on preference for oral administration (vignette commissions by manufacturer) => too high, ERG's estimate of 0.05 more plausible	**List - Patient Access Scheme** Cost-consequence model Model driven by QoL (mode of administration)

MEDICINE Generic name, indication	**HSUV** Technique, appraisal	DECISION ICER, reasons
Asfotase alfa Paediatric-onset hypophosphatasia	**Vignettes** **-** 9 clinical experts completing EQ-5D for each level of severity (6MWT) => reasonable face validity (suitability of measure in capturing concept of interest) => not collected in trials - health states in the Markov model defined based on severity levels of 6MWT that, however, may not capture all the relevant symptoms => measure accepted due to lack of available evidence => HSUV for most severe health state very low (0.23), potentially overestimating benefits (more space for HSUV gain) => lack of correspondence between vignettes and model health states **EQ-5D (European patient survey)** => aligned with values in vignette study	**List - Managed Access Agreement + commercial agreement** Cost-consequence model ~14-25 QALYs HSUV considered to reasonably capture impact on QoL, risk of underestimation compensated by carer disutility not included in model

MEDICINE Generic name, indication	**HSUV** Technique, appraisal	DECISION ICER, reasons
Strimvelis Adenosine deaminase deficiency–severe combined immunodeficiency	Trial QoL data not included in model because limited **HSUV QoL (published literature - no detail)** - Full health HSUV from general population => since no data on long term effect, these were explored within sensitivity and scenario analyses. The committee agreed lower values should be used **HSUV intravenous immunoglobulin (IVIG) or severe infections** - ERG: 0.75 HSUV included - plausibility confirmed by clinical experts **HSUV carer** **-** improved fast after treatment - no approach to measure - to be considered qualitatively during deliberations	**List** £12-120K/QALY (14.0-19.6 QALY gained) Impact of changes of QoL on model not reported
Burosumab X-linked hypophosphataemia	**Vignettes** - 6 clinicians value QoL of patients with XLH aged 18, 40 and 60 years using EQ-5D 5L - some missing data, company inferred 1 for healed health states - scored by clinicians not patients, not from trials => approach deemed appropriate (in absence of alternatives), but highly uncertain **HSUV carer (literature)** - published literature on people with limited mobility => acceptable, not robust	**List - Managed Access Agreement + commercial agreement** £113-£150K/QALY (5.52-15.99 QALYs gained) Most/less conservative assumptions included/excluded carer disutility (and different stopping ages) resulting in ICERS ranging from £112-149k/QALY. Unclear to what extent variation due to inclusion/exclusion of carer disutility

MEDICINE Generic name, indication	**HSUV** Technique, appraisal	DECISION ICER, reasons
Inotersen Hereditary transthyretin amyloidosis	**EQ-5D (Brazilian registry converted with UK tariffs, source model HSUVs)** - modelling of values from dataset with a number of assumptions, e.g. cap to ensure HSUVs do not exceed the general population => model could generate implausible health state classifications => not ideal, but acceptable, considered uncertain **HSUV carer** - 1 in stages 1-2, 2 in stage 3	**List - commercial agreement** £96,697-£150,636/QALY (no QALY weighing) HSUV values did have some effect on model, but generally uncertain => unclear if driving the model => time-dependent HSUVs used within each health state
Mannitol Cystic fibrosis	**HUI2 (trial)** - mean disutility at baseline (0.988), average change at each timepoint added to baseline to calculation HSUV for each health state => HUI2 baseline considered high given multiple comorbidities => EQ-5D measure preferred => difficulty to value health states in chronic conditions. Standard method of using general population's valuation of QoL descriptions to generate HSUVs appropriate **HSUV lung transplant and pulmonary exacerbations (literature)**	**Restrict - clinical parameters, 2nd line** ICER<£30K Model changes with extension of life, little with changes in QoL - patients confirmed treatment improved QoL, considered important => HSUVs values very uncertain

MEDICINE Generic name, indication	**HSUV** Technique, appraisal	DECISION ICER, reasons
Colistimethate sodium and tobramycin dry powders for inhalation (DPI) [=antibiotics] Pseudomas lung infection in cystic fibrosis	**HSUV Colistimethate sodium DPI** **CFQ-R mapped to EQ-5D** => no preference-based model considered a methodological limitation **Health utility study linking EQ-5D responses to FEV% health states** => issue around establishing relationship, but considered more appropriate compared to manufacturer's model (mapping) **HSUV Tobramycin DPI (patient input)** => DPI to improve QoL in terms of speed and adherence compared to nebuliser	**List - Patient Access Scheme** Drivers of cost-effectiveness model: cost of interventions and their comparators, QALY gains/losses Colistimethate sodium DPI: small QALY loss (based on HSUV/QoL evidence) but substantial cost savings over nebuliser Tobramycin DPI: dominant - small QALY gain (no HSUV/QoL evidence, based on patient input) and cost saving (DPI dominated nebuliser)
Nintedanib Idiopathic pulmonary fibrosis	**EQ-5D (trial)** - model based on predicted FVC changes and rate of exacerbations **HSUV adverse events** - serious gastro-intestinal events, rash related events => model did not include diarrhoea-adverse events as not severe and affected a small proportion of patients => committee did not agree, and considered it to affect QoL **HSUV exacerbations** => possible gains in QOL not captured in QALY (tolerability profile, reduced dosing frequency) => lack of sensitivity to change	**Restrict - clinical parameters + Patient Access Scheme** Dominant over pirfenidone (survival equal, differences in QALYs) Committee recognised that additional impact on QoL not captured in model

MEDICINE Generic name, indication	**HSUV** Technique, appraisal	DECISION ICER, reasons
Lumacaftor–ivacaftor Cystic fibrosis	**HSUV QoL (multivariate mixed model)** - repeated regression analysis to model relationship between EQ-5D, lung function and pulmonary exacerbations in trials - no change in EQ-5D + little opportunity to demonstrate improved QoL due to ceiling effect - clinical experts state that EQ-5D capture most important effects in cystic fibrosis - committee tested model with values from another study (Lancaster) that better captured changes in QOL using EQ-5D in patients with similar levels of severity, resulting in increased ICER by ~65K/QALY => HSUV not captured adequately, uncertainty in model => however, trial data used, which is the biggest trials conducted in cystic fibrosis to date **HSUV lung transplant (literature)**	**Reject** ~218-349K/QALY Model mostly driven by changes in life years gained When HSUVs from other study were used (Lancaster), ICER increased by 65K
Mepolizumab Severe refractory eosinophilic asthma	**SGRQ (MENSA trial) mapped to EQ-5D** - mapping algorithm based on population with chronic obstructive pulmonary disease - used as baseline value, adjusted due to differences between treatment arms and ages => considered acceptable **EQ-5D (DREAM trial)** - values adjusted for differences in baseline utilities values => baseline adjustment considered appropriate **HSUV exacerbation**	**List - Patient Access Scheme** ~£29k/QALY Little effect of QoL on ICER. EQ-5D mapped from SGRQ considered in model, EQ-5D values from DREAM trial accounted for in the interpretation of QoL impact. Drivers included exacerbation rates, age-related mortality estimates and attrition rates

MEDICINE Generic name, indication	**HSUV** Technique, appraisal	DECISION ICER, reasons
	- mid-point between trial data and published value => little change when using different disutility values, approach acceptable	
Obeticholic acid Primary biliary cholangitis	No HSUVs data collected in trials **Published literature and expert assessment** - Chronic Hepatitis C and previous Technology Appraisal reports => some issues raised, but accepted	**List - Patient Access Scheme** ~£33K/QALY, additional factors considered: ICER underestimated in trial due to lack of adjustment up to recommended dose in some patients + innovative nature + potential to return to normal life + opportunity cost of liver transplant on other patients needing it
Holoclar Limbal stem cell deficiency after eye burns	**Mapping (HSUV visual acuity)** - combination of visual acuity in both best and worst seeing eyes - published mapping algorithm => model did not capture: negative effect on donor eye => if donor disutility captured, ICER likely to decrease **HSUV from pain, burning, photophobia** - base case value attached to presence of moderate or severe pain/burning/ photophobia derived from EQ-5D 3L tariff and uses the level 2 and 3 decrements of -0.123 and -0.386 respectively. Alternative values of no decrement and that derived from the general population SG method of -0.291 for	**Restrict - subgroups and 1 eye + Patient Access Scheme** £6,948-£30,415-£42,139/QALY (lower values with 1 eye) Best plausible ICER was above £20K/QALY (includes ERG's estimate of disfigurement decrement). The committee accepted that if the model had considered a negative impact on donors, it would most likely be cost-effective => accepted for reimbursement

MEDICINE Generic name, indication	**HSUV** Technique, appraisal	DECISION ICER, reasons
	both moderate and severe were used **Disfigurement HSUV** - Bespoke standard gamble exercise performed by 520 UK participants who were presented with various clinical scenarios describing moderate to severe limbal stem cell deficiency, including an image of a patient's eye with this condition showing the extent of the disfigurement typically present - estimated at 0.308 => applied from non-reference case methods and likely to be exaggerated => patients with one eye may prioritise impact of disfigurement over visual acuity, and those with two eyes affected may prioritise visual acuity over disfigurement => cataract disutilities considered more appropriate estimate of impact on QoL => HSUV of 0.840 as base case for visual acuity and HSUV decrement of 0.140 for disfigurement	
Pirfenidone Idiopathic pulmonary fibrosis	no info (resubmission, no new data)	**Restrict - clinical parameters + Patient Access Scheme** £32,643-£38,687/QALY

MEDICINE Generic name, indication	**HSUV** Technique, appraisal	DECISION ICER, reasons
Darvadstrocel Crohn's disease	**Vignette** => considered robust given significant number of participants (n=835 general public and n=162 patients with Crohn's disease) => reliable estimates of HSUVs => vignettes used considered appropriate (even if EQ-5D not collected in trial), also aligns with values in literature => HSUVs in some heath states might be too low, and that correctly derived HSUVs for these 3 health states could result in higher ICERs	**Reject** £143,131/QALY Very uncertain model. HSUVs may have some influence on ICER levels

MEDICINE Generic name, indication	**HSUV** Technique, appraisal	DECISION ICER, reasons
Nusinersen Spinal muscular atrophy	**HSUV expert elicitation** => not based on formal elicitation methods (may differ if other clinicians were to redo exercise) => questions asked to clinicians not available, making it difficult to interpret => health states based on motor function may not have captured QOL impact, differences in HSUVs between health states small **HSUV PedsQL mapped to EQ-5D** - published algorithm for later onset, and HSUVs adapted for the early onset model based on assumed correspondence of health states (values confidential) => limited face validity, not considered appropriate => challenge in babies and children => HSUV techniques not ideal, results highly uncertain **HSUV carer** - best health state based on general population HSUV, worse health state based on cross-sectional study of SMA patients, adjusted for each health state - equal transitions between these 2 points (values confidential) => based on assumptions and not on evidence => key driver in ICER (better ICER for later onset, worse for early onset due to carer disutility "saved" from early death - seen as "perverse" effect) => to be included, but highly uncertain **Disutility due to bereavement** **-** applied as -0.04	**Restrict - Types 1,2,3 + Managed Access Agreements** ICER not specified Key driver in models - may impact differently early and late onset models: carer disutility (highly uncertain, difficult to quantify), resource costs

MEDICINE Generic name, indication	**HSUV** Technique, appraisal	DECISION ICER, reasons
Letermovir Cytomegalovirus	**EQ-5D-3L (published literature)** - Long term disutility associated with haematopoietic stem cell transplant derived from a mix of EQ-5D 5L and 3L values from two published studies - ERG proposed alterative approach based on difference between mean HSUVs of patients in trial (PN001, 48 weeks) and the general population from another study => ERG approach preferable	**List - commercial agreement** <£24,269/QALY likely <£20,000/QALY ICER likely to decrease due to QoL not captured in evidence (when considering PROM data)
Lanadelumab Hereditary angioedema	**Published literature** Committee accepted alternative approach to EQ-5D-5L (recognised as insufficiently sensitive). Published study used to derive HSUVs, which collected EQ-5D-5L about health state today and health state during last attack	**Restrict - indication + commercial agreement** <£20,000/QALY QALY gains small relatively to costs, ICER could change with different clinical scenarios

*No HSUVs were reported for one treatment (pirfenidone) given it was a re-assessment; therefore, it was excluded from this analysis, which focuses on the 23 remaining treatments.

Legend: HSUV: health state utility values; QALY: quality-adjusted life years gained; ICER: incremental cost-effectiveness ratio; EQ-5D: EuroQol-5 Dimension; EQ-5D-3L: EuroQol-5 Dimension-3 Level; EQ-5D-5L: EuroQol-5 Dimension-5 Level; GI: gastro-intestinal; QoL: quality of life; ERG: Evidence Review Group; IRD: Inherited retinal dystrophies ; TTO: time-trade off; PedsQL: Paediatric Quality of Life Inventory - Parent Report for Toddlers; DCE: discreet choice experiment; ERT: enzyme replacement therapy; 6MWT: 6-minute walk test; IVIG: intravenous immunoglobulin; HUI2: Health Utility Index Mark 2; DPI: tobramycin dry powders for inhalation; CFQ-R:cystic fibrosis questionnaire revised; FEV: Forced Expiratory Volume; SGRQ: St George Respiratory Questionnaire

Sources: [16-39]

A number of issues were raised about the vignettes. For voretigene, poor convergent validity between EQ-5D and HUI2 and preference for EQ-5D (considered to better capture overall QoL over HUI2) were highlighted. For alfotase alfa, trial data would have been preferred over vignettes by the appraisal committee; however, QoL results from the vignette were compared to results from a patient survey and considered aligned. Additionally, given the health states were based on the surrogate outcome "six-minute walking test" (6MWT), all of the relevant symptoms that would produce lower HSUVs in the more severe states may not have been captured (likely underestimate). The HST Committee was also concerned with clinicians responding to the vignettes instead of patients (burosumab). Furthermore, there was concern about the uncertain robustness of the vignettes given an unclear association of other elements (e.g., pain) to health states (cerliponase).

Published literature was used in three cases. This was because QoL was not measured in the trials (strimvelis, obeticholic acid) or the available mapping algorithm was conducted on a healthy population and thus unsuitable (ataluren). No detail on the published literature was provided for strimvelis and ataluren, whereas for obeticholic acid, values from an analogue disease (Hep C) were used.

In one case (elosulfase alfa), HSUVs were derived by converting improvement in 6MWT and forced vital capacity (FVC) collected in natural history studies and combining these with the correlation observed between 6MWT, FVC and QoL from the patient and families survey. For each additional benefit reported by patients not captured in 6MWT or FVC, an HSUV increment was derived from the literature. The HST Committee highlighted that the data were not collected within a trial but recognised the challenges in collecting QoL data from children alongside the lack of validated PROMs.

Use and influence of PRO evidence and HSUV estimates in HAS, G-BA and ZIN appraisals

Comparing the appraisal of PRO evidence by NICE with those by ZIN, G-BA and HAS, a number of observations arose (Table 5). First, a proportion of the appraisal reports did not include any detail about QoL evidence (38% for ZIN, 61% for HAS, and 16% for G-BA). Second, a vast majority of those that did report QoL data were deemed inconclusive. The main reasons were the lack of statistical significance (ZIN, HAS, G-BA), the exploratory nature of the evidence, e.g. secondary endpoint (HAS), the non-inclusion of a hierarchical test (HAS), the lack of validated or non-clinically relevant endpoint (G-BA). Third, in the few cases when QoL was considered to be improved by treatment in one country, a different outcome was determined in the other countries. Only one treatment appraised by HAS (inotersen) was considered to provide a moderate improvement in QoL, as it was one of the trial's co-primary endpoints; whereas no meaningful clinically relevant change was recognised by NICE and G-BA. Two treatments appraised by G-BA, patisiran and lanadelumab, were considered to provide some benefit as they were both validated and clinically relevant endpoints. For ZIN, it was unclear whether the PRO evidence had any influence on the decisions and the HSUVs appraised for three treatments were considered very uncertain.

Table 5. Use and influence of PRO evidence in HAS, G-BA and ZIN appraisals of non-oncology rare disease treatments

MEDICINE Generic name - indication	PRO EVIDENCE AND APPRAISAL		
	HAS (France)	G-BA (Germany)	ZIN (Netherlands)
Asfotase alfa Paediatric-onset hypophosphatasia	no details provided	no trial QoL data, no conclusion	no details provided
Eculizumab Atypical haemolytic uraemic syndrome (aHUS)	no details provided	NA	no details provided
Patisiran Hereditary transthyretin amyloidosis	no details provided	Norfolk QoL-DN: statistically improved; validity and reliability confirmed; possible bias from higher missing values after 18 months in control group; no MID, effect size's hedges calculated for dossier; clinically relevant difference	NA
Voretigene Inherited retinal dystrophies	VFQ: not demonstrated. Secondary judgment criterion, no hierarchical test	VFQ: unsuitable. Transferability and MID from NEI VFQ-25 to new VFQ inappropriate	Vignettes, EQ-5D-5L, HUI3: not adequately collected
Cerliponase Nuronal ceroid lipofuscinosis type 2	PedsQL, CLN2-QoL, EQ-5D 5L: exploratory consideration of QoL, stabilisation in treatment group versus degradation in natural history data	PedsQL: no benefit in QoL recognised due to lack of comparative data and clinical relevance of change CLN2-QoL: not considered as no data on its development (by company) and validation provided	NA

MEDICINE Generic name - indication	PRO EVIDENCE AND APPRAISAL		
	HAS (France)	**G-BA (Germany)**	**ZIN (Netherlands)**
Elosulfase alfa Mucopolysaccharidosis type IVa	no details provided	no details provided	no PROM data collected in trial
Ataluren Duchenne muscular dystrophy	no details provided	PODCI: not statistically significant. Quality and patient relevance not demonstrated due to lack of information	PedsQL, PODCI: not statistically significant
Migalastat Fabry disease	no details provided	SF-36: inconclusive	SF-36: inconclusive
Eliglustat Gaucher disease	no details provided	BPI, FSS, SF-36: no significant differences	SF-36, BPI, FSS, DS3: clinically relevant and crucial, no significant differences
Strimvelis Adenosine deaminase deficiency–severe combined immunodeficiency	NA	NA	NA
Burosumab for X-linked hypophosphataemia	SF-36, PROMIS: exploratory, not usable	SF-10: lack of information on questionnaire development, restrictions in content validity, reliability and validity. Results not accounted for	NA
Inotersen Hereditary transthyretin amyloidosis	Norfolk QoL-DN: modest improvement as co-primary endpoint SF-36: not discussed	SF-36: biased due to missing values Norfolk-DN: no valid MID based on hedge's g, effects not clinically relevant. Statistically significant improvement, but not clinically relevant C-SSRS: not discussed	NA

MEDICINE Generic name - indication	PRO EVIDENCE AND APPRAISAL		
	HAS (France)	**G-BA (Germany)**	**ZIN (Netherlands)**
Mannitol for cystic fibrosis	no details provided	NA	CFQ-R: no significant improvements. Overall effect around improving QoL and reducing pulmonary exacerbations
Colistimethate sodium and tobramycin dry powders for inhalation (DPI) [=antibiotics] Pseudomas lung infection in cystic fibrosis	no details provided	NA	no details provided
Nintedanib Idiopathic pulmonary fibrosis	EQ-5D, EORTC QLQ-30, QLQ-LC13: no expected improvement	G-BA/IQWiG EQ-5D VAS: statistically improved, benefit not proven given hedge's g SGRQ: not discussed	SGRQ: not clinically relevant
Lumacaftor–ivacaftor Cystic fibrosis	no details provided	not collected in trial	EQ-5D: used to derive HSUVs
Mepolizumab Severe refractory eosinophilic asthma	NA	no details provided	no details provided
Obeticholic acid for primary biliary cholangitis	no details provided	PBC-40: validated measure. Responsiveness and MID not examined. Marginal change, but clinical relevance not determined	PBC-40: no improvement

MEDICINE Generic name - indication	PRO EVIDENCE AND APPRAISAL		
	HAS (France)	**G-BA (Germany)**	**ZIN (Netherlands)**
Holoclar for limbal stem cell deficiency after eye burns	NA	no details provided	NA
Pirfenidone Idiopathic pulmonary fibrosis	no details provided	SGRQ, WHO QoL: no proof of added benefit	EQ-5D, SGRQ: from published paper. Unclear benefit as baseline values and validation difficult to verify
Darvadstrocel Crohn's disease	Van Assche Score, IBDQ: exploratory secondary endpoints, no change captured	IBDQ: not designed or validated for target population, no information on MID. Inconclusive QoL benefit	NA
Nusinersen Spinal muscular atrophy	PedsQL: not possible to quantify QoL benefit due to low response rates	PedsQL: QoL not demonstrated. Caregiver experience included	PedsQL mapped to EQ-5D
Letermovir Cytomegalovirus	EQ-5D-3L: unsuitable, used to derive HSUVs for different health states rather than change in QoL associated with an illness	EQ-5D, FACT-BMT FACT-BMT considered validated in patient population	not details provided
Lanadelumab for hereditary angioedema	AE-QoL: unusable as exploratory endpoint	AE-QoL: statistically improved, considered clinically relevant based on Hedge's g	NA

Impact on carers

Eighteen of the treatments were considered to have an impact on carers (Table 1), whereas evidence on carer impact was considered for only nine of these by NICE (8 HST and 1 TA). Impact of disease and treatment on carers was considered either qualitatively or quantitatively through HSUVs. In the former case, the relevant committees discussed the burden on carers during the deliberative process (mepolizumab, strimvelis, asfotase alfa), and in other cases, considered evidence from patient/carer surveys (eculizumab, elosulfase alfa). In the latter cases, HSUVs were derived from various sources (e.g. published literature, number of carers affected, report on challenges from living and caring for a sick child, or cross-sectional surveys). Some of the HSUVs submitted were changed so as to better align with previous appraisals (patisiran), to only include HSUVs for children (voretigene), to reflect a shorter timeframe (cerliponase), or to reflect a different number of carers (ataluren). In four of these cases, carer disutility was uncertain (also in the decision). Carer QoL was not reported in the other countries.

Discussion

This study explored the appraisal of QoL in all the non-oncology rare disease treatments considered by NICE. It is the first study of this type, which furthers our understanding of the nature of QoL evidence and the nuances of its use in HTA of rare disease treatments.

Our results primarily enable a better understanding of whether the QoL evidence was actually considered. The vast majority of conditions investigated, particularly in NICE's HST programme, are life-threatening and/or debilitating. For all of the treatments investigated, their added benefit was also considered to improve QoL. Measuring their impact on QoL is therefore critical in determining their added benefit, particularly for those treatments aiming solely to improve QoL. This, however, is not reflected in our results. PRO evidence was not reported for a large number of treatments across all of the study countries, and when reported, most of the PROMs and results were not discussed (and therefore we assume not accounted for). In the other study countries, no PRO evidence was reported in 16%, 38% and 61% respectively in Germany, the Netherlands and France. It was not clear from the appraisal reports why this evidence was not reported nor accounted for. When PRO evidence was reported, it was limited to one or two PROMs (versus more in the NICE reports).

Overall, a large amount of QoL data was collected, but these data were barely reported or referred to in the appraisal reports across the different study countries. However, the 28 different PROMs identified and collected in the trials are most likely covering concepts important for patients [5]. Their lack of use points either to a loss of valuable information on the patient perspective, issues in capturing meaningful change in rare diseases, or issues in accounting for all of these PROMs within the HTA approach adopted. Results illustrate that different QoL evidence would be considered depending on the HTA approach. For cost-effectiveness oriented approaches, HSUVs are

considered within the incremental cost-effectiveness ratio and are derived from PRO data using indirect techniques (e.g. generic preference-based instruments, mapping), or measured directly from patient responses using direct techniques (e.g. time-trade-off) [44]. In countries with an added clinical benefit assessment approach, the PRO data would be considered and interpreted as is without being derived into a numerical HSUV. To help with the comparability and interpretation of the PRO data, generic PROMs are often preferred. Consideration should therefore be given to how this information could be better used in HTA. This could be achieved through greater involvement in early multi-stakeholder dialogues and early scientific advice to better align across HTA bodies and agree on what QoL evidence would be accepted, and a greater acceptance of registry data to leverage early on data on natural history on the disease.

Second, our results enable a better understanding of whether the QoL evidence actually considered was impactful. Results point to a limited influence of PRO evidence in general. In the NICE appraisals, this was because QoL is mainly measured by HSUVs used in the economic models. PRO evidence was considered to support the interpretation of HSUVs included in the model in one case, and potentially in a few other cases; but overall, its influence was fairly limited. Just over 1/3 of the HSUVs were accepted, even if, in some cases, they were recognised as not ideal. In the remaining cases, the HSUVs were highly uncertain and in most cases the relevant committee recognised that all benefits were not captured. In these cases, interpretation was informed by information from patient and clinicians in four cases, and a patient survey in one case.

Only three disease-specific PROMs were reported, but their consideration had a limited influence on the decision and in only one case, it was mapped to derive HSUVs. This confirms the issue of a lack of validated disease-specific preference-based PROMs and their conversion into HSUVs through mapping [8, 45, 46]. Disease-group PROMs were more frequently used and may constitute a suitable alternative for rare diseases; however, their influence was also limited. A similar situation was seen around the use of symptom-specific PROMs. By contrast, there were a number of cases where the relevant committees recognised that the QoL evidence did not capture the full range of dimensions important to patients. These related to improvements in QoL, such as the ability to return to work, to perform daily activities, to have a social life, to maintain independence and dignity, improving in walking, better tolerability profile, reduced dosing frequency, or improved patient choice, as well as decrements in QoL, such as the impact from relying on wheelchairs, or adverse events not captured. However, considering that many of these domains are typically covered in PROMs, the issue may be more around the lack of sensitivity of these measures rather than domains not being captured.

In Germany and France, most of the PRO evidence was considered inconclusive due to the frequent lack of a statistically significant improvement and/or they did not meet the country-specific evidentiary requirements. In Germany, PROMs need to be validated and PRO evidence clinically relevant (based on a minimally important difference (MID)). However, a treatment failing to meet the MID criterion does not imply lack of improvement across all patients, where there may be some patients improving above the MID and others under [47]. This may be more frequent in heterogeneous and small patient

populations [48]. In France, the PRO endpoint should be a significant one (e.g. primary endpoint). In only one case in France and two cases in Germany was QoL considered improved, and this concerned different treatments. Similarly in the Netherlands, the PRO evidence was generally inconclusive and the HSUVs reported in three cases were considered very uncertain.

Overall, findings suggest that a big proportion of the PRO evidence and HSUVs appraised are either not considered or provide inconclusive uncertain outcomes. The main contrast between NICE and the other countries is their willingness to account for other forms of evidence, such as patient surveys or expert input to provide additional and complementary information on QoL impact. They also appear to be more flexible when interpreting QoL evidence, e.g. in recognising that all benefits are not captured by the measures used, and account for that when making their decisions.

We then tried to understand whether the issues highlighted by the relevant committees related to nature of rare disease treatments. One main distinction seen in NICE's HST Programme is a greater likelihood of treatments targeting children/infants or treating heterogeneous and/or multi-systemic conditions. In the 15 NICE appraisals affecting children, only three considered children-specific PROMs (PedsQL) and none considered any proxy-reported PRO evidence. This confirms the frequent lack of validated measures in children [10], but does not reflect the common reliance on proxy-reported data [9]. In only one case was the PedsQL mapped to EQ-5D, but results were limited and the challenges in collecting data from children recognised (together with another case).

The extent to which it may be more difficult to capture meaningful and generalisable outcomes in heterogenous populations and conditions affecting multiple organs [9, 10, 49] was not entirely clear from the results. There were, however, cases where evidence on QoL was lacking to estimate the HSUVs required by the model (ataluren), to capture all relevant symptoms (asfotase alfa), or to deal with multiple co-morbidities (mannitol).

Patient numbers for three HST treatments were small (an incidence of 1-7 patients/year in England), possibly resulting in uncertain aggregated results [9]. In one case (cerliponase), the HST Committee recognised an initial improvement in QoL based on PRO evidence. However, vignettes were used to derive HSUVs due to the lack of correspondence of PRO evidence with health states. The other two cases either did not report (asfotase alfa), nor collect (strimvelis) any PRO evidence, and published literature was used to derive HSUVs.

No existing treatments were available for almost 60% of the 12 HST and 17% of the 12 TA treatments (in total, 9 of 24 treatments). Current standards of care for these diseases require multi-disciplinary specialised services and are considered burdensome for patients and their carers. They generally entail monitoring of disease, management of symptoms, complications or disability, and/or supportive care (e.g. counselling, occupational therapy, physiotherapy, social care, palliative care, etc.). This may create additional challenges in identifying the relevant domains of QoL to measure in the comparative arm [50].

Three quarters of the conditions appraised affect QoL of families and carers, and the treatments were considered to improve their QoL. None of the PRO evidence collected and reported related to carer burden. However, the NICE Committees did account for the impact on carers either qualitatively or in cases where impact on carer's QoL was collected within a patient and carer survey (eculizumab). On the other hand, carer HSUVs were estimated in only eight cases for which more than half the data were uncertain or inconclusive. This further emphasises the tendency for inconsistent inclusion of carer HSUVs and the variety of approaches used for their measurement [51]. There is a need for methodological guidance on when and how to include carer HSUVs in QALY and non-QALY approaches to HTA [52]. Considering that 80% of rare diseases affect children, and are often severe and disabling, including carer QoL is crucial in determining the added benefit of a new treatment.

Limitations

This study is not without limitations. First, it relies on information from a small number of appraisals, which is unavoidable given the small number of RDTs (excluding oncology treatments) considered each year. Secondly, it relies on official reports, which may not comprehensively depict the full appraisal process. This was more pronounced for some study countries that do not provide detail of their appraisal of the evidence. Based on expectations around transparency, we considered that the items documented in the HTA reports included the most important determinants of decisions. Further, there may have been some limitations relating to language barriers given the use of google translator for some of the countries. However, no inconsistencies across countries were identified that could indicate missing or misinterpreted information. Additionally, our document analysis was qualitative and as a result, we may have missed or misinterpreted some aspects leading to the decision. Given the complexity of some of these appraisals, it was challenging to identify explanations for some of the limitations highlighted, and how they related to the nature of rare diseases. However, we attempted to identify some possible explanations and examples on some of the implications. Finally, this study highlights some of the nuances in considering QoL evidence in rare diseases. It is possible that some of the same issues could arise in the HTA of more common diseases. Further research would be needed to compare the results from this analysis with those from a similar analysis of HTAs for common non-cancer treatments.

Conclusions

This study highlights some of the limitations and challenges in appraising PRO evidence and HSUVs to understand the impacts of a rare condition and treatments on QoL, and the influence of these aspects on determination of value. In many cases, PRO evidence did not have a major influence in HTA decisions, as it often did not demonstrate meaningful change or was inconclusive. The HSUVs were often very uncertain due to numerous reasons, such as being insensitive to change, ceiling effects, limited face validity, not capturing all domains important to patients, lack of long-term data or

methodological issues. This emphasises the need for improved development, testing, use and reporting of PRO evidence, and use of HSUVs that are better adapted to rare disease specificities, such as small sample sizes. HTA bodies would also benefit from greater flexibility in accepting less conventional techniques to derive HSUVs, for example, using vignettes, but there is a need to develop methodologies that support their robust development and application. Additionally, patient evidence, including patient surveys, focus groups, interviews, and expert testimony, have shown to be crucial for providing information about the burden of illness, treatment benefits including outcomes that matter most, and in supporting the interpretation of uncertain aspects of the QoL evidence considered important for the decision.

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