CARERS' HEALTH-RELATED QUALITY OF LIFE IN NICE GUIDANCE

REPORT BY THE DECISION SUPPORT UNIT

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I (Becky Pennington) was funded by an NIHR doctoral fellowship studying carers' HRQoL (NIHR300160) until Feb 2026. Many of the papers cited here are my own research from that fellowship and express my views on this topic. I have an ongoing project researching carers' HRQoL in cancer for which my employer (University of Sheffield) is receiving funding from Pfizer.

EXECUTIVE SUMMARY

There is a growing need for further guidance on how carers' health-related quality of life (HRQoL) should be included in health technology assessment (HTA). This is highlighted by the papers and commentaries published over the last five years calling for clearer guidance, as well as the variation in methods and data used in economic evaluation, and the difficulties faced by National Institute for Health and Care Excellence (NICE) Appraisal Committees.

Through a targeted review of recent literature, consideration of five NICE appraisals and a systematic review of the evidence for the effect of bereavement on HRQoL, we identified key areas where NICE can currently make evidence-informed recommendations about the inclusion of carers' HRQoL, and priority areas for further research.

The inclusion of carers' HRQoL in NICE appraisals has typically been limited to paediatric and rare diseases, dementia, and multiple sclerosis. This is despite evidence of carers' HRQoL impacts across other areas such as cancer. We therefore suggest that NICE could recommend evidence is presented to demonstrate that the carers' HRQoL burden for the condition under consideration is particularly pertinent. Relatedly, there has been some recognition that there are carers' HRQoL effects in some displaced interventions and that consideration of opportunity costs may be important, but there is little evidence to inform adjusting the threshold to account for this. Instead, we propose that the evidence on carers' HRQoL for a specific appraisal needs to demonstrate that the impacts are larger than average to justify their inclusion. We suggest further research is required to establish the average carers' HRQoL burden across health conditions.

Guidance from the literature recommends using the same HRQoL measure for carers as patients, and EQ-5D has been found to be valid in caregivers and commonly used in measuring carers' HRQoL. We therefore recommend that NICE continues to state a preference for EQ-5D for measuring carers' HRQoL.

The literature recognises that spillover effects can affect multiple people, and that effects to different people will vary in size and by context, but there is little published evidence studying carers' HRQoL beyond the primary caregiver. Some NICE appraisals considered the HRQoL effects to multiple carers. We propose that NICE should recommend that where multiple carers are included, evidence needs to be provided for an HRQoL impact beyond the primary carer, and the size of HRQoL impact should not be assumed to be the same for all carers/family members. Scenario analyses should be presented including only the HRQoL impact for the primary carer.

Carers' HRQoL may not be typically collected in clinical trials. There are calls in the literature for studies to more robustly identify a causal effect of caring on HRQoL, using well-matched controls and/or longitudinal studies. Study design for studies collecting data on carers' HRQoL has not typically been discussed in detail in NICE appraisals, with committees making pragmatic decisions using the data available. We suggest that NICE could clarify that the same hierarchy of HRQoL methods applies to carers and patients, and that carers' HRQoL should be collected from carers directly in a relevant study.

There is variation in the methods used to quantify carers' HRQoL in economic models used to inform NICE appraisals. The "utility" method includes carer's utilities as well as patient utilities, while patients are alive. The "disutility" method includes a utility decrement, relative to non-carers, for carers while patients are alive. The "increments" method includes the difference between carers' HRQoL in each health state and the worst health state. The "decrements" method includes the difference between carers' HRQoL in each state and the best health state. The literature discusses some of these methods and additionally multiplier-based methods and notes the differences between their implications. We propose that these need to be considered in the context of bereavement, and that the priority is that the models accurately reflect carers' HRQoL. We propose that NICE may need to recognise that decision rules for some of the conditions affecting carers may differ from strict quality-adjusted life year (QALY) maximisation, given that carers may not be utility maximisers in this context.

Our systematic review of the effect of bereavement on HRQoL included seven studies. Four studies considered adults bereaved by other adults (typically widows), and

generally found a small, statistically significant effect of bereavement, but that this did not differ by whether the bereaved was previously caring for the deceased. We therefore propose NICE should not recommend the inclusion of a bereavement effect where adults were caring for other adults. Three studies considered adults bereaved by the death of a child and generally found larger effect sizes that persisted over time. We suggest that bereavement should be accounted for in evaluations where parents would be bereaved by their children, and that this should be reflected in the modelling methods. We suggest further research is needed to establish the potential interaction between parental bereavement, decision-making rules for paediatric populations and severity modifiers. This should build upon ongoing research into societal preferences for valuing health benefits in people with severe diseases to consider whether these already capture that the health condition may affect children and lead to parental bereavement, or if these should be considered as additional factors.

There are some calls in the literature to consider the distributional consequences of including carers' HRQoL, particularly where conditions have differing numbers of carers. This has not been previously considered in NICE appraisals, and it is unclear what the impact would be. However, we propose that consideration of distributional consequences is particularly important in the context of equity and health inequalities which NICE committees now consider and may use as justification for applying flexibility to the cost-effectiveness threshold (National Institute for Health and Care Excellence. 2022). We suggest further research is needed to consider the potential equity and health inequality impacts associated with including unpaid carers' HRQoL.

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ABBREVIATIONS AND DEFINITIONS

AIFA	Agenzia Italiana del Farmaco
AQoL	Assessment of Quality of Life
ASCOT	Adult Social Care Outcomes Toolkit
CHTE	Centre for Health Technology Evaluation
CEA	Cost effectiveness analysis
EAG	External Assessment Group
EDSS	Expanded Disability Status Scale
EQ-HWB-S	EQ Health and Wellbeing Scale
GID	Guidance In Development
HAS	Haute Autorité de Santé
HIQA	Health Information and Quality Authority
HRQoL	Health-related quality of life
HST	Highly Specialised Technology
HTA	Health Technology Assessment
HUI	Health Utilities Index
ICECAP-A	ICEpop CAPability measure for Adults
ICER	Institute for Clinical and Economic Review
ICERs	Incremental Cost-Effectiveness Ratios
IQWIG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
MS	Multiple sclerosis
MSOP	Modular updates Selection and Oversight Panel
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PBAC	Pharmaceutical Benefits Advisory Committee
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
QALY	Quality-Adjusted Life Year
SF-6D	Short Form 6 Dimension
SHEER	Spillovers in Health Economic Evaluation and Research
SMA	Spinal Muscular Atrophy
SMC	Scottish Medicines Consortium

SPMS	Secondary Progressive Mulitple Scleroris
TA	Technology Appraisal
TLV	Tandvards Och Lakemedelsformansverket
VAS	Visual Analogue Scale
ZIN	Zorginstituut Nederland

1. INTRODUCTION

The National Institute for Health and Care Excellence's (NICE's) health technology evaluations manual specifies that the reference case perspective on outcomes includes *"all health effects, whether for patients or, when relevant, carers"* in Section 4.3.17 and Table 4.1, or *"all relevant health effects, whether for patients, or when relevant, other people (mainly carers)"* in Section 4.2.8. We note this to highlight that the term carer is not defined, and there is potential that people other than carers may be included depending on interpretation. The multiplicity of meanings in the terms "family", "carer", and "spillovers" are noted in the literature, and the Spillovers in Health Economic Evaluation and Research (SHEER) guidelines provide a definition of family (a network of persons) and caregivers (people providing informal care) and specify that their recommendations consider spillover effects to both family and caregivers (Henry et al. 2024).

The manual specifies that health effects should be expressed in quality-adjusted life years (QALYs) (Section 4.2.14), which reflect length of life and health-related quality of life (HRQoL) (Section 4.3.2) (National Institute for Health and Care Excellence. 2022). NICE's manual does not define what HRQoL is, but the NICE glossary defines health-related quality of life as "*A combination of a person's physical, mental and social well-being; not merely the absence of disease"* (National Institute for Health and Care Excellence. 2025f).

Many methods working groups, task forces and commentators have similarly recommended that carers' health effects should be included in economic evaluation. A Health Economics Methods Advisory report on Defining Appropriate Benefits for Economic Evaluation of Health Technologies notes that if a health technology assessment (HTA) organisation such as NICE decides that health effects are the appropriate benefit they asses, there is no reason why health effects to people beyond the patient themselves should not be included (McQueen et al. 2025). Elsewhere, there appears to be broad support for including spillovers in economic evaluation, but recommendations relating to carers' HRQoL effects vary depending on the perspective. The SHEER taskforce *"advocates for the consideration of health spillovers in all economic evaluation conducted from this [payer perspective] and those*

more inclusive perspectives" (Henry et al. 2024). Leech and colleagues state that *"Caregiver HRQoL spillover effects should be included in CEAs conducted from both healthcare and societal perspectives"* (Leech et al. 2023). Campbell and colleagues recommend that *"Family spillover effects should be considered for all HTAs"*, but then further recommend that the societal perspective should include spillover health effects, but only specify that the healthcare/payer perspective should include spillover effects on direct cost (Campbell et al. 2024). This seems at odds with Campbell's description that participants recommended that family spillover effects should be consistent with patient effects.

It should be noted that the NICE manual discusses carers' HRQoL within the context of carer health effects. For patients, HRQoL may be used to refer to the impact a health technology has on the patients' functioning and wellbeing (YHEC. 2026) and is connected to the patients' health or disease status (BMJ Blog. 2014). The NICE manual does not differentiate between the definition of HRQoL for patients and carers, so it may be assumed that the same definition applies, and that only aspects of carers' quality of life that are affected via the carers' own health effects are relevant. Caring can affect people's lives in many different ways, including finances, physical health (for example lifting and supporting someone or sleep deprivation), mental health (including stress and depression), relationships, emotions, and social isolation (Carers Trust. 2026.). Measuring HRQoL will not necessarily identify impacts across all these areas. For example, the domains in C-DEMQOL, a measure of dementia carers' quality of life, are carer responsibilities and personal needs, carer wellbeing, carer role, feelings about the future and carer support. It contains 30 questions and only one relates to the impact of caring on health (Brighton and Sussex Medical School. 2026.).

The NICE manual provides only limited guidance on methods for incorporating carer health effects (Section 4.3.17). Carers' HRQoL was one of the areas examined in NICE's health technology evaluations methods review that resulted in the current manual. A task and finish group reviewed the evidence available at the time and produced a draft list of minimum evidence requirements. However, it was concluded that more research was needed for NICE to issue detailed methods guidance in this area.

NICE’s 2024/2025 Modular updates Selection and Oversight Panel (MSOP) recently concluded that producing clearer guidance on when and how to incorporate carers’ HRQoL in economic evaluations is a high priority (National Institute for Health and Care Excellence. 2026).

This project will provide NICE with an up-to-date overview of the evidence. The intention is to use this information as the basis for a modular update to the manual, providing more detailed guidance on when and how to incorporate carers’ HRQoL into technology appraisals. It is anticipated that this will lead to more consistent and higher quality evidence being submitted and give committees clearer grounds for accepting or rejecting proposals.

2. AIMS AND OBJECTIVES

The aim of this project is to determine if there are sufficient changes to the evidence base on unpaid/informal carers'/caregivers' HRQoL since the 2020 Centre for Health Technology Evaluation (CHTE) methods review to warrant a modular update.

The objectives are to answer the following questions:

1. What methods have been used to include carers' HRQoL in economic evaluation, including historically and more recently?
2. Is there new (since 2020) guidance or evidence to suggest how carers' HRQoL should be included in economic evaluation?
3. Is there new (since 2020) evidence on the factors affecting the size of carers' HRQoL impacts (health conditions, caring relationships, number of carers)?
4. How does bereavement affect HRQoL, considering evidence since database inception?

3. METHODS

3.1. Targeted literature review

To address objectives 1, 2 and 3 in Section 2, we sought to identify review papers, guidance, or commentaries that related to unpaid carers' HRQoL and its inclusion in HTA since 2020. This included studies that reviewed international HTA guidance related to unpaid carers' HRQoL, and any updates to those international HTA methods guides since publication of the review.

3.2. Review of NICE appraisals

To understand methods and evidence used in NICE appraisals, we reviewed a sample of five case studies. The sample was agreed with the NICE team and aimed to cover a range of health conditions (including oncology, multiple sclerosis, and life-limiting conditions) in children and adults, drawn from both the Technology Appraisal (TA) and Highly Specialised Technologies (HST) programmes, including recent and historic appraisals. We extracted data related to the committee's preferences for whether carers' HRQoL was included in the base case analysis and the reasons for this, the number of carers and evidence to support this, the source of carers' HRQoL data, and the approach used to model carers' HRQoL.

The case studies were:

- GID-TA11220: Lecanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease (National Institute for Health and Care Excellence. 2025d) *Note that this case study was ongoing at the time of writing and information presented here is accurate to February 2026 based on final draft guidance prior to appeal panel decision.*
- TA1053: Cladribine for treating active relapsing forms of multiple sclerosis (National Institute for Health and Care Excellence. 2024)
- HST28: Birch bark extract for treating epidermolysis bullosa (National Institute for Health and Care Excellence. 2023a)
- HST15: Onasemnogene abeparvovec for treating spinal muscular atrophy (National Institute for Health and Care Excellence. 2023b)

- TA386: Ruxolitinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis (National Institute for Health and Care Excellence. 2016).

3.3. The effect of bereavement on HRQoL

There is a need to better understand the relationship between bereavement and HRQoL to address objective 4 in Section 2. We conducted a systematic literature review to identify published evidence to support or refute an effect of bereavement on HRQoL. The search strategy is included as an appendix. We searched Ovid MEDLINE from inception until 3 October 2025. One reviewer screened and extracted data from all records. Inclusion and exclusion criteria are shown in Table 1.

Table 1: Inclusion and exclusion criteria

	Include	Exclude
Population	People who have been bereaved (adults, children, any age) No restriction on when they were bereaved, or relationship to deceased	People who have not been bereaved (living caregivers, families of people receiving palliative care, people with anticipatory grief) Animals, or people bereaved by animal death Professionals (doctors, nurses etc.)
Outcome	Generic preference-based measure of health-related quality of life, for example EQ-5D, SF-6D, HUI, AQoL	Other health outcomes (e.g., depression, anxiety) Non-preference-based measures of HRQoL (e.g., VAS, direct elicitation) Views, experiences (e.g., of palliative care)
Study design	Quantitative studies that include comparison to control group for example pre-bereavement, non-bereaved controls Cross-sectional studies with comparator Longitudinal studies Trials Surveys Analysis of observational data Study protocols	Qualitative studies Non-comparative studies Cross-sectional studies without comparator Studies assessing factors that affect bereavement outcomes, only in bereaved people Interventional studies for bereaved people Interventions to improve symptoms in bereaved people
Language	English	Non-English
Country	Any	No exclusion
Publication type	Peer-reviewed research articles Peer-reviewed conference abstracts	Commentary Editorial

4. RESULTS

4.1. Targeted literature review

We identified twelve publications that reviewed or discussed the inclusion of family and caregiver spillover HRQoL effects in economic evaluation, relevant to NICE appraisals. These are:

1. A systematic literature review update of spillover effects on informal and carers' utility (Theaktson and Mott 2025)
2. A review of the inclusion of carers' HRQoL in NICE assessments up until 2022 (Kanters et al. 2024)
3. An updated review of the inclusion of carers' HRQoL in NICE appraisals up until 2023 (Ahmadu et al. 2025)
4. A review of methods for including spillovers in economic evaluations for children (Lamsal et al. 2024)
5. An international taskforce which provides recommendations and research priorities (Henry et al. 2024)
6. Recommendations from a stakeholder workshop (Campbell et al. 2024)
7. A commentary that proposes recommendations in considering carers' HRQoL effects (Leech et al. 2023)
8. A conceptual framework for including carers' HRQoL in HTA (Bourke et al. 2024)
9. A paper describing the challenges in modelling carers' HRQoL (Pennington and Al-Janabi 2024)
10. A paper discussing the issues in carers' HRQoL in the context of rare progressive paediatric conditions (Powell et al. 2025)
11. A paper proposing a new approach for modelling carers' HRQoL (Pennington, Davis, and Cranmer 2025)
12. A paper reviewing international HTA guidance and case studies of carers' HRQoL and providing recommendations (Pennington et al. 2022)

Since the publication of the review of international HTA guidance, seven of the included HTA bodies have updated their guidance (Canada's Drug Agency have additionally produced a draft guidance on informal caregivers), and so we included revised guidance from:

13. Zoorginstituut Nederland (Netherlands), Guideline for economic evaluations in healthcare 2024 version (Zoginstituut Nederland. 2024)
14. Tandvards Och Lakemedelsformansverket (Sweden), Calculation and payment 2022 (Tandvards Och Lakemedelsformansverket. 2022)
15. Institute for Clinical and Economic Review (USA), Reference case for economic evaluations 2025 (Institute for Clinical and Economic Review. 2025)
16. Canada's Drug Agency (Canada), Guidelines for the Economic Evaluation of Health Technologies 2025 (Canada's Drug Agency. 2025)
17. Canada's Drug Agency (Canada). New Guidance on Expanding Economic Evaluations to Reflect Impacts on Informal Caregivers DRAFT 2026. (Canada's Drug Agency. 2026)
18. Scottish Medicines Consortium (Scotland), Guidance on completing the new product assessment form 2022 (Scottish Medicines Consortium. 2022.)
19. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Germany), General methods 2025 (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen 2025)
20. Agenzia Italiana del Farmaco (Italy), Guidelines for filling in the dossier to support HTA 2026 (Agenzia Italiana del Farmaco. 2025)

4.2. NICE appraisal case studies

The five case studies of NICE appraisals are summarised in Table 2, and discussed in further detail in the individual sections.

Table 2: Summary of NICE appraisals case studies - inclusion of carers' HRQoL

	Carers' HRQoL in company base case?	Carers' HRQoL included in committee preferred ICER?	HRQoL measure used for carers	Number of carers included	Opportunity cost explicitly considered?	Carers' HRQoL study design – committee preferred	Modelling approach – committee preferred
Lecanemab for Alzheimer's disease	Yes	Yes	EQ-5D	1.8	No	Observational study of 1,483 caregivers in France, Germany and UK	Increments
Cladribine for multiple sclerosis	Yes	Yes	EQ-5D	1	No	200 MS carers and 200 matched controls in UK	Disutilities
Birch bark extract for epidermolysis bullosa	Yes	Yes	Vignette, time trade-off	Varies by state from 0.5 to 1.78	No	Vignette description 6 health states, 120 members of public valued using time trade-off	Utilities
Onasemnogene abeparvovec for spinal muscular atrophy	No -scenario only	No, noted as complex	Quality of Wellbeing scale	1	No	96 primary caregivers of children with spina bifida, compared to 49 controls in the US	Disutilities
Ruxolitinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis	No – scenario only	No	SF-36, no HRQoL value	1.76	Yes	No HRQoL value reported, assumption made	Treatment-specific utility

4.3. What evidence is there that caring affects HRQoL?

Wittenberg and colleagues systematically reviewed carers' HRQoL studies in February 2012 and then updated their review in April 2018. Wittenberg and colleagues found 15 studies in 2012, and 80 in the period until 2018 (since inception) (Wittenberg, James, and Prosser 2019). Wittenberg and colleagues concluded that utilities generally indicated a loss in HRQoL associated with being a caregiver or family member of an ill patient. Theakston and Mott updated this review in 2024 and found 96 studies since April 2018 (Theaktson and Mott 2025). This suggest that the evidence base for carers' HRQoL is expanding, and more studies are being published every year.

4.4. When should carers' HRQoL be included in economic evaluation?

4.4.1. Literature

There is some variation amongst recommendations for where carers' HRQoL should be included, and whether this should be considered for all evaluations or specific cases. The SHEER guidelines seem to support including carers' HRQoL in all economic evaluations, and Campbell and colleagues further recommend that a rationale should be provided when family spillover effects are not included (Henry et al. 2024, Campbell et al. 2024), a suggestion echoed by Kanters and colleagues (Kanters et al. 2024). Pennington and colleagues recommend that justification should be provided for including carers' HRQoL (Pennington et al. 2022), with evidence and explanation of the causal mechanism by which the intervention is anticipated to affect carers' HRQoL (Pennington and Al-Janabi 2024). Kanters and colleagues discuss that while the consideration of carer utilities is always justified and preferred, it may have limited relevance where the anticipated treatment effect on carers' HRQoL is negligible (Kanters et al. 2024). Lamsal and colleagues encourage researchers to identify criteria for inclusion of family spillover effects such as the type of conditions or diseases that significantly impact carers' health and wellbeing (Lamsal et al. 2024). Bourke and colleagues propose a "carer burden framework", suggesting that carers' HRQoL is most relevant for conditions with a high caregiving intensity and long duration (such as chronic conditions) (Bourke et al. 2024). There is less discussion in the literature about consideration of carers' HRQoL in opportunity costs / displaced interventions – this is discussed further in Section 4.5.

Theakston and Mott reviewed evidence for spillover effects on caregivers or family members, and found that some studies focussed on specific diseases, and others covered a range conditions. Of the studies that focussed on specific diseases, the most common conditions were dementia (n=23) and Alzheimer's (n=7), cancer (n=8), autism spectrum disorders (n=7) and mental health disorders (n=7). Sixty-three studies focussed on care for adults, 22 on care for children, and 11 spanned both populations (Theaktson and Mott 2025). Pennington and colleagues analysed patient-carer dyads where carers self-reported providing care to the patient at some time point and did not restrict by health condition. They found that inclusion of the specific health condition had no statistically significant impact on the results (Pennington, Alava, and Strong 2025), but their analysis differs from the review by Theakson & Mott in that it was specific to the HRQoL of unpaid caregivers and not family members. It did not analyse whether different patient health conditions may have different spillover effects to family members who did not self-identify as caregivers.

In their review of paediatric cost-utility analyses, Lamsal and colleagues primarily identified studies of infectious diseases (18 of 35 studies), with mental and behavioural disorders (n=5) and endocrine disorders (n=4) also featuring prominently (Lamsal et al. 2024). Powell and colleagues also focussed on paediatric conditions, but specifically chronic, progressive, life-limiting conditions (Powell et al. 2025).

Kanters and colleagues describe that appraisals in their review predominantly included orphan indications, paediatric populations and neurological conditions, noting this was similar to the review by Pennington in 2020 (Kanters et al. 2024). Ahmadu and colleagues state that NICE committees accepted the inclusion of carers' HRQoL in 27 clinical areas, but do not discuss this further aside from noting carers' HRQoL was included in 14 appraisals in multiple sclerosis (Ahmadu et al. 2025).

A 2022 review of international HTA guidance concluded that NICE, Haute Autorité de Santé (HAS) in France, Health Information and Quality Authority (HIQA) in Ireland, and Zorginstituut Nederlands (ZiN) all clearly indicated that carers' HRQoL should be included in the base case analysis, and that the Pharmaceuticals Benefits Advisory Committee (PBAC) in Australia and Pharmac in New Zealand were clear that carers' HRQoL should be excluded. They noted that guidance from Canada, Germany, the

USA, Sweden and Scotland was less clear, and that guidance from Wales and Italy did not mention carers (Pennington et al. 2022).

The ZiN in the Netherlands updated its guidance in 2024 to state that carers should be considered in scenario analysis where interventions affect the volume of informal care required or the carers' HRQoL (Zoginstituut Nederland. 2024).

The Tandvards Och Lakemedelsformansverket (TLV) in Sweden state that previously, it had not considered carers' HRQoL in their reference case analysis, and it had not formed the basis for the assessment but included it in scenario analysis only. It noted that the issues including quality of data on carers' HRQoL, methodological considerations, and whether carers' HRQoL gains should be prioritised. They commissioned a research group to study these challenges (Tandvards Och Lakemedelsformansverket. 2022). The TLV concluded that it is reasonable to consider family members' HRQoL where the patients' condition leads to a "significant impact" and "reliable" evidence to demonstrate the effect of the treatment on the family members' HRQoL, but that this needs to be done in a way that minimises introducing additional uncertainty (Tandvards Och Lakemedelsformansverket. 2022).

The most recent guidance from the Institute for Clinical and Economic Review (ICER) states that a societal perspective, including a disutility for caregivers, should be included as a co-base case, alongside a health system perspective, where the impact of treatment on societal domains such as caregiver productivity is substantial (it does not offer guidance as to how to quantity a substantial impact). It advises also considering the impact on caregiver quality of life when "compelling and appropriate" data are available, but again, these terms are not defined (Institute for Clinical and Economic Review. 2025).

Canada's Drug Agency, in its 2025 guidance, maintains the standpoint that spillover impacts to caregivers from interventions targeted at patients should be addressed in non-reference case analysis. (Canada's Drug Agency. 2025).

Guidance from 2022 from the Scottish Medicines Consortium (SMC) states that QALYs for carers are outside its preferred perspective, and refers to "appropriate" data

which may be provided as additional evidence (Scottish Medicines Consortium. 2022.).

The 2025 Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG) general methods note that interventions may affect families and caregivers and state this should be included, but do not specify whether caregiver HRQoL should be included (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen 2025).

New guidelines from Agenzia Italiana del Farmaco (AIFA) now recommend that caregiver's HRQoL can be considered in scenario analysis where justified by the pathology or type of treatment considered (Agenzia Italiana del Farmaco. 2025).

4.4.2. NICE appraisals

Caregivers' HRQoL was included in the company submission and Evidence Assessment Group (EAG) report for lecanemab for Alzheimer's disease, and the principle of including caregiver's HRQoL was accepted in the committee base case.

Caregivers' HRQoL does not appear to have been discussed in the cladribine for multiple sclerosis appraisal but was included in both the company and EAG base cases, so it seems reasonable to assume the committee accepted it. In a previous cladribine appraisal (TA616), the committee included carers' HRQoL in the base case, despite the EAG removing this and stating it was inconsistent with the NICE reference case. The committee cited precedence from previous multiple sclerosis appraisals, and recognition of the impact of caring for people with multiple sclerosis on caregivers (National Institute for Health and Care Excellence. 2024).

The committee agreed it was appropriate to include carers' HRQoL in the birch bark extract appraisal. (National Institute for Health and Care Excellence. 2023a)

The committee discussed carers' HRQoL in the onasemnogene abeparvovec appraisal and concluded that accounting for carers' HRQoL was important in appraisals of spinal muscular atrophy (SMA) treatments. The committee understood that the intervention was likely to reduce caregiver burden in the short term, but that it

was possible that it may increase the level of care required over a lifetime horizon, and that the subsequent effect on carers' HRQoL was uncertain. It noted that inclusion of caregiver disutilities increased the ICERs. The committee concluded that the inclusion of carers' HRQoL in SMA is complex. The company did not include caregiver HRQoL in its base case (National Institute for Health and Care Excellence. 2023b).

The committee did not favour factoring in carers' HRQoL in the base case in the ruxolitinib appraisal. Although it agreed that caring could affect HRQoL, it did not consider that myelofibrosis had a more profound carer burden than other conditions. Further, it was concerned that the opportunity cost of the carers' burden (the carers' HRQoL impacts relieved by other currently funded treatments) had not been considered (National Institute for Health and Care Excellence. 2016).

Kanters and colleagues highlight four recent case studies where the NICE committee did not accept the company's preferred assumptions for modelling carers' HRQoL: mexiltine for symptoms of myotonia (TA784), mogamulizumab for mycoisis funcoides and Sezary syndrome (TA754), cenobamate for seizure in epilepsy (TA753) and berotralstat for hereditary angioedema (TA738). In TA784, TA754 and TA753, the committee acknowledged that there would be some impact on carers but felt that the data provided was not sufficiently robust to include it in the base case. Ahmadu and colleagues further note that committees declined to quantitively consider carers' HRQoL in the HST appraisal of ataluren for Duchenne Muscular Dystrophy (HST22) because of the disconnect between patient and carer testimony and the disutility modelling approach (see Section 4.9) proposed by the external assessment group (Ahmadu et al. 2025).

HST appraisals may be expected to differ from TAs with respect to carers' HRQoL, since routing criterion 1 defines that the disease is debilitating in part due to its *"exceptional negative impact and burden on people with the ultra-rare disease, and their carers and families"* (National Institute for Health and Care Excellence. 2025e). Since the impact and burden on families and carers is explicitly stated in the HST criteria (since April 2025), we may therefore expect that carers' HRQoL is included as standard.

4.4.3. Discussion

Based on the published literature, there appear to be some general trends for including carers' HRQoL in economic evaluations in paediatric conditions, dementia and multiple sclerosis but it is not entirely clear why this is, when there is also evidence of carers' HRQoL effects in cancer (which NICE Technology Appraisals frequently appraise) and mental health disorders (less commonly appraised by NICE). There has been some consideration of whether certain conditions pose a particularly large HRQoL burden in NICE appraisals, but this has not been supported by empirical evidence. We suggest that precedent from previous appraisals in the same or similar disease area alone is not sufficient justification for including carers' HRQoL.

Pennington and Al-Janabi discuss potential alternatives to modelling carers' HRQoL, including qualitative consideration, which has been done in some NICE appraisals, for example where the modelling led to the carer QALY trap (see Section 4.9). They note that while this may allow committees to assign additional weights to interventions that affect carers and to consider qualitative evidence, it is not transparent, consistent or unbiased without a formally defined process (Pennington and Al-Janabi 2024).

Guidance from other HTA bodies also suggests that there are likely to be particular conditions or treatments that affect carers' HRQoL, with terms like "significant", "substantial" or "compelling" used to describe evidence that would be required to support the inclusion of carers' HRQoL effects. However, there are no definitions or guidance as to what evidence is required, or how NICE and appraisal committees should determine in which circumstances carers' HRQoL is particularly relevant.

NICE could consider whether it wishes to provide guidance on specific (aspects of) health conditions where carers' HRQoL is recognised to be relevant (for example, paediatric populations and life-limiting conditions (Powell et al. 2025) or chronic conditions with a high caregiver burden (Bourke et al. 2024)), or what evidence is required to demonstrate carers' HRQoL should be included.

NICE may also wish to review evidence on carers' health impacts more broadly (not limited to HRQoL) to understand if there are health conditions with a particularly pertinent carer burden, and where carers' HRQoL evidence should be collected.

Relatedly, NICE may wish to provide further clarity on whose spillover effects should be included, and whether this is limited to caregivers, or if analyses can consider family members who may not provide care but who are affected by the patient's health condition by caring *about* them.

4.5. Should opportunity cost / displaced carers' HRQoL effects be considered?

4.5.1. Literature

The potential displacement of carers' HRQoL benefits currently provided by funded health interventions (opportunity cost) has not been widely discussed in the past five years. The SHEER guidelines note that displacement should ideally be considered but note that healthcare interventions that are displaced or forgone are typically unknown and so little is known about lost spillover effects from these activities. They make a future research recommendation to calculate average family and caregiver spillovers from displaced activities (Henry et al. 2024).

The TLV discuss that theoretically, if the effect on family members is taken into account in many decisions, it may be necessary to lower the accepted threshold, since the inclusion of caregiver's HRQoL will lead to a lower incremental cost-effectiveness ratios (ICERs) and therefore higher prices for medicines. However, the TLV believes that changing the threshold is not necessary if carers' HRQoL is only considered in specific cases with clear evidence for a family HRQoL gain (Tandvards Och Lakemedelsformansverket. 2022).

4.5.2. NICE appraisals

Two NICE appraisals explicitly discuss the issue of displaced carers' HRQoL effects. In the ruxolitinib appraisal, the committee concluded that the scenario the company proposed including carers' HRQoL did not account for the opportunity cost of carers' burden (National Institute for Health and Care Excellence. 2016). Similarly, the committee felt that it was not appropriate to include HRQoL for carers in the appraisal of berotralstat because there was no clear evidence to suggest that the utility gains for carers would be substantially greater than with displaced treatments (National Institute for Health and Care Excellence. 2021). The committee did not appear to explicitly discuss displaced carers' HRQoL effects in the other case studies considered here or by Kanters and colleagues.

4.5.3. Discussion

There is some recognition that there is an opportunity cost of carers' HRQoL that would otherwise have been affected by other displaced interventions, and an indication of the need to consider whether the intervention under consideration has a larger carers' HRQoL impact than average.

There does not appear to be strong support for considering displaced carers' HRQoL effects through adjusting the cost-effectiveness threshold used by NICE – this would require that the displaced activities were known, and their average spillovers calculated (and this would likely be challenging to estimate accurately). For consistency, this would require that the threshold was based on the opportunity costs of intervention within the NHS, which evidence suggests they are not (Lomas, Martin, and Claxton 2019, Naci et al. 2025). The focus may therefore need to be on demonstrating that the carers' HRQoL effects from the intervention under appraisal are higher than average and supported by evidence.

4.6. What measures should be used for carers' HRQoL?

4.6.1. Literature

The SHEER taskforce recommends that analysts "*Consider the use of the same measure for spillover and patient outcomes if the aim is to aggregate both in the analysis" (Henry et al. 2024).* Campbell and colleagues recommend that *"The same generic preference-based measures of health should be used for patients and family or informal caregivers. A family/informal carer specific measure should be added where possible"* (Campbell et al. 2024). Neither recommend a specific measure, instead supporting consistency between patient and caregiver HRQoL measures. This is because different HRQoL measures cannot be considered interchangeable, even if they all produce utilities anchored between 0 and 1. Different HRQoL instruments contain different domains and response levels and have different scoring algorithms and so do not necessarily produce the same score for the same health state.

Kanters and colleagues state that EQ-5D appears to be the most appropriate choice for this purpose in the UK context, and cite two studies that assessed the construct validity and responsiveness of EQ-5D and found it to be a valid measure of HRQoL in

carers. In both these cases, EQ-5D-5L was mapped to 3L using the 2012 van Hout interim scoring (Kanters et al. 2024, Bhadhuri et al. 2017, McLoughlin, Goranitis, and Al-Janabi 2020). Leech and colleagues similarly discuss and highlight evidence on the validity of EQ-5D in caregivers (Leech et al. 2023), citing examples where EQ-5D has been found to be valid for carers of people with autism (Khanna, Jariwala, and Bentley 2013), meningitis (Bhadhuri et al. 2017), dementia, stroke, mental illness and rheumatoid arthritis (McLoughlin, Goranitis, and Al-Janabi 2020). Kanters and colleagues and Leech and colleagues both note that caregiver-specific QoL instruments may measure other benefits that may be relevant to carers, that the HRQoL-focus of the EQ-5D may not capture (Kanters et al. 2024, Leech et al. 2023). McLoughlin and colleagues found that the Adult Social Care Outcomes Toolkit (ASCOT)-Carer Questionnaire or ICEpop CAPability measure for Adults (ICECAP-A) were more sensitive than EQ-5D to changes in contextual constructs about the caring situation and discuss that this is because ICECAP-A and ASCOT-Carer have a broader scope than health. The ASCOT-Carer questionnaire contains seven domains: occupation, control over daily life, self-care, personal safety, social participation, space and time to be yourself, and feeling supported and encouraged (Rand et al. 2015). ICECAP-A has five domains: feeling settled and secure, love and friendship and support, being independent, achievement and progress, and enjoyment and pleasure . Clearly, these are broader measures of wellbeing than the health-focussed EQ-5D. However, the relative value of these other benefits versus the HRQoL outcomes captured by EQ-5D has not been quantified (for example through time trade-off measures), and so it remains unclear if and how they should be combined with HRQoL.

A systematic review of the psychometric performance of generic preference-based measures in informal carers concluded that the available evidence suggest that generic preference-based measures do have acceptable validity in informal carers, and that the EQ-5D has a particularly wide evidence base across populations including carers of children. The authors note an absence of studies of carers of certain population such as people with mental health conditions (Faller et al. 2025).

Powell and colleagues present an opposing view, arguing that a generic model of HRQoL is inappropriate for carers of children with rare, progressive conditions and

suggest that content validity has not been demonstrated for the EQ-5D (although this is a commentary article not original research: they do not provide or cite any evidence demonstrating that the EQ-5D is not valid) (Powell et al. 2025).

EQ-5D was the most commonly used measure in Theakston and Mott's review (n=71), with SF-6D, HUI, EQ-HWB-S and AQoL-4D used in fewer studies (total 77 studies used generic measures). Twenty-three studies used carer-specific measures, with CarerQol-7D being the most common (n=21). They note that the continued focus on certain conditions limit the applicability of the data (Theaktson and Mott 2025).

An abstract from the International Society for Pharmacoeconomics and Outcomes Research 2024 European conference found that the effect of unpaid caring was statistically significant for people providing 5 or more hours of care per week, and that the disutility was greater using EQ-5D-3L than using EQ-5D-5L mapped to 3L (Pennington and Hernandez 2024).

The ZiN notes that there are multiple instruments and methods for measuring and valuing carers' HRQoL, but it considers that there is insufficient evidence about their validity and sensitivity and defer to NICE's guidance to use EQ-5D, noting this allows patient and care outcomes to be combined (Zoginstituut Nederland. 2024).

The draft methods guidance on informal caregivers from CDA states that HRQoL impacts on caregivers should be obtained from indirect measurement methods based on generic classification systems (with EQ-5D, SF-6D and HUI-3 cited as examples), with health preferences reflective of the Canadian population. Both statements are aligned with guidance for measuring HRQoL of patients, and the CDA note that this enables comparability and alignment with the QALY framework. They further specify that expert opinion should not be used to value caregiver HRQoL. This guidance recognises that generic health utility instruments may not capture the full breadth of caregiver experiences and propose that the if caregiver HRQoL is included in economic evaluation (using HRQoL), the full impact on caregivers should be acknowledged and deliberated in interpreting results (Canada's Drug Agency. 2026). McLoughlin and colleagues note that if broader measures of caregiving impacts are

included in addition to HRQoL, care should be taken to avoid double-counting when presenting the results (McLoughlin, Goranitis, and Al-Janabi 2020).

4.6.2. NICE appraisals

The values used for caregivers' HRQoL in the lecanemab appraisal were measured using the EQ-5D. The committee discussed whether EQ-5D might underestimate carers' HRQoL effects in Alzheimer's disease, and that NICE's methods specify that only health effects should be incorporated (rather than broader quality of life effects). The committee for the contemporaneous appraisal of donanemab in Alzheimer's disease had acknowledged the limitations of EQ-5D, but noted that these were not unique to Alzheimer's disease (in the context of caregiving) (National Institute for Health and Care Excellence. 2025d).

The cladribine appraisal used EQ-5D for caregivers (National Institute for Health and Care Excellence. 2024).

The birch bark extract appraisal used a vignette study, valued using time trade-off (National Institute for Health and Care Excellence. 2023a).

The carers' HRQoL data considered in a scenario analysis for onasemnogene abeparvovec used the Quality of Wellbeing Scale to measure HRQoL (National Institute for Health and Care Excellence. 2023b).

The evidence cited by the company to support inclusion of carers' HRQoL for ruxolitinib was a study of SF-36 of 50 caregivers of patient with gliomas in France. The study does not appear to report an HRQoL value (National Institute for Health and Care Excellence. 2016).

4.6.3. Discussion

The evidence is broadly supportive of continuing NICE's preference for using EQ-5D to measure the HRQoL of unpaid carers, with no quantitative evidence suggesting it was inappropriate. There is no evidence to indicate that NICE's hierarchy of preferred HRQoL methods should not apply equally to carers as to patients, with the preference for carers HRQoL being EQ-5D reported by carers in a relevant study.

The NICE manual notes that in some circumstances, EQ-5D may not be appropriate, and provides guidance on how to make a case that EQ-5D is not appropriate:

> *"In some circumstances the EQ-5D may not be the most appropriate measure. To make a case that the EQ-5D is inappropriate, provide qualitative empirical evidence on the lack of content validity for the EQ-5D, showing that key dimensions of health are missing. This should be supported by evidence that shows that EQ-5D performs poorly on tests of construct validity (that is, it does not perform as would be expected) and responsiveness in a particular patient population. This evidence should be derived from a synthesis of peer-reviewed literature. In these circumstances alternative health-related quality-of-life measures may be used. These must be accompanied by a carefully detailed account of the methods used to generate the data, their validity, and how these methods affect the utility values."*
>
> NICE Manual 4.3.10 (National Institute for Health and Care Excellence. 2022).

We suggest that this same guidance applies to demonstrating that EQ-5D is not appropriate for carers. Carer-specific QoL measures exist, and some, such as CarerQoL-7 Dimensions can be used to generate utilities. However, this measures quality of life rather than specifically HRQoL (see Section 1), so while EQ-5D may not capture all aspects of caregiving, there does not appear to be any evidence that key dimensions of *health* are missing from EQ-5D that would be captured in other HRQoL measures. There is a further challenge in aggregating patient and carer QALYs if the same HRQoL measures is not used for both.

4.7. How many carers should be included?

4.7.1. Literature

Many studies acknowledge that spillover effects can affect more than one family member, and that the impacts to different family members will vary in size and by context (Henry et al. 2024, Kanters et al. 2024, Lamsal et al. 2024, Pennington and Al-Janabi 2024, Pennington et al. 2022, Leech et al. 2023).

There is little published evidence on the size of HRQoL impacts on carers beyond the primary caregiver – most studies of carers' HRQoL collected data from the primary caregiver only (Theaktson and Mott 2025). It is therefore unclear whether the same size HRQoL impact can be applied to multiple carers. SHEER guidelines recommend that either evidence should be collected for specific family members, or that the HRQoL of the closest and second closest network members (primary and secondary caregivers) should be measured, and a mathematical function applied to estimate the full network. The use of a mathematical function or multiplier, as proposed by Al-Janabi in a meningitis case study (Al-Janabi et al. 2016) is also recommend by Pennington and Al-Janabi (Pennington and Al-Janabi 2024), whereas Lamsal recommended future studies should measure HRQoL on multiple family members (Lamsal et al. 2024). Powell and colleagues echo the need for consideration of HRQoL impacts beyond the primary caregiver and propose the use of qualitative HRQoL research to identify impacts to wider family members (Powell et al. 2025). However, we note that qualitative evidence alone cannot provide estimates for use in economic evaluation.

The TLV considered it unreasonable to consider differential numbers of family members for different patient groups, due to potential distributional effects (see Section 4.11). Instead, it proposes only one family member should be considered, noting that this avoids need for discussion of who can be considered a family member (Tandvards Och Lakemedelsformansverket. 2022). AIFA advise that generally, one caregiver should be assumed per patient (Agenzia Italiana del Farmaco. 2025).

The CDA state that the proportion of patients who have an informal caregiver and the number of informal caregivers should be informed by disease-specific evidence, and that in the absence of evidence about the number of caregivers, one caregiver should be assumed. They further specify that where multiple carers are assumed, increasing caregiver utility losses or gains by a fixed number is inappropriate as it assumes each caregiver is the sole caregiver. Instead, the analysis must demonstrate that the utility measurement accounted for multiple carers (for example with surveys demonstrating multiple caregivers were included and weighted) (Canada's Drug Agency. 2026).

4.7.2. NICE appraisals

In the final draft guidance after the third committee meeting, the committee for lecanemab preferred to include 1.8 caregivers, for consistency with donanemab for the same indication (GID-11221), and because people in the GERAS study, which provided caregiver's HRQoL data, had an average of 1.8 carers. This is referenced to the donanemab appraisal and a 2019 publication by Belger and colleagues that describes the GERAS study (Belger et al. 2019), but we were unable to find the number of 1.8 within the study, or any reference to the number of carers. GERAS was an observational study in patients with dementia and their caregivers, other publications about the same study seem to suggest it only included primary caregivers so it is unclear where the figure of 1.8 came from. The committee for donanemab discussed that it was unclear how the average of 1.8 would be distributed over the population without more robust evidence (National Institute for Health and Care Excellence. 2025d).

The cladribine appraisal appears to include 1 carer, but this is not explicitly discussed (National Institute for Health and Care Excellence. 2024).

In the birch bark extract appraisal, the committee agreed it was appropriate to include 1.78 carers (the average number of parents per household) in the more severe states (states 5 and 6) where the body surface area percentage covered in wounds was highest. From the company submission, it appears the states with the lowest body surface area percentage covered in wounds (states 1 and 2) had 0.5 carers (50% of patients had one carer), and people in states 3 and 4 had one carer. The committee concluded that the company's approach to modify the HRQoL effects for the secondary caregiver in stages 5 and 6 such that they had 77% of the HRQoL reduction of the primary carer was appropriate, based on a survey submitted by the company (National Institute for Health and Care Excellence. 2023a).

The company's scenario analysis including carers' HRQoL for onasemnogene abeparvovec appears to include 1 carer (National Institute for Health and Care Excellence. 2023b).

The company's proposed analysis for ruxolitinib included a carers' HRQoL decrement whilst on the comparator, for 57.48% of patients each requiring 1.76 caregivers (both figures referenced to an unpublished report on myelofibrosis) (National Institute for Health and Care Excellence. 2023b)

4.7.3. Discussion

While there is recognition that patient health conditions can impact the HRQoL of multiple people, the evidence for carers' HRQoL effects has primarily/exclusively been for the primary caregiver. The inclusion of HRQoL effects to multiple people requires consideration of whether these people are carers or family members more broadly (see Section 4.4) and how people transition between these roles where the number of carers differs between health states. Inclusion of multiple cares also requires evidence to inform the size of the carers' HRQoL effects beyond the primary caregiver. There is some evidence to support decreasing HRQoL effect size beyond the primary carer, with suggestions of using arithmetic progression to estimate successive family members' HRQoL effects (Al-Janabi et al. 2016).

4.8. How should studies be designed to include assessments of carers' HRQoL?

4.8.1. Literature

Papers discuss the different options for collecting carers' HRQoL data, and some express preferences. Campbell and colleagues propose that HTA organisations should provide an evidence hierarchy in guidance on the inclusion of family spillovers (Campbell et al. 2024).

Primary studies which collected patient and carers' HRQoL for an intervention and comparator could directly inform carers' HRQoL in economic evaluation. However, typically, economic models have linked carers' HRQoL to patient health states using secondary data and therefore assume that the intervention affects carers' HRQoL by affecting patients' health.

The SHEER taskforce recommends collecting primary data "where possible", with justification provided where secondary data is use (Henry et al. 2024). Pennington and colleagues recommend that evidence for carers' HRQoL should come from the

population under consideration, and justification for transferability should be provided where evidence comes from different populations, including consideration of both the volume and type of care (Pennington et al. 2022). Leech and colleagues suggest carers' HRQoL data could be collected in clinical trials or registries (Leech et al. 2023). Kanters and colleagues state the primary data collection is preferred, but note that this might be difficult (Kanters et al. 2024). Powell and colleagues note that the generation and inclusion of carers' HRQoL impacts is particularly challenging in rare, progressive, paediatric conditions where this evidence is limited (Powell et al. 2025). As alternatives to primary data collection, some papers propose the use of vignettes and mapping from non-preference based measures (Leech et al. 2023, Kanters et al. 2024, Campbell et al. 2024), but it is unclear why this would be preferable to collecting caregivers' HRQoL data directly. Kanters and colleagues compare the advantages and disadvantages of primary data, secondary data/literature, vignette studies and mapping. They highlight concerns about transferability using secondary data, particularly where caring contexts may differ between countries. Kanters and colleagues note that while vignette studies are convenient since they do not require direct measurement of carer-level data, the disadvantage is that they are not able to fully reflect experiences in each state and so are inferior to direct EQ-5D, and they state that his criticism applies equally to carer and patients. They further note that while vignettes may allow assessment of the impact of specific attributes on carers' HRQoL, they are treatment and disease specific, so their transferability is limited. They discuss that mapping between carer-specific and HRQoL instruments is complicated by lack of conceptual overlap (Kanters et al. 2024). Ahmadu and colleagues note that carers' HRQoL data proposed for inclusion in NICE appraisals included observational studies, surveys, vignette studies, previous appraisals HTAs and clinical trials (Ahmadu et al. 2025).

Theakston and Mott describe that the majority (n=58) of the studies they identified were primary studies that collected new data (typically online surveys), 16 were secondary data analyses of existing datasets, 15 were from trials, and 7 were direct elicitation studies (often rare conditions) (Theaktson and Mott 2025).

Some studies recognised that most carers' HRQoL studies to date used a cross-sectional design, which has limitations in identifying a causal effect of caring on

HRQoL because of selection bias: people who become carers may be different to people who do not become carers, and the same factors that affect whether someone becomes a carer may also influence their HRQoL (for example, older people and people with pre-existing health conditions may be more likely to become carers and also more likely to have worse HRQoL) . Lamsal and colleagues suggested that cross-sectional studies needed comparison to a matched-comparison group (Lamsal et al. 2024). Longitudinal studies which compared someone's HRQoL before and after they became a carer would also address selection bias, and would also provide insight into the temporality of the relationship between caring and HRQoL over time (for example whether carers "adapt" to the change in HRQoL, or whether HRQoL continues to decline over time) (Pennington 2020, Henry et al. 2024, Lamsal et al. 2024, Powell et al. 2025) (Henry et al. 2024). This was a particular concern in the papers specifically discussing informal carers' HRQoL in paediatric conditions (Powell et al. 2025, Lamsal et al. 2024).

Theakston and Mott found that longitudinal studies were relatively uncommon, both in primary (n=9) and secondary research (n=3). Some studies compared to the general population's HRQoL (n=5) to estimate a carer disutility, and two compared carers of patients with different severity to estimate differential carer disutilities. Theakston and Mott noted that cross-sectional data cannot capture all relevant impacts of the health condition and intervention (Theaktson and Mott 2025).

Pennington and colleagues' 2025 longitudinal analysis found that there was a statistically significant relationship between carers' and patients' HRQoL, and between duration of caregiving and carers' HRQoL. This indicated that there is a causal relationship between caregiving and HRQoL, and that changes in patient's HRQoL can also be expected to change carers' HRQoL (Pennington, Alava, and Strong 2025). There is some evidence that patients may be able to act as proxies for carers' HRQoL (reporting carers' HRQoL, not their own), with fair-to-moderate agreement, but that care recipients consistently overestimate carers' HRQoL (Kuharic, Su, and Pickard 2025).

4.8.2. NICE appraisals

In the final draft guidance after the third committee meeting, the committee for lecanemab preferred to use the GERAS study for caregivers' HRQoL data (Wimo et al. 2013). The company had initially used EQ-5D-3L estimates from Clarity AD (the clinical trial) for the MCI and mild AD states, supplemented with estimates from the literature for more severe states (Black et al. 2018) and residential care (Farina et al. 2020). GERAS was used in the donanemab appraisal and was an observational study of Alzheimer's disease patients and their caregivers and included the EQ-5D at baseline of 1,483 Alzheimer's disease caregivers in France, Germany and the UK. The committee considered this was a large study and gave "UK-relevant" estimates, so preferred to use GERAS in its final guidance (National Institute for Health and Care Excellence. 2025d).

The cladribine appraisal used caregiver HRQoL data from a UK study of EQ-5D in 200 carers of people with multiple sclerosis and 200 matched controls (Acaster et al. 2013) (National Institute for Health and Care Excellence. 2024).

The trial for birch bark extract did not collect carers' HRQoL data, so the company did a separate study. They provided vignette descriptions of six health states, and 120 members of the public undertook a time trade-off exercise to provide utilities for each health state (National Institute for Health and Care Excellence. 2023a).

The carers' HRQoL data considered in a scenario analysis for onasemnogene abeparvovec was from a US study that reported the disutility for 98 primary caregivers of children with spinal bifida, compared to a control sample of 49 parents of unaffected children. HRQoL was measured using the Quality of Wellbeing Scale and valued using a categorical rating scale method and a multi-attribute utility model. The company stated that this was an explorative scenario only and noted the lack of robust SMA-specific UK caregiver utility data (National Institute for Health and Care Excellence. 2023b).

4.8.3. Discussion

Evidence demonstrates that it is feasible to collect carers' HRQoL. Carers' HRQoL data should be collected directly from carers and should not be assumed to be identical to patients' HRQoL.

There is recognition of the need for robust, UK-appropriate data in the literature and NICE appraisals. However, the literature has generally called for a higher standard of evidence to demonstrate a causal effect of caring on HRQoL, whereas NICE appraisals have made pragmatic decisions with the available data.

The NICE manual states that the preferred source of EQ-5D for patients is a "relevant study" and recommends that if EQ-5D is not available in the relevant clinical trials, EQ-5D can be sourced from the literature. It is possible that clinical trials could collect EQ-5D for carers as well as patients, and this would help to determine whether the treatment, or change in patient's health status, affected carers' HRQoL. However, NICE may wish to consider whether they can make recommendations about potential preferred study designs where carers' HRQoL was not collected in clinical trials.

4.9. How should carers' HRQoL be modelled?

4.9.1. Literature

Studies note that there are different methods for modelling carers' HRQoL, including the "utility" and "disutility" methods commonly used in NICE appraisals (Lamsal et al. 2024, Kanters et al. 2024, Pennington et al. 2022, Ahmadu et al. 2025). Lamsal also points to the use of a multiplier to estimate carer QALYs, although this has been less commonly used in NICE appraisals (Pennington 2020). Pennington, Davis and Cranmer (Pennington, Davis, and Cranmer 2026) describe these methods, and also the "increments" or "decrements" approach considered in NICE's recent appraisals in Alzheimer's disease (National Institute for Health and Care Excellence. 2025d) and Duchenne Muscular Dystrophy (National Institute for Health and Care Excellence. 2025c), and the "multipliers" approach used in the literature.

No studies provide definitive guidance as to whether any of these approaches are preferable to others, and the SHEER guidance and Powell and colleagues recommend further research on this topic (Henry et al. 2024, Powell et al. 2025). The CDA draft methodological document provides guidance on their preferred modelling approach,

noting that the decrement and increment approaches are appropriate, and the "additive" utility approach is only appropriate where caregiver QALYs are measured across the full caregiver lifespan with sufficient evidence to inform the caregiver's HRQoL after patient death (Canada's Drug Agency. 2026). The TLV discuss the utility approach and use of multipliers as well as multicriteria decision analysis, and conclude that none are fully optimal, mostly due to a lack of reliable data on the magnitude of the HRQoL effect of treatment on family members. AIFA and the ZIN do not discuss specific approaches but describe that carers' HRQoL should be related to patient health states (Agenzia Italiana del Farmaco. 2025) (Zoginstituut Nederland. 2024).

The methods are described below and compared in Table 3.

- The "utility" method includes utility values for caregivers, as well as utility values for patients, as long as the modelled patient is alive. This necessarily results in more total QALYs (assuming caregiver utilities are positive) than including patient HRQoL alone, and interventions which extend patient survival lead to more caregiver QALYs (as well as more patient QALYs). Caregiver utilities are typically linked to patient health states and are higher where patient health is better, so interventions that improve patient morbidity also lead to a caregiver QALY gain. This is sometimes termed the "absolute utility" methods since it includes the absolute value of the caregiver utility, or the "additive utility" method since it adds together patient and caregiver utilities. Mathematically, this is equivalent to assuming that the carer dies (or their HRQoL becomes equivalent to death) when the patient dies. The interpretation of only including caregiver QALYs while the patient is alive varies, since it suggests caregiver's utility becomes 0 when patients die, with some arguing that this is because carers are no longer relevant, and others stating this implies bereaved caregivers are not valued (National Institute for Health and Care Excellence. 2023c). In their guidance, the ZiN noted that caregivers' HRQoL should not be considered beyond the patient's life expectancy (Zoginstituut Nederland. 2024).
- The "disutility" method includes a disutility for caregivers as long as patients are alive. The disutility is calculated as the difference between utility values for caregivers and either full health or the utility expected for the (age- and sex-matched) general population. These differences are negative, since caregivers

generally have worse HRQoL than people who do not provide care. Caregiver disutilities are linked to patient health states and are smaller in magnitude (but still negative) for better patient health states. This necessarily results in fewer total QALYs (assuming caregiver utilities are lower than non-caregiver utilities) than including patient HRQoL alone, and interventions which extend patient survival lead to fewer caregiver QALYs. This has been termed the “carer QALY trap” (Mott et al. 2023).

- The “increments” approach includes, for each patient health state, the difference between caregiver utility in that health state and the caregiver utility in the worst/most severe patient health state. This uses the caregiver health state utilities associated with the patient health states, without making comparison to full health or the general population. The increment in the worst health state is zero and is positive for all other health states. This necessarily results in more total QALYs than including patient HRQoL alone, as long as patients are not in the worst health state (where there is no impact). Interventions that extend patient survival lead to more caregiver QALYs unless the extended survival is solely in the worst health state. Interventions that improve patient morbidity lead to more caregiver QALYs. This approach assumes that caregivers are indifferent to the patient dying or living in the worst health state. It is mathematically equivalent to applying the caregivers’ HRQoL in the worst health state to the patient death health state and therefore implies a bereavement effect that is equal in size to the caregiving effect in the worst health state and lasts for the patient’s lifetime on the intervention.
- The “decrements” approach includes, for each patient health state, the difference between caregiver utility in that health state and the caregiver utility in the best patient health state. Like the increments approach, this does not make comparison to general population/full health. The decrement in the best health state is zero and is negative for all other health states. If the caregiver utility in the best patient health state was equal to the general population/full health, this approach would be the same as the disutility approach. If the caregiver utility in the best health state is lower than the general population/full health then the decrements are smaller than the disutilities would be. This approach necessarily results in fewer total QALYs than including patient

HRQoL alone unless patients are in the best health state (where there is no impact). Interventions that extend patient survival lead to fewer caregiver QALYs unless the extended survival is solely in the best health state. Interventions that improve patient morbidity lead to a small caregiver QALY loss and hence more caregiver QALYs. Bereavement is assumed to have no negative HRQoL impact on the caregiver and this approach can therefore also lead to the carer QALY trap, but the QALY gain is typically smaller than using the disutility approach.

- The “multiplier” approach multiplies the patient QALYs by a number (typically between 0 and 1) to estimate the caregiver QALYs. This number is typically estimated from the ratio of caregiver to patient HRQoL. This requires patients’ and carers’ HRQoL data at one time point but assumes a constant relationship between patient and carer HRQoL, regardless of patient health state and time. This assumption may not be true, for example if the caregiving burden increases more rapidly in worse health states. If a multiplier is applied to the patient QALY gain to estimate carer QALY gain, then this implicitly assumes carers’ HRQoL is only relevant/valued/affected while they are caregiving, and not after bereavement. While this may avoid the carer QALY trap, its interpretation is unclear as it suggests any changes to carers’ HRQoL during the patient life extension offered by a new treatment have no impact on carers’ HRQoL. The TLV propose an approach that they term the “standard rate”, which multiplies a number between 0 and 1 by the patient’s QALY improvement over the patient’s life expectancy with standard care. They propose a value of 0.5 but note that it is not based on actual measurements and the magnitude needs to be determined (Tandvards Och Lakemedelsformansverket. 2022).
- The “family and caregiving” approach includes a multiplier for the patient HRQoL to represent the family effect or “caring about” someone, and an additional caregiving effect (disutility or increment) specific to each health state to represent the caregiving effect of “caring for” someone. This requires data on the relationship between patients’ and caregivers’ HRQoL for each patient health state but allows for flexibility in modelling the relationship between patient and carers’ HRQoL, and transparency in disentangling positive and negative impacts. Whether extending patient survival leads to a QALY gain or

loss for carers depends on whether the caregiving effect is positive or negative, and on the relative size of the caregiving and family effects (Pennington, Davis, and Cranmer 2025).

Ahmadu and colleagues also discuss appraisals where treatment-specific caregiver utility increments were proposed, but these were not considered appropriate by NICE committees (Ahmadu et al. 2025).

Table 3 Comparison of modelling approaches

	Direction of impact on total QALYS of including carers' HRQoL	**Size of impact on total QALYS of including carers' HRQoL**	**(Implied) effect of patient death on caregiver QALYs**
Utility	Increase	Large	Loss
Disutility	Decrease	Small – Large, depends on size	Gain
Increments	Increase, except in worst state	Small	Loss, except in worst state (no impact)
Decrements	Decrease, except in best state	Small	Gain, except in best state (no impact)
Multiplier	Increase	Depends on multiplier	Loss or no impact
Family and caregiving effects	Depends on relative sizes	Small	Depends on relative sizes

4.9.2. NICE appraisals

The committee for lecanemab preferred to use the company's "incremental approach" to model utility, which used the worst alive health state as a reference and applied caregiver's utility increments for each better state relative to this. The committee noted that this approach avoided the carer QALY trap, and had no impact on carer QALYs

from extending survival in the worst state (National Institute for Health and Care Excellence. 2025d).

The company submission and EAG report for cladribine refer to “carer disutility”, indicating that the modelling included a negative carers’ HRQoL effect for caring for someone with multiple sclerosis, the magnitude of which increases as disease progresses (National Institute for Health and Care Excellence. 2024).

The committee discussion does not comment on the modelling approach in the birch bark extract appraisal, which appeared to use carer utilities. The benefit of treatment was through improving morbidity rather than extending survival, so different modelling approaches would lead to the same carer QALY gain (either through carer QALY gains, or avoiding carer QALY losses) (National Institute for Health and Care Excellence. 2023a).

The scenario analysis in the onasemnogene abeparvovec appraisal included caregiver disutilities. The company considered that including caregiver disutilities produced “counterintuitive” results, as it made the intervention less cost-effective. The committee noted that while the intervention would reduce short-term caregiver burden, the effect of potentially increasing the level of care needed in the future on carers’ HRQoL was uncertain (National Institute for Health and Care Excellence. 2023b).

The company model for ruxolitinib assumed that caregivers of patients on the comparator treatment would have a utility decrement of 0.1, whereas ruxolitinib would relieve this (a treatment-specific approach), which the committee did not favour including in its preferred analysis (National Institute for Health and Care Excellence. 2016).

4.9.3. Application of modelling methods to case studies

We applied the modelling methods described in Section 4.9.1 to three of the models for the case studies in the NICE appraisals. We discuss the results and implications of these, to understand whether NICE can make recommendations about any preferred or inappropriate methods. NICE provided access to models submitted by

the company during the appraisal process. The settings within these models do not necessarily reflect the final committee-preferred assumptions, and the QALY gains do not represent those used in decision-making, but they provide real-life examples of how models developed for HTA.

The methods in the examples use the following assumptions:

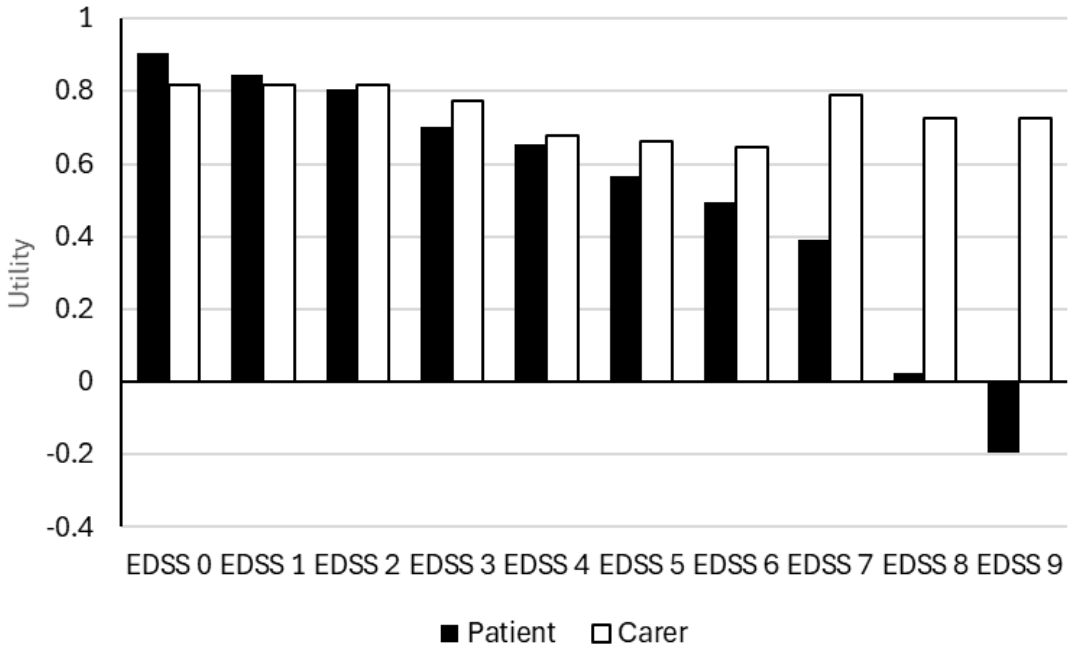
- Carer utilities are applied for as long as patients are alive. Carer utilities are assumed to be zero or excluded after patients die.
- Carer disutilities are applied for as long as patients are alive. There is no bereavement effect, carers' HRQoL reverts to full health/no negative effect immediately upon patient death.
- Carer increments are caclulated as the difference between the carer utility for each health state, and the carer utility for the worst carer health state. They are applied whilst patients are alive.
- Carer decrements are caclualted as the difference between the carer utility for each health state, and the carer utility for the best carer health state. They are applied whilst patients are alive.
- The multiplier calculates the carer QALYs as 16% of the patient QALYs, using the 0.16 positive spillover coefficeint from a study of families exposed to the after-effects of meningitis (Al-Janabi et al. 2016)
- The family and caregiving effects assumes a family effect multiplier of 12.3% and calculates the caregiving effects for each health state using the patient and carer utilities in the model and the calculations described by Pennington and colleagues (Pennington, Davis, and Cranmer 2026)

4.9.3.1. Cladribine for multiple sclerosis

The model for clardiribine uses health states defined by the Expanded Disability Status Scale (EDSS), a higher number indicates worse health. Each EDSS health state has a patient utility value, and a caregiver disutility value. There are additionally patient disutilities associated with transitionig to Secondary Progressive Mulitple Scleroris (SPMS), relapse events, and adverse events. We calculated caregiver utilities by adding the (negative) disutility to the mean utility for controls (0.82) in the source study (Acaster et al. 2013). The patient and caregiver utilities are shown in

Figure 1. One carer is assumed per patient, in each health state. The guidance does not discuss different approaches for modelling carers' HRQoL, and only the carer disutility approach is included in the analysis.

Figure 1: Patient and carer utilities in cladribine case study

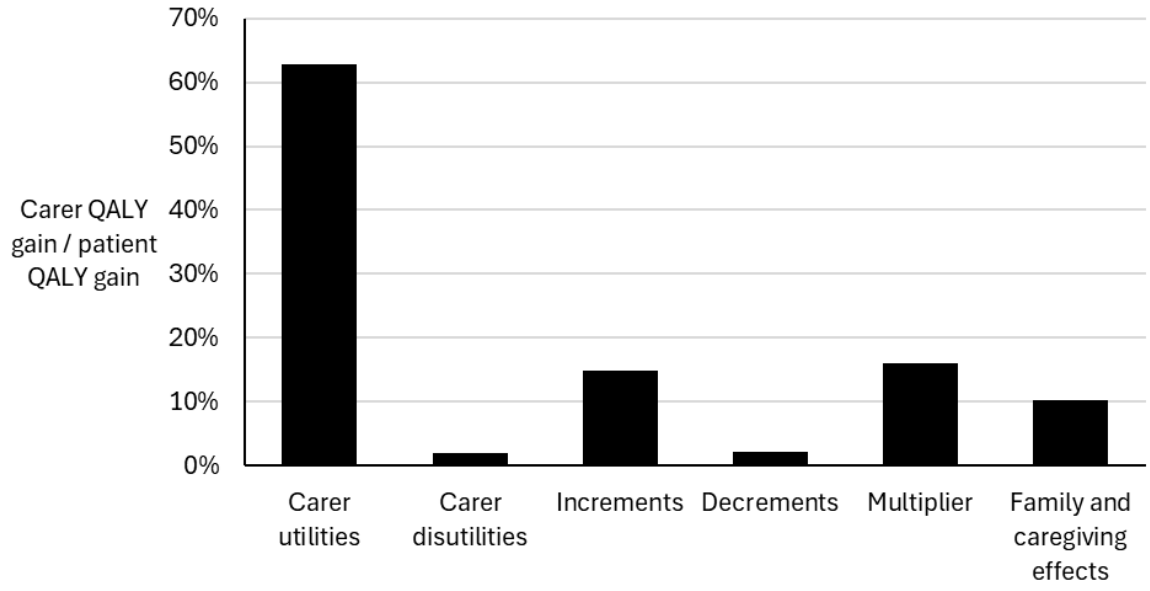


Cladribine is compared to ocrelizumab and ofatumumab (National Institute for Health and Care Excellence. 2024). In the final guidance, the committee found that cladribine led to fewer QALYs than the comparators but was cost-saving and cost-effective in the South-West quadrant. The model including committee's preferred assumptions was not available. The version of the model we had reported that cladribine led to more QALYs than the comparator due to different assumptions, so here we refer to intervention and comparator, where intervention leads to more QALYs than the comparator. Worse EDSS health states are associated with higher mortality ratios (National Institute for Health and Care Excellence. 2024), so interventions that delay progression to more severe EDSS states lead to a QALY gain through extended survival and improved HRQoL.

The total and incremental QALYs are redacted within the documents available publicly, and so they are not reported here. Instead, we report the incremental carer QALYs as a percentage of the incremental patient QALYs in Figure 2. All of the

modelling methods lead to a carer QALY gain for the intervention versus the comparators. In this case study, the carer disutilities approach does not lead to the carer QALY trap (negative incremental carer QALYs) – this is because of the relative size of the mortality and morbidity gains. The carer utilities approach leads to the most carer QALYs. The disutilities and decrements approaches lead to similar results – this is because the carer utility in the best state is very close to that of the general population, so the magnitude of the disutilities and decrements for the worse states are similar. The multiplier here is applied as 16% of the patient QALY gain. The result of the family and caregiving effect is slightly less than the multiplier – this is because the family effect is slightly smaller at 12.3% (applied per health state), and the caregiving effect is negative.

Figure 2: Cladribine case study results

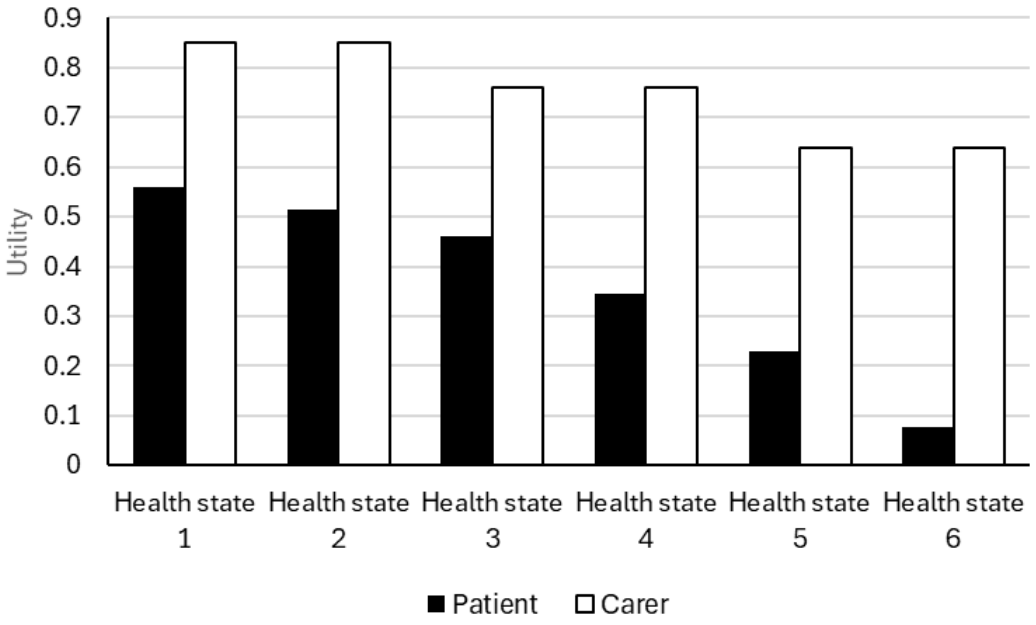


It is worth noting that while the patient utilities decrease monotonically as the EDSS states worsen, the caregiver utilities do not – the caregiver utility for the most severe EDSS states are higher than for states EDSS 4-6. This complicates the relationship between caregivers HRQoL and treatment effectiveness, but this applies equally to all of the carer HRQoL methods (except the multiplier).

4.9.3.2. Birch bark extract for epidermolysis bullosa

The model has six health states, defined by wound burden severity, with health state 1 the least severe and health state six the most severe. The intervention does not affect mortality. The patient and caregiver utilities are shown in Figure 3. The guidance refers to carer disutility, but the model includes utilities and QALYs for patient and carers, suggesting that the carer utility approach was used in this appraisal.

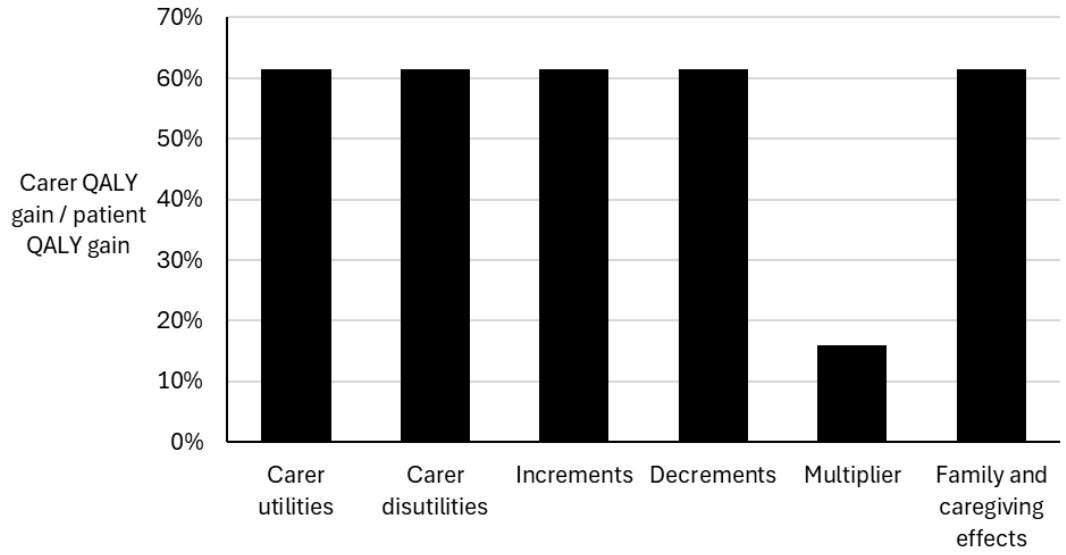
Figure 3: Patient and carer utilities in birch bark extract case study



The committee's preferred assumptions involved different numbers of carers in different health states. For clarity, we first present the results for the different methods assuming 1 carer in each health state, in Figure 4. The incremental carer QALYs are the same for all of the methods except the multiplier (which is 16% of the patient QALYs) since they all use the same data source, and there is no survival difference between intervention and comparator. All of the carer QALYs are from

transitions between the different carer utilities, so it does not matter how the difference between these utilities is implemented in the model.

Figure 4: Birch bark extract case study results - assuming one carer



The inclusion of multiple carers, and specifically different numbers of carers for different health states, complicates matters. The model submitted to NICE uses the carer utilities approach, and allows for a maximum of 1.78 carers per health state. Where there are fewer than 1.78 carers, the health-state specific carer utility is applied to the number of carers, and the general population utility is applied to the remaning number of potential carers (so for example, in health state 1 where there are 0.5 carers, the carer utility is applied to 0.5 carers and the general population utility to 1.28 carers). The carer utility and disutility approaches generate the same incremental QALYs as each other when multiple carers are included, as shown in Figure 5.

There are two potential options for calculating the increments and decrements which lead to different results. One option, labelled 1 in Figure 5, is to calculate the increment (decrement) as the difference between the carer QALYs for each health state and the carer QALYs for the worst (best) health state – this gives results consistent with the utility and disutility approaches. Alternatively, calculating the incremental (or decremental) carer utility by looking at the carer utility values (not the carer QALYs) and multiplying this by the number of carers per state, leads to a bigger increment (or decrement) in states that have more carers – this is labelled 2 in

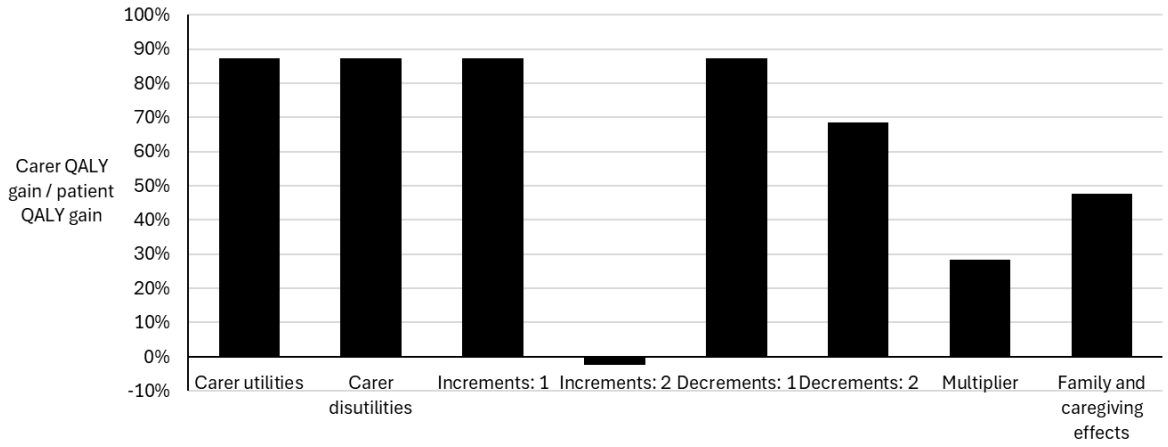
Figure 5. For the increment approach, the increment is zero for the severe states (1.78 carers) and smaller for the best states (0.5 carers) but highest for the middling states (1 carer), so interventions that move patients from worse to better states are penalised. For the decrement approach, the decrement for the more severe states is compared to the utility assuming one carer in the best state, so the relative decrement for worse states with more carers is smaller than in the first method. For consistency with the carer utility and disutility apporach, and to avoid counterintuitive results, we suggest increments and decrements should be calculated using the first method.

The multiplier method also warrants consideration where multiple carers are involved. Al-Janabi et al propose mathematical functions that can be applied to estimate the spillovers to additional family members (Al-Janabi et al. 2016), and this would be straightfoward to apply where the number of additional family members is constant throughout the disease. However, applying a bigger multiplier to QALYs gained in health states with more carers would place more weight on QALYs gained in more severe health states, and penalise interventions which moved patients from worse to better states, which would seem counterintuitive. A more pragmatic option may be to apply the multiplier to the patient QALY gain assuming the maximum number of carers, since the additional people who would become carers in more severe states also benefit from delaying progression to these states. In this example we use a multiplier of 0.29 (0.16*1.78).

The family and caregiving effects do not give the same results as the other methods when applied to multiple carers. This is because the relative sizes of the two effects differ for different health states, and so applying these to differing numbers of carers

changes the results. The carer QALY gain using the family and caregiving effects is slightly smaller in this example.

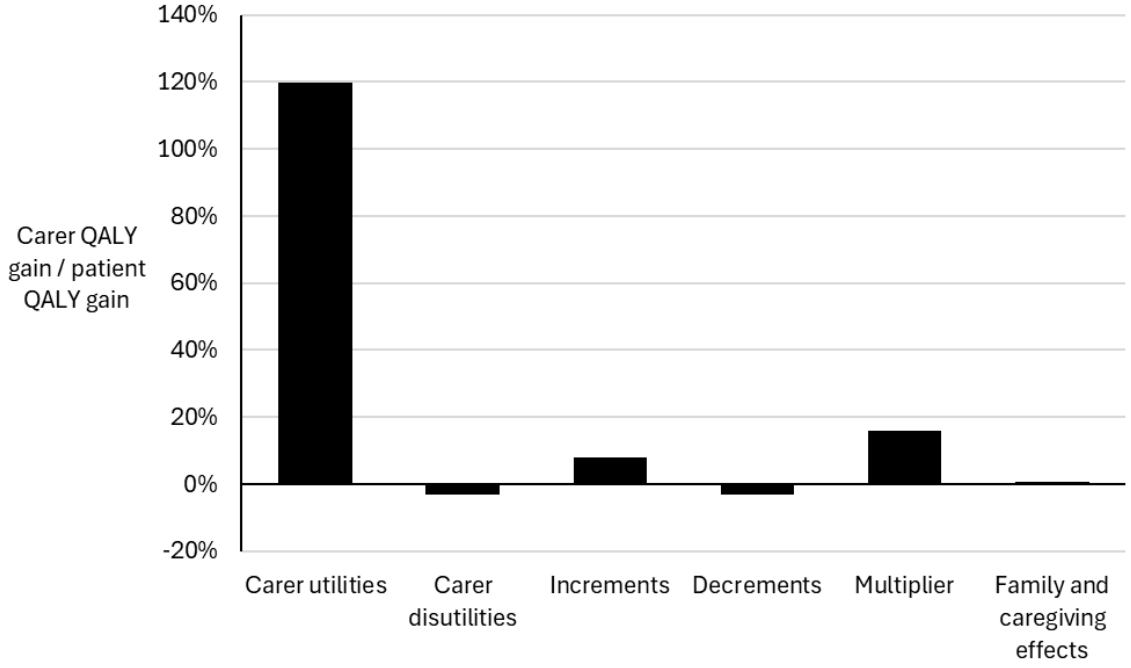
Figure 5: Birch bark extract case study results - assuming multiple carers



4.9.3.3. Onasemnogene abeparvovec for spinal muscular atrophy

The evidence assessment group included carer disutilities for the three most severe health states in a scenario analysis. We used these values and assumed that carers of patients in the two best health states had no HRQoL impact for the carer utilities, increments and decrements approaches as this was equivalent to zero disutilities and avoided the scenario where carer QALYs were maximised where patients spent more time in worse states than in better states. We excluded the family and caregiving effects from the best health states since it is unclear whether the family effect should be included where no caregiving is required. The results are shown in Figure 6. The carer utilities approach leads to more QALYs than patient QALYs, since carers are in better health than patients and the treatment substantially extends survival. The extended survival also leads to the carer QALY loss using the disutilities approach, and the decrements approach. The family and caregiving effect here is small – note that this case study assumes the same family and caregiving effects for the treatment and comparator. The increments approach is positive and small. The committee's preferred base case did not include carer's HRQoL, due to the complexities discussed in Section 4.4.2.

Figure 6: Onasemnogene abeparvovec case study results



4.9.4. *Discussion*

Modelling of carers' HRQoL is needed to estimate the full health effects of interventions and comparators, but there is no consensus as to which method is optimal, and the different methods lead to different results. In our selection of case studies, we demonstrate that where the intervention does not lead to a survival gain, the utility, disutility, increments, decrements, and family and caregiving effects led to the same results. This is unsurprising since they use the same data and apply the same carers' HRQoL benefits of delaying disease progression. The multiplier approach led to a different result since it used different data.

In case studies where the intervention extended patient survival, the utilities approach consistently led to the most carer QALYs and the disutilities approach led to the least. The disutilities approach did not always lead to a QALY loss (for example in the cladribine case study) since it depends on the relative sizes of the disutilities and the life extension. The increments and decrements approaches consistently led to a small impact on carer QALYs (smaller than utilities or disutilities), and the increments approach always led to more carer QALYs than the decrements approach which was sometimes negative. The multiplier approach necessarily led to a consistent carer

QALY gain of 16% of the patient QALY gain. The family and caregiving approach was more variable in terms of the size of the carer QALY gain.

For consistency between appraisals and for transparency, it is important that committees understand how any extension to patient survival impacts carer QALYs in the model. If NICE cannot recommend one preferred modelling approach across appraisals, they may prefer to request that analyses are presented using (some of) the different modelling approaches. This would allow committees to understand the sensitivity of results to these different approaches and allow consistency with other appraisals. The committee should state which approaches should or should not be presented.

The consideration of multiple carers raised further questions for the different approaches, particularly in the case where the number of carers was not consistent throughout the model. For the utilities and disutilities approach it may seem reasonable to assume full health/no decrement where carers aren't included in the model, since the alternative (effectively assuming HRQoL equivalent to 0) favours interventions that require carers – see discussion on distributional consequences in Section 4.11. For the increments and decrements approach there is an additional consideration of how to estimate the increments/decrements for multiple people. The family and caregiving effects and multipliers raised questions about whether these effects should be included for people who are not yet carers, which may lead to concerns about distributional consequences. NICE may wish to provide further clarity for appraisals where the number of carers changes throughout the model (see Section 4.7 for discussion on number of carers).

As demonstrated in the case studies, the different methods imply different effects of bereavement and lead to different carer QALY gains for life-extending treatments (see Section 4.9.1. This is a key concern in the literature and is well discussed in Mott's paper on the "carer QALY trap" (Mott et al. 2023). Other studies point to the relationship between bereavement and HRQoL as a key area for research (Landfeldt and Sandhu 2024, Henry et al. 2024, Powell et al. 2025). The relationship between bereavement and HRQoL is explored further in Section 4.10.

It is, however, important to distinguish between accurately measuring and predicting the full HRQoL effects of an intervention, and the decision rules used to determine whether interventions should be funded. Methods and decision rules should be consistent across appraisals, but the decision rule should not dictate the method: it is feasible that society (and NICE) chooses to fund interventions that have a detrimental impact on carers' QALYs but a positive impact on patients' QALYs. The decision rule of QALY maximisation should not dictate calculation of carers' HRQoL.

NICE may also wish to consider the interaction between modelling carers' HRQoL and the severity modifier. Severity is defined as the future health lost by people living with the condition with standard care in the NHS (National Institute for Health and Care Excellence. 2022). There has been some debate as to whether carers should be classed as "living with the condition", but committees have preferred not to apply the severity modified to carers (National Institute for Health and Care Excellence. 2025b, a). Committees have noted that the severity modifier could only be applied to carers as well as patients if they met the same requirements for the modifier (National Institute for Health and Care Excellence. 2025a). Some research has explored calculating carer QALY shortfall, but noted that judgement is required to determine whether patient and carer QALY shortfall can be combined, whose lifetime to consider, and whether the same thresholds and weights apply as for patient QALY shortfall (McCarthy and Pennington 2024). Committees additionally noted that there is potential conceptual overlap between the societal preference to give more weight to severe conditions and the effects of severe conditions on carers, which could lead to double counting (National Institute for Health and Care Excellence. 2025b). Under a QALY maximisation framework, it would seem inconsistent to recognise that current and new interventions can negatively impact carers' HRQoL and that extending patient survival may detrimentally affect carers' QALYs (using the disutility or decrements approaches) without also recognising the negative carers' HRQoL impact within the QALY shortfall calculations. However, this may require further research into whether the societal preferences that determine the severity modifiers apply equally to patients and carers. A 2025 NICE Listens project found that participants generally supported NICE considering impacts on carers when prioritising treatments, but some people thought this would be impractical and some suggested alleviating carer burden was outside NICE's remit (which would support excluding carers' HRQoL, but contrasts with

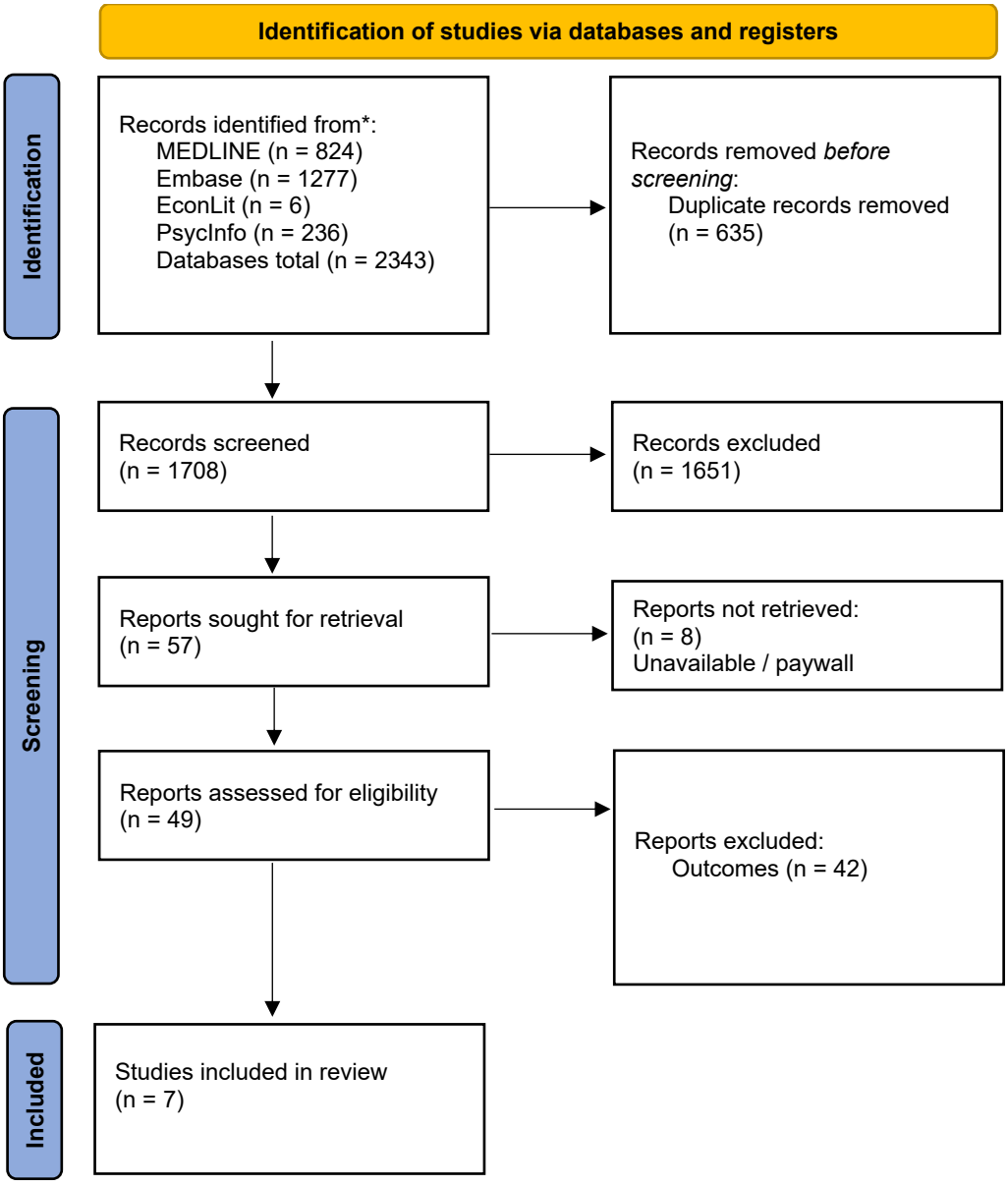
recommendations in Section 1) (NICE Listens. 2025b). The project recommended that NICE should explore whether factors other than QALY shortfall could be considered in determining severity weightings, including impacts on families and carers (NICE Listens. 2025a).

4.10. Bereavement

The SHEER guidelines implicitly recommend including bereavement effects, noting that “bereavement may be an important consideration” but that the lack of established methods for including bereavement and the unpredictability of those effects make is consideration challenging (Henry et al. 2024). Bourke and colleagues note that a greater understanding of the dynamics of bereavement is needed (Bourke et al. 2024). Landfeldt and Sadhu go as far as to propose that including bereavement effects could overcome the carer QALY trap (Landfeldt and Sandhu 2024). Kanters and colleagues note that NICE committee explicitly noted the importance of including the bereavement effect in TA755 but it proved too complex (Kanters et al. 2024). The TLV recognised that bereavement could affect HRQoL but concluded that familial grief should not be included in economic evaluation, since there were too many uncertainties about the duration of grief and number of people affected, and because life-extending treatments delay rather than avoid grief (Tandvards Och Lakemedelsformansverket. 2022). In their draft methodological guidance, the CDA state that where there are differences in patient mortality between interventions, the impact of patient life extension on caregiver QALYs should be transparently reported (Canada's Drug Agency. 2026).

Our systematic review aimed to address this evidence gap and related issues. The PRISMA diagram is shown in Figure 7.

Figure 7: PRISMA diagram



The systematic literature review identified seven papers which reported the HRQoL of people who were bereaved. These studies were:

- Measuring EQ-5D-5L utility values in parents who have experienced perinatal death. (Camacho et al. 2024)
- Quality of life and loneliness post-bereavement: Results from a nationwide survey of bereaved older adults. (Engel et al. 2023)
- Mental Health, Quality of Life, and Work Functioning of Parents of Children Who Have Died from Spinal Muscular Atrophy. (Lavelle et al. 2025)

- How Does Bereavement Affect the Health-Related Quality of Life of Household Members Who Do and Do Not Provide Unpaid Care? Difference-in-Differences Analyses Using the UK Household Longitudinal Survey. (Pennington, Hernandez Alava, and Strong 2025)
- Quality of life and mental health in the bereaved family members of patients with terminal cancer (Song et al. 2012)
- Long-term Effects of Child Death on Parents' Health Related Quality of Life: A Dyadic Analysis. (Song et al. 2010)
- The impact of widowhood on the quality of life of older adults: the mediating role of intergenerational support from children. (Zhu et al. 2024)

A summary of the seven papers is provided in Table 4.

Table 4: Summary of bereavement studies

Study	Sample size	Population	Country	Comparator	HRQoL measure	Finding
Camacho et al 2024	256 bereaved adults	Parents (93% mothers) who have experienced perinatal death.	UK	General population, based on age and sex	EQ-5D-5L	Whole sample utility decrement: -13% Decrement by time since death ranges from -26% (0 – 6 months) to -5% (121+ months)
Engel et al, 2023	575 bereaved adults	Adults aged 65 or older who were bereaved by significant person at least 6 months ago	Australia	Population norms, matched by age. Regression analysis within bereaved sample	AQoL-4D	Mean AQoL-4D = 0.58, versus general population = 0.76. Higher QoL loss in people bereaved by death of partner.
Lavelle et al, 2025	70 bereaved people	Parents whose child had died of spinal muscular atrophy type 1	United States	Population norms, matched by age and gender	SF-6D (EQ-5D for population norms)	Mean SF-6D utility lower where child had died <5 years ago (0.64) than 5-10 years ago (0.70) and >10 years ago (0.73). All

						values below population norms.
Pennington et al, 2025	55,745 total (1,447 bereaved carers, 721 bereaved non-carers)	Bereaved carers and bereaved non-carers	UK	Non-bereaved carers and non-bereaved non-carers	SF-36 converted to SF-6D	Carers HRQoL loss = 0.0283 in year 1 following bereavement, non-carers = 0.0383. No sustained effect beyond 2 years.
Song et al, 2012	501 bereaved, 353 controls	Bereaved family members of patients with terminal cancer	Korea	Participants in national survey, matched using propensity scores	EQ-5D-3L	Bereaved HRQoL = 0.88 vs controls = 0.93.
Song et al, 2010	233 bereaved couples, 229 controls	Couples who experienced death of a child	US	Couples whose children were all alive. Multilevel modelling	HUI-3	Bereavement reduced HRQoL by -0.04. When considering cause of death, only violent death was significant.
Zhu et al, 2024	4,555 total	Widows aged 45 or older	China	Non-widowed adults* from the same study. Regression model.	EQ-5D-3L	Widowhood decrement of -0.08 in regression

*excluding divorced, separated, or never married

4.10.1. Size of HRQoL loss

The seven studies use different populations, different HRQoL instruments and different analytical methods to estimate the impact of bereavement on HRQoL.

All studies found a statistically significant negative impact of bereavement on carers' HRQoL, but the size of the HRQoL loss varied from -0.0283 (Pennington, Hernandez Alava, and Strong 2025) to -0.22 (Lavelle et al. 2025).

Three studies used EQ-5D (Camacho et al. 2024, Song et al. 2012, Zhu et al. 2024), one used SF-6D (Lavelle et al. 2025) and compared this to EQ-5D for the general population, one used SF-36 converted to SF-6D (Pennington, Hernandez Alava, and Strong 2025), one used HUI-3 (Song et al. 2010) and one used AQoL-8D (Engel et al. 2023). The domains of the different measures are shown in Table 5. There is limited overlap between the four measures, and it is not immediately clear how bereavement would affect many of the domains in most of the measures or which measure would optimally measure the effect of bereavement. This highlights the difficulty in comparing the size of bereavement impacts across studies that use different measures, and in estimating a bereavement impact where the control group uses a different measure.

Table 5: Domains of HRQoL measures in bereavement studies

EQ-5D	SF-6D	HUI-3	AQoL-8D
Mobility	Physical functioning	Ambulation	
Self-care			Independent living
Usual activities	Role limitations		
Pain / discomfort	Pain	Pain	Pain
Anxiety / depression	Mental health	Emotion	Mental health
	Social functioning		
	Vitality		
		Vision	
		Hearing	
		Speech	
		Dexterity	
		Cognition	
			Happiness
			Coping
			Relationships
			Self Worth
			Senses

Three studies compared bereaved people's HRQoL to general population norms at the average age (and sex distribution) of the sample (Camacho et al. 2024, Engel et al. 2023, Lavelle et al. 2025). While this provides some indication of the differences between bereaved people's HRQoL and that of the general population, it does not account for other potential confounders that may cause issues of comparability between these populations and lead to biased results. For example, women experiencing perinatal loss may have a higher prevalence of obesity and smoking (Gardosi et al. 2013), and may be more likely to be from socioeconomically deprived areas (Seaton et al. 2012) – all of these factors may also lead to lower HRQoL, and so would confound (and likely overestimate) the relative utility loss of perinatal death.

In the study of bereaved SMA caregivers, the general population HRQoL is measured using a different instrument, further limiting the comparability (Lavelle et al. 2025).

Three studies compared bereaved and non-bereaved populations from the same survey (Song et al. 2010, Zhu et al. 2024, Pennington, Hernandez Alava, and Strong 2025), matching/adjusting for characteristics. One study matched the bereaved population to controls from a separate survey, using propensity scores (Song et al. 2012). These four studies may provide a less biased estimate of the impact of bereavement on HRQoL.

4.10.2. Relationship between deceased and bereaved

Three studies considered parental bereavement (Camacho et al. 2024, Song et al. 2010, Lavelle et al. 2025) but in quite different populations. Song et al (2012) found a much smaller impact of bereavement than the other two studies. The difference in HRQoL impact may be due to the comparison method (see Section 4.10.1) or the time since bereavement, which was an average of 21.1 years in the Song et al (2012) study (see Section4.10.3).

One study focused specifically on widows (Zhu et al. 2024) and three studies considered mixed populations (Engel et al. 2023, Pennington, Hernandez Alava, and Strong 2025, Song et al. 2012). All three of the mixed population studies found that the HRQoL loss was numerically largest (but not statistically significantly different) for bereaved spouses/widows. This finding may be subject to confounding, for example because widows would be typically older than adults whose parents died, and there may be within-household effects (such as socioeconomic status) that only apply to cohabiting dyads.

One study specifically considered whether caregivers and non-caregivers had different bereavement effects and considered that both were similar and their confidence intervals overlapped (Pennington, Hernandez Alava, and Strong 2025). One study of caregivers found that none of the caregiving characteristics were significantly associated with HRQoL (Song et al. 2012). Another study found that being a carer for the deceased was not statistically significantly associated with the size of bereavement effect (Engel et al. 2023).

4.10.3. Time since bereavement

Three studies reported HRQoL scores/losses at different time points since bereavement (Camacho et al. 2024, Lavelle et al. 2025, Pennington, Hernandez

Alava, and Strong 2025). They generally found that the impact of bereavement decreased as time since death increased, suggesting some adaptation or return to baseline HRQoL. However, the duration of this adaptation period differed: one study found no statistically significant effect after two years (Pennington, Hernandez Alava, and Strong 2025), the others found sustained (and in some cases statistically significant) effects up to 10 years later (Camacho et al. 2024, Lavelle et al. 2025). These differences may be due to differences in population and comparison but suggest that the effect of bereavement does diminish over time. This is supported by the Song et al (2012) study that found no statistically significant effects of bereavement at an average of 38.4 years since infant death and 15.6 years since death due to illness (Song et al. 2012).

4.10.4. Cause of death

The cause of death was not reported in three studies (Pennington, Hernandez Alava, and Strong 2025, Zhu et al. 2024, Engel et al. 2023). One study considered death due to terminal cancer (Song et al. 2012).

The causes of death across the three paediatric studies varied: perinatal death (Camacho et al. 2024), death from spinal muscular atrophy (Lavelle et al. 2025) and death from different causes (Song et al. 2010). One study found that bereavement only had a statistically significant impact on HRQoL when children died from violent deaths (Song et al. 2010). This may indicate that bereavement HRQoL impacts are not generalizable across populations with different conditions.

4.10.5. Conclusion

There is evidence that bereavement negatively affects HRQoL, but the size and duration of this effect differ between studies. This may be due to differences in the population, but is also confounded by differences in study designs, comparators, and measures of HRQoL. For adults bereaved by other adults, there appears to be a statistically significant bereavement effect of spousal bereavement, but the size is relatively small, and the duration is unclear. This may apply equally across all populations, regardless of whether the surviving spouse was providing care to the deceased. This suggests that there is no rationale for including a differential

bereavement effect only for conditions that require informal carers. It may be appropriate to include this effect for all interventions where patients die as adults, if the affected relevant other people are assumed to include family members rather than specifically caregivers.

It seems likely that there is a significant and sustained bereavement effect in parents whose children die, but this may return to baseline/reach non-significance in the longer-term. It is less clear whether this is an effect limited to caregivers or more broadly affects parents, since some of the evidence is for sudden deaths where children would not have long-term conditions and require an additional level of caregiving beyond that expected of parents. However, the comparison of children who do not require carers is limited since NICE does not typically evaluate interventions to prevent premature death in children where parents would not take on some caregiving role prior to the death (for example, prevention of violent death would not be a NICE technology appraisal). It may be more relevant to differentiate between the relevance of a bereavement effect for premature death in paediatric populations and in adults, than between caregivers and non-caregivers. However, it is unclear whether the severity modifiers and use of a higher threshold (in HST) already capture any element of avoiding bereavement. It may be important to consider the implications of any bereavement effect in the context of these other decision-making adjustments.

In paediatric conditions, while the inclusion of a bereavement effect has been proposed as a “solution” to the carer QALY trap (Landfeldt and Sandhu 2024), the QALYs gained by delaying bereavement may not be sufficient to entirely offset the carer QALYs lost by extending patient survival where models use the disutility approach. Interventions may theoretically be able to avoid the QALY loss from bereavement altogether by extending patient survival to such an extent that the patient outlives their parent carers, otherwise there is still a bereavement effect to parents from the death of a child, but this QALY loss is smaller due to discounting (since death occurs further into the future with the intervention).

NICE should therefore consider whether the bereavement effect should be explicitly modelled, or whether instead it has implications for the modelling method used. If bereavement was included, it would be necessary to identify evidence or justify

assumptions about who bereavement effects apply to, and the magnitude and duration of bereavement effects to each person. If bereavement is explicitly modelled (for example, whenever a patient dies in an economic model), NICE should consider whether the current evidence is of sufficient quality and transferable between populations with different health conditions. Alternatively, NICE may prefer to consider what the bereavement implies about proposed modelling approaches and decision-making rules.

4.11. Distributional consequences

4.11.1. Literature

Henry and colleagues note that the inclusion of distributional consequences related to spillovers (potential for inclusion of family and carers' HRQoL to impact the equity of resource allocation) has sparked debate and recognize the challenges in systematically exploring distributional consequences within individual economic evaluations. However, they recommend that distributional consequences are considered explicitly (Henry et al. 2024). They cite examples that including more caregivers in some patient health conditions could result in interventions for those conditions being funded over interventions which primarily provide health benefits only to patients.

Kanters and colleagues also acknowledge that the inclusion of carers' HRQoL in HTAs may have distributional impacts, but further note that excluding carers' HRQoL will also have distributional impacts (Kanters et al. 2024).

Leech and colleagues also highlight potential concerns with distributional effects, discussing that where spillovers are selectively included for some health conditions that have substantial family involvement (for example paediatric conditions) and not for conditions where diminished family ties are common (for example substance misuse), interventions may appear artificially cost-effective. They note that care may be shifted to formal social care services where the costs and effects may not be quantified in economic evaluation (Leech et al. 2023).

The TLV noted that there are ethical considerations with including carers' HRQoL, since it may potentially discriminate against people with few or no family members, but concluded that they were not able to consider this aspect (Tandvards Och Lakemedelsformansverket. 2022).

The CDA notes that not all individuals providing care may identify as "caregivers", which may affect the extent to which HRQoL measures capture caregiving impacts. They further note that patient and caregiver preferences may not always align (citing an example of a hypothetical intervention that improves patient's symptoms but substantially increases the time required by caregivers to administer treatment) and that the treatments primarily aim to benefit patients, which may conflict with decision maker priorities (Canada's Drug Agency. 2026).

4.11.2. NICE appraisals

None of the case studies of NICE appraisals specifically discussed distributional consequences of including or excluding carers' HRQoL.

4.11.3. Discussion

The distributional consequences of including carers' HRQoL has only been considered briefly in the literature, and seemingly not considered in NICE appraisals. However, this is an important area of consideration, particularly within the context of equity and health inequalities.

There is potential asymmetry in including carers' HRQoL impacts but excluding the costs of formal care provided by social services, local authorities or self-funded by patients and their families. This may mean that we include carers' HRQoL impacts for specific population groups which are differentiated by wealth. There are further considerations as to whether the provision of formal care differs by geographical region (different local authorities) and for different health conditions (for example greater availability of formal care for older people than for paediatric populations).

NICE should consider further research into this area, to ensure that the inclusion of unpaid carers' HRQoL is not inadvertently affecting some populations more than others, or worsening health inequalities. This would require further research into the provision of formal care and requirement for informal care across health conditions,

locality, and sociodemographic groups, noting that the health inequalities impact for carers may not be identical to those for the patients they care for.

5. RECOMMENDATIONS

Based on the available evidence, NICE could make the following recommendations:

- Companies should provide evidence to demonstrate that carers' HRQoL is particularly relevant (greater than average across all health conditions) for the health condition and they should provide an explanation of how the intervention affects carers' HRQoL
- The EQ-5D is the preferred measurement method to measure carers' HRQoL. To make a case that EQ-5D is not appropriate, evidence should be provided to show that EQ-5D is missing key dimensions of health and performs poorly on tests of construct validity and responsiveness in the specific caregiving population.
- The same hierarchy of evidence for patients' HRQoL should apply to carers' HRQoL. The literature suggests a need for it and papers broadly seem agreed on this.
- If multiple carers are included, this needs to be supported by empirical evidence of an HRQoL impact beyond the primary carer, and empirical evidence is also required to inform relative effect sizes. Effect sizes for multiple people should not be assumed to the same for all carers. Scenario analysis should be presented assuming only one carer.
- Do not include HRQoL bereavement effects for older people caring for their spouse/partner, unless they are also routinely included for populations where patients do not have caregivers.
- It is appropriate to include a short-term effect of bereavement on the HRQoL of bereaved parents, but this effect should reduce over time. None of the currently used modelling methods adequately reflect this (but could potentially be adapted to relax the strong assumptions they currently make, to include bereavement effects):
    - The absolute utility and multiplier approaches assume bereaved parents' HRQoL is equivalent to zero. Evidence suggests bereaved parents' HRQoL is above zero.
    - The disutility and decrements approaches assume bereaved parents' HRQoL immediately reverts to general population. Evidence suggests that there is an immediate impact.

    - The increments approach assumes bereaved parents' HRQoL is identical to that of parents caring for children in the worst health state and remains at that level indefinitely. Evidence suggests the bereavement effect is not sustained forever.
- If a preferred approach to modelling carers' HRQoL cannot be agreed, analyses should be presented showing the impact of different approaches.
- Cost effectiveness analysis should seek to accurately estimate and reflect the differential impact of health interventions on carers' HRQoL.

NICE should undertake further research to be able to make recommendations regarding:

- Estimation of average carers' HRQoL burden across NHS-funded interventions, to understand the opportunity cost / displaced carers' HRQoL. This will help determine whether specific conditions have a particularly large impact on carers' HRQoL. This could include analysis of the average number of unpaid carers in the UK population, in combination with published estimates of carers' HRQoL.
- Guidance for decision-making in situations where the implications of including carers' HRQoL are challenging.
- The distributional consequences and importantly, potential equity and health inequalities impacts of including carers' HRQoL.
- Whether decision rules differ for paediatric and adult populations, and whether the decision rule captures the effect of bereavement on parent's HRQoL
- The interaction between the severity modifier and carers' HRQoL, whether the severity modifiers implicitly or explicitly capture carers' QALY shortfall, and the evidence to determine whether the shortfall calculation should include carers' QALY shortfall.

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APPENDIX – Search Strategy

Ovid MEDLINE(R) ALL <1946 to October 03, 2025>

1 "Quality of Life"/ 311643
2 quality of life.ti,kf. 141590
3 (sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kf. 34229
4 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6 or sf-6d).ti,ab,kf. 3890
5 (sf8 or sf 8 or sf eight or sfeight or short form 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kf. 845
6 (sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kf. 8946
7 (sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kf. 44
8 (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kf. 488
9 (hql or hqol or h qol or hrqol or hr qol).ti,ab,kf. 29265
10 (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kf. 19004
11 disutilit*.ti,ab,kf. 748
12 (hui or hui1 or hui2 or hui3).ti,ab,kf. 2277
13 (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kf. 28225
14 (15D or AQoL21 or AQoL).ti,ab,kf. 2468
15 or/1-14 398661
16 exp Bereavement/ 16441
17 (bereave* or grief or griev* or widow*).ti,kf. 12590
18 ((loss or losing or death*) adj2 ("loved one*" or parent* or mother* or father* or grandparent* or grandmother* or grandfather* or sibling* or brother* or sister* or child or children or daughter* or son* or spouse* or wife or wives or husband* or partner*)).ti,ab. 15850
19 or/16-18 35245
20 15 and 19 823