Inclusion of carer health-related quality of life in national institute for health and care excellence appraisals.

Article:

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Abstract

Objectives

Health interventions for patients can have effects on their carers too. For consistency, decision-makers may wish to specify whether carer outcomes should be included. One example is the National Institute for Health and Care Excellence (NICE), whose Reference Case specifies that economic evaluations should include direct health effects for patients and carers where relevant. We aimed to review the methods used in including carer health-related quality of life (HRQL) in NICE appraisals.

Methods

We reviewed all published Technology Appraisals (TAs) and Highly Specialised Technologies (HSTs) to identify those that included carer HRQL, and discussed the methods and data sources.

Results

Twelve of 414 TAs (3%) and four of eight HSTs (50%) included carer HRQL in cost-utility analyses. Eight were for multiple sclerosis, the remainder were each in a unique disease area. Twelve of the 16 appraisals modelled carer HRQL as a function of the patient's health state, three modelled carer HRQL as a function of the patient's treatment and one included family quality-adjusted life year (QALY) loss. They used five source studies: two compared carer EQ-5D scores with controls, two measured carer utility only (one HUI and one EQ-5D), and one estimated family QALY loss from a child's death. Two used disutility estimates not from literature. Including carer HRQL increased the incremental QALYs and decreased incremental cost-effectiveness ratios (ICERs) in all cases.

Conclusions

The inclusion of carer HRQL in NICE appraisals is relatively uncommon and has been limited by data availability.

Keywords

Carer, spillover, cost-utility, NICE, appraisal

Highlights

- NICE states that economic evaluations should include direct health effects for all individuals, including carers where relevant, yet the inclusion of carer health outcomes in NICE technology appraisals and highly specialised technologies is relatively uncommon.
- The studies used to estimate carer health outcomes in NICE appraisals used various utility measures, some used non-UK populations, some were from other disease areas or populations, and some required comparison to general population utilities.
- In the absence of clear guidance from health technology assessment bodies such as NICE, inclusion of carer health outcomes will be inconsistent between appraisals.

Body of article

Introduction

Health interventions for patients can affect outcomes for informal carers too. For example, an intervention may reduce the amount of informal care required and so improve the quality of life of the informal carer[1]. Conversely, an increased requirement for care may entitle the patient to formal (paid) care, which may alleviate the burden on informal carers. Furthermore, a patient's health may directly influence the wellbeing of others who care *about* them as well as those who care *for* them[2]. Economic evaluations of health interventions have traditionally focused on outcomes for the patient, but a small proportion of studies have also included outcomes for carers[3, 4]. Ignoring the potentially large impacts to carers may be inequitable and inefficient[5].

Variation in how costs and outcomes are included will cause inconsistency in comparing between different economic evaluations. Health Technology Assessment (HTA) agencies may therefore produce a "Reference Case", specifying the methods that should be used. One example of this is the Reference Case for Technology Appraisals produced by the National Institute for Health and Care Excellence (NICE) in England[6]. NICE's Reference Case stipulates that cost-utility analyses should be used, with costs relating to those under the control of the National Health Service and personal social services and outcomes measured in quality-adjusted life years (QALYs). Outcomes should be direct health effects, whether for patients or, when relevant, carers. The EQ-5D is NICE's preferred measure of health-related quality of life (HRQL) in adults, and changes in HRQL should be valued using a representative sample of the UK population. The Reference Case does not specify how carer HRQL should be included in cost-utility analyses, or how the relevance of health effects for carers should be determined[6]. The Second Panel on Cost-Effectiveness in Health and Medicine in the US similarly recommend that health effects should be those accruing to patients and other affected parties including caregivers[7]. By comparison, Guidelines for submissions to the Pharmaceutical Benefits and Advisory Committee in Australia[8] specify that health outcomes for carers should only be included in sensitivity analysis and not in the base case, and guidelines for the Canadian Agency for Drugs and Technologies in Health do not mention carers[9]. We were therefore interested, given NICE's global role in HTA, in the extent to which carer HRQL has been included in NICE appraisals.

Our aim was to understand how carer HRQL has been considered in the analyses and recommendation of NICE Technology Appraisals (TAs) and Highly Specialised Technologies (HSTs) (for which the NICE Reference Case also applies). In both the TA and HST process, the company submits principal evidence on cost-effectiveness which is critiqued by an independent assessment group and then discussed by the committee. There may then be further evidence submitted by the company and further critique by the assessment group before the committee make their final recommendation in the Final Appraisal Determination (FAD) for TAs or Final Evaluation Document (FED) for HSTs. The FAD/FED reports the committee discussion in developing recommendations and reviewing the cost-effectiveness evidence, so reviewing NICE appraisals provides an opportunity to understand not only how analysts have included carer HRQL in economic evaluation, but also how independent review groups have viewed it and how decision makers have considered carer HRQL in reimbursement decisions.

Our objectives were to review:

1. Which appraisals and clinical areas have included carer HRQL (in addition to patient HRQL)
2. How carer HRQL has been included in cost-utility analyses

3. Which sources of evidence have been used to report carer HRQL
4. How the inclusion of carer HRQL affects incremental QALYs and incremental cost-effectiveness ratios (ICERs)
5. Whether NICE committees considered that the inclusion of carer HRQL was relevant and appropriate in decision-making

Methods

On 11 January 2019, we searched for the terms “carer” and “caregiver” within the FAD/FED for every TA and HST published on the NICE website since inception in 2000. We read the FADs/FEDs that included these terms and included appraisals where the committee specifically discussed carer HRQL and its impact on QALYs or ICERs. We excluded appraisals that mentioned carers without specifying carer HRQL, for example those that acknowledged only that patients with the condition need a carer, or those that discussed there are “benefits” or “effects” to carers but without specifying HRQL as these do not clearly fall within NICE’s reference case of direct health effects measured in QALYs. We categorised included appraisals by those where the cost-utility analysis included carer HRQL in any stage of the process, and those where carer HRQL was not included in the cost-utility analysis but where the committee did discuss the impact of carer HRQL.

We reviewed the company submission(s) and independent assessment group report(s) for each appraisal and one reviewer extracted data on the clinical area, date of publication, how carer HRQL was included in cost-utility analysis, size of carer HRQL impact and number of modelled carers, source of carer HRQL data, and the impact of the inclusion of carer HRQL on incremental QALYs and ICERs. As there are several stages in which the company and independent assessment group may conduct cost-utility analyses and both groups may undertake scenario analyses (and in multiple TAs there are several submitting companies), it is possible that multiple methods and sources of data could be used to model carer HRQL within each appraisal. We extracted data on each method and data source considered within the appraisals. From the FAD/FED, we extracted data on the committee discussion and conclusion regarding the inclusion of carer HRQL.

Results

Of 414 published TAs and eight published HSTs, we identified a total of 73 appraisals where the FED/FAD included the term "carer" or "caregiver". Of these, 12 TAs and four HSTs included carer HRQL in the cost-utility analysis. In a further 11 appraisals, the committee discussed carer HRQL but it was not included in the cost-utility analysis [see Supplement 1]. In the remaining 46 appraisals, the committee discussed carers but not specifically in the context of HRQL. A PRISMA flow diagram is provided in Figure 1.

Clinical areas

The 12 TAs that included carer HRQL in cost-utility analyses were for interventions to treat multiple sclerosis (n=8), Alzheimer's disease, juvenile idiopathic arthritis, atopic dermatitis and myelofibrosis. The four HSTs were in mucopolysaccharidosis type IVa (MPS IVa), Duchenne muscular dystrophy (DMD), adenonsine deaminase deficiency-severe combined immunodeficiency (ADA-SCID) and X-linked hypophosphataemia (XLH). The appraisals where carer HRQL was discussed but not included in cost-utility analyses were in plaque psoriasis in children, juvenile idiopathic arthritis, asthma (n=3), non-small-cell lung cancer, cystic fibrosis, alcohol consumption, chronic hepatitis C in children, neuroblastoma and paediatric-onset hypophosphatasia.

Of the appraisals that included carer HRQL in the cost-utility analyses, six of the 12 TAs and all four HSTs were for either exclusively paediatric populations or combined paediatric and adult populations. Furthermore, seven of the 11 appraisals that discussed carer HRQL but did not include it in cost-utility analyses included paediatric populations.

How carer HRQL was included in cost-utility analysis

Table 1 describes how carer HRQL was included in the cost-utility analysis in the TAs and HSTs. In each appraisal, the cost-utility analysis used an economic model to simulate patients' experience of a disease with the intervention and comparator. Carers were included by modelling carer's HRQL as a function of either patients' disease status/health state, patients' treatment or patients' death. Eleven appraisals used disutilities (utility decrements or losses) for carers, modelled as a function of the patient's health state [10-20]. Three appraisals modelled carer HRQL as function of the treatment the patient received (either as utility increments or disutilities), independent of the patient's health state [21-23]. One appraisal modelled carer utilities as a function of patient's disease severity[24], and one appraisal included a QALY loss to the family when the patient died[25]. The size of the carer HRQL impact ranged from an increase of 0.01 for a treatment-related increment in the appraisal of atopic dermatitis[23] to a disutility of 0.173 in two appraisals in multiple sclerosis[16, 17] and a lifetime QALY loss of 1.8 to 2.1 in the appraisal that modelled family QALYs as a function of patient death[23].

Most of the appraisals included one carer, with the exception of the TA in myelofibrosis which included 1.76 carers for 57.48% of patients (based on an unpublished study), the HST in DMD which included up to three carers in the company's analysis[19], and the HST in ADA-SCID which did not specify the number of family members[25].

Figure 2 reports the number of appraisals that included and excluded carer HRQL over time, using different approaches. Since the first TA in 2000, the number of NICE appraisals conducted annually has generally increased over time. The first appraisal to include carer HRQL was in 2007 (TA127), and the next appraisal to include carer HRQL was not until 2012, and since 2014, more appraisals have included carer HRQL.

Source of carer HRQL data

Five sources provided the estimates of carer HRQL used in the 16 appraisals: Neumann et al (2000)[26], Acaster et al (2013)[27], Kuhlthau et al (2010)[28], Landfeldt et al (2014)[29] and Christensen et al (2014)[30]. Table 2 reports the country, carer and control population, the utility measures and valuation sets used, the outcomes, and which appraisals used the different sources. [31-44]

Acaster et al (2013) generated disutilities as the mean difference between the controls and carers, reported by the Patient Determined Disease Steps (PDSS) state[27]. The disutilities displayed a non-monotonic pattern, with PDSS 7 and 8 (the most severe states) having smaller carer disutilities than PDSS 4-6. The study authors noted this finding and discussed that the reasons for it were unclear, with post-hoc analyses suggesting that this was not due to reduced burden from external caregiver support. These carer disutilities were used in two multiple sclerosis appraisals which modelled patient health using the EDSS, by converting the PDSS states from Acaster et al (2013) to the EDSS states in the model[38, 41].

Kuhlthau et al (2010)[28] analysed data from the US Medical Expenditure Panel Survey data using regression analysis considering multiple variables[40]. This study was used in the juvenile idiopathic arthritis TA[40] and in the HST for XLH[42] (although in this case the disutility included was 0.08, which is the difference between the mean EQ-5D scores for the two groups).

Landfeldt et al (2014)[29] was used in the HST for DMD, which included a caregiver disutility for non-ambulatory patient health states[43, 44].

Neumann et al (2000)[26] appears to have been first used to inform carer utilities in TA111 for Alzheimer's disease and later used in TA217[31], which superseded TA111 (the FADs for superseded appraisals are not published on NICE's website so were not included in our review). The same source was also used in seven multiple sclerosis appraisals, calculating the difference between the lowest HUI3 score and full health to give a disutility of 0.14, which was applied to the most severe Expanded Disability Status Scale (EDSS) health state[32-38]. A linear interpolation was applied to estimate carer disutilities for the remaining health states, with a carer disutility of 0 for the state representing no disability. The same source was used in the HST for MPS IVa, linking the health states in the multiple sclerosis appraisals with wheelchair usage in the model for MPS IVa[39], and in the TA for juvenile idiopathic arthritis[40].

Christensen et al (2014) [30] refer to a study by Al-Janabi et al (2015) which reports HRQL losses using EQ-5D-5L to the families of meningitis sequalae survivors[45], but note that this study did not measure the impact of patient death of family members' HRQL, so used evidence on the impact of bereavement on parent's HRQL using HUI3[46] and comparison of HRQL loss for meningitis sequalae survivors with HRQL loss from death. Numerical calculations are not provided. The estimate of 9% was used in the HST for ADA-SCID in a scenario analysis to incorporate family QALY loss.

The Alzheimer's disease TA also considered carer utilities generated from the Short-Form 36 questionnaire, but no further information was available on this source. The TA for atopic dermatitis and the TA for myelofibrosis included increments for carer utility (0.01 and 0.1 for atopic dermatitis and 0.1 for myelofibrosis) when patients received treatment[47, 48]. The TA for atopic dermatitis refers to a literature review of caregiver disutilities across disease areas[49] and the JIA appraisal[21]. The TA for myelofibrosis describes a utility decrement for cancer carers of "about -0.10 as measured by the SF-6D" (pp.13 [48]), referenced to a study of SF-36 scores which reports a difference of -0.09 between general health scores, measured on the 0 to 100 scale[50], and refers to Acaster et al (2013)[27]. Neither TA provided evidence for how the treatment itself would improve carer utility.

Impact on incremental QALYs and ICERs

Information on the impact of including carer HRQL on incremental QALYs and/or on ICERs was available for 10 of the appraisals and is presented in Table 3. In the other appraisals, either scenarios were not presented or results were confidential. In all cases, including carer HRQL increased incremental QALYs and decreased ICERs. Including carer HRQL generally increased incremental QALYs by less than 0.03 – although in some cases this represented over a 20% increase. Two appraisals (HST3 and HST7) considered scenario analyses where carer HRQL had a bigger absolute impact on incremental QALYs, but these were for HSTs with high incremental QALYs initially, so the percentage change is less.

The biggest impact on the ICER was for TA534, where including a utility increment of 0.1 for all patients on treatment decreased the ICER by £9,498 (33%). In other appraisals where caregiver disutilities were included as a function of patient health states, the impact on the ICER was less, with decreases of up to £2,900 (10%).

Committee discussion

In 11 of the 16 appraisals that included carer HRQL in cost-utility analyses, the committee felt that carer HRQL should be included in the base-case cost-effectiveness evidence. In the Alzheimer's disease appraisal, the committee used the assessment group's model in decision-making, which excluded carer HRQL in the base case, but noted the impact of including carer HRQL[10]. In the ADA-SCID and XLH appraisals, the committee felt that the scenarios did not fully capture HRQL benefits to carers, and so stated that they would consider carer HRQL qualitatively[20, 25]. In the atopic dermatitis appraisal, the committee considered that there may be an impact on carer HRQL, but that there was no robust evidence to support this[23]. In the myelofibrosis appraisal, the committee concluded that carer HRQL should not be included in the estimation of the ICER because the results were not robust; they did not consider that the carer burden from myelofibrosis was more profound than that of other severe illnesses; and the analysis did not account for the opportunity cost of carer's burden (that is, the carer burden currently relieved by other interventions which would be displaced if ruxolitinib were funded) [22].

Discussion

Clinical areas

We found that appraisals that included carer HRQL covered a range of clinical areas. While there were a high number in multiple sclerosis representing all published multiple sclerosis appraisals, the appraisals in Alzheimer's disease, atopic dermatitis, myelofibrosis and all four HSTs were each the only published appraisal in that disease area. TA373 which included carer HRQL in the cost-utility analysis is one of two published appraisals in juvenile idiopathic arthritis, but the committee did discuss the impact of carer HRQL on the ICER in the other (TA238).

Whether carer HRQL is included in economic evaluation may be a function of data availability, but we note that Wittenberg et al's 2019 systematic literature review of family and carer HRQL identified carer utilities/disutilities in disease areas other than these appraisals[50]. However, the inclusion of carer HRQL in economic evaluations does not appear to be routine even in disease areas with substantial data – Wittenberg et al (2019) found 15 (of 80) studies reported carer HRQL in Alzheimer's disease, but Lin et al (2019) found that only nine of 63 published economic evaluations in Alzheimer's disease or dementia included carer HRQL[51].

Although TA386 is the only NICE appraisal in myelofibrosis (a type of blood cancer), none of the many other NICE appraisals in cancer included carer HRQL. This is consistent with a 2015 systematic review across four disease areas which found no economic evaluations in metastatic colorectal cancer included either carer HRQL or carer costs, compared to 64% in Alzheimer's disease, 13% in Parkinson's disease and 14% in rheumatoid arthritis. However, in Wittenberg et al's 2019, cancer was the second most commonly reported disease area, with six of 80 studies[50].

A substantial proportion of appraisals that considered carer HRQL (either in cost-utility analyses or in discussion) included paediatric populations. Wittenberg et al (2019) found less data was available for caregivers and family members of ill children than ill adults[50]. However, in a separate piece of work we identified 31 TAs which included children in their populations[52], so it is clearly not the case that appraisals of interventions in children routinely consider carer HRQL. Indeed, Lavelle found that only 15 of 142 identified paediatric economic evaluations considered carer HRQL[53].

How carer HRQL was included in cost-utility analysis

Methods were largely similar between appraisals, with some notable exceptions. Modelling carer HRQL as a function of patients' health status appears consistent with the data sources in most cases, whereas assuming that treatment itself increases a carer's HRQL without linking this to a change in the patient's health appears to be a simplistic assumption not underpinned by evidence in the cases where this was done. Only one appraisal explicitly considered the impact of the patient's death on carer's HRQL[25], but the data to support this are not well-reported[30]. The company submissions and assessment group reports did not always clearly describe how HRQL was included or how data was used – greater transparency in reporting would be beneficial in future cost-utility analyses.

The number of carers included also appears to be important. In almost all cases, the number of carers was assumed to be one. Consideration should be given to the number of carers likely to be affected, and how the evidence on the size of carer HRQL should be applied to them. For example, Kuhlthau et al (2010) report the effect of having a child with activity limitation on HRQL of parents [28] – where children have more than one parent, multiple carer impacts could be included. In the two appraisals where this source was used, it was only applied to one carer. Canaway et al (2019) found that the impact of care at the end of life impacted a median of eight individuals, and suggested that economists should prioritise including the three closest individuals[54]. This is much higher than was usually included in NICE appraisals. This raises the question as to whether economic evaluations should include carer HRQL effects from caring *about* the individual or only caring *for* the individual[2].

Source of carer HRQL data

In many cases, there are serious concerns relating to the measurement of carer HRQL, the geographic origin and valuation of the source data and the comparison used to derive disutilities. We note similar concerns regarding patient HRQL: a 2011 review found only 56% of company submission and assessment group reports contained utility data that conformed to the NICE Reference Case[55].

The utilities from Neumann et al (2000) used the HUI, whereas NICE specifies that it prefers the EQ-5D. HTA bodies should consider whether utility measures for carers should be the same as those for patients, or whether different measures better capture the impact on carers[56-60]. In terms of data availability, Wittenberg et al (2019) found that the EQ-5D was the most common instrument used to measure carer utility (used in 69% of cases)[50].

Two studies (Neumann et al (2000) and Kuhlthau et al (2010)) were from the US rather than the UK, and one study included a mix of countries (Landfeldt (2014)). Differences in formal care provided in the different jurisdictions may impact carer effects. Furthermore, Neumann et al (2000) and Kuhlthau et al (2010) use the US value set for EQ-5D and Landfelft (2014) do not report which they used, whereas NICE states that the UK value set should be used [6].

Comparing carer utilities to full-health (utility of 1), as in the appraisals that used the Neumann et al (2000) study, does not account for comorbidities in the general population. The use of age-adjusted utilities or comparison to general population utility (as in the Landfeldt (2014) study) partly addresses this, but limitations remain. More robust estimates of carer disutility would result from comparison to a control group (as in Acaster et al (2010) and Kuhlthau et al (2010)) or longitudinal studies reporting carer HRQL over time (effectively using carers of patients with different health status as the control group). Using longitudinal data of carer's utility would have further benefits, as other evidence has found that carer's health differs from that of non-carers, at least partly because of differences in the populations who become or do not become carers[61]. Assuming that carers' HRQL becomes equivalent to that of non-carers if the patient becomes cured ignores these differences between the populations. Similarly, it is feasible that people who become carers of people with more severe disease differ from people who become carers of people with less severe disease, so assuming that a carer's HRQL improves/worsens as the health of the person they care for improves/worsens is not necessarily appropriate. To understand how carer HRQL changes over time (as modelled in cost-utility analyses) would require longitudinal studies.

Impact on incremental QALYs and ICERs

Including carer HRQL consistently increased incremental QALYs and so interventions appeared more cost-effective where carer HRQL was included. Other studies found similar results: including carer health outcomes/costs led to less favourable cost-effectiveness results in pairwise ICER comparisons for only two of 43 paediatric studies[53] and two of 33 Alzheimer's disease/dementia studies [51].

Committee discussion

In the cases where the committee did not consider that carer HRQL should be considered in decision-making, this was due to a lack of evidence or concern about displacing the carer burden currently relieved by other funded interventions. The routine inclusion of carer HRQL in economic evaluation would allow for consistency in decision-making, as discussed by Brouwer (2019)[5] and McCabe (2019)[62]. This would require evidence on carer HRQL across clinical areas. Wittenberg et al (2019) highlight existing publications which report carer HRQL [50], but to provide values across clinical areas requires either new studies (for example, measuring carer HRQL along with patient HRQL in clinical studies) or prediction of carer HRQL from patient HRQL. While it is possible to predict the number of informal hours required from the patient’s EQ-5D score and health condition[63, 64], no evidence currently exists to predict carer EQ-5D from patient EQ-5D across health conditions, or to predict carer EQ-5D from hours of informal care provided (although attempts have been made, for example in Alzheimer's disease[65] and meningitis[66]).

Strengths and limitations

Our study is the first to systematically search and review the inclusion of carer HRQL in NICE appraisals. It is possible that other NICE appraisals have included carer HRQL in cost-utility analysis at some stage, but that this was not discussed in the FAD/FED, and so these appraisals may have been missed in our searching. However, our aim was to understand what has been done to date, rather than to synthesise evidence, so we do not consider that this has biased the findings of our review. Our methodology is sufficient to highlight the current issues and challenges in incorporating carer HRQL into cost-utility analyses for interventions appraised by NICE.

Conclusions

The inclusion of carer HRQL in NICE appraisals is relatively uncommon and there does not appear to be a systematic consideration for when this is relevant. The source data used to provide carer HRQL values has been limited to few studies which do not necessarily conform to the NICE Reference Case, may be from other disease areas, and are limited in the comparison used to derive carer disutilities. For consistency in decision-making, there is a need for better quality evidence for carer HRQL across clinical areas and careful consideration as to how this should be included in economic evaluation.

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