

EUR Research Information Portal

Including carer health-related quality of life in NICE health technology assessments in the United Kingdom

Published in:

Health Economics, Policy and Law

Publication status and date:

E-pub ahead of print: 08/10/2024

DOI (link to publisher):

[10.1017/S1744133124000124](https://doi.org/10.1017/S1744133124000124)

Document Version

Publisher's PDF, also known as Version of record

Document License/Available under:

CC BY

Citation for the published version (APA):

Kanters, T. A., van Hezik-Wester, V., Boateng, A., Cranmer, H., Kvamme, I., Santi, I., Al-Janabi, H., & van Exel, J. (2024). Including carer health-related quality of life in NICE health technology assessments in the United Kingdom. *Health Economics, Policy and Law*. Advance online publication. <https://doi.org/10.1017/S1744133124000124>

[Link to publication on the EUR Research Information Portal](#)

Terms and Conditions of Use

Except as permitted by the applicable copyright law, you may not reproduce or make this material available to any third party without the prior written permission from the copyright holder(s). Copyright law allows the following uses of this material without prior permission:

- you may download, save and print a copy of this material for your personal use only;
- you may share the EUR portal link to this material.

In case the material is published with an open access license (e.g. a Creative Commons (CC) license), other uses may be allowed. Please check the terms and conditions of the specific license.

Take-down policy

If you believe that this material infringes your copyright and/or any other intellectual property rights, you may request its removal by contacting us at the following email address: openaccess.library@eur.nl. Please provide us with all the relevant information, including the reasons why you believe any of your rights have been infringed. In case of a legitimate complaint, we will make the material inaccessible and/or remove it from the website.

ARTICLE

Including carer health-related quality of life in NICE health technology assessments in the United Kingdom

Tim A. Kanters^{1,2} , Valérie van Hezik-Wester^{1,2}, Andy Boateng³, Holly Cranmer³, Ingelin Kvamme^{1,2}, Irene Santi^{1,2}, Hareth Al-Janabi⁴ and Job van Exel²

¹Institute for Medical Technology Assessment, Erasmus University Rotterdam, Rotterdam, Netherlands, ²Erasmus School for Health Policy & Management, Erasmus University Rotterdam, Rotterdam, Netherlands, ³Takeda UK Ltd, London, UK and ⁴Institute of Applied Health Research, University of Birmingham, Birmingham, UK

Corresponding author: Tim A. Kanters; Email: kanters@imta.eur.nl

(Received 30 January 2024; revised 10 May 2024; accepted 25 May 2024)

Abstract

The impact of health technologies may extend beyond the patient and affect the health of people in their network, like their informal carers. The National Institute for Health and Care Excellence (NICE) methods guide explicitly allows the inclusion of health-related quality of life (HRQoL) effects on carers in economic evaluations when these effects are substantial, but the proportion of NICE appraisals that includes carer HRQoL remains small. This paper discusses when inclusion of carer HRQoL is justified, how inclusion can be substantiated, and how carer HRQoL can be measured and included in health economic models. Inclusion of HRQoL in economic evaluations can best be substantiated by data collected in (carers for) patients eligible for receiving the intervention. To facilitate combining patient and carer utilities on the benefit side of economic evaluations, using EQ-5D to measure impacts on carers seems the most successful strategy in the UK context. Alternatives to primary data collection of EQ-5D include vignette studies, using existing values, and mapping algorithms. Carer HRQoL was most often incorporated in economic models in NICE appraisals by employing (dis)utilities as a function of the patient's health state or disease severity. For consistency and comparability, economic evaluations including carer HRQoL should present analyses with and without carer HRQoL.

Keywords: carer health-related quality of life; carer HRQoL; informal care; spillover

1. Introduction

While health technologies aim to improve patients' health, it is increasingly acknowledged that their impact may extend beyond the patient. These effects are also known as spillover effects (Al-Janabi *et al.*, 2016a; Mendoza-Jiménez *et al.*, 2024). Patients' health may, for instance, affect the health of people in their network indirectly through the burden of providing informal care – the 'caregiving effect' – but also directly through anxiety or grief from the health prospects of a loved one – the 'family effect' (Bobinac *et al.*, 2011). In addition, the death of a patient may affect the health and well-being of their loved ones directly through bereavement (Stroebe *et al.*, 2007).

In the UK, more than 9.3 million people (14.2 per cent of the population) together provided approximately 9.5 billion hours of informal care in 2016, which averages at 19.7 h per week (Pena-Longobardo and Oliva-Moreno, 2021). More than 70 per cent of these carers reported feeling tired and 60 per cent reported feeling stressed due to providing care (Adult Social Care Statistics Team, 2022). The burden of caregiving is associated with the health status of patients (e.g. Van Exel *et al.*, 2004; Chiao *et al.*, 2015). Interventions that improve patient health can

© The Author(s), 2024. Published by Cambridge University Press. This is an Open Access article, distributed under the terms of the Creative Commons Attribution licence (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted re-use, distribution and reproduction, provided the original article is properly cited.

also reduce the volume and gravity of informal care patients require and, therefore, reduce the burden for carers. As such, interventions aimed at improving patient health can also impact patients' carers. Considering the various impacts of patient health not only on informal carers, but also on others, taking spillover effects into account in economic evaluations of new health technologies and subsequent funding decisions seems relevant from both a societal and health-care system perspective (Brouwer, 2019; Henry *et al.*, 2024). After all, if the aim of a healthcare system is to maximise population health from a given budget, this should also assess the health of those experiencing health effects as a direct or indirect consequence of changes in patients' health. In this paper, the focus is on including the health effects for informal carers in economic evaluations.

In a systematic literature review, Krol *et al.* (2015) found that including informal care in cost-effectiveness analyses can influence the incremental cost-effectiveness ratio (ICER) significantly (Krol *et al.*, 2015). A more recent systematic review of UK cost-utility analyses (CUAs) conducted between 1999 and 2021 showed that ICERs were mostly lower when spillover effects on carers were included (Scope *et al.*, 2022). This review further showed that the methods used to include carer health-related quality of life (carer HRQoL) in economic evaluations varied considerably and argued for more consistency in methodology. A systematic literature review showed that only a few CUAs included family spillover effects, and also showed that applied methodologies varied substantially between included studies (Lamsal *et al.*, 2024). Again, the authors concluded that more guidance is needed on how to include spillover effects in economic evaluations.

Although including carer HRQoL effects in economic evaluations was mentioned by the National Institute for Health and Care Excellence (NICE) in its methods guide for health technology evaluation in 2013 (National Institute for Health and Care Excellence, 2013), it was not specified how to include carer HRQoL effects. To inform revisions of the NICE guidelines, various Task & Finish Groups were established in 2020 in different methodological areas (Dawoud *et al.*, 2022). One such group, the Health-Related Quality of Life Task & Finish (HRQoL T&F) Group, provided input on the inclusion of carer HRQoL, and proposed a set of minimum evidence standards (MES) for considering carer HRQoL in appraisals (National Institute for Health and Care Excellence, 2020). Their MES summarise the type of evidence that might be useful, such as published carer burden studies, and suggest that carer HRQoL should be measured using EQ-5D for consistency with patient HRQoL data and comparability among appraisals. Additionally, the MES suggest that carer HRQoL effects should only be considered for the 'primary carer' and that family and bereavement effects should not be included in economic models.

These MES were consulted for the most recent NICE methods guide published in 2022 (National Institute for Health and Care Excellence, 2022), but were not integrated in the guidelines because information was considered still incomplete (Dawoud *et al.*, 2022). The methods guide states that 'all relevant health effects, whether for patients, or, when relevant, other people (mainly carers)' should be included. The methods guide further states that 'evidence should be provided to show that the condition is associated with a substantial effect on carer's health-related quality of life and how the technology affects carers', but without specifying what is considered 'substantial'. This could, e.g. refer to a certain minimum absolute effect on carers, but also to a relative effect on carers compared to the effect of the intervention on patients. The methods guide also does not provide guidance on how effects on carers (or others) should be included. Considering the relevance of including carer HRQoL in economic evaluations combined with the lack of methodological guidance for when and how to do so, this paper addresses two questions by examining past appraisals and available literature on the topic. First, when is inclusion of carer HRQoL justified and how could inclusion be substantiated? Second, how should carer HRQoL be measured and included in health economic models? The UK makes an interesting case study for three reasons. First, while NICE guidelines allow for the inclusion of carer HRQoL in economic evaluations, carer HRQoL is included in only a small proportion of appraisals (Scope *et al.*, 2022). It can be helpful for future submissions to investigate these cases and

determine which factors can enhance the chances for acceptance of inclusion of carer HRQoL. Second, previous appraisals are readily available on NICE's website in English language. Third, NICE's eminent position in the health technology assessment (HTA) landscape results in their methodologies and assessments having a global impact, both through NICE and NICE Decision Support Unit guidance, and because global health economic models are frequently designed for implementation in the UK and country adaptations consequently build on modelling choices made for the UK.

2. To what extent has carer HRQoL been included in recent appraisals?

To answer the two research questions, it is important to know to what extent carer HRQoL has been used in prior appraisals in the UK. In this respect, prior to the 2022 publication of the NICE methods guide, Pennington (2020) reviewed NICE appraisals from NICE's website inception in 2000 to January 2019 for the inclusion of carer HRQoL in economic evaluations (Pennington, 2020). For this purpose, Pennington first searched the final appraisal determinations (FADs for all technology appraisals [TAs]) and final evaluation documents (FEDs for all highly specialised technologies [HSTs]) for the terms 'carer' and 'caregiver'. Subsequently, those FADs and FEDs that included carer or caregiver were screened for eligibility (step 2) and final inclusion of carer HRQoL in the CUA (step 3). Table 1 summarises the results of Pennington's review and also provides an update of the same review until March 2022, performed for this current study and using the same methodology. A PRISMA flow diagram of the updated review is presented in Figure 1. Pennington showed that 3 per cent (12/414) of TAs and 50 per cent (4/8) of HST evaluations included carer HRQoL (as submitted by the company). Since then, the proportion of appraisals that included carer HRQoL has increased (6 per cent [13/226] of TAs and 78 per cent [7/9] of HST evaluations). Also, carer HRQoL was more often included in base-case analyses rather than scenario analyses, indicating a growing role of carer HRQoL in NICE appraisals. Similar to the Pennington review, the appraisals that include carer HRQoL predominantly concern orphan indications, paediatric populations, and/or neurological conditions. Since the Pennington review, when all HRQoL estimates originated from published sources, 35 per cent of submissions used *de novo* estimates (either from EQ-5D or vignette studies). Carer HRQoL was most commonly included in economic models by linking carer disutilities to patient health states.

3. When should carer HRQoL be included in economic evaluations?

Including carer HRQoL in economic evaluations was found to be supported by public preferences in the UK, although the public gave less weight to HRQoL effects in carers than in patients (Al-Janabi *et al.*, 2022). Inclusion can be justified on several grounds, regardless of the perspective of the economic evaluation (e.g. healthcare or societal). From an efficiency argument, all health effects of interventions are important, including effects on others than the patient (Brouwer, 2019). In addition, there is an equity argument for including these broader health effects, as carers are more frequently female and often have lower socio-economic status (Pena-Longobardo and Oliva-Moreno, 2021). Moreover, as society expects people in the network of the patient to contribute to their care, the impact on the health of carers and any spillover effects should be monitored and considered in HTAs, particularly if these effects are substantial. This may be especially relevant in situations where patients require higher levels of assistance, e.g. when a large proportion of patients receives informal care, caregiving time is substantial or multiple carers are involved. Therefore, the relevance to consider carer HRQoL might be dependent on the therapeutic indication or the context in which care is required, and interventions can impact carer HRQoL through various mechanisms (Al-Janabi *et al.*, 2019). For instance, providing care to your elderly partner might be considered a normal part of life, whereas

Table 1. Carer HRQoL in NICE appraisals

	Pennington (2020)		Update (2022)		Total	
Review period	2000 ^a –Jan 2019		Feb 2019–March 2022		2000 ^a –March 2022	
	Number	Proportion ^b	Number	Proportion ^b	Number	Proportion ^b
Number of appraisals	16		20		36	
• Technology appraisals	12/412	3%	13/226	6%	25/638	4%
• Highly specialised technologies	4/8	50%	7/9	78%	11/17	65%
	Number	Proportion ^c	Number	Proportion ^c	Number	Proportion ^{c,d}
Patient population						
Adult only	6	38%	10	50%	16	44%
Paediatric or paediatric + adult	10	62%	10	50%	20	56%
Position in company submission						
• Base-case analyses	11	69%	18	90%	29	81%
• Scenario analysis	5	31%	2	10%	7	19%
Source of HRQoL estimates						
• <i>De novo</i> EQ-5D	0	0%	3	15%	3	8%
• <i>De novo</i> vignette study	0	0%	4	20%	4	11%
• Values from published sources	16	100%	13	65%	29	81%
Use of EQ-5D based values (5L or 3L)						
• Yes, direct application of published or measured values	5	31%	9	45%	14	39%
• Yes, new values derived from measured EQ-5D values based on assumptions or mapping	1	6%	6	30%	7	19%
• No	8	50%	4	20%	12	33%
• Not reported	2	13%	1	5%	3	8%

Number of carers						
• 1 carer	13	81%	8	40%	21	58%
• >1 carer	2	13%	9	45%	11	31%
• Not reported	1	6%	3	15%	4	11%
Modelling technique						
• (Dis)utilities as a function of patient's health state or disease severity	12	75%	13	65%	25	69%
• (Dis)utilities as a function of patient's treatment	3	19%	3	15%	6	17%
• Disutility as a function of an adverse event	0	0%	2	10%	2	6%
• QALY loss linked to patient's death	1	6%	0	0%	1	3%
• Combination of techniques above	0	0%	2	10%	2	6%

HRQoL, health-related quality of life; QALY, quality-adjusted life years.

^aSince inception of NICE website.

^bProportion of total appraisals.

^cProportion of appraisals that included carer HRQoL.

^dSome proportions do not add to 100 per cent due to rounding.

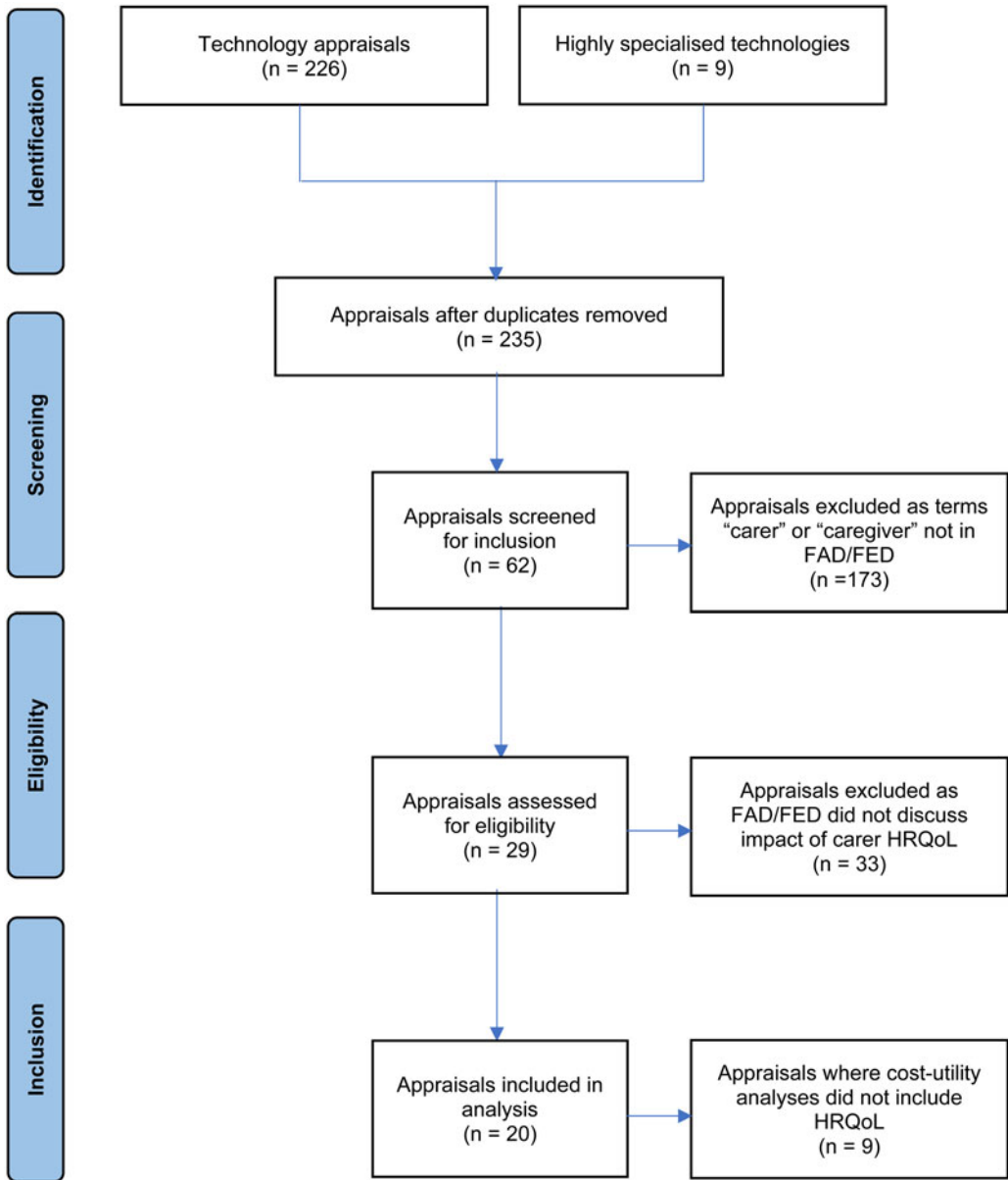


Figure 1. PRISMA flow diagram.

providing care to your seriously or chronically ill child is not. On the other hand, considering carer HRQoL might be less relevant when there is no plausible treatment effect on carers, either directly or indirectly (i.e. when there is no clear relation between patient health and carer HRQoL) or in populations with limited social networks, but these situations are likely to be the exception rather than the rule. Hence, while theoretically the consideration of carer utilities is always justified, and preferred for reasons of efficiency, equity, and comparability, the relevance of its inclusion may be limited if the treatment effect on carer HRQoL is expected to be negligible. The relevance of including carer HRQoL should therefore be weighted against the burden of collecting data in carers.

When values or assumptions are uncertain or of disputable quality, NICE might question the appropriateness of including carer HRQoL. In one instance (TA738), the Evidence Review Group (ERG) expressed doubts on the clinical plausibility of the values and the poor reporting of the methods. In such cases, values from high-quality *de novo* studies and literature (including previous appraisals) can be argued to best substantiate the clinical plausibility of the proposed approach. Focus should be on the plausible causal link between the intervention and carer HRQoL, and on the plausibility of the magnitude of the carer impact relative to the patient impact.

The distinction between the caregiving effect (i.e. the indirect effect of providing informal care on carer HRQoL) and the family effect (i.e. the direct effect of having an ill family member on carer HRQoL) is important to consider when determining the effects on carers (Bobinac *et al.*, 2010). The HRQoL T&F Group proposed not to consider family effect in economic evaluations since evidence in this area is scarce. The NICE methods guide does not specifically exclude non-carers from the evaluation, although it mentions that ‘other people’ affected by the intervention are mainly carers. However, excluding family effects could mean that a real and substantial effect is not accounted for in appraisals. Moreover, previous studies showed that disentangling the carer and family effects is complicated (Bobinac *et al.*, 2010; Hoefman *et al.*, 2013), making guidance to exclude family effects – which may also occur in informal carers, next to the caregiving effect – challenging to implement in practice.

4. How should carer HRQoL be measured and included in health economic models?

4.1 Prospective measurement using existing measures

There is an abundance of instruments available for measuring the impact of providing care on carers’ lives (Deeken *et al.*, 2003; Hoefman *et al.*, 2013; Mosquera *et al.*, 2016; McLoughlin *et al.*, 2020). These include disease-specific and generic measures of carer outcomes, and also generic measures of (non-carer specific) outcomes. Disease-specific, like the C-DEMqOL for carers of people with dementia (Brown *et al.*, 2019), CAREqOL-MS for carers of people with multiple sclerosis (Benito-León *et al.*, 2011), and carer-specific instruments, like the caregiver strain index (CSI) (Robinson, 1983) and Self-Rated Burden (SRB) scale (Van Exel *et al.*, 2004), may have the advantage of being more sensitive to context-specific effects but complicate the comparison of effects across contexts and the incorporation of effects in economic evaluations (Hoefman *et al.*, 2013). Generic measures of HRQoL, like the health utilities index (Horsman *et al.*, 2003) or the EQ-5D (Brooks, 1996), which is NICE’s preferred measure for patient HRQoL (National Institute for Health and Care Excellence, 2022), facilitate the aggregation of carer and patient effects and inclusion of these effects in an ICER. The use of the same outcome measure for patients and carers has also been advocated by the Spillovers in Health Economic Evaluation and Research Task Force (Henry *et al.*, 2024). However, such generic measures have been argued to lack sensitivity to capture effects relevant to carers, although empirical evidence is mixed (e.g. Bhadhuri *et al.*, 2017; Reed *et al.*, 2017; McLoughlin *et al.*, 2020; Valcárcel-Nazco *et al.*, 2022). A recent qualitative study showed that although the error rate of EQ-5D is low, carers prefer a care-related QoL measure (McLoughlin *et al.*, 2023). These broader care-related QoL measures, such as the ASCOT-Carer, CarerQoL, or Carer Experience Scale (Brouwer *et al.*, 2006; Al-Janabi *et al.*, 2008; Rand *et al.*, 2015), are argued to be more sensitive for use in carers. These instruments generate preference-weighted scores (in contrast to carer-specific instruments like CSI and SRB), allowing for comparisons of carer experiences across diseases and caregiving contexts. However, these measures do not generate utility values in terms of quality-adjusted life years, as measured from patient HRQoL instruments, necessary for economic evaluations. Lacking utility values hampers aggregation with patient health effects and their use in economic evaluations of patient interventions. Exchange rates between care-related scores and EQ-5D utilities have been estimated in an exploratory UK study, but these are still of limited use due to methodological issues (Dhanji *et al.*, 2021). Alternatively, generic measures of well-

being could be used for measuring the effects on carers and family members. For example, a recent study demonstrated the construct validity of the EQ Health and Well-being in a sample of informal carers (Kuharic *et al.*, 2024). Although these are conceptually the broadest measures, including them in economic evaluations would only work if effects in patients are also measured in well-being terms, which currently is not common practice. Therefore, to facilitate combining patient and carer utility values on the benefit side of economic evaluations, the use of EQ-5D for measuring carer HRQoL appears to be the most successful strategy in the UK context. This is substantiated with the conclusions of McLoughlin *et al.*, stating that EQ-5D(-5L) is a valid outcome measure when the focus of economic evaluations is on health maximisation (McLoughlin *et al.*, 2020). Likewise, Bhadhuri *et al.* (2017) concluded that EQ-5D is a valid measure for incorporating carer HRQoL impacts in economic evaluations (Bhadhuri *et al.*, 2017).

Pennington's review of NICE appraisals (Pennington, 2020) and its update showed that most evaluations that included carer HRQoL used EQ-5D to measure carer HRQoL or derived estimates based on mapping of, or assumptions on, EQ-5D values (Table 1). Use of EQ-5D is also in line with HRQoL T&F Group's proposed MES (National Institute for Health and Care Excellence, 2020).

Primary data collection is preferred to obtain EQ-5D estimates in carers because this ensures that the carer population corresponds to the indication and intervention of interest. It also enables necessary subgroups (e.g. patients' health states) to be studied, although stratification for subgroups may require larger sample sizes. However, depending on the indication and the intervention, primary data collection may be difficult. Carers are not always easy to identify or reach and completing a survey might be burdensome for them next to the caregiving tasks and their other responsibilities (Whitebird *et al.*, 2011; Horrell *et al.*, 2015).

In recent cases, concerns for including carer HRQoL in the base-case analysis by NICE has often focused on the (perceived) low quality and uncertainty of the evidence, including the clinical plausibility of (*de novo*) values (e.g. TA748, TA754), the magnitude of effects (e.g. TA738, TA753, TA754), number of caregivers (e.g. TA753), and proportion of patients receiving care (e.g. TA748), leading to rejection of inclusion of carer HRQoL as modelled in the base-case analysis. This highlights the importance of robust studies.

4.2 Measurement when EQ-5D data cannot be collected

There are some alternatives to collecting primary EQ-5D data in carers. One frequently used option is a vignette study, in which (hypothetical) health state descriptions or scenarios are used to obtain HRQoL estimates (Matza *et al.*, 2021). The descriptions are informed by expert input (e.g. patients, carers, clinicians) and valued in a preference elicitation task. A disadvantage of vignettes is that they are not able to fully reflect patient experiences in each state, and therefore are inferior to primary EQ-5D data in eliciting patient HRQoL for NICE submissions (Brazier and Rowen, 2011); the same applies for carer HRQoL estimates. Nonetheless, a vignette study is convenient, as it does not require direct measurement of carer-level data. This may particularly be an advantage in subgroups where data collection is challenging, e.g. for practical or ethical reasons (e.g. rarely occurring health states, paediatric indications, end-of-life health states) (Matza *et al.*, 2021). Also, vignettes allow assessing the impact of specific attributes on carer HRQoL. However, the comparability and transferability of estimates obtained using vignettes is limited, as the descriptions are treatment and indication specific. In 4 out of 20 of NICE appraisals that included carer HRQoL, estimates were derived from vignette studies (Table 1). In three of these appraisals, the values used in the health economic models were criticised by the committee and in two appraisals the inclusion of carer HRQoL was transferred to the scenario analyses in response to committee's critique.

Another alternative to primary data collection is using estimates from the literature or previous appraisals, albeit HRQoL data might be scarcely available, especially by health state. Using

estimates that have been accepted by NICE in previous appraisals may also be accepted in later appraisals for the same indication, depending on the comparability of the health states and intervention. In the absence of indication-specific data, models used for NICE submissions have been populated using carer HRQoL values from other indications. In one NICE appraisal (HST16), estimates from another indication have been accepted, while in another NICE appraisal (TA748), estimates from another indication were deemed not transferable. In such cases, it is crucial to corroborate the similarities between indications. When using international data, researchers should take caution of differences between countries (e.g. cultural, healthcare system, valuation of health states) (Pennington *et al.*, 2022).

Finally, carer HRQoL estimates could be obtained by mapping other instruments onto EQ-5D, as it is often done for HTA submissions in situations where patient EQ-5D data are unavailable (Longworth and Rowen, 2013). However, the development of mapping algorithms has proven to be complex and available evidence largely concerns mapping to patient EQ-5D values. Mapping requires conceptual overlap between instruments, which complicates mapping carer-specific instruments, focusing on care-related quality of life, onto EQ-5D, focusing on HRQoL. Gheorghe *et al.* (2019) succeeded in mapping patients' EQ-5D to caregiving hours, but their attempt to map to the carer-specific CarerQoL instrument did not lead to satisfying results (Gheorghe *et al.*, 2019). Dixon *et al.* (2006) also found explanatory power for relationships between patient and carer utilities to be low (Dixon *et al.*, 2006). In addition, Al-Janabi *et al.* (2017) tried to predict carer EQ-5D using patient EQ-5D in a sample of 497 carer-patient dyads with long-term disabilities stemming from meningitis, which provided some evidence for relations between patient and carer HRQoL on an aggregate level, but did not allow for predictions on an individual level (Al-Janabi *et al.*, 2017). Given the lack of empirical evidence, further research into estimating carer HRQoL impacts based on commonly measured patient outcomes is recommended.

Table 2 provides an overview of advantages and disadvantages of different methods to obtain carer HRQoL estimates.

4.3 Number of carers

Next to carer utility values, data are needed on the proportion of patients receiving informal care and the number of carers providing care per patient. The HRQoL T&F Group proposed that only a single carer should be considered, particularly because evidence on the primary carer is likely to be more robust. Nonetheless, 45 per cent of recent NICE appraisals included more than one caregiver (Table 1), which NICE accepted in several cases. Ideally, the effects for the entire network of the patient are considered, as all health effects in the population should be equally important when maximising health. However, the identification of a patient's informal care network can

Table 2. Advantages and disadvantages of methods to obtain carer HRQoL estimates

	Advantages	Disadvantages
Prospective measurement using existing measures	<ul style="list-style-type: none"> • In line with proposed MES (EQ-5D) • Population corresponds to indication/intervention • Enables studying subgroups 	<ul style="list-style-type: none"> • Data collection issues (identification of carers, low response)
Vignette study	<ul style="list-style-type: none"> • Convenient • Possible for 'complex' patient populations • Possible to assess distinct features 	<ul style="list-style-type: none"> • Does not fully reflect patient experiences in each health state • Comparability issues
Literature/previous appraisal	<ul style="list-style-type: none"> • Convenient, especially when approved in prior submissions 	<ul style="list-style-type: none"> • Availability of data • Transferability issues
Mapping	<ul style="list-style-type: none"> • Convenient 	<ul style="list-style-type: none"> • Availability of valid mapping functions

be complicated, because of the subjective nature of defining informal care (e.g. some carers might not identify themselves as such) and the diversity of care relationships (e.g. some carers might remain out of scope of researchers). The size and composition of a patient's network may depend on the condition and the patient's health state; particularly in paediatric and elderly care, the network might be larger than in other conditions. When including multiple carers, it is important to acknowledge that not all carers may experience similar effects on providing care (Broese van Groenou *et al.*, 2013). In particular, the size of health effects is likely to decline with increasing social distance from the patient. This has been shown in a case study on meningitis (Al-Janabi *et al.*, 2016b), but this distance-decline can be expected more generally. Extrapolating data collected in the primary carer to the caregiving network, e.g. by multiplying the obtained disutility value by the number of carers involved, is likely to overestimate the total carer HRQoL impact. Preferably, HRQoL estimates that reflect the relationship between patient and carer would be used, but this would require a higher level of granularity in the data.

4.4 Carer HRQoL in health economic models

Economic models are generally developed to represent the disease and patient HRQoL effects as accurately as possible, and carer HRQoL effects are added to this structure, if at all. Several options exist for including carer HRQoL in existing models, dependent on model structure. The review of NICE appraisals showed that carer HRQoL was previously included in economic models in different ways (Table 1): (dis)utilities as a function of the patient's health state or disease severity (25/36), (dis)utilities as a function of the patient's treatment (6/36), and (dis)utilities related to an adverse event (2/36). Pennington *et al.* (2022) showed that both utilities and disutilities were used in different countries, and did not consider either approach superior (Pennington *et al.*, 2022).

When carer HRQoL estimates are appended to existing health states, carer HRQoL estimates per health state are required. However, more mechanisms might play a role in this relationship and might not be represented in the model health states, including management of care and timing or location of services (Al-Janabi *et al.*, 2019). Also, if it can be argued that the intervention affects carer HRQoL both directly (e.g. through factors such as location, timing, information provision, and involvement of family) and indirectly (i.e. through changes in patient health), treatment-dependent carer HRQoL data might be applied to model health states. The underlying mechanisms at play are ideally corroborated by data, so that the treatment's impact on carer HRQoL can be correctly integrated in economic models.

Finally, carer utility values, the proportion of patients receiving informal care, and the number of carers involved are all surrounded with uncertainty. This uncertainty should be included in the model like other parameters (Henry *et al.*, 2024).

5. Consistency and comparability of outcomes

To maintain comparability of cost-effectiveness outcomes across diseases, interventions, and over time, it is important that the rationale and method for including carer HRQoL in economic evaluations is applied consistently. Therefore, future economic evaluations should preferably present analyses with and without carer HRQoL (Pennington *et al.*, 2022). In this way, evidence is provided on the impact of the intervention on carers while comparability is maintained with evaluations that exclude carer HRQoL, either conducted in the past or for which carer HRQoL is not relevant, and with common cost-effectiveness thresholds.

6. Directions for future research

Attention towards carer HRQoL is growing, but there still are several unsolved issues. Important issues concern substantiating when inclusion of carer HRQoL is relevant and capturing elements

that affect carer HRQoL adequately and comprehensively. Disease, interventions and patient group-specific elements play a role here.

Although the utilitarian approach in cost-effectiveness studies provides a systematic framework for evaluating new interventions, maximising health benefits under a budget constraint may not fully capture societal and individual preferences or the subjective experiences of patients and their carers related to the disease, the intervention, and their impacts. There is a difference in what is relevant for carers (e.g. the patient's and their own well-being, or their employment, career prospects, and financial situation) and for decision makers (i.e. HRQoL in the healthcare perspective). As the EQ-5D focuses on HRQoL, such other aspects of value to carers may not be adequately captured. The use of other instruments can be particularly valuable if these instruments can be used to produce utility values. This requires additional research into how such utilities can be combined with utilities derived from EQ-5D. Until then, carer-specific utilities could be included in scenario analyses.

It is also important to consider that inclusion of carer HRQoL in HTAs may have distributional impacts, if they are considered in decision-making. After all, because an outcome category is added to the evaluation, interventions that have a positive effect on carer HRQoL may then result in more (health) value for money than interventions that have no, or a negative, impact on informal carers. The magnitude and direction of this effect may depend on characteristics of the patient group, their condition, the number of carers included in the economic evaluation, the context, and the intervention, and could be relevant to both a healthcare and a societal perspective. Of course, ignoring carer HRQoL is also associated with distributional impacts, albeit implicitly, as potentially relevant health effects in carers are left out of consideration in decision-making (Brouwer, 2019), skewing decision-making away from interventions that benefit carers and patients with conditions associated with informal care.

Another important aspect is how bereavement affects carers and families (Henry *et al.*, 2024). In one appraisal (TA755), NICE explicitly mentioned that accounting for the bereavement effect was important, but it proved to be complex to incorporate this in a health economic model. Dealing with grief in health economic models is largely unexplored but could entail modelling beyond patients' lifetime time horizon, as carers and family members may experience grief for long after a patient's death, especially in paediatric indications. Interventions that greatly improve life expectancy could, therefore, result in a significant impact on carer and family HRQoL. The HRQoL T&F Group argued that bereavement should not be considered, because the methods to quantify these effects are not well developed and the impact is unpredictable. Further research is thus needed on how to measure and model the effects of bereavement in HTAs and the way in which decision-makers may want such data presented.

Finally, it may be helpful to shift the burden of proof for future appraisals from demonstrating that effects on carers are substantial and hence relevant, as is currently advised by NICE, for demonstrating that this is not the case, reiterating the conclusions from the review by Goodrich *et al.* (2012). This would acknowledge the importance of incorporating carer HRQoL in economic evaluations and consequently promote the consideration of carer HRQoL routinely in economic evaluations, in line with the aim of maximising population health.

Acknowledgement. The authors thank Matthijs Versteegh, PhD, for his role in the concept and design of the study.

Financial support. The study was sponsored by Takeda UK, Ltd. The deliverable of the project was a publication. Two employees of the sponsor are co-authors of the publication. The publication of the study results was not contingent on the sponsor's approval or censorship of the manuscript.

Competing interests. Kanters and van Hezik-Wester received grants from Biogen Netherlands outside the submitted work. Boateng and Cranmer were employed by Takeda UK, Ltd. Al-Janabi received personal fees from Ferring, Curta, Roche, and PHMR. Van Exel received grants from National Institute for Public Health and the Environment, ZonMw, European Commission, Erasmus Trustfonds, Convergence Health & Technology, and GSK. Kvamme and Santi have no competing interests.

References

- Adult Social Care Statistics Team ND** (2022) *Personal Social Services Survey of Adult Carers in England, 2011–22*. NHS Digital.
- Al-Janabi H, Coast J and Flynn TN** (2008) What do people value when they provide unpaid care for an older person? A meta-ethnography with interview follow-up. *Social Science & Medicine* **67**, 111–121.
- Al-Janabi H, van Exel J, Brouwer W and Coast J** (2016a) A framework for including family health spillovers in economic evaluation. *Medical Decision Making* **36**, 176–186.
- Al-Janabi H, Van Exel J, Brouwer W, Trotter C, Glennie L, Hannigan L and Coast J** (2016b) Measuring health spillovers for economic evaluation: a case study in meningitis. *Health Economics* **25**, 1529–1544.
- Al-Janabi H, Manca A and Coast J** (2017) Predicting carer health effects for use in economic evaluation. *PLoS ONE* **12**, e0184886.
- Al-Janabi H, McLoughlin C, Oyeboode J, Efstathiou N and Calvert M** (2019) Six mechanisms behind carer wellbeing effects: a qualitative study of healthcare delivery. *Social Science & Medicine* **235**, 112382.
- Al-Janabi H, Wittenberg E, Donaldson C and Brouwer W** (2022) The relative value of carer and patient quality of life: a person trade-off (PTO) study. *Social Science & Medicine* **292**, 114556.
- Benito-León J, Rivera-Navarro J, Guerrero AL, de las Heras V, Balseiro J, Rodríguez E, Belló M and Martínez-Martín P** (2011) The CAREQOL-MS was a useful instrument to measure caregiver quality of life in multiple sclerosis. *Journal of Clinical Epidemiology* **64**, 675–686.
- Bhadhuri A, Jowett S, Jolly K and Al-Janabi H** (2017) A comparison of the validity and responsiveness of the EQ-5D-5L and SF-6D for measuring health spillovers: a study of the family impact of meningitis. *Medical Decision Making* **37**, 882–893.
- Bobinac A, Van Exel NJA, Rutten FFH and Brouwer WBF** (2010) Caring for and caring about: disentangling the caregiver effect and the family effect. *Journal of Health Economics* **29**, 549–556.
- Bobinac A, Van Exel NJA, Rutten FFH and Brouwer WBF** (2011) Health effects in significant others: separating family and care-giving effects. *Medical Decision Making* **31**, 292–298.
- Brazier J and Rowen D** (2011) NICE DSU Technical Support Document 11: Alternatives to EQ-5D for generating health state utility values. Sheffield, United Kingdom: School of Health and Related Research, University of Sheffield, UK.
- Broeze van Groenou MI, de Boer A and Iedema J** (2013) Positive and negative evaluation of caregiving among three different types of informal care relationships. *European Journal of Ageing* **10**, 301–311.
- Brooks R** (1996) EuroQol: the current state of play. *Health Policy* **37**, 53–72.
- Brouwer WB** (2019) The inclusion of spillover effects in economic evaluations: not an optional extra. *PharmacoEconomics* **37**, 451–456.
- Brouwer WBF, Van Exel NJA, Van Gorp B and Redekop WK** (2006) The CarerQol instrument: a new instrument to measure care-related quality of life of informal caregivers for use in economic evaluations. *Quality of Life Research* **15**, 1005–1021.
- Brown A, Page TE, Daley S, Farina N, Basset T, Livingston G, Budgett J, Gallaher L, Feeney Y, Murray J, Bowling A, Knapp M and Banerjee S** (2019) Measuring the quality of life of family carers of people with dementia: development and validation of C-DEMQOL. *Quality of Life Research* **28**, 2299–2310.
- Chiao C-Y, Wu H-S and Hsiao C-Y** (2015) Caregiver burden for informal caregivers of patients with dementia: a systematic review. *International Nursing Review* **62**, 340–350.
- Dawoud D, Lamb A, Moore A, Bregman C, Rupniewska E, Paling T, Wolfram V, Lovett RES and Dent R** (2022) Capturing what matters: updating NICE methods guidance on measuring and valuing health. *Quality of Life Research* **31**, 2167–2173.
- Deeken JF, Taylor KL, Mangan P, Yabroff KR and Ingham JM** (2003) Care for the caregivers: a review of self-report instruments developed to measure the burden, needs, and quality of life of informal caregivers. *Journal of Pain and Symptom Management* **26**, 922–953.
- Dhanji N, Brouwer W, Donaldson C, Wittenberg E and Al-Janabi H** (2021) Estimating an exchange-rate between care-related and health-related quality of life outcomes for economic evaluation: an application of the wellbeing valuation method. *Health Economics* **30**, 2847–2857.
- Dixon S, Walker M and Salek S** (2006) Incorporating carer effects into economic evaluation. *PharmacoEconomics* **24**, 43–53.
- Gheorghe M, Hoefman RJ, Versteegh MM and Van Exel J** (2019) Estimating informal caregiving time from patient EQ-5D data: the informal CARE effect (iCARE) tool. *PharmacoEconomics* **37**, 93–103.
- Goodrich K, Kaambwa B and Al-Janabi H** (2012) The inclusion of informal care in applied economic evaluation: a review. *Value in Health* **15**, 975–981.
- Henry E, Al-Janabi H, Brouwer W, Cullinan J, Engel L, Griffin S, Hulme C, Kingkaew P, Lloyd A, Payakachat N, Pennington B, Peña-Longobardo LM, Prosser LA, Shah K, Ungar WJ, Wilkinson T and Wittenberg E** (2024) Recommendations for emerging good practice and future research in relation to family and caregiver health spillovers in health economic evaluations: a report of the SHEER task force. *PharmacoEconomics* **42**, 343–362.

- Hoefman RJ, Van Exel J and Brouwer W (2013) How to include informal care in economic evaluations. *PharmacoEconomics* 31, 1105–1119.
- Horrell B, Stephens C and Breheny M (2015) Online research with informal caregivers: opportunities and challenges. *Qualitative Research in Psychology* 12, 258–271.
- Horsman J, Furlong W, Feeny D and Torrance G (2003) The health utilities index (HUI[®]): concepts, measurement properties and applications. *Health and Quality of Life Outcomes* 1, 1–13.
- Krol M, Papenburg J and Van Exel J (2015) Does including informal care in economic evaluations matter? A systematic review of inclusion and impact of informal care in cost-effectiveness studies. *PharmacoEconomics* 33, 123–135.
- Kuharic M, Mulhern B, Sharp LK, Turpin RS and Pickard AS (2024) Comparison of EQ health and well-being long and short with other preference-based measures among United States informal caregivers. *Value in Health* 27, 967–977.
- Lamsal R, Yeh EA, Pullenayegum E and Ungar WJ (2024) A systematic review of methods used by pediatric cost-utility analyses to include family spillover effects. *PharmacoEconomics* 42, 199–217.
- Longworth L and Rowen D (2013) Mapping to obtain EQ-5D utility values for use in NICE health technology assessments. *Value in Health* 16, 202–210.
- Matza LS, Stewart KD, Lloyd AJ, Rowen D and Brazier JE (2021) Vignette-based utilities: usefulness, limitations, and methodological recommendations. *Value in Health* 24, 812–821.
- McLoughlin C, Goranitis I and Al-Janabi H (2020) Validity and responsiveness of preference-based quality-of-life measures in informal carers: a comparison of 5 measures across 4 conditions. *Value in Health* 23, 782–790.
- McLoughlin C, Goranitis I and Al-Janabi H (2023) The feasibility and validity of preference-based quality of life measures with informal carers: a think-aloud study. *Value in Health* 26, 1655–1664.
- Mendoza-Jiménez MJ, van Exel J and Brouwer W (2024) On spillovers in economic evaluations: definition, mapping review and research agenda. *The European Journal of Health Economics* 25, 1239–1260.
- Mosquera I, Vergara I, Larrañaga I, Machón M, Del Rio M and Calderón C (2016) Measuring the impact of informal elderly caregiving: a systematic review of tools. *Quality of Life Research* 25, 1059–1092.
- National Institute for Health and Care Excellence (2013) *Guide to the methods of technology appraisal 2013. Process and methods*. National Institute for Health and Care Excellence. www.nice.org.uk/process/pmg9.
- National Institute for Health and Care Excellence (2020) *CHTE methods review. Health-related quality of life. Task and finish group report*. National Institute for Health and Care Excellence.
- National Institute for Health and Care Excellence (2022) *NICE health technology evaluations: the manual. Process and methods*. National Institute for Health and Care Excellence. www.nice.org.uk/process/pmg36.
- Pena-Longobardo LM and Oliva-Moreno J (2021) The economic value of non-professional care: a Europe-wide analysis. *International Journal of Health Policy and Management* 11, 2272–2286.
- Pennington BM (2020) Inclusion of carer health-related quality of life in national institute for health and care excellence appraisals. *Value in Health* 23, 1349–1357.
- Pennington B, Eaton J, Hatswell AJ and Taylor H (2022) ‘Carers’ health-related quality of life in global health technology assessment: guidance, case studies and recommendations’. *PharmacoEconomics* 40, 837–850.
- Rand SE, Malley JN, Netten AP and Forder JE (2015) Factor structure and construct validity of the adult social care outcomes toolkit for carers (ASCOT-carer). *Quality of Life Research* 24, 2601–2614.
- Reed C, Barrett A, Lebreck J, Dodel R, Jones RW, Vellas B, Wimo A, Argimon JM, Bruno G and Haro JM (2017) How useful is the EQ-5D in assessing the impact of caring for people with Alzheimer’s disease?. *Health and Quality of Life Outcomes* 15, 16.
- Robinson BC (1983) Validation of a caregiver strain index. *Journal of Gerontology* 38, 344–348.
- Scope A, Bhadhuri A and Pennington B (2022) Systematic review of cost-utility analyses that have included carer and family member health-related quality of life. *Value in Health* 25, 1644–1653.
- Stroebe M, Schut H and Stroebe W (2007) Health outcomes of bereavement. *The Lancet* 370, 1960–1973.
- Valcárcel-Nazco C, Ramallo-Fariña Y, Linertová R, Ramos-Goñi JM, García-Pérez L and Serrano-Aguilar P (2022) Health-related quality of life and perceived burden of informal caregivers of patients with rare diseases in selected European countries. *International Journal of Environmental Research and Public Health* 19, 8208.
- Van Exel NJA, Scholte op Reimer WJ, Brouwer WB, van den Berg B, Koopmanschap MA and van den Bos GA (2004) Instruments for assessing the burden of informal caregiving for stroke patients in clinical practice: a comparison of CSI, CRA, SCQ and self-rated burden. *Clinical Rehabilitation* 18, 203–214.
- Whitebird RR, Kreitzer MJ, Lewis BA, Hanson LR, Crain AL, Enstad CJ and Mehta A (2011) Recruiting and retaining family caregivers to a randomized controlled trial on mindfulness-based stress reduction. *Contemporary Clinical Trials* 32, 654–661.