MODELLING CARER HEALTH-RELATED QUALITY OF LIFE IN NICE TECHNOLOGY APPRAISALS AND HIGHLY SPECIALISED TECHNOLOGIES

REPORT BY THE DECISION SUPPORT UNIT

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EXECUTIVE SUMMARY

NICE's Reference Case for the methods of Technology Appraisal (TA); also used in Highly Specialised Technologies (HSTs); states that "all direct health effects, whether for patients, or when relevant, carers" should be considered. NICE's Reference Case states that health effects should be measured in quality-adjusted life years (QALYs). Our aim was to review all published NICE TAs and HSTs to identify which appraisals have considered the impact of an intervention on QALYs for carers or family members.

Of 422 appraisals, we found 12 TAs and four HSTs where carer QALYs had been included in the economic evaluation, either by the submitting company or the Evidence Review Group (ERG)/Assessment Group (AG), either in the base case or scenario analyses. Eight of the TAs were in multiple sclerosis (MS), one in Alzheimer's disease, one in atopic dermatitis, one in juvenile idiopathic arthritis (JIA) and one in myelofibrosis. The HSTs were in mucopolysaccharidosis type IVa (MPS IVa) in adults and children, Duchenne muscular dystrophy (DMD) in people aged 5 years and older, adenosine deaminase deficiency-severe combined immunodeficiency (ADA-SCID) and X-linked hypophosphataemia (XLH) in children and young people.

The approach to modelling carer QALYs differed between appraisals. The eight MS TAs and the HSTs in MPS IVa, DMD and XLH included carer disutilities associated with the patient's health states whilst alive, whereas the Alzheimer's disease TA included carer utilities. The JIA, atopic dermatitis and myelofibrosis TAs modelled a carer utility increment by the patients' treatment. The ADA-SCID HST included a family QALY loss when the patient died. The approaches differ mathematically and conceptually, particularly in terms of the implied effect on carers' health-related quality of life (HRQL) when a patient dies.

Carer utility in the Alzheimer's TA was based on an unpublished Short-From 36 data, and a non-comparative study measuring the quality of life of carers of Alzheimer's patients using the Health Utilities Index. This same study was used to estimate carer disutility in seven of the MS TAs, the JIA TA and the MPS IVA HST. A study estimating EQ-5D disutilities of carers of patients with MS relative to matched controls was used in two MS TAs (one MS TA was a multiple TA with multiple models). The JIA TA also considered disutilities from a study

analysing EQ-5D in parents of children with and without an activity limitation, which was used in the XLH HST. The DMD HST used carer disutility values from a study comparing EQ-5D of carers of patients with DMD relative to the general population. The ADA-SCID HST estimated family QALY loss relative to patient QALY loss due to premature death, based on a study relating family QALY loss relative to patient QALY loss from death due to meningitis. The treatment utility increments in the atopic dermatitis and myelofibrosis TAs were estimates not rooted in data.

Most TAs and HST considered the health impact on 1 carer only, but the DMD HST considered between 2 and 3 carers, the myelofibrosis TA considered 1.76 carers for 57.48% of patients (based on a burden of illness study), and the ADA-SCID HST considered a family with an unspecified number of members.

In all cases where scenario analyses were presented, including carer QALYs decreased the incremental cost-effectiveness ratio (ICER) for the intervention.

In the appraisals where quantitative analysis including carer QALYs were presented, the committee felt that they should be included in decision-making in most cases (although in the atopic dermatitis they noted there was no evidence to support this). Furthermore, in 11 additional appraisals, the committee felt that there were benefits to carers not captured in the QALY estimation (we excluded appraisals in which the committee discussed the impact of the condition or intervention on carers but not in the context of the economic evaluation). The one notable exception is the TA for myelofibrosis, where the committee felt that the ICER should not be modified to incorporate carer QALYs. In this appraisal, the committee felt that the carer HRQL data was not robust, the carer HRQL burden in myelofibrosis was no more profound than other severe illness, and that the analysis did not account for the carer HRQL burden relieved by other NHS treatments that might be displaced if the intervention were funded. The issue of displaced carer QALYs raises an important issue, especially when considering how few appraisals have considered carer QALYs. Where multiple interventions may be funded from the same budget, the impact on carer QALYs for all potential interventions should be considered in order to maximise QALYs for the population. If carer HRQL burden is not consistent across interventions, it may be necessary for the decision-making process to explicitly consider displaced carer HRQL burden in the opportunity cost. Carer QALYs are not routinely considered for most NICE appraisals and it is unclear why this is. It may be partly

due to paucity of evidence, noting the few studies that have been used across disease areas, or due to confusion amongst analysts as to whether carer QALYs should be included (there was some confusion amongst ERGs/AGs in TA493 and TA527 as to whether carer QALYs should be included in Reference Case analyses).

The following issues need to be considered in order to develop consistent approaches to the incorporation of carer health impacts in cost effectiveness and subsequent decision making:

- When carer health effects should be included in economic evaluations, including consideration of:
    - How to determine when carer health effects are "relevant"
    - Clarification on the meaning of "direct" health effects
    - Which, and how many, carers/family members should be included
    - Whether there are specific populations where carer/family health should routinely be included
- What evidence is required to determine whether carer/family health outcomes should be included in economic evaluation, including consideration of:
    - Specific disease where carer/family health should routinely be included
    - Whether evidence can be used from other disease areas
    - Which measures should be used to measure family/carer health
    - The most appropriate comparison for estimating carer health effects
- How carer/family health should be modelled, including consideration of:
    - Whether carer/family health should be linked to the patient's disease status or treatment
    - The duration of the impact on carer/family health
    - The impact of patient death of carer/family health

Further research would be valuable to explore:

- The family/carer health outcomes of NHS interventions
- Family/carer health outcomes across disease areas
- The change in carer HRQL over time.

Addressing these issues would provide guidance and evidence to support a consistent approach to including carer/family health outcomes across NICE appraisals.

CONTENTS

TABLES

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ABBREVIATIONS AND DEFINITIONS

ACD	Appraisal consultation document
AG	Assessment Group
CDR	Clinical Dementia Rating scale
ECD	Evaluation consultation document
EDSS	Expanded Disability Status Score
EQ-5D	EuroQol-Five Dimension
ERG	Evidence Review Group
FAD	Final appraisal determination
FED	Final evaluation document
HRQL	Health-related quality of life
HST	Highly Specialised Technology
HUI	Health Utilities Index
ICER	Incremental cost-effectiveness ratio
MMSE	Mini Mental State Examination
MS	Multiple sclerosis
MTA	Multiple Technology Appraisal
NICE	The National Institute for Health and Care Excellence
PDDS	Patient Determined Disease Steps
QALY	Quality-adjusted life year
TA	Technology Appraisal
SD	Standard deviation
SE	Standard error
SF-36	Short Form 36
STA	Single Technology Appraisal

1. INTRODUCTION

1.1. BACKGROUND

Health interventions can affect the health of carers as well as the person receiving the intervention. This could be because the intervention changes the patient's requirement for informal care (for example by improving a patient's mobility and reducing their need for lifting reduces a carer's back pain); because of the carer's emotional response to the patient's condition; because the intervention substitutes, complements, or increases the patients' informal care; or because the intervention changes the carer's attitude, emotional response or health-related behaviours [1]. These elements may affect a carer's health-related quality of life (HRQL) and may therefore be relevant for inclusion in economic evaluation. The 2013 National Institute for Health and Care Excellence (NICE)'s reference case for Technology Appraisal (TA) states that the perspective on outcomes should be all direct health effects (p32)[2]. In the summary of the reference case, this is expanded as "whether for patient or, when relevant, carers" (p32), and in the text this is expanded as "whether for patients or other people" (p33) (although a definition for direct or indirect effects is not provided). In both the 2004[3] and 2008[4] reference cases, the perspective on outcomes is stated to be "all health effects on individuals" (p21 of 2004, p30 of 2008) and this is expanded as "…all direct health effects whether for patients or, where relevant, other individuals (principally carers)" (p22 of 2004, p32 of 2008). The HST Interim Methods and Process Guide additionally states that in forming its guidance, the committee will consider the nature of the disease (including impact on carers' quality of life), clinical effectiveness (including magnitude of health benefits to patients, and when relevant, carers) as well as value for money and impact beyond direct health benefits [5].

NICE's reference case states that health effects should be expressed in quality-adjusted life years (QALYs)[2]. QALYs combine quality of life and quantity of life, by assigning a utility value to a person's HRQL, anchored between 1 (perfect health) and 0 (equivalent to death). Economic evaluations for interventions appraised by NICE may therefore include carer QALYs.

Whilst all cost-utility analyses consider the direct health effects (measured in QALYs) for the patient, the inclusion of health effects for other people is less common. A 2012 systematic review found only six published economic evaluations that included carer QALYs [6], and a

2015 study found only three of 100 economic evaluations in Parkinson's, Alzheimer's, metastatic colorectal cancer and rheumatoid arthritis included carer QALYs[7]. As NICE does not specify the methods by which health effects to other people should be included, there is interest in reviewing and critiquing the approaches and data sources used in NICE TAs and Highly Specialised Technologies (HSTs) (where the TA Reference case is referenced as the preferred methods evaluating cost-effectiveness [5]).

1.2. THIS REVIEW

This review examines published documentation from NICE's TA and HST programmes to identify economic evaluations that included health effects for carers in economic evaluation, or which discussed the impact of including carer health effects on the ICER. The methods and data sources for incorporating carer HRQL are described and critiqued.

2. METHODS

An information specialist (RW) hand-searched the online Final Appraisal Documents (FADs) and Final Evaluation Documents (FEDs) published TAs and HSTs on the NICE website on 10th January 2019, to identify appraisals where the terms "carer" or "caregiver" were mentioned in the text. A health economist (BP) then reviewed these TAs and HSTs and included those where the Committee discussed the inclusion of carer or family quality of life in relation to economic analysis or HRQL, utilities or disutility, or the incremental cost-effectiveness ratio (ICER). The health economist extracted data related to the intervention, condition, approach to modelling carer HRQL, number of carers included, source of carer HRQL data, size of carer HRQL impact, and information on the impact of including HRQL on cost-effectiveness results.

3. RESULTS

3.1. SUMMARY RESULTS

There were 414 published TAs and eight published HSTs on 10th January 2019. We identified 16 appraisals in total which included carer HRQL in economic analyses: 12 TAs and four HSTs. The TAs included three multiple technology appraisals (MTAs) - one for multiple sclerosis[8], one for juvenile idiopathic arthritis[9] and one for Alzheimer's disease[10] - and nine single technology appraisals (STAs): seven in multiple sclerosis[11-17], one in atopic

dermatitis[18] and one in myelofibrosis[19]. The HSTs were for adenosine deaminase deficiency-severe combined immunodeficiency[20], Duchenne muscular dystrophy[21], mucopolysaccharidosis type IVa[22] and X-linked hypophosphataemia[23].

The appraisals where carer HRQL was quantitatively included are summarized in Table 1 and discussed in Sections 3.2 to 3.9.

In 12 appraisals carer HRQL was linked to patient's disease severity, in three appraisals carer HRQL was linked to the patient's treatment, and in one appraisal carer QALY loss was linked to the patient's death.

Carer HRQL was included for one carer in 13 appraisals. In one appraisal, the company assumed that 57.48% of patients have 1.76 carers. In one appraisal, the number of carers varied between 1 and 3 in the company and ERG analysis. One appraisal applied a family QALY loss without specifying the number of carers/family members.

Most appraisals used carer disutilites - the size of these ranged from 0.01 to 0.173 per year. One appraisal used carer utility, ranging from 0.85 to 0.94. In all appraisals, it appears that the carer disutility or utility was included for the duration of the model (until the patient died), except in one appraisal where family QALY loss was included as a one-off event due to a child's death, valued at 9% of the child's QALY loss, equal to a family loss of 1.8 or 2.1 QALYs depending on the type of donor for stem cell transplant.

The 16 appraisals referred to five original studies which reported HRQL for carers (some studies used multiple sources):

- A study reporting Health Utilities Index (HUI) 2 and 3 scores for carers of patients with Alzheimer's disease[24] – used in 10 appraisals
- A cross-sectional survey comparing EQ-5D scores for carers of people with MS and controls[25] – used in 2 appraisals
- A study analyzing the impact of having a child with activity limitations on EQ-5D scores for parents[26] – used in 2 appraisals
- A study measuring the EQ-5D of carers of patients with Duchenne muscular dystrophy[27] – used in 1 appraisal

- A cost-effectiveness analysis reporting the family QALY loss to a family due to the premature death of a child[28] – used in 1 appraisal

The submitting company for the Alzheimer's appraisal also referred to an analysis of Short-Form 36 (SF-36) data, but further information was unavailable. Two appraisals included estimates of carer disutility not rooted in data. Figure 1 shows how the original studies have been used in the TAs and HSTs.

In 11 appraisals, the committee used the economic analysis including carer disutilities in their decision-making. In four appraisals, the committee considered the impact on carer HRQL in their decision-making but did not cite the results of the economic analysis including the carer disutility as their preferred cost-effectiveness estimate (the reasons for this varied). In one appraisal, the committee felt that the cost-effectiveness analysis results should not include the impact on carer's HRQL [19].

In 11 additional appraisals, the Committee discussed the impact of including carer or family HRQL on the ICER, but it was not formally included in economic evaluation [29-35]. These appraisals are summarized in Table 2. Appraisals in which the Committee discussed the impact of the condition or intervention on carers, but not in the context of inclusion in economic evaluation were excluded from our review. Including these would have increased the number of appraisals in which carers were considered qualitatively. These considerations may not be limited to health or health-related quality of life and may include effects not included in ICERs.

The impact of the inclusion of carer HRQL on cost-effectiveness results is summarised in Table 3. This is limited as some appraisals did not report any scenario analysis testing these assumptions, and in some appraisals the information was redacted for confidentiality. Furthermore, in the appraisals where this information was available, the format varied, and so for consistency we report the change in incremental QALYs and ICER. The decision whether to include or exclude carer HRQL generally changed the incremental QALYs by less than 0.03, but up to 22%. Varying the number of carers included, as in HST3, made a much bigger difference to the incremental QALYs – with changes of up to 0.884 for one versus three carers. Including family QALY loss due to patient premature death in HST8 had the biggest impact on incremental QALYs – with a change of 1.3 incremental QALYs. The impact on the ICER depends on the incremental cost (which does not change when carer HRQL is

included/excluded) as well as the incremental QALYs, and so is more variable across appraisals.

Table 1: Summary of appraisals that quantitatively include carer health-related quality of life

TA /HST	Indication / population	Carer HRQL included quantitatively in economic analyses?	Method for including carer HRQL	Size of carer HRQL effect	Population to whom carer HRQL applied	Source of carer HRQL data	Measure of utility	Committee conclusion
TA217	Alzheimer's disease	In base case for 1 company model. In scenario analysis for AG model.	Carer utility modelled by patient's disease severity	Unclear in company model. In AD model, utility ranged from 0.85 to 0.94.	1 carer	Company: unpublished data. Neumann et al (2000) study of 679 utility of carers of patients with Alzheimer's Disease[24]	Company: SF-36 transformed into utilities. AG: HUI 2	Used assessment group model in decision-making, but noted carer quality of life.
TA127 TA254 TA312 TA303 TA320 TA533	Multiple sclerosis	Yes	Carer disutility modelled by patient's disease severity	Disutility ranged from 0.00 to 0.14.	1 carer	Neumann et al (2000) study of 679 utility of carers of patients with Alzheimer's Disease[24]	HUI 3	Used company's model in decision-making.
TA493	Multiple sclerosis	Yes	Carer disutility modelled by patient's disease severity	Disutility ranged from 0.002 to 0.173	1 carer	Acaster et al (2013) survey of 200 carers of people with MS and 300 matched controls [25]	EQ-5D	Quality of life decrements for carers should be considered in cost-effectiveness analysis.
TA527	Multiple sclerosis	In base case for 3 company models.	Carer disutility modelled by patient's	1 company: same as TA127	1 carer	Neumann et al (2000) [24] and Acaster et al (2013) [25]	HUI 3 and EQ-5D	Disutility to carers should be included in cost-effectiveness analysis.

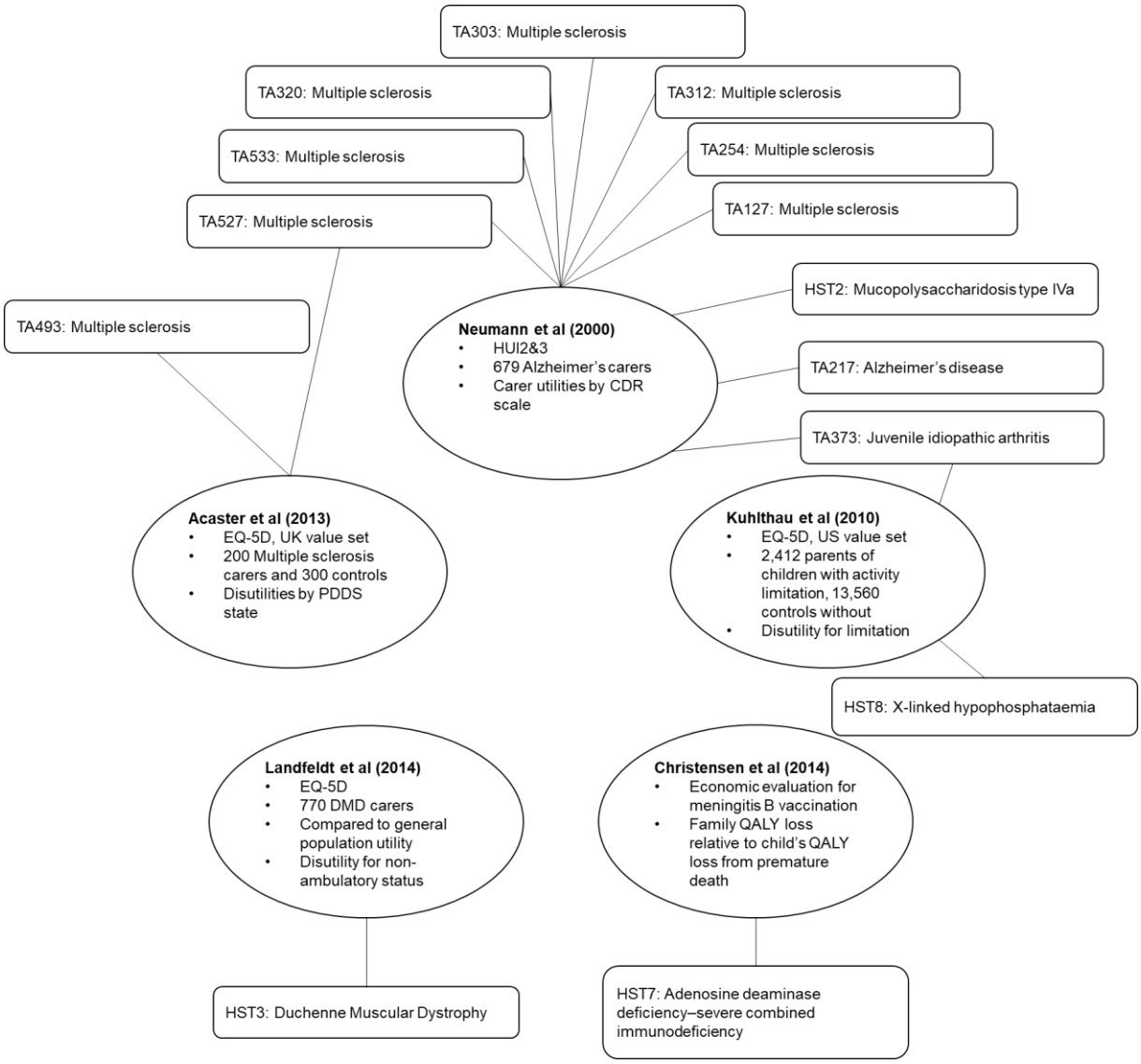
TA /HST	Indication / population	Carer HRQL included quantitatively in economic analyses?	Method for including carer HRQL	Size of carer HRQL effect	Population to whom carer HRQL applied	Source of carer HRQL data	Measure of utility	Committee conclusion
		In scenario analysis for AG model.	disease severity	2 companies: same as TA493				
TA373	Juvenile idiopathic arthritis	In scenario analysis for AG model only.	Carer disutility – patient being on treatment halves carer disutility	Two scenarios - carer disutility when patient off treatment: 0.02 or 0.07	1 carer	1 scenario: data used in TA127 1 scenario: Kuhlthau et al (2010) survey of 15,972 patients including some whose children had activity limitation [26]	EQ-5D	Carer utility should be included in modelling, but unclear which of the 2 scenarios should be used.
TA386	Disease-related splenomegaly or symptoms in adults with myelofibrosis	In company's revised analysis after ACD	Carer utility increment for patients receiving treatment	Increment of 0.1	57.48% of patients have 1.76 carers	Refers to study measuring quality of life of carers of patients with glioma[36] and Acaster et al 2013c[25]	Study uses SF-36, and Acaster uses EQ-5D	ICER should not be modified to reflect carer's quality of life.
TA534	Moderate to severe atopic dermatitis	In company's revised analysis after ACD	Carer utility increment for patients	Increment of 0.01 or 0.1	1 carer	No source specified	NA	There could potentially be an effect on quality of life of

TA /HST	Indication / population	Carer HRQL included quantitatively in economic analyses?	Method for including carer HRQL	Size of carer HRQL effect	Population to whom carer HRQL applied	Source of carer HRQL data	Measure of utility	Committee conclusion
			receiving treatment					carers, but no evidence to support this.
HST2	Mucopolysaccharidosis type IVa	In company's base case	Carer disutility modelled by patient's disease severity	Disutility ranged from 0.00 to 0.14.	1 carer	Neumann et al (2000) [24]	HUI3	Company's model used in decision making.
HST3	Duchenne muscular dystrophy	In company's base case	Carer disutility modelled by patient's ambulatory status	Disutility of 0.11	Company original submission: 1 carer. Company revised model: 3 carers. ERG analysis: 2 carers.	Landfeldt et al 2014 study of 770 pairs of patients and their carers [27]	EQ-5D	Company's increased care disutility (3 carers) partially addressed patient organizations' comments, but concern about the disutility values. Imperative that future review of guidance includes carer utility data.
HST7	Adenosine deaminase deficiency–severe combined immunodeficiency	In company's scenario analysis	Family QALY loss due to patient premature death	Family QALY loss 9% of child's QALY loss	Not stated – family	Christensen et al 2014 economic evaluation of vaccination for meningitis B [28]	Not stated	Scenario would not fully reflect quality-of-life benefit to carers after successful treatment. Improvement to carer's quality of life should be considered qualitatively.

TA /HST	Indication / population	Carer HRQL included quantitatively in economic analyses?	Method for including carer HRQL	Size of carer HRQL effect	Population to whom carer HRQL applied	Source of carer HRQL data	Measure of utility	Committee conclusion
HST8	X-linked hypophosphataemia	In company's scenario analysis after ECD	Carer disutility modelled by patient's disease severity	Disutility of 0.08	1 carer	Kuhlthau et al (2010)[26]	EQ-5D	It would take into account estimates including a quantitative estimate of carer burden, but because the estimate was not robust, it would also consider carer burden qualitatively.

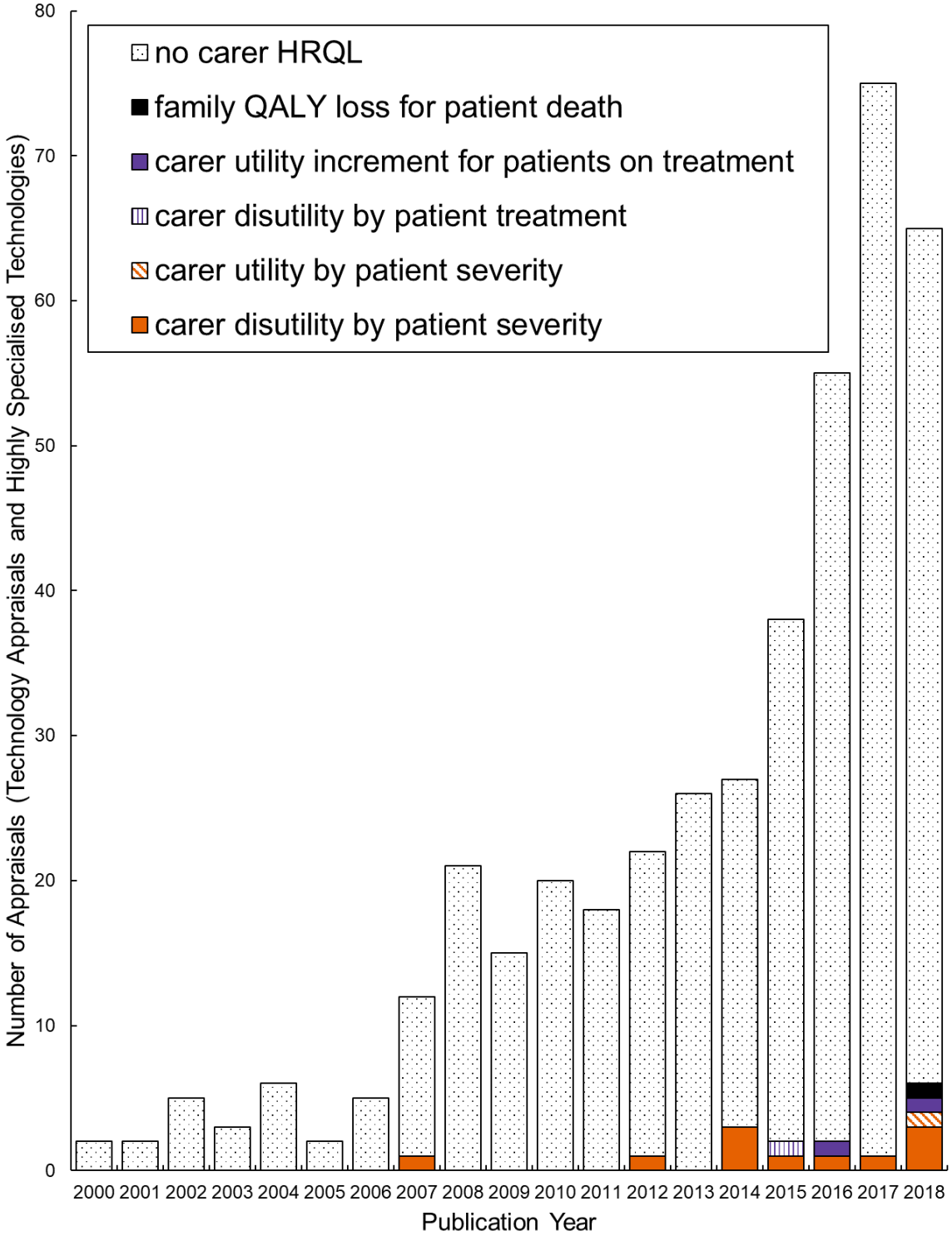
ACD: Appraisal consultation document, ECD: Evaluation consultation document, EQ-5D: EuroQol-Five Dimension, HST: highly specialized technology, HUI: health utilities index, ICER: incremental cost-effectiveness ratio, MS: multiple sclerosis, QALY: quality-adjusted life year, SF-36: Short Form 36, TA: technology appraisal

Figure 1: Use of data sources in appraisals



CDR: Clinical Dementia Rating, DMD: Duchenne Muscular Dystrophy, EQ-5D: EuroQol-Five Dimension, HST: highly specialized technology, HUI: health utilities index, ICER: incremental cost-effectiveness ratio, PDDS: Patient Determined Disease Steps, QALY: quality-adjusted life year, SF-36: Short Form 36, TA: technology appraisal

Figure 2: Inclusion of carer HRQL in NICE appraisals over time



HRQL: health-related quality of life, QALY: quality-adjusted life year

Table 2: Summary of appraisals that discuss but do not quantitatively include carer health-related quality of life

TA /HST	Indication / population	Committee conclusion
TA538	Dinutuximab beta for treating neuroblastoma	The committee acknowledged that there were uncaptured health-related benefits. These included reduced quality of life because of the effect of stress and depression caused by the disease on young patients and their families, as well as the devastating effects of bereavement on families.
TA455	Plaque psoriasis in children and young people	Carer disutility should be considered, but no quantitative estimates available.
TA238	Juvenile idiopathic arthritis	If carer utility were considered, ICER would be lower.
TA278	Severe persistent allergic asthma	There are benefits to carers not captured in the QALY gain.
TA431	Severe refractory eosinophilic asthma	There are benefits to carers not captured in the QALY gain.
TA479	Severe eosinophilic asthma	There are benefits to carers not captured in the QALY gain.
TA406	Untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer	Company did not incorporate the expected benefits to patients' carers in the model, but no evidence was presented on the extent of these benefits. No evidence was presented of benefits not captured in QALYs.
TA398	Cystic fibrosis homozygous for the F508del mutation	Effects on carers had not been taken into account in company's economic model, but these would not change recommendations given the very high ICER.
TA325	Reducing alcohol consumption in people with alcohol dependence	The utility values in the model may have underestimated the true benefit of the intervention because the model did not take into account health-related quality of life of family and carers.
TA300	Chronic hepatitis C in children and young people	There were health benefits not captured by the QALY, including alleviating a mother's burden of psychological guilt of mother-to-child transmission. These did not need further action because of the favourable cost-effectiveness results.
HST6	Asfotase alfa for treating paediatric-onset hypophosphatasia	The committee also acknowledged that the company had not included the health-related quality-of-life benefits for carers of people with the condition and that, if included, they were likely to increase the quality-adjusted life year (QALY) gain for asfotase alfa compared with best supportive care.

HST: highly specialized technology, ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life year, TA: technology appraisal

Table 3: Impact of inclusion of carer health-related quality of life on cost-effectiveness results

TA /HST	Indication / population	Carer HRQL included quantitatively in economic analyses?	Impact of including carer HRQL on incremental QALYs	Impact of including carer HRQL on ICERs
TA217	Alzheimer's disease	In base case for 1 company model. In scenario analysis for AG model.	Removing caregiver disutility for patients in institutional care decreased incremental QALYs by 0.026 QALYs (mild) and 0.021 QALYs (moderate)	
TA127	Multiple sclerosis	Yes		Removing caregiver disutility increased ICER by £2,600.
TA254				
TA312				
TA303				
TA320			Removing caregiver utility decreased incremental QALYs by 0.024	Removing caregiver analysis increased ICER by £11,498.
TA533				Limiting the caregiver disutility to 0.05 increased ICER vs. beta-interferon by £1,579 and vs. teriflunomide by £599.
TA493	Multiple sclerosis	Yes		
TA527	Multiple sclerosis	In base case for 3 company models. In scenario analysis for AG model.		
TA373	Juvenile idiopathic arthritis	In scenario analysis for AG model only.		Including the lower disutility decreased the ICERs by £951 to £1,478. Including the higher disutility decreased the ICERs by £3,637 to £4,723.
TA386	Disease-related splenomegaly or symptoms in adults with myelofibrosis	In company's revised analysis after ACD	Including carer utility benefit increased incremental QALYs by 0.03.	Including carer utility benefit decreased ICER by £4,030.

TA /HST	Indication / population	Carer HRQL included quantitatively in economic analyses?	Impact of including carer HRQL on incremental QALYs	Impact of including carer HRQL on ICERs
TA534	Moderate to severe atopic dermatitis	In company's revised analysis after ACD		Including the lower carer utility benefit decreased ICER by £1,244 or £2,248. Including the higher carer utility benefit decreased ICER by £8,933 or £9,498.
HST2	Mucopolysaccharidosis type IVa	In company's base case	Removing caregiver disutility decreased incremental QALYs by 0.03	
HST3	Duchenne muscular dystrophy	In company's base case	Reducing the number of carers from three to two decreased the incremental QALYs by 0.442. Reducing the number of carers from three to one decreased the incremental QALYs by 0.884.	
HST7	Adenosine deaminase deficiency–severe combined immunodeficiency	In company's scenario analysis	Including family QALY loss increased the incremental QALYs by 1.3.	Including family QALY loss decreased the ICER by £3,159.
HST8	X-linked hypophosphataemia	In company's scenario analysis after ECD		

HST: highly specialized technology, ICER: incremental cost-effectiveness ratio, MS: multiple sclerosis, QALY: quality-adjusted life year, TA: technology appraisal

3.2. TA217: DONEPEZIL, GALANTAMINE, RIVASTIGMINE AND MEMANTINE FOR THE TREATMENT OF ALZHEIMER'S DISEASE

3.2.1.1. Company submission

TA217 was an MTA of four technologies for Alzheimer's disease in adult patients: donepezil, galantamine, rivastigmine and memantine, published in March 2011. Economic models were submitted by the companies for two technologies: memantine and donepezil. The company model for donepezil included utility for one caregiver, using an equation that predicted caregiver utility based on caregiver age and sex and patient age and disease state[37]. This was based on analysis of donepezil trial data that measured caregiver quality of life using the short-form 36 questionnaire (SF-36), transformed into utilities. The company submission references a technical appendix for further information, which is not available, and so further information on the caregiver utilities cannot be provided or critiqued here.

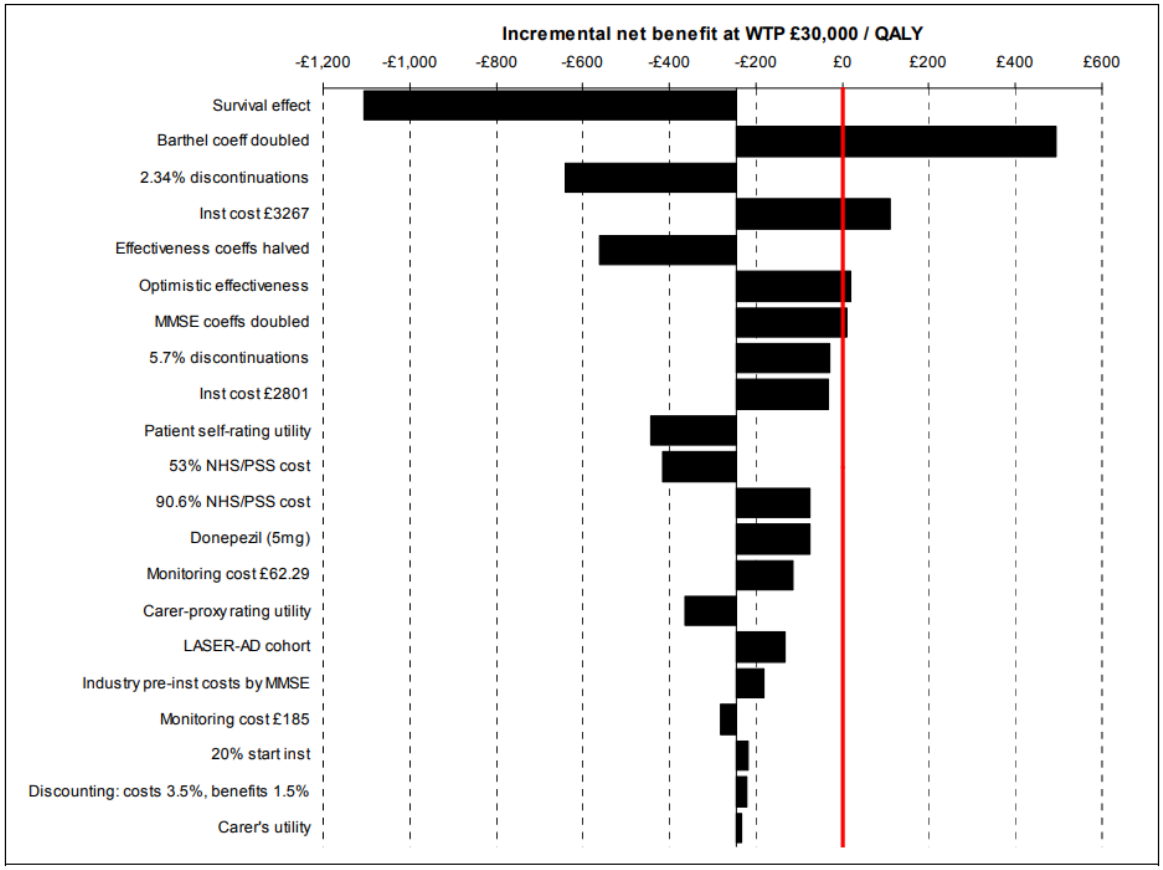
The company conducted scenario analysis in which they removed the caregiver utility decrement associated with disease severity for patients receiving institutional care. This increased the carer QALYs for both intervention and comparator, but decreased the incremental QALYs from 0.164 to 0.138 for mild and from 0.111 to 0.091 for moderate. As the incremental costs remained negative, the ICERs were dominant in all cases.

3.2.1.2. Independent assessment

The Assessment Group (AG) developed an economic model that used the Mini Mental State Examination (MMSE) scale to model Alzheimer's disease. Their model included carer utility in scenario analysis, but not in the base case[38]. Information about their method for including carer utility is not provided.

They used HUI2 utilities from Neumann et al (2000)[24], mapping the Clinical Dementia Rating scale (CDR) onto MMSE. They modelled carer utility by the patient's MMSE score and mapped onto time prior to institutionalisation for the patient. Scenario analysis including caregiver utility slightly increased the incremental net benefit at £30,000 per QALY, as shown in 3.

Figure 3: Effect of carer utility on cost-effectiveness of Alzheimer's intervention



Reproduced from TA217

Neumann et al (2000) report HUI2 and HUI3 scores for patients with Alzheimer's disease and their caregivers from a cross-sectional study in the US. The mean age of caregivers was 63 (standard deviation (SD) 14) and 65% of caregivers were female. 39% of caregivers were the patient's spouse, 48% were the patient's child, and 13% were another relation to the patient (including sibling, other relative or friend). The caregiver utilities, categorized by the CDR, are reproduced in Table 4. Neumann et al found in linear regression analysis that patient disease stage was not a significant predictor of caregiver utility.

Table 4: Utility scores for carers of patients with Alzeimer's Disease

	Overall sample (n=679)	Questionable CDR=0.5 (n=52)	Mild CDR=1 (n=194)	Moderate CDR=2 (n=230)	Severe CDR=4 (n=50)	Profound CDR=4 (n=50)	Terminal CDR=5 (n=13)
HUI 2 mean	0.87	0.88	0.87	0.86	0.85	0.91	0.94
HUI 2 SD	0.18	0.10	0.12	0.11	0.11	0.09	0.03
HUI 3 mean	0.87	0.88	0.87	0.87	0.86	0.90	0.93
HUI 3 SD	0.14	0.12	0.15	0.14	0.16	0.10	0.04

CDR: Clinical Dementia Rating, HUI: health utilities index, SD: standard deviation
Reproduced from Neumann et al (2000)

3.2.1.3. Committee discussion

The committee considered the AG's model in developing recommendations, but noted the results from the company's model for donepezil and that the impact of including carer utility and that the differences between the models may be partially due to carer utility[10].

3.3. MULTIPLE SCLEROSIS

3.3.1. TA127: Natalizumab for highly active relapsing-remitting multiple sclerosis

3.3.1.1. Company submission

TA127 appraised natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis (RRMS), published in August 2007. In their submission, the company included a disutility for one caregiver. The size of the caregiver disutility depended upon the health state (defined by Expanded Disability Status Score (EDSS)) that the patient was in, up to a maximum disutility of 0.14[39]. The company reported that this was based on a mean caregiver utility of 0.86 quoted in the NICE assessment for treatment of Alzheimer's disease, so it appears that the disutility was calculated by subtracting the caregiver utility from 1 – thus assuming that caregivers would otherwise have full health if they were not caregivers. The reference cited by the manufacturer is no longer available as the NICE

appraisal it refers to (TA111) has been superseded, but there is a published Health Technology Assessment (HTA) report describing the appraisal of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease [40]. This HTA report provides estimates of utilities for carers of patients with Alzheimer's disease using the HUI2 and HUI3. The utilities are referenced to a number of publications by Neumann et al, one of which contains the same HUI2 and HUI3 utilities[24], reproduced in Table 5.

Table 5: Disutilities for carers of patients with Multiple Sclerosis

EDSS score	Average caregiver disutility
0.0	0.00
1.0	0.00
1.5-2.0	0.00
2.5-3.0	0.01
3.5-4.0	0.01
4.5-5.0	0.02
5.5-6.0	0.03
6.5-7.0	0.05
7.5-8.0	0.11
8.5-9.5	0.14

EDSS: Expanded Disability Status Score.

Reproduced from Loveman et al [40]

In the manufacturer's scenario analysis, removing caregiver disutility decreased the ICER by £2,600 (from £27,000).

3.3.1.2. Independent assessment

The Evidence Review Group (ERG) noted that the estimation of caregiver disutility was based on sparse data and assumptions and raised concern with including it in the base case analysis[41], but noted it made little difference to the cost-effectiveness results. The company responded that caregiver disutility was added to the reference case at NICE's suggestion in a meeting to discuss the decision problem, based on the conclusion that caregiver utility was relevant in TA111 for Alzheimer's disease[42].

3.3.1.3. Committee discussion

The FAD does not explicitly refer to carer quality of life. The FAD describes that the committee considered the company's cost-effectiveness results and the ERG comments[11].

3.3.2. TA254, TA312, TA303, TA320, TA533: relapsing-remitting multiple sclerosis

This section describes the following five TAs:

- TA254: fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis in adults (published in April 2012)
- TA312: alemtuzumab for the treatment of relapsing–remitting multiple sclerosis in adults (published in May 2014)
- TA303: teriflunomide for the treatment of relapsing–remitting multiple sclerosis in adults (published in June 2014)
- TA320: dimethyl fumarate for the treatment of relapsing–remitting multiple sclerosis in adults (published in August 2014)
- TA533: ocrelizumab for treating relapsing–remitting multiple sclerosis in adults (published in July 2018)

3.3.2.1. Company submissions

The company submissions for these five TAs for relapsing-remitting multiple sclerosis used the same caregiver disutilities and approach as TA127 in the base case analyses[43-47]. TA320 presented a scenario analysis excluding caregiver disutility – this decreased the incremental QALYs from 0.23 to 0.206 and increased the ICER from £122,105 to £133,603.

3.3.2.1. Independent assessment

The ERGs for these five TAs did not challenge the inclusion of, or data source for, caregiver disutilities [48-52]. The ERG for TA533 presented a scenario analysis limiting the caregiver disutility to a maximum of 0.05 – this increased the ICER of ocrelizumab versus interferon from £26,436 to £28,015 and versus teriflunomide from £9,833 to £10,432.

3.3.2.2. Committee discussion

The FADs for TA320 and TA303 discuss the caregiver disutilities, noting that the values had been used in previous appraisals of technologies for relapsing-remitting multiple sclerosis and that including these disutility values was appropriate. In TA303, the committee noted that the disutility values did not have a large impact on the cost-effectiveness results and

concluded therefore that they did not need to consider them further. The FADs for TA254 and TA312 do not explicitly discuss carer quality of life [12, 16, 14, 15, 17].

3.3.3. TA493: Cladribine for the treatment of relapsing–remitting multiple sclerosis

3.3.3.1. Company submission

TA492 appraised cladribine for the treatment of relapsing-remitting multiple sclerosis in adults, published in December 2017. The company included a disutility for one caregiver in their base case, using data from a study by Acaster et al, and mapping Patient Determined Disease Steps (PDDS) to EDSS[53] to link caregiver disutility to the patient's disease state. Acaster et al conducted a cross-sectional survey of 200 carers of people with MS and 300 controls in the UK, matched on age, sex, employed status and habitation status[25]. 25.0% of caregivers cared for a patient with relapsing-remitting MS, 43.5% for a patient with secondary progressive MS and 31.5% for a patient with primary progressive MS. 76.5% of caregivers were the patient's partner/spouse, 6.5% were the patient's parent, 2.0% were the patient's child, 9.5% were another family member and 5.5% were a friend. Health utilities were derived using the EQ-5D (with UK general population values) for the control and caregiver groups, and the difference between groups assessed. The difference between caregiver and general population EQ-5D scores are reproduced in Table 6. Acaster et al note that only the differences are only significant for Patient determined Disease Steps (PDSS) 4, 5 and 6. Acaster et al note that the disutilities for PDDS 7 and 8 are comparable with PDDS 1 and 2, and that in PDDS 7 a patient would typically require use of a wheelchair, and in PDDS 8 a patient would be bed-ridden. Acaster et al explored whether this difference is related to the impact of receiving external caregiver support, but found no difference in utilities for caregivers receiving versus not receiving support[25].

Table 6: Disutilities for carers of patients with multiple sclerosis

	PDSS 0-1 (n=28)	PDSS 2-3 (n=24)	PDSS 4 (n=20)	PDSS 5 (n=26)	PDSS 6 (n=27)	PDSS 7 (n=62)	PDSS 8 (n=13)
Mean	0.002	0.045	0.142	0.160	0.173	0.030	0.095
SE	0.053	0.057	0.062	0.055	0.054	0.038	0.75

SE: standard error, PDDS: Patient Determined Disease Steps

Reproduced from Acaster et al [25]

3.3.3.2. Independent assessment

The ERG excluded carer disutility in their base case analysis, on the grounds that the NICE reference case states "all direct health benefits" and they considered that the impact to the carer was indirect[54].

3.3.3.3. Committee discussion

The FAD discusses that the committee were aware that previous NICE guidance for RRMS had included caregiver utility. The committee agreed it was important to recognise the impact of caring for people with MS on carer's quality of life, and concluded that quality of life decrements should be taken into account in the cost-effectiveness analysis[13].

3.3.4. TA527: Beta interferons and glatiramer acetate for treating multiple sclerosis

3.3.4.1. Company submissions

TA527 was an MTA of five technologies for multiple sclerosis in adults: interferon beta 1a (manufactured by two different companies), peginterferon beta 1a, interferom beta 1b and glatiramer acetate, published in June 2018. Three companies submitted economic models., all of which included a disutility for one caregiver, linked to the patient's disease state – one used the same disutilities as TA127, and two used the same disutilities as TA493 (based on Acaster et al)[55].

3.3.4.2. Independent assessment

The AG excluded carer disutilities from their base case analysis, on the grounds that they represent unpaid/informal carers. In scenario analysis they presented results including carer disutilities based on Acaster et al combined with other changes, but the impact of carer disutilities alone was not considered [55].

3.3.4.3. Committee discussion

The FAD discusses the committee's consideration of the burden on carers and noted that previous NICE TAs in MS included carer disutility. The committee concluded that it would include disutility to carers[8].

3.4. TA373 ABATACEPT, ADALIMUMAB, ETANERCEPT AND TOCILIZUMAB FOR TREATING JUVENILE IDIOPATHIC ARTHRITIS

3.4.1.1. Company submissions

TA373 appraised abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis in paediatric patients, published in December 2015. Only one company submitted a cost-utility analysis, and this did not include caregiver utility[56].

3.4.1.2. Independent assessment

The AG considered a disutility for one caregiver in scenario analyses, where they assumed that caregiver disutility for patients on abatacept, adalimumbab, etanercept or tocilizumab is half the size of the caregiver disutility for patients not on treatment[56]. The AG considered two sources of disutility data: a publication by Gani et al[57] which describes the model used in NICE TA127, and a study by Kuhlthau et al (2010) [26] which reports the well-being of parental caregivers of children with activity limitations. Kuhlthau analysed EQ-5D scores from the US Medical Expenditure Panel Survey for 13,560 parents without a child with an activity limitation, and 2,412 parents of a child with an activity limitation. The AG noted that in Gani et al, the caregiver disutility was relatively small until the patient entered a state of severe immobility, and considered a disutility of 0.02. Including the disutility of 0.02 reduced the ICERs by £951-£1,478 (from £32,256-£38,656).
Kuhlthau used EQ-5D data from 15,972 parents in the Medical Expenditure Survey in the US, to explore the association of parent outcomes with having a child with an activity limitation and found a coefficient of 0.07. The AG therefore considered a disutility of 0.07. Including the disutility of 0.07 reduced the ICERs by £3,637-£4,723.

3.4.1.1. Committee discussion

The FAD notes that the committee concluded it was relevant to include caregiver utility in the modelling, but was unclear which of the two values considered by the AG in scenario analyses should be used[9].

3.5. TA386: RUXOLITINIB FOR TREATING DISEASE-RELATED SPLENOMEGALY OR SYMPTOMS IN ADULTS WITH MYELOFIBROSIS

3.5.1.1. Company submission

TA386 appraised ruxolitinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis, published in March 2016. In their original submission, the company

stated that the economic analysis did not include the impact on carers and therefore underestimated the benefit of ruxolitinib[58]. In response to the ACD, the company submitted revised economic analyses including a scenario which considered carer QALYs[59]. This analysis assumed that 57.48% of patients had 1.76 carers, based on a study of the burden of illness[60]. The company assumed that the utility of the carer would increase by 0.1 for patients receiving treatment with ruxolitinib. The company describe that a study of quality of life among caregivers of patients with glioma showed the utility decrement was around 0.10 using SF-6D – the study reports a non-significant difference between SF-36 scores for caregivers of patients with glioma and caregivers of patients with other cancers[36]. The company also refer to the caregiver utility decrements in MS from Acaster et al[25]. Including the caregiver utility increment in the company's analysis increased the incremental QALYs from 2.51 to 2.54 and decreased the ICER from £34,865 to £30,835.

3.5.1.2. Independent assessment

The ERG expressed a number of concerns regarding the assumptions and data used in the scenario considering a caregiver utility. Specifically, the ERG was concerned with the use of non-UK data, the use of utilities from different disease areas, the limited support from the studies, and the optimistic assumption that caregiver quality of life returns to the general population level when patients are treated with ruxolitinib. The ERG therefore advised that the ICER incorporating caregiver quality of life is subject to substantial uncertainty and should be considered cautiously[61].

3.5.1.3. Committee discussion

Although the committee agreed that carer's health could be affected by caring, the committee did not favour factoring in a modification to the ICERs to reflect carers' quality of life for three reasons. Firstly, the committee did not consider the results of the company's scenario robust. Secondly, the committee did not consider that myelofibrosis had a more profound carer burden than other severe illnesses. Finally, and most importantly for the committee, the committee concluded that the company's scenario did not account for the opportunity cost of carer's burden (that is, the carer's burden currently relieved by other treatments currently funded by the NHS that may be displaced if ruxolitinib were reimbursed)[19].

3.6. TA534: DUPILUMAB FOR TREATING MODERATE TO SEVERE ATOPIC DERMATITIS

3.6.1.1. Company submission

TA534 appraised dupilumab for treating moderate to severe atopic dermatitis in adults, published in August 2018. In their original economic analyses, the company did not include carer quality of life, but discussed that improving patient's symptoms may improve the HRQL for those close to them. In their revised analysis following the ACD, the company conducted scenario analyses including a utility benefit to one carer of 0.01 or 0.1 whilst patients are on dupilumab[62]. These utility benefits are not referenced to specific studies, instead, the company refer to TA373 (see Section 3.4) and a review of carer HRQL effects in different conditions[63].

Including a carer utility benefit of 0.01 decreased the company's ICER from £28,495 to £26,247 or £27,251 depending on the approach to modelling treatment discontinuation. Including a carer utility benefit of 0.01 decreased the company's ICER to £18,997 or £19,562 depending on the approach to modelling treatment discontinuation.

3.6.1.2. Independent assessment

The ERG did not comment on the scenario analysis including caregiver utility benefit[64].

3.6.1.3. Committee discussion

The committee heard from stakeholders that the effect of atopic dermatitis on the quality of life of families and carers should be considered. The committee acknowledged that there could potentially be an effect on the quality of life of families and carers, it had not seen any evidence to support this[18].

3.7. HST2: ELOSULFASE ALFA FOR TREATING MUCOPOLYSACCHARIDOSIS TYPE IVA

3.7.1.1. Company submission

This HST appraised elosulfase alfa for treating mucopolysaccharidosis type IVa in adults and children and was published in December 2015. The company included caregiver disutility for one carer in its base case analysis, using the caregiver disutilities reported by Gani et al[57] (TA127) and linking EDSS states with wheelchair usage such that caregiver disutility decreased as patient's health status improved[65]. The company described an alternative approach using Acaster data and present a scenario analysis that is labelled 'removal of caregiver disutility (based on Acaster)', which the ERG noted appears to be an error.

Removing caregiver disutilities in the manufacturer's analysis decreased the incremental QALYs by 0.03.

3.7.1.2. Independent assessment

The ERG conducted additional analyses, but none of these related to the caregiver disutility[66].

3.7.1.3. Committee discussion

The committee did not discuss the caregiver disutility in the FED, but considered the results of the company's model so are assumed to accept it as appropriate[22].

3.8. HST3: ATALUREN FOR TREATING DUCHENNE MUSCULAR DYSTROPHY

3.8.1.1. Company submission

This HST appraised ataluren for treating Duchenne muscular dystrophy in people aged 5 years and older and was published in July 2016. The company included a caregiver disutility in its economic model for the non-ambulatory patient health states[67], thus assuming that the impact on carers is the same for all non-ambulatory patients and that there is no negative impact on carers for ambulatory patients. The disutility value was 0.11, from a study by Landfeldt et al which reported the mean loss of caregiver quality of life in relation to the general population[27]. Landfeldt et al used EQ-5D (value set not specified) to measure caregiver quality of life in 770 pairs of Duchenne muscular dystrophy patients and their caregiver in Germany (n=173), Italy (n=122), the UK (n=191) and the US (n=284). 97.8% of caregivers were parents of the patient, and the majority were the patient's mother. Initially, the company subtracted the disutility of 0.11 from the patient's utility[67], but later revised their analysis to subtract a disutility of 0.33, to represent the equivalent of three primary carers, comprised of two primary carers (with the full disutility) and two secondary carers (with half the disutility)[68]. In the company's revised analysis, there were 11.747 incremental QALYs with three caregivers compared to 11.305 with two caregivers and 10.863 with one caregiver.

3.8.1.1. Independent assessment

The ERG did not initially dispute the inclusion of caregiver disutilities[69], but after the company revised its analysis to include the equivalent of three primary carers, the ERG revised its analysis to incorporate two primary carers[70].

3.8.1.1. Committee discussion

In its FED, the committee noted that the company's increased caregiver disutility partially addressed comments from patient organisations that the original model did not appropriately reflect the impact of the condition and technology on caregiver's quality of life. The committee was concerned about the caregiver disutility values, and noted the proposal in the managed access agreement to capture carer utility, and concluded it was imperative that its future review of guidance includes carer utility data[21].

3.9. HST7: STRIMVELIS FOR TREATING ADENOSINE DEAMINASE DEFICIENCY–SEVERE COMBINED IMMUNODEFICIENCY

3.9.1.1. Company submission

This HST appraised strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency (ADA–SCID), and was published in February 2018. The company did not include caregiver disutility in its base case analysis, but included a scenario which considered the QALY loss to a family due to the premature death of a child[71]. This was set to be equivalent to 9% of the child's QALY loss from premature death, referenced to a study by Christensen et al (2014) which is an economic evaluation of vaccination for meningitis B[28]. In their analysis, Christensen et al (2014) incorporated the impact of meningitis sequalae on family members' quality of life, referencing unpublished work by Al-Janabi et al which estimated QALY losses to the family network were approximately 48% of the QALY losses to the meningitis survivor. The study by Al-Janabi did not measure the impact of bereavement on family members' quality of life, so Christensen et al made a modification using evidence on the impact of bereavement on parent's quality of life from a study by Song et al[72]. Song et al compared the quality of life of 233 couples who had experienced a child death with 229 comparison couples. Quality of life was measured using HUI3. Stratified random sampling was used to select the matched comparison group, using gender, age and education as stratification variables. A multilevel model found that, controlling for demographic factors, bereaved parents HRQL was 0.04 lower than the control group. Including family QALY loss decreased the company's base case ICER from £36,360 to £33,201 and increased incremental QALYs from 13.6 to 14.9.

3.9.1.2. Independent assessment

The ERG did not include the family QALY loss due to premature child death, or any other caregiver disutility in their analysis[73].

3.9.1.3. Committee discussion

In the FED, the committee considered the scenario analysis, but felt it would not fully reflect the quality-of-life benefit to carers after successful treatment as described by the patient experts. The committee heard from the company and ERG that there were no specific care-related utilities that could be identified for use in the model, and concluded that improvements to carer's quality of life should be considered qualitatively in the decision making[20].

3.10. HST8: BUROSUMAB FOR TREATING X-LINKED HYPOPHOSPHATAEMIA IN CHILDREN AND YOUNG PEOPLE

3.10.1.1. Company submission

This HST appraised burosumab for treating X-linked hypophosphataemia (XLH) in children and young people and was published in October 2018. In their initial submission, the company discussed that having a child with medical needs such as X-linked hypophosphataemia affected the quality of life of families and carers, but did not include quantitative estimates of carer HRQL in their economic analysis[74]. Following publication of the ECD, the company provided a further scenario analysis including a carer disutility for one carer[75]. The disutility was 0.08, applied to patients in the moderate and severe health states up to the age of 18, referenced to a study by Kuhlthau et al (2010)[26] (used in TA373).

3.10.1.2. Independent assessment

The ERG included the carer disutility in reporting the company's revised analysis, and commented that the disutility was deemed a reasonable estimate[76], but it is unclear if this means that the ERG or the company considered the estimate to be reasonable.

3.10.1.3. Committee discussion

In the FED, the committee concluded that it was important to consider carer burden. It further concluded that it would consider the results including the quantitative estimate of carer burden, but that since the estimate was not robust, it would also consider the burden qualitatively[23].

4. DISCUSSION

This review identified a number of issues in relation to the inclusion of carer HRQL in NICE appraisals that warrant discussion.

4.1. INCLUSION OF CARER HRQL IN NICE APPRAISALS

Firstly, it is perhaps surprising that so few appraisals have quantitatively considered health effects beyond the patient when NICE's Reference Case specifically permits this and has done since 2004 [3, 4, 2]. At the time of our search, there were 414 TAs published, of which only 12 quantitatively considered carer HRQL and a further 11 discussed the impact of including carer HRQL on the ICER. However, we note that the number of appraisals would have increased if we had included those in which carers were considered qualitatively.

Secondly, there do not appear to be clear trends or rules for where carer HRQL may be relevant (for example, specific interventions, populations or disease areas). Although all MS appraisals have included carer HRQL, it is not clear why this is or what the particular characteristics of MS are that make the inclusion of carer HRQL more relevant than many other disease areas. It appears that the inclusion of carer HRQL in MS was not first determined by the availability of evidence in this area, since the first MS appraisals to consider carer HRQL used evidence from Alzheimer's disease[11]. Six of the TAs and the four HSTs included paediatric populations, where we may expect a substantial burden for parents or carers. Additionally, 7 of the 11 appraisals where the impact of carer HRQL on the ICER was discussed by the committee but not quantitatively included were in paediatric populations. This suggests that appraisals in paediatric populations are more likely to consider carer HRQL than those in adult populations. However, in a separate piece of work we identified 31 TAs which included children in their populations[77], so it is clearly not the case that appraisals of interventions in children always consider carer HRQL. There does not appear to be a systematic consideration at any stage of whether the inclusion of carer HRQL is particularly relevant within an individual appraisal.

A greater proportion of HSTs than TAs included carer HRQL either quantitatively or in committee discussion (HST: 50% quantitatively and 12.5% in discussion, TA: 2.9% quantitatively and 2.4% in discussion). While the number of HSTs may be too small for

meaningful analysis, this is an interesting finding. This could be partially related to the higher frequency of paediatric populations in HSTs (as discussed in the paragraph above), or because of the specific references to carer HRQL in addition to value for money in decision-making in the HST Methods and Processes Guide – this may be particularly the case where carer HRQL is discussed but not included in the economic evaluation. We also note that this may be a feature of the newness of HSTs - the inclusion of carer HRQL has become more common in recent years, and that the first HST was published in 2015.

The variation in whether carer HRQL is included may be partially due to interpretation of the NICE reference case and differences in understanding. In TA493, the ERG believed that effects to carers were not 'direct' and therefore should not be included[54]. In the health economics literature there does not appear to be a definition of what 'direct health effects' are, nor is this defined in NICE's glossary. Similarly, in TA527 there was confusion whether carer utilities should be included, with the AG excluding them on the grounds that they represent unpaid or informal carers (we note that this would usually be a reason to exclude the costs, whereas the costs and not the health effects for formal/paid carers would be included)[55]. In future revision to NICE's reference case it may be prudent to more clearly define whose health effects can (and should be) included in economic evaluations.

A further issue lies within the definition of 'health effects', and to what extent the methods for generating QALYs capture the impacts of carer burden. Brazier et al (2019) note that the EQ-5D was not intended to cover all dimensions of health, and that other sectors which measure the impact of interventions on carers use different measures (for example, Carer-QoL and the Carer Experience Scale) [78]. Where the impact of interventions on carers is relevant for inclusion, the EQ-5D may not be the best instrument to measure this.

The impact of including carer HRQL was always to increase incremental QALYs and therefore decrease ICERs. While this may seem obvious, it is worth considering that interventions could theoretically decrease carer QALYs, for example if they delayed the patient moving into residential care and thus actually increased the carer burden. If incremental QALYs always increase when carer HRQL is included, interventions where carer HRQL is included will appear more cost-effective than those where carer HRQL is excluded. To ensure consistency in decision making therefore requires that the criteria for determining whether carer HRQL should be included must be common across appraisals.

The impact of including or excluding disutilities for one carer appears relatively modest, at around 0.03 or less. However, in the cases where incremental QALYs were reported, this equated to increasing the QALY gain by up to 22% and so this can have a large impact on the ICER. For example, the company's analysis in TA534 found that including a carer utility benefit could decrease the ICER from £28,495 to £18,997 – a change that could impact recommendations at a willingness to pay threshold of £20,000 – £30,000 per QALY.

Varying the number of carers for whom carer HRQL is included had a larger impact on cost-effectiveness results, changing the incremental QALYs by 0.88 in HST3. This suggests that careful consideration should be given to the number of carers affected by a condition, and how the size of carer HRQL effects in the evidence relates to the number of carers. For example, Kuhlthau et al[26] reported HRQL for parents – suggesting that this could be applicable to multiple people, but in both cases where it was used (TA373 and HST8), it was applied to only one carer.

Including the impact of a child's death on family QALYs had the largest impact on incremental QALYs, in the scenario in HST7. This is unsurprising given the magnitude of the QALY loss (1.8 or 2.1) applied as a one-off compared to the magnitude of disutilities (0.01 to 0.173), which would be discounted over time. Since the death of a child is not specific to one condition, this could potentially be included across multiple appraisals. Furthermore, many interventions appraised by NICE delay death, so could influence family QALY loss through discounting. It may therefore be important for NICE to decide whether the family HRQL impacts of a patient's death should be included in any circumstances.

4.2. Evidence for carer HRQL

Whether specific appraisals consider carer HRQL may be a feature of the available evidence. Indeed, TA455, TA300 and TA278 all noted that while carer health-related quality of life was relevant for inclusion in the modelling, there was no evidence available to provide estimates of the size of the benefit[35, 30]. Other appraisals, however, borrowed carer quality of life estimates from other disease areas to populate models (as shown in Figure 1). Most notably, the company in TA127 estimated disutilities for carers of MS patients from utilities for carers of patients with Alzheimer's disease[11]. These estimates were not only used in several

further MS appraisals, but additionally in TA373 for juvenile idiopathic arthritis[9], and HST2 for mucopolysaccharidosis[22]. It is unclear to what extent carer quality of life estimates are transferable between disease areas. Whilst there is some evidence estimating informal care time associated with EQ-5D scores and disease area [79], there does not appear to be a generic approach available to estimate carer HRQL across disease areas.

The quality of the evidence for carer HRQL varies between appraisals. The disutilities used in TA127 are estimated assuming that carers would otherwise be in full health, using HUI3 rather than NICE's preferred EQ-5D. The disutilities calculated by Acaster et al used EQ-5D, but from relatively small sample sizes in some states[25]. Other appraisals made assumptions about the size of carer disutility, and committees in some appraisals considered carer HRQL qualitatively.

4.2.1. Evidence from the wider literature

In their review of economic evaluations that included informal care [6], Goodrich et al identified five economic evaluations of interventions for patients that used QALYs and valued carer outcomes [80-84]. Three considered vaccination for rotavirus in children and its impact on carer QALY loss[82, 80, 84], referencing the same source [85]. The carer QALY loss is reported to be 0.0020-0.0022, measured using EQ-5D [80, 84]. One study appears to be related to the manufacturer model in TA217 for Alzheimer's disease that used an equation to estimate caregiver utility based on SF-36 collected in clinical trials[81]. The other study is also an evaluation in Alzheimer's disease, which was not freely available, but by Neumann et al so we expect used the same carer utility data as the HUI2 and HUI3 study[83]. Wittenberg and Prosser conducted a systematic review of caregiver and family disutility [63]. They identified (or calculated from reported data) disutilities for families, household members or carers across a range of diseases including prostate cancer, rheumatoid arthritis, Alzheimer's disease, congenital abnormalities in children, MS, rotavirus-associated gastroenteritis in children, activity limitations in children, spinal bifida in children, stroke and other diseases in elderly people[63].

4.3. APPROACH TO MODELLING CARER HRQL

The approach to modelling carer HRQL differs between models. In TA217, carer utility was included, linked to patient disease severity. In the eight MS appraisals, HST2, HST3 and

HST8, a disutility was applied to each health state to represent the carer burden. In TA373, a different disutility was applied for different interventions to represent the carer burden. In TA386 and TA354, an additional utility increment for the intervention and not the comparator was applied to represent the improvement in carer quality of life. In HST8, a family QALY loss was included when a child died. These represent different approaches to modelling health effects and generating QALYs for the patient and carer. In Table 3, there does not appear to be a difference in the impact incremental QALYs between the different modelling approaches, so we consider further the implications of the different approaches.

Reducing a carer disutility or including a carer utility increment when a patient receives a specific treatment assumes that the carer's HRQL is not linked to the patient's disease severity, but to the treatment received. This means that the carer would have the same HRQL benefit regardless of the size of the benefit the patient received from treatment. This contradicts the way in which models typically consider patient HRQL, which is linked to disease severity (which treatment affects) rather than the treatment itself. Validating this approach would require evidence that the HRQL benefit to carers is dependent only on treatment and not on the patient's disease status. Such evidence was not provided in any of the case studies where this approach was used. Mathematically, linking a reduction in carer disutility or a utility increment to an intervention would generate the same incremental QALYs, but report different total QALYs for intervention and comparator. Modelling a carer HRQL benefit linked to treatment would always result in an additional QALY gain for the treatment. The size of the additional QALY gain would depend on the size of the utility increment/reduction in disutility and the duration of treatment, but not on the change in patient's disease severity.

Modelling carer HRQL by patient disease status appears more consistent with the typical approach to model patient HRQL than modelling carer HRQL by patient's treatment. This approach may also better explain the change in HRQL for the carer: a person caring for a patient with more severe disease may have to spend more time performing caring tasks or worry more about the patient, and so the HRQL impact would be higher. Validating this approach would require evidence that the HRQL of carers varies by the patient's disease severity. This evidence was presented in the cases where this approach was used – although in several cases the data were from different disease areas. However, while the evidence generally showed that carers of patients with more severe disease had worse HRQL, it did not

show that changing a patient's disease severity would impact a carer's HRQL – this would require longitudinal studies.

Modelling carer HRQL by patient disease status requires consideration as to what happens to carer HRQL when the patient dies. When a patient dies, they stop treatment, so it is clear that any treatment-related carer HRQL benefit would stop, but it is not clear whether or how carer HRQL should be included once the patient dies if carer HRQL depends on patient disease severity. Including a utility value for the carer member linked to the patient's disease status while they are alive, would assume that the HRQL of the carer/family member is equivalent to being dead once the patient dies. By comparison, modelling a carer disutility linked to patient health status while alive assumes that there is no negative impact on carer HRQL when the patient dies. In reality, it is likely that neither of these are realistic. The size of the additional QALY gain from including carer HRQL linked to patient disease severity therefore depends on how the intervention and comparator impact patient disease severity and mortality; the size of the relative carer HRQL impact of increasing patient disease severity; whether carer utilities or disutilities are included; and the assumption about carer HRQL after the patient dies.

Evidence from a study of Song et al indicates that utility, as measures by HUI3, is 0.04 lower for people who have experienced a child death than for matched controls [72]. Basu et al found that the disutility, measured by time trade-off, for partners of people with prostate cancer was larger when the partner died (0.718) than when the partner was alive (range: 0.295 to 0.503)[86]. One HST considered the QALY loss for families when a child dies (Section 3.9). The impact of patient death on carer HRQL may be an area that requires further research to determine which modelling approach is most appropriate.

4.4. DISPLACED CARER BURDEN

In TA386, the committee did not favour factoring carer utility into the economic analysis, for a number of reasons, but most importantly because the scenario did not account for the opportunity cost of the carer's burden. In their 2016 publication, Al-Janabi et al discuss that displacing health activity may displace carer HRQL benefits and that to take account of carer HRQL in a consistent manner, both carer HRQL effects generated and those displaced should be considered[87]. Al-Janabi et al demonstrate that if carer HRQL effects are not constant

across the health system, then explicitly incorporating carer HRQL in the decision-making process is necessary to maximise health benefits. They propose including two multipliers to represent the ratio of incremental total health benefits to incremental patient health benefits, one relating to the health benefits generated by an intervention and one relating to the health benefits displaced. Carer HRQL effects become more important in economic evaluation as the two multipliers diverge, as in the case when the intervention being evaluated has particularly large impact on carer HRQL, or in the case that the carer HRQL benefits are small or even negative (the intervention increases or introduces a burden to carers/families). It is therefore important to consider whether the size of carer HRQL impacts associated with the intervention relative to the carer HRQL impacts associated with intervention typically funded by the same budget. It is therefore pertinent to the committee's decision not to include carer quality of life in appraising TA386 that they did not consider myelofibrosis had a more profound carer burden than other severe illnesses. It is unclear from the available evidence whether the disease areas where NICE appraisals have considered carer HRQL represent a greater carer burden than other disease areas where NHS funds would otherwise be spent. Further research analysing the impact of different conditions on carer HRQL would therefore be valuable.

5. CONCLUSION

Relatively few TAs and HSTs have quantitatively included carer HRQL quantitatively in cost-utility analysis. Within those that have included carer HRQL, the evidence has not often been of good quality or necessarily appropriate to the disease area, and consideration has rarely been given to the carer HRQL benefits displaced. Key areas where carer HRQL has been included are in MS and Alzheimers, where it is unclear whether the carer HRQL impacts are substantially greater than in other conditions, and interventions for children, where we note not all TAs or HSTs have considered the impact on families.

In all cases, including carer HRQL increases incremental QALYs and therefore decreases ICERs. Therefore, using the same decision-making criteria between appraisals will favour interventions where carer HRQL is included. It is therefore important that the approach to considering carer HRQL is consistent between appraisals, and that carer HRQL is modelled accurately.

It would be helpful if NICE could provide clarity on:

- Whose health outcomes should be included in economic evaluation (including a definition or explanation of "direct" and "indirect")
- Whether there are specific diseases areas where carer/family health outcomes should be routinely included
- What evidence is required to determine whether carer/family health outcomes should be included in economic evaluation. This could include guidance on:
    - Whether there are specific populations where carer/family health outcomes should be routinely included (for example, paediatric populations)
    - Whether the evidence needs to be specific to that intervention or disease area
    - Which measures should be used for measuring carer/family health outcome
    - The most appropriate comparator for carer HRQL (for example, general population, full health, matched controls, carers of less severe patients)
- How carer/family health should be modelled. This could include guidance on:
    - Whether family/carer health should be linked to the patient's treatment or disease status.
    - Over what duration family/carer health should be included.
    - What should be assumed about family/carer health after the patient dies.
    - Whether the impact of death of family/carer health should be routinely included in economic evaluation.

To improve accuracy in modelling family/carer health, we recommend that research is conducted in the following areas:

- What is the family/carer HRQL improvement from currently funded NHS interventions?
- What is the carer HRQL impact across different disease areas?
- How does carer HRQL change over time (including when the patient's health improves or worsens, and the patient dies)?

Addressing these issues would provide guidance and evidence to support a consistent approach to including carer/family health outcomes across NICE appraisals.

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