The methods for incorporating carer HRQoL should be more clearly defined by NICE

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INTRODUCTION

- The broader societal benefits offered by new technologies in terms of quality-adjusted life-years (QALYs) accrued by carers (e.g., a partner, parent, or other family member) are accepted for inclusion in the reference case for National Institute for Health and Care Excellence (NICE) technology appraisals (TAs) and highly specialised technology (HST) assessments (i.e., within the base-case incremental cost-effectiveness ratio [ICER] calculation).[1]
- A targeted literature search identified a comprehensive review conducted by the NICE Decision Support Unit (DSU), which reviewed 414 NICE TAs and eight HST assessments published up to 10 January 2019 for inclusion of carer health-related quality of life (HRQoL) in economic evaluations.[2] This study highlighted a lack of formal, quantitative consideration for carer QALYs within economic evaluations across TAs (3%; 12/414) and HST assessments (50%; 4/8). The majority of economic evaluations that considered carer HRQoL targeted neurological conditions, in particular multiple sclerosis (8/12 TAs). This research was updated and expanded within this study.

Objective

- To review all published TAs and HST assessments to identify those that considered the impact of an intervention on QALYs for carers and how these have incorporated carer HRQoL.

METHODS

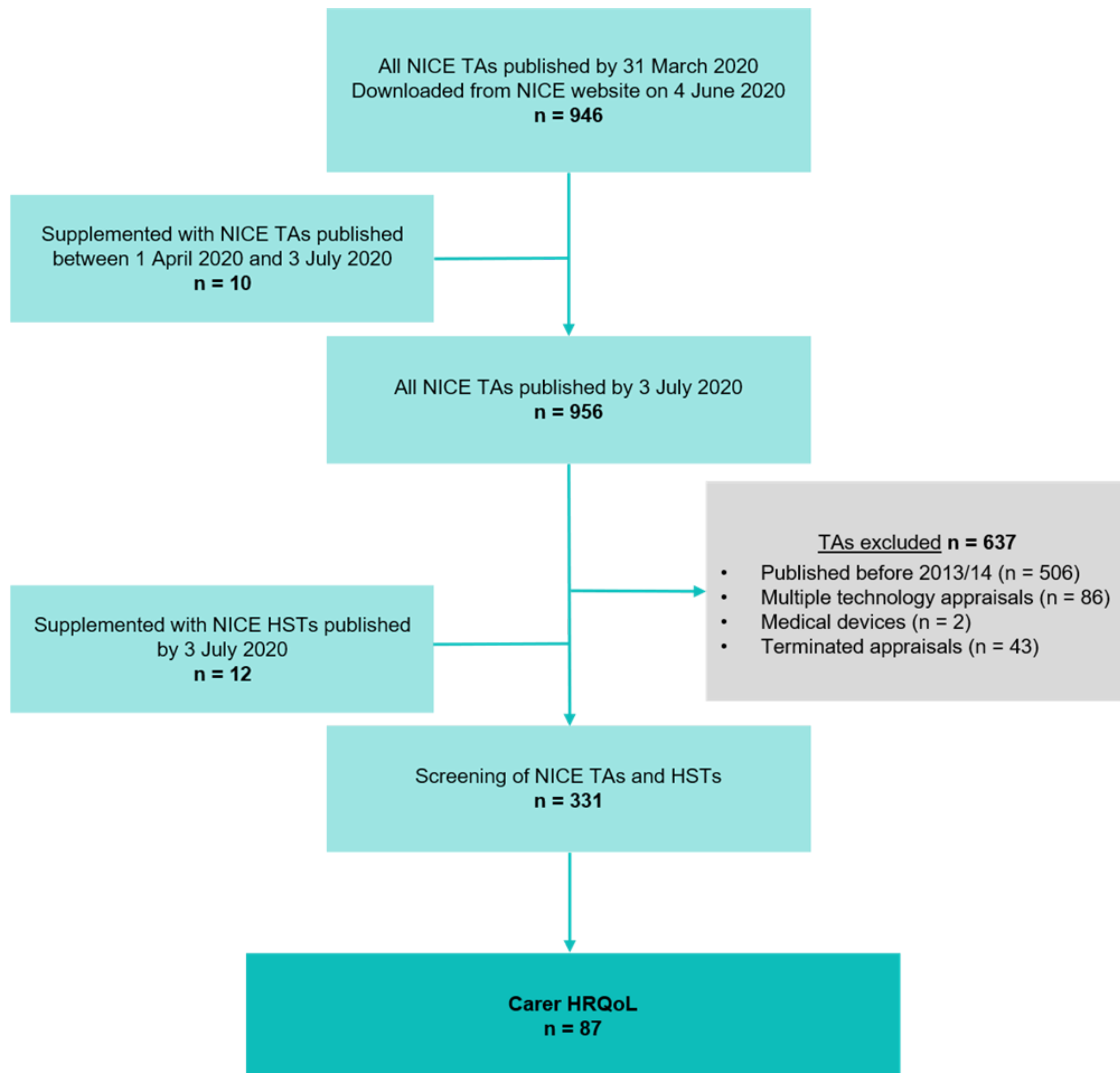
- All TAs published by 31 March were downloaded from the NICE website. These TAs were supplemented with manual searches to identify NICE TAs published between 1 April 2020 and 3 July 2020, and NICE HST assessments published by 3 July 2020.
- TAs published before the publication of the current NICE methods guidance in April 2013, multiple technology appraisals, assessments of medical devices, and terminated appraisals were excluded.
- For each of the included TAs or HST assessments, the company evidence submission was screened to identify whether the manufacturer had considered carers' HRQoL data in the economic modelling, in the value narrative, or solely to support the unmet need of the disease area. Where carers' HRQoL data were included in the economic modelling, the following documents were screened:
  - Final scope document
  - Evidence review group (ERG) report and associated documents
  - Technical report and responses, where applicable
  - Final Appraisal Determination document.

IDENTIFICATION OF NICE TAS AND HST ASSESSMENTS

Identification and selection of NICE TAs and HST assessments

- A total of 946 TAs were published by 31 March 2020 on the NICE website, and manual searches identified a further 10 TAs published between 1 April 2020 and 3 July 2020.
- TAs identified for inclusion were screened alongside 12 HST assessments (n = 331) to identify submissions that included carers' HRQoL data (Figure 1).

Figure 1 Flow chart describing the identification and selection of NICE TAs and HST assessments



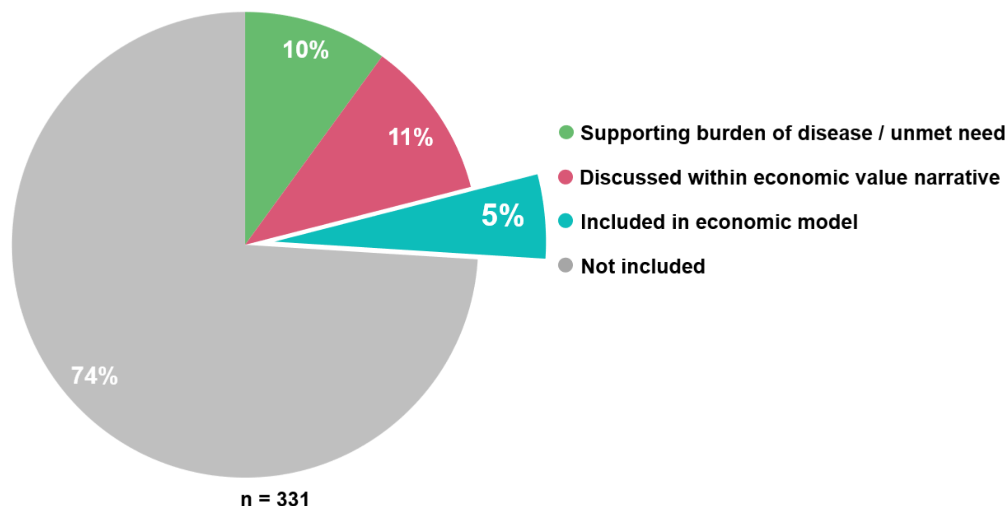
HRQoL, health-related quality of life; HST, highly specialised technology; NICE, National Institute for Health and Care Excellence; TA, technology appraisal.

INCORPORATION OF CARER HRQOL WITHIN ECONOMIC MODELS

Only 5% of NICE TAs and HST assessments considered carer disutilities within economic models

- Carer HRQoL was considered in 26% (87/331) of all screened NICE TAs and HST assessments. A small fraction included carer disutilities within economic modelling (5%; 17/331) (Figure 2).

Figure 2 Sections within manufacturer submissions including considerations of carer HRQoL



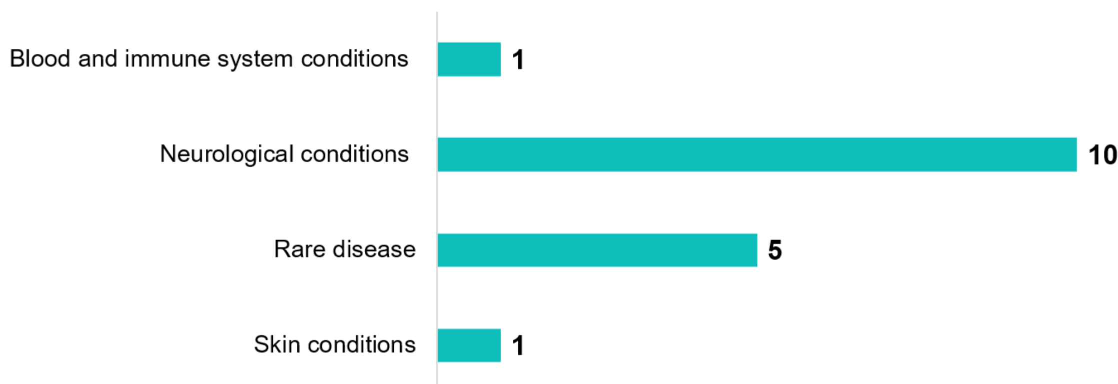
n = 331

Exclusive categories (economic model, economic value narrative, burden of disease / unmet need) were used to derive the numbers. For example, while it is likely that submissions which incorporated carer HRQoL within the economic model would also consider carer HRQoL within the economic value narrative and burden of disease / unmet need, these submissions would only fall under 'included in economic model'. Likewise, submissions that did not include carer HRQoL within the economic model but argued that this was relevant within the economic value narrative would only fall under 'included in the economic value narrative' even if this was also set up in the burden of disease/unmet need. Submissions categorised as including carer HRQoL within the burden of disease / unmet need did not include carer HRQoL within the economic narrative or model. Review of NICE/ERG critique was only performed on TAs and HST assessments that included carer HRQoL within economic modelling.
ERG, evidence review group; HRQoL, health-related quality of life; HST, highly specialised technology; NICE, National Institute for Health and Care Excellence; TA, technology appraisal.

Over half (53%) of NICE TAs and HST assessments with economic models that included carer HRQoL were for interventions targeting neurological conditions

- TAs and HST assessments that included carer HRQoL in economic modelling were often for interventions targeting neurological conditions (53%; 10/17) (Figure 3), in particular multiple sclerosis (7/10).

Figure 3 Number of NICE TAs or HST assessments that include carer HRQoL in the economic modelling by disease area



Methods for inclusion of carer HRQoL in the economic modelling varied

- Methods varied across the 17 TAs and HST assessments identified: a total of 9 included carer disutilities in the base case, 6 as a scenario analysis, and 2 included carer disutilities in both.
- In all cases, carer HRQoL was applied as disutilities rather than utilities, for one or more carers based on the care requirements of the patient assessed by the patients' age, disease severity, or activity level. In 1 submission (HST7), the QALY loss to a family due to the premature death of a child was considered.
- Carer disutility values were derived using vignettes valued through the EuroQol Five-Dimension Visual Analogue Scale (EQ-5D VAS) in 2 TAs (TA614, TA615; both for cannabidiol for treating seizures associated with Lennox-Gastaut syndrome). Carers valued three vignettes defined by the number of seizures and seizure-free days per month in consideration of their own HRQoL. The plausibility of these values was validated with data published in literature.
- The remaining 15 TAs and HST assessments relied exclusively on values from the literature, with little consistency in methods. Studies in the literature either reported disutilities directly or calculated from utilities, measured by EQ-5D, Health Utilities Index, or 36-item Short Form Health Survey, and data sources were not always from the same patient population as those assessed in the TA or HST. For example, across submissions for multiple sclerosis, a study by Gani *et al*. (2008) was commonly cited (6/7 cases), which estimated utility decrements for the carers of patients with Alzheimer's disease.[3]

NICE ACCEPTANCE OF CARER HRQOL IN ECONOMIC MODELLING

Despite often not being explicitly included within the scope, the NICE committee accepted that carer disutilities should be reflected in the economic model in 76% of cases

- Inclusion of carer HRQoL was not explicitly stated in the NICE defined scope for 71% of TAs or HST assessments (12/17); however, the NICE committee commented on the majority of TAs and HST assessments where carer HRQoL had been considered (94%; 16/17).
- Assuming that a lack of NICE commentary indicates acceptance that carer disutilities should be reflected in the economic model, the overall acceptance rate was 76% (13/17). Table 1 provides an overview of the methods used and the NICE commentary across these accepted TAs and HST assessments.
  - NICE accepted all TAs and HST assessments that included carer HRQoL considerations in the base case (9/17), or in both the base case and scenario analyses (2/17).
  - Among the 6 TAs and HST assessments that included carer HRQoL considerations only in the scenario analyses, NICE rejected 4 of them within the economic modelling; however, in 2 cases carer HRQoL was considered qualitatively (rejected: TA534, TA386; rejected in economic modelling but considered qualitatively: HST7, HST8).
- The ERG commented on 76% of assessments (13/17), accepting the inclusion of disutilities for carers in 69% of these cases (9/13; 6 in base case, and 3 in scenario analyses).
- The 2 TAs that derived carer disutility values using an EQ-5D vignette study (TA614, TA615; Table 1) were rejected by the ERG in the base-case analyses, given that this methodology is not in line with NICE guidance; however, NICE accepted the vignette study approach in both cases due to the importance of considering carer HRQoL in these conditions and the lack of evidence in the literature.

Table 1 Methods used and NICE commentary across accepted NICE TAs and HST assessments incorporating carer HRQoL in economic modelling

ID Indication Analysis		
HST11 Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations Base case	Methods	•Carer disutility for one person providing care for children and adults using EQ-5D score; based on literature. Carer disutility values varied according to health states of children and adults •In the ERG's preferred base case, the disutility for carers was multiplied by 1.78 (mean number of parents in a household) •In the ERG's scenario disutility values for adults were excluded; however, disutility values were included for carers of children in all health states
	Commentary	•Noted that there was little difference between the company's and ERG's values •Concluded that the ERG's scenario was more appropriate and would be used in decision making
HST2 Elosulfase alfa for treating mucopolysaccharidosis type Iva Base case and scenario analyses	Methods	•Carer disutility for one person providing care; based on literature •Linked EDSS states (number of hours spent caring) with frequency of wheelchair usage •The ERG conducted additional analyses but none related to carer disutility
	Commentary	•Did not discuss carer disutility in the final evaluation determination document, but considered the results of the company's model
HST3 Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene Base case	Methods	•Revised analysis to include carer disutility for three primary carers (comprising two primary carers and two secondary carers with half the disutility of a primary carer) for non-ambulatory patient health states using EQ-5D score from literature •The ERG incorporated disutility for two primary carers in its revised analysis
	Commentary	•Noted that the company's increased carer disutility partially addressed comments from patient organisations regarding the impact of the condition and technology on carers' HRQoL •Concluded that it would use the company's and the ERG's analyses in its decision making
TA303 Teriflunomide for treating relapsing-remitting MS Base case	Methods	•Carer disutilities per EDSS state accounted for within the model; based on literature •Not discussed by the ERG
	Commentary	•Discussed the disutility values incorporated in the model to reflect carer disutility, as in previous MS appraisals, and considered this to be appropriate
TA312 Alemtuzumab for treating highly active relapsing-remitting MS Base case	Methods	•Carer disutilities per EDSS state accounted for within the model; based on literature •Not discussed by the ERG
	Commentary	•Noted that the manufacturer applied disutilities to carers based on Gani *et al.* (2008)[3] but had no further comments
TA320 Dimethyl fumarate for treating relapsing-remitting MS Base case	Methods	•Carer disutilities per EDSS state accounted for within the model; based on literature •The ERG noted carer disutilities were estimated from MS survey data and there is no published source that can allow these estimates to be evaluated, but the estimates are the same as in previous TAs
	Commentary	•Noted that model included carer disutility that increased with increasing disability of the patient •Aware that carer disutility had featured in TA254 and TA127 and concluded that including carer disutility values was appropriate
TA533 Ocrelizumab for treating relapsing-remitting MS Base case	Methods	•Carer disutilities based on data from TA127 •The ERG did not challenge the inclusion of carer disutility or the data source used •The ERG presented a scenario analysis that limited the carer disutility to a maximum of 0.05
	Commentary	•Stated that the company's model structure was based on advancing disability (EDSS states) but included disutility for relapses and carers •Accepted the ERG's modifications to the economic model
TA585 Ocrelizumab for treating primary progressive MS Base case	Methods	•Carer disutilities per EDSS state accounted for within the model; based on literature •The ERG agreed with the inclusion of carer disutility, but rejected the inclusion of other disutility given this may be overestimating the impact on QALYs
	Commentary	•In agreement with the ERG, rejected inclusion of other disutility but accepted inclusion of carer disutility in the economic model
TA588 Nusinersen for treating spinal muscular atrophy Base case and scenario analysis	Methods	•Carer disutilities derived using EQ-5D scores (carer utility) and multiplying by patient life-years; based on literature •The ERG expressed concerns with the company's approach, their preferred ICER included patient health gains only. They noted a lack of face validity regarding whether patient utilities affects calculation of carer utilities
	Commentary	•The committee considered that including carer disutility in its decision making was appropriate •The ERG model was not supported by patient experts, because it made a life-extending treatment appear to be less cost-effective
TA614 Cannabidiol with clobazam for treating seizures associated with Lennox-Gastaut syndrome Base case	Methods	•Carer disutility for one person providing care **derived using vignettes** valued through EQ-5D VAS. •The ERG discarded carer disutilities within their base-case analysis. They argued the vignette study was not in line with the NICE reference case and there are limitations associated with this study design
	Commentary	•Agreed that the vignette approach was justified given the lack of data in the literature but did note several limitations
TA615 Cannabidiol with clobazam for treating seizures associated with Lennox-Gastaut syndrome Base case	Methods	•Carer disutility for one carer **derived using vignettes** valued through EQ-5D VAS •Assumed that each patient has 1.8 carers (informed by literature) •The ERG did not consider carer HRQoL in their base-case but explored inclusion within a scenario analysis; however, expressed several concerns, e.g., multiple carers may not have the same disutility, and limitations around study design
	Commentary	•Concluded that it was appropriate to consider HRQoL in the economic model and that, although limited, the vignette approach was the best available source for disutility values •Agreed that 1.8 carers was a plausible assumption in line with evidence •Challenged the uncertainty around the values and need for validation from the literature
TA616 Cladribine for treating relapsing-remitting MS Scenario analyses	Methods	•Lost income and disutility associated with EDSS states and progression •Identified health utilities based on EQ-5D and SF-6D for people with MS from two studies •The ERG removed HRQoL decrement for carers from the company's economic model because it was considered inconsistent with the NICE reference case
	Commentary	•Aware that previous NICE guidance for relapsing-remitting MS included utility values for carers •Agreed that it was important to recognise the impact that caring for people with MS has on carers, and concluded that carer HRQoL decrements should be included in cost-effectiveness analysis
TA624 Peginterferon beta-1a for treating relapsing-remitting MS Scenario analyses	Methods	•Financial burden and impact to carers' ability to work; based on literature •The ERG considered using the disutilities from Gani *et al.* (2008)[3] more appropriate
	Commentary	•Agreed that carer utility decrements should rise with worsening EDSS health state (ERG model), and that the company should have used the baseline population from the MS risk sharing scheme rather than the trial •Agreed to consider the various company and ERG base cases and scenario analyses in its decision making

Please note, table only considers NICE TAs and HST assessments which incorporated carer HRQoL in their economic modelling and were accepted within the economic model by the NICE committee. Number of carers included for submissions where the number of carers included was explicitly stated.
EDSS, Expanded Disability Status Scale; EQ-5D EuroQoL-5 Dimension; ERG, evidence review group; HRQoL, health-related quality of life; HST, highly specialised technologies; ICER, incremental cost-effectiveness ratio; ID, identification; MS, multiple sclerosis; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life-year; SF-6D, Short-Form 6-Dimension; TA, technology appraisal; VAS, Visual Analogue Scale.

CONCLUSIONS

- Even though in the current NICE methods guidance, QALYs accrued by carers are accepted for inclusion in the reference case for TAs and HST assessments, this study confirms that carer HRQoL is not routinely submitted to NICE, and so the broader health benefit is not being considered by NICE when evaluating the majority of new interventions.
  - Although the findings of this study indicate a greater proportion of NICE TAs and HST assessments include carer HRQoL considerations in either the economic model or only the value narrative compared with the findings of the DSU report (economic model: 5% vs 3%; value narrative: 11% vs 3%, respectively),[2] this discrepancy is likely due to differences in screening criteria. The NICE DSU specifically included appraisals that discussed the impact of including carer HRQoL on the ICER, whereas this study considered any submission describing a benefit with the intervention on carer HRQoL. In addition, this review excluded multiple technology appraisals and had a more recent time frame.
- In the cases where NICE accepted carer HRQoL, various methods were applied besides EQ-5D to derive utility decrements. There is a lack of clear guidance from NICE on what method manufacturers should use to capture carers' HRQoL, and how it should be incorporated into the cost-effectiveness analyses.[1]
  - In some cases there were clear inconsistencies between ERG and NICE evaluations. For example, in the appraisals deriving carer disutility values using EQ-5D vignettes, the ERG rejected these in the base case while NICE accepted the approach.
- NICE should provide further guidance and evidence to support a consistent approach to including carer/family health outcomes in appraisals.

DISCLOSURES

This work was funded by Pfizer Ltd, UK.

ABSTRACT

Objectives: The broader societal benefits offered by new technologies in terms of quality-adjusted life-years (QALYs) accrued by carers (e.g., a partner, parent, or family member) are accepted for inclusion in the Reference Case for National Institute for Health and Care Excellence (NICE) technology appraisals (TAs) and highly specialised technology (HST) guidance.[1] The research presented here reviews all published TAs and HST assesssments to identify those that considered the impact of an intervention on QALYs for carers and how these have incorporated carer health-related quality of life (HRQoL).

Methods: All TAs and HST assessments published between the publications of the current NICE methods guidance in April 2013 and July 2020 were reviewed.

Results: Manufacturers included carer HRQoL in their economic models in 5% (17/331) of NICE TAs and HST assessments. Most of these (10/17) concerned neurological conditions; 7/10 were for multiple sclerosis, 6 of which used utility decrements for carers of patients with Alzheimer's disease referenced from Gani *et al.* (2008).[3] In 2/17 submissions, carer disutilities were derived using vignettes valued through the EuroQol five-dimension questionnaire (EQ-5D) visual analogue scale (VAS). One submission included the QALY loss to a family due to the premature death of a child. The remaining studies used disutilities from the literature. Of the 17 submissions, 9 included carer HRQoL in the base case only, and 2 in the base case and scenario analyses. NICE accepted inclusion of disutilities for carers in all of these. Six included carer HRQoL only in a scenario analysis. NICE rejected 2 of them.

Conclusions: Carer HRQoL is not routinely submitted for NICE decision making. In the cases where NICE accepted it, various methodologies were applied besides EQ-5D to derive utility decrements. NICE should provide further guidance and evidence to support a consistent approach to including carer/family health outcomes in appraisals.

Corrigendum: In the original abstract, the number of assessments concerning neurological conditions was stated as 9. This has now been updated to 10.

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Top 5%