SYSTEMATIC REVIEW OF COST-UTILITY ANALYSES THAT HAVE INCLUDED CARER AND FAMILY MEMBER HEALTH-RELATED QUALITY OF LIFE

REPORT BY THE DECISION SUPPORT UNIT

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EXECUTIVE SUMMARY

Health interventions for patients can also affect the health of informal carers who provide unpaid care for patients, by changing the patient's condition and therefore changing the carer's emotional response; by substituting, complementing, reducing or increasing the informal care provided; or by changing the carer's attitude, or behaviours. Family members who do not provide care may also experience negative impacts to their mental health from being witness to a patient's illness. These changes in carer or family member health, sometimes referred to as health spillovers, could be reflected in economic evaluation through the measurement and inclusion of their quality-adjusted life years (QALYs) in cost-utility analysis (CUA). In its Guide to the Methods of Technology Appraisals the National Institute for Health and Care Excellence (NICE) recommend economic evaluations include all direct health effects, whether for patients or other people. A comprehensive overview of the existing CUAs that have included health utilities for family members or carers to date is required, in order that this can be used to facilitate inclusion of carer QALYs in future CUAs. The first objective, therefore, is to conduct a systematic review to identify all CUAs of published cost-utility analyses that have included health utilities for family members or carers published up to 2019. The second objective is to determine and outline the methods that have been used in these studies to measure family member or carer utilities and to include them in the CUA, and to report the results with and without family member or carer utilities, where available. This reports adds to body of literature identified in the April 2019 review of NICE appraisals that identified NICE TAs and HSTs that considered the impact of an intervention on QALYs for carers or family members.

The systematic review identified 38 CUAs that met the inclusion criteria. CUAs were published between 1999 and 2019 and conducted in 15 different countries including 11 in the UK. The studies examined several different conditions. Fifteen examined vaccination, four examined Alzheimer's disease, two examined Parkinson's disease, three referred to the condition examined as dementia and two examined terminal illness. Fifteen further studies each examined a different condition. The EQ-5D was the most common utility measure used for carer quality of life, applied in 23 studies.

Most CUAs included changes in QALYs for one carer per patient, but some included changes in QALYs for two carers, and two studies included changes in QALYs for four family members per patient.

In 11 of the included studies, it was not possible to assess the impact of including health spillovers, for various reasons. Where it was possible (27 studies), there was considerable variation in the impact of including health spillovers on cost-effectiveness. QALY gains for carers were similar to or greater than QALY gains for patients in 3 studies. In 10 studies by including carer QALYs the incremental cost-effectiveness ratio (ICER) was reduced relative to patient QALYs alone. However, in 6 studies QALY gains for carers were very small compared to patients, or made little difference to the ICER. Only four studies provided information on both the impact of including family member QALYs and how this changed the ICER. Greater uncertainty in the estimation of carer QALYs compared to patient QALYs was noted across a number of studies.

Several factors may have had an effect on the impact of including health spillovers in the analysis, including the number of carers, and whether informal care costs were simultaneously included, and the measures and methods used. The justification for the number of carers included was not always clear, and it was not always possible to determine the methods by which carer QALYs were included in the analyses. Four CUAs incorporated QALY losses in bereaved family members in addition to QALY losses for family members of ‘living’ patients; this raises the question of whether bereaved family member QALYs should be included routinely or not. It was difficult to examine the impact of including carer QALYs on cost-effectiveness, as QALYs for patients and carers were frequently not reported separately. Generally, including carer QALYs appeared to increase the difference in QALYs between the intervention and comparator, consistent with the findings from the review of NICE appraisals.

This review highlights similar issues to the April 2019 review of NICE appraisals, in that, very few economic evaluations have included carer QALYs and the methods for doing so are not consistent and data sources are often limited. The rationale for why carer QALYs were included in studies was not always clear or consistent. It is therefore difficult to understand how analysts determine when carer QALYs should be included, and whether there are general rules that can be made for specific conditions, populations or interventions. Many of the studies we identified considered chronic conditions such as Alzheimer's disease, this was also the case for the studies included in the NICE review. This may suggest that there are some conditions and populations where the inclusion of carer QALYs is particularly common, but it is not clear to what extent these are influenced by precedents set and data availability in these conditions or populations. A key difference between output of this review and the NICE review is that this review included several within-trial economic evaluations, whereas the CUAs in the NICE review were all model-based. The models included here faced similar challenges to those observed in the NICE review, with multiple studies using the same source but interpreting the data differently (as in the rotavirus examples), or in relying on source data from a different disease area.

This review adds to the growing body of literature regarding the inclusion of carer health outcomes in economic evaluation. It provides a full systematic review of CUAs of patient interventions including carer or family member QALYs, and identifies a number of issues pertinent for analysts conducting CUAs and decision-makers appraising them. A key limitation of the review lies in the level of information available. Developers of future guidance for the reporting of economic evaluations may wish to consider specifying that justification for including or excluding carer QALYs should be provided, the methods for doing so should be described, and results should be reported separately for patients and carers.

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ABBREVIATIONS AND DEFINITIONS

Abbreviation	**Definition**
ACD	Appraisal consultation document
AG	Assessment Group
CDR	Clinical Dementia Rating scale
ECD	Evaluation consultation document
EDSS	Expanded Disability Status Score
EQ-5D	EuroQol-Five Dimension
ERG	Evidence Review Group
FAD	Final appraisal determination
FED	Final evaluation document
HRQL	Health-related quality of life
HST	Highly Specialised Technology
HUI	Health Utilities Index
ICER	Incremental cost-effectiveness ratio
MMSE	Mini Mental State Examination
MS	Multiple sclerosis
MTA	Multiple Technology Appraisal
NICE	The National Institute for Health and Care Excellence
PDDS	Patient Determined Disease Steps
QALY	Quality-adjusted life year
TA	Technology Appraisal
SD	Standard deviation
SE	Standard error
SF-6D	Short Form 36
STA	Single Technology Appraisal

1. INTRODUCTION

1.1. BACKGROUND

Health interventions for patients can also affect the health of informal carers who provided unpaid care for patients (henceforth referred to as ‘carers’), by changing the patient’s condition and therefore changing the carer’s emotional response; by substituting, complementing, reducing or increasing the informal care provided; or by changing the carer’s attitude, or behaviours.(1). Family members who do not provide care may also experience negative impacts to their mental health from being witness to a patient’s illness. These changes in carer or family member health, also referred to as health spillovers, could be reflected in economic evaluation through the measurement and inclusion of their quality-adjusted life years (QALYs) in cost-utility analysis (CUA).

In its Guide to the Methods of Technology Appraisals the National Institute for Health and Care Excellence (NICE) states that the perspective on outcomes of the economic evaluation should be all direct health effects (p32)(2). In the summary of the reference case, this is expanded as “whether for patient or, when relevant, carers” (p32), and in the text this is expanded as “whether for patients or other people” (p33) (although a definition for direct or indirect effects is not provided). However, a review of the inclusion of carer QALYs in NICE appraisals in April 2019 found that only 16 of 422 published Technology Appraisals (TAs) and Highly Specialised Technologies (HSTs) included carer QALYs (3) This review considered carer QALYs quantitatively in the ICER and not qualitative consideration of carer effects, which may be included in a wider number of appraisals. The review showed that in those that did include carer HRQL, the evidence has not often been of good quality or necessarily appropriate to the disease area, and consideration has rarely been given to the carer HRQL benefits displaced. Key areas where carer HRQL was included were in MS and Alzheimer’s disease, and interventions for children, where not all TAs and HSTs considered the impact on families. The review showed that including carer HRQL increases incremental QALY’s and therefore decreases ICERs. The approach to modelling carer QALY’s differed between appraisals, both mathematically and conceptually, particularly in terms of the implied effect on carers’ health related quality of life (HRQL) when a patient dies This review further found inconsistencies in whether carer QALYs were included, differences in the methods to include carer QALYs in economic modelling and a limited number of data sources used to include carer QALYs.

In this report, we aim to better understand the potential methods for including carer QALYs in economic evaluations through reviewing the wider literature. A 2012 systematic review found only six published economic evaluations that included carer QALYs(4), and a 2015 systematic review found only three of 100 economic evaluations in Parkinson's, Alzheimer's, metastatic colorectal cancer and rheumatoid arthritis included carer QALYs(5). Our aim is to carry out a 2019 systematic review to identify all CUAs of patient interventions which have included carer health-related QALYs and have been published as journal articles. This will provide a comprehensive overview of the existing CUAs that have included health spillovers to date, in order that this can be used to facilitate inclusion of carer QALYs in future CUAs.

1.2. THIS REVIEW

In 2015, AB (Bhadhuri, 2018) conducted a systematic review to assess the extent to which existing CUAs included health spillovers(6). AB identified 3270 records and included 29 studies published up to 2015. This review updates the AB review to 2019.

The first objective of the systematic review is to identify all cost-utility analyses of patient interventions that have included QALYs of informal carers and family members published from database inception-2015 and from 2015 - 2019. To include in principle, all significant others such as parents and spouses. The second objective is to determine and outline the methods that have been used in these studies to measure health spillovers and to include them in the cost-utility analysis, and to report the results with and without family member or carer QALYs, where available.

This report describes the methods and reports the findings of the combined review. This report does not make recommendations on what models should assume about spillover effects nor on data sources that should be used.

2. METHODS

Searches

Four bibliographic databases were searched to retrieve studies where cost utility analyses have included health spillover effects. These were searched from inception for the original review (6) with searches conducted in 2015, therefore for the update, the searches were limited from 2015 until March 2019. The databases searched were: MEDLINE (Ovid, 1946 to 2019), Embase (Ovid, 1974 to 2019), EconLit (Ovid, 1986 to 2019) and NHS EED (CRD, 1995-2019). (For full search strategies see Appendix 1).

Screening and eligibility

A two-stage sifting process for inclusion of studies, (title/abstract then full paper sift) was undertaken, as was the case in the original review. Titles and abstracts were scrutinised by one systematic reviewer (AS) according to the inclusion and exclusion criteria developed by Bhadhuri (2018) (AB) in the original review (6). There was no exclusion on the basis of quality. All studies identified for inclusion using the abstract alone, plus any study in which a decision on inclusion is not possible only from the abstract, were retrieved for more detailed appraisal. The eligibility criteria listed in Table 1 below was applied in order to select studies at title and abstract, and full text sift, and reflects the inclusion and exclusion criteria applied in the original review(6).

Table 1 Inclusion and exclusion criteria

	Inclusion criteria	***Exclusion criteria***
Study design	Full economic evaluations; cost-effectiveness analysis; must include a cost-utility analysis	Exclude if the paper is not a full economic evaluation (e.g. reviews, systematic reviews, clinical effectiveness studies, costing studies). not an obvious cost-effectiveness analysis (no incremental cost per outcome) not an obvious cost-utility analysis (no utility measure in list of outcomes)

	Inclusion criteria	***Exclusion criteria***
		conference abstract, study protocol, not English language
Population	family, carer, informal care	Exclude if population terms (e.g. family, carer, informal care) were not mentioned in a relevant part of the abstract
Intervention	Patients intervention	Exclude if they clearly and specifically relate to the economic evaluation of a family/carer intervention.
Comparator	Any	
Outcomes	Measure of family member healthy utility	Exclude if they do not use a measure of family member health utility

Data extraction strategy

Data extraction was performed by one reviewer (AS) into a standardised data extraction form, in the same way as it was undertaken in the original review(6). Data extracted included: condition, intervention, population, country, perspective, number or type of people other than the patient whose health effects were included, size of health effects for people other than the patient, source of health effects for people other than the patient, approach to modelling health effects (where available), assumptions inherent in the modelling approach. Data extracted included which people beyond the patient have been included in models, the data used to populate the models, and the assumptions made within the models about how the intervention affected people beyond the patient. Basic demographic information for participants was also extracted.

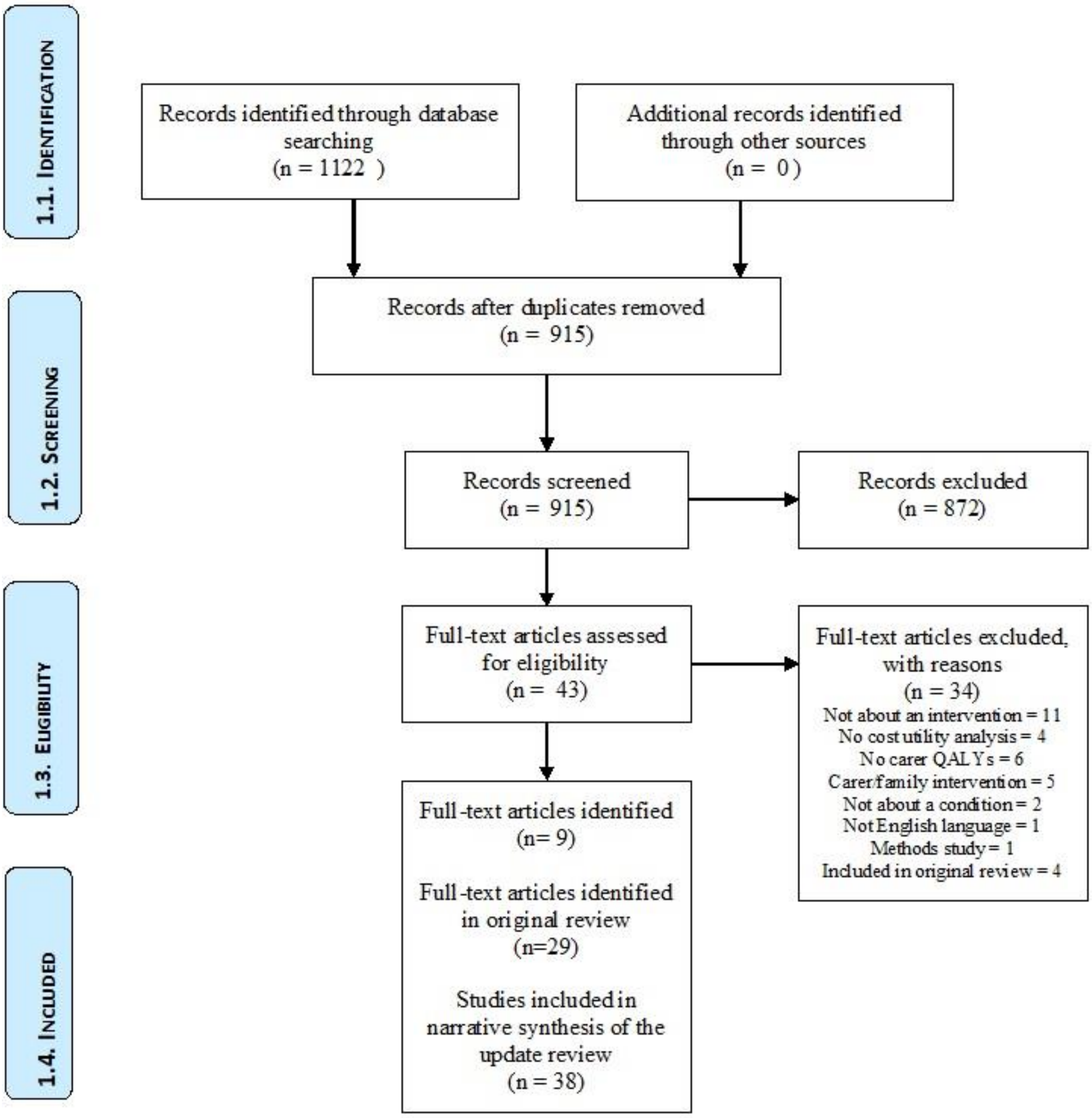
Methods of data synthesis

A narrative synthesis of the evidence was performed. The key areas that were documented are the number of cost-utility analyses that have included health spillovers, the disease areas in which health spillovers have been accounted for, the methods used to estimate health spillover and incorporate them into decision analyses, and the impact of including health spillovers on the cost-effectiveness of the interventions. As this is an update review, the studies included in the previous review were retrieved and included in the synthesis of the results.

3. RESULTS

Quantity of research available

Figure 1 PRISMA flow diagram for updated (2019) review



The original search from 2015 identified 3270 records and included 29 CUAs. The updated search from 2019 identified 1122 records and included 9 additional CUAs

(Figure 1). Therefore, a total of 38 CUAs were identified from the consolidated searches. See the PRISMA flowchart Figure 1 for details.

Characteristics of included studies

Key characteristics of the included studies are provided below (Table 2, Table 3).

Table 2 Characteristics of included studies

Author	**Year**	**Country**	**Underpinning condition**	**Intervention**
Studies identified in the update searches				
Chatterton et al(7)	2019	Australia	Childhood Anxiety Disorders	Stepped Care CBT programme (vs manualised CBT)
Forster et al(8)	2015	UK	Stroke	Post discharge system of care - LoTS care system of care.
Isenberg et al(9)	2017	USA	Palliative care patients	Inpatient palliative care programs
Kalabina et al(10)	2019	Scotland and Wales	Advanced Parkinson's disease (aPD)	Levodopa carbidopa intestinal gel (LCIG)
Lamb et al(11)	2018	England	Dementia (mild to moderate)	Aerobic strength training exercise programme for cognitive impairment.
Orgeta et al(12)	2015	UK	Dementia	Cognitive stimulation therapy (carer led)
Partridge et al(13)	2015	USA	Neonates at 23 weeks gestation	Resuscitation – universal and selective
Tiberg et al(14)	2016	Sweden	Children with type 1 diabetes	Home based hospital care (HBHC)
Zuluaga-Sanchez et al.(15)	2019)	Sweden	Infantile-Onseat and Later-Onset Spinal Muscular Atrophy	Nusinersen
Studies identified in the original review				
Bilcke et al(16)	2009	Belgium	Rotavirus	Vaccination
Christensen et al(17)	2014	UK	Meningitis	Vaccination
Creswell et al(18)	2015	UK	Anxiety disorder	Mother anxiety treatment

Author	**Year**	**Country**	**Underpinning condition**	**Intervention**
Fisman et al(19)	2012	Canada	Rotavirus	Vaccination
Flood et al(20)	2005	UK	Frail older patients	Occupational therapy
Gani et al(21)	2008	UK	Multiple Sclerosis	Natalizumab
Getsios et al(22)	2010	UK	Alzheimer’s	Donepezil
Getsios et al(23)	2012	UK	Alzheimer’s	Early assessment & donepezil
Greer et al(24)	2011	Canada	Pertusiss	Pertussis vaccination
Hartz et al(25)	2012	Germany	Alzheimer’s	Donepezil
Hornberger et al	2012	USA	Cancer (leukemia)	Rituximab
Itzler et al(26)	2011	Taiwan	Rotavirus	Vaccination
Jit et al(27)	2009	5 countries	Rotavirus	Vaccination
Jit et al(28)	2007	England and Wales	Rotavirus	Vaccination
Little et al	2005	USA	Herpes Simplex	Acyclovir prophylaxis
Meeuwsen et al(29)	2013	Netherlands	Dementia	Memory clinic care
Melliez et al(30)	2008	France	Rotavirus	Vaccination
Milne et al	2009	New Zealand	Rotavirus	Vaccination
Neumann et al(31)	1999	USA	Alzheimer’s	Donepezil
Newall et al(32)	2007	Australia	Rotavirus	Vaccination
Perez-Rubio et al(33)	2011	Spain	Rotavirus	Vaccination
Pham et al(34)	2014	Canada	Terminally ill	Palliative team care, patient planning
Poirier et al(35)	2009	Canada	Pneumococcal	Pneumococcal conjugate vaccination
Salize et al(36)	2013	Germany	Alcoholism	Alcohol dependence treatment
Schawo et al(37)	2015	Netherlands	ADHD	Methylphenidate osmotic release oral system
Shim et al	2009	USA	Rotavirus	Vaccination
Sturkenboom et al(38)	2015	Netherlands	Parkinson’s	Occupational therapy
Tilson et al	2011	Ireland	Rotavirus	Vaccination
Tu et al(39)	2012	Vietnam	Rotavirus	Vaccination

Table 3 Methods for accounting for health spillovers on family members (FMs) in included studies

Author	Year	Study design for measuring family member health	Number of FMs included in the primary analysis	FMs included in synthesis of benefits	Measure of family member outcome	Data collection dates
Studies identified in the update searches						
Chatterton et al(7)	2019	RCT	1	Yes	AQoL-8D	2012-2014
Forster et al(8)	2015	RCT	1	Yes	GHQ-12 (using threshold ranges for point gains)	Not stated
Isenberg et al(9)	2017	Observational	2.5 carers per patient encounter (PE) (from previous literature estimating average individual at the end of life has 2.5 carers.	Yes	Estimated Mean QoL improvements for carers from 3 studies as 0.05 to estimate QALYs (40-42) (these studies used Quality of Life in Life Threatening Illness-Family Carer Version (QOLLTI-F), City of Hope QOL-Family instrument.)	2013-2014
Kalabina et al(10)	2019	Observational	1	Yes	EQ-5D	2012 data
Lamb et al(11)	2018	RCT	1	Yes	EQ-5D	2013-2015
Orgeta et al(12)	2015	RCT	1	Yes	EQ-5D	2012-2013
Partridge et al(13)	2009	Observational	1	Yes	Surrogate used from previous study(43) – (Direct elicitation using standard gamble)	2009
Tiberg et al(14)	2016	RCT	2 (parents)	Yes (no patients)	SF-6D	2008-2011

Author	Year	Study design for measuring family member health	Number of FMs included in the primary analysis	FMs included in synthesis of benefits	Measure of family member outcome	Data collection dates
Zuluaga-Sanchez et al(15)	2019	Observational (data from SRs)	1	Yes	EQ-5D	Not stated
Studies identified in the original review						
Bilcke et al(16)	2009	Observational	1	Yes	EQ-5D	2005
Christensen et al(17)	2014	Observational	4	Yes	EQ-5D	2012
Creswell et al(18)	2015	RCT	1	Yes (no patients)	EQ-5D	2008-2013
Fisman et al(19)	2012	Observational	Not stated	Yes	EQ-5D	2005
Flood et al(20)	2005	RCT	Not stated	No	EQ-5D	2000-2001
Gani et al(21)	2008	Not stated	1	Yes	Not stated	Not stated
Getsios et al(22)	2010	RCT (pooled estimate)	1	Yes	SF-6D	Not stated
Getsios et al(23)	2012	RCT (pooled estimate)	1	Yes	SF-6D	Not stated
Greer et al(24)	2011	Observational	2	Yes	Direct elicitation	1997-1998
Hartz et al(25)	2012	RCT (pooled estimate)	1	Yes	SF-6D	Not stated
Hornberger et al	2012	Unclear	1	Yes	Direct (time trade-off)	1986-1994
Itzler et al(26)	2011	Observational	1.9 (average)	Yes	EQ-5D	2005
Jit et al(27)	2009	Observational	1	Yes	EQ-5D	2005
Jit et al(28)	2007	Observational	2	Yes	EQ-5D	2005
Little et al	2005	Observational	1	Yes	Direct elicitation	1997-1998
Meeuwsen et al(29)	2013	RCT	1	Yes	EQ-5D	2007-2010
Melliez et al(30)	2008	Observational	1	Yes	EQ-5D	2005
Milne et al	2009	Observational	1	Yes	EQ-5D	2005
Neumann et al(31)	1999	Observational	1	Yes	HUI:2	1996-1997
Newall et al(32)	2007	Observational	1	Yes	EQ-5D	2005

Author	**Year**	**Study design for measuring family member health**	**Number of FMs included in the primary analysis**	**FMs included in synthesis of benefits**	**Measure of family member outcome**	**Data collection dates**
Perez-Rubio et al(33)	2011	Observational	2	Yes	EQ-5D	2005
Pham et al(34)	2014	Observational	1	Yes	EQ-5D	2004
Poirier et al(35)	2009	Not stated	1	Yes	Not stated	Not stated
Salize et al(36)	2013	Observational	1	Yes (no patients)	WHO-BREF (difference between total scores at t0 and t1 used to measure the gain QALYs – total scores treated as scale which was treated as a preference measure)	2005-2008
Schawo et al(37)	2015	Observational	4	Yes	EQ-5D	2012
Shim et al	2009	Observational	1	Yes	EQ-5D	2005
Sturkenboom et al(38)	2015	RCT	1 / 2	Yes	EQ-5D	2011-12
Tilson et al	2011	Observational	1	Yes	EQ-5D	2005
Tu et al(39)	2012	Observational	1	Yes	EQ-5D	2005

Table 4 Summary of findings of the included studies

Author	Date	Indication / population	Type of analysis in which Carer HRQL is included.	Method for including carer HRQL and for combining patient and carer QALYs	Size of carer HRQL effect	Impact on ICER (where available in the study)	Source of carer HRQL data and carer QALY information
Studies identified in the update searches							
Chatterton(7)	2019	Childhood anxiety disorders	Base case (societal perspective) Secondary analysis - health sector perspective	Carer utility measured at baseline and at 12 month follow up. QALYs presented separately for patients and parents, for each arm.	Carer QALY - Improved in both arms from baseline. Slightly more but not significantly improved QALYs in comparator group (adjusted mean difference -0.011, 95% CI=[-0.037, 0.015] for patients; -0.002, 95% CI=[-0.014, 0.010] for parents) Patient and parent QALYs not combined.	NR.	Utility values for patients and parents (AQoL-8D) at the 12 month follow up reported separately, for both arms of the RCT. (n=281 patient-parent dyads)
Forster (8)	2015	Stroke	Base case from both health and social care and societal perspective	Base case included carer utilities. QALYs - utility scores at each time point for intervention and control group and mean difference - patient and carer combined.	QALY gains reported for patients and carers combined (not separately).	ICERs NR – authors reported as unnecessary because no cost-outcome combination suggested statistically significant between-group increases, in both costs and outcomes.	Utility estimates for carers using the GHQ-12 generated through RCT data from this study. (n=208 carers)
Isenberg (9)	2017	Palliative care patients	Threshold analysis using a provider (hospital) perspective.	Base case included carers. Mean utility for carers was converted into QALYs, by multiplying the number of carers (assuming 2.5 carers per patient encounter) by the QoL score and average length of stay in years.	Intervention potential to save 3.06 QALYs for carers. Combing the QALYs generated from patient encounters (0.05 QALY) and carers (3.06 QALYs), the intervention could yield 3.11 QALYs.	NR.	Estimated QoL improvements for carers (0.05) (value generated from 3 previous trials using Quality of Life in Life Threatening Illness-Family Carer Version (QOLLTI-F), City of Hope QOL-Family instrument. (Juarez et al 2008; Groh et al 2013; Sun et al 2015).

Author	**Date**	**Indication / population**	**Type of analysis in which Carer HRQL is included.**	**Method for including carer HRQL and for combining patient and carer QALYs**	**Size of carer HRQL effect**	**Impact on ICER (where available in the study)**	**Source of carer HRQL data and carer QALY information**
Orgeta(12)	2015	Dementia	Base case, sensitivity analyses	Carer utility increment for patients receiving treatment. QALYs only reported for carers.	Carer QALY difference 0.05	Carer ICER, health and social care perspective £3100 (95%CI -71,000 to 84,200) societal - £38,400 (95%CI -236,000 to 47,300). Did not included patient QALYs.	Utility estimates for carers using the EQ-5D generated through RCT data from this study (n=264 carer patient dyads).
Kalabina(10)	2019	Advanced Parkinson's disease (aPD)	Base case; scenario analysis	Base case included patients, scenario analysis included impact on carer. Carer disutility modelled by patient's disease severity and included in scenario analysis.	Carer utility decrement ranged from 0.00 to - 0.12. QALY gain for patients 1.26	Base case ICER £52,110. When carer disutility included as a scenario analysis the ICER was reduced to £47,266	Carer disutility estimated using patient level data and carer EQ-5D - using a Tobit regression. From several studies: Adelphi Real World Parkinson's DSP 2012, DAPHNE, GLORIA.
Lamb(11)	2018	Dementia (mild to moderate)	Base case; sensitivity analysis	Base case analyses related to patient QALYs. Sensitivity analysis - wider societal perspective - including families and informal carers. Carer utility measured at each time point in each group.	Carer QALY estimate intervention 0.758 (SE 0.014) v control 0.782 (SE 0.020). Incremental QALYS base case -0.0220; adjusted for carer QALYs - 0.00665	ICER was dominated with and without carer QALYs.	RCT data from this study. (n = 416 carers) Exercise versus control carer reported QALYs presented.
Partridge(13)	2009	Neonates at 23 weeks gestation	Base case; sensitivity analysis	Base case includes neonatal and carer QALYs. Sensitivity analyses explored the concept that the increase in neonatal survivors' QALYs (nQALYs) after universal or selective resuscitation could outweigh maternal QALYs. Combined QALYs for this perspective.	Carer utilities range from 1 - 0.75 depending on neonatal outcome. (intact survival, death, impairment).	From the neonatal perspective universal and selective resuscitation are cost-effective at $55713 or $55844 per nQALY. Combined maternal neonatal perspective ICER for universal resuscitation $88537 (when probability of neonatal death is <0.95).	Used median maternal utilities for a child affected by trisomy 21 as a surrogate (Grobman et al., 2002). Applied maternal utilities to discounted life expectancy to generate maternal QALYs.
Tiberg (14)	2016	Children with type 1 diabetes	Base case	Base case analyses relate to effectiveness in terms of patient's disease severity in terms of HbA1C and utility in	Carer utility values presented for control and intervention group at three time points, no significant	NR.	76 parents completed SF-6D at all three time points in the trial. QALYs were not reported.

Author	**Date**	**Indication / population**	**Type of analysis in which Carer HRQL is included.**	**Method for including carer HRQL and for combining patient and carer QALYs**	**Size of carer HRQL effect**	**Impact on ICER (where available in the study)**	**Source of carer HRQL data and carer QALY information**
				terms of SF-6D. No patient utility values were collected.	differences. No patient utility values were reported.		
Zuluaga-Sanchez(15)	2019	Infantile-Onset and Later-Onset Spinal Muscular Atrophy	Base case societal perspective	Patient and carer QALYs presented separately then combined in the ICER.	Health-state carer disutility values (based on disease severity) ranged from -0.160, to - 0.00. QALY gains for patients - infantile-onset 3.86; Later-onset 9.54. QALY gains for carers- infantile-onset 0.02; Later-onset 2.39.	ICER only reported for combined QALYS.	Utility estimates were informed by clinical and economic SRs reviewed by clinical experts using the EQ-5D. Model outcomes included incremental cost per QALY gained (base-case scenario included QALYs gained for both patients and carercarers).
Studies identified in the original review							
Bilcke et al(16)	2009	Rotavirus	Base case	Health care perspective- included QALYs for children and one parent, and excluded carer productivity losses; justified as necessary to prevent double counting Societal perspective- included QALYs for children only, and included carer productivity losses	Scenario analysis evaluated impact of excluding carer QALYs under the health care payer perspective.	Probability of Rotarix being cost-effective was reduced from 81% to 8% as a result of excluding carer QALYs. Conversely, another scenario analysis found that including QALYs of two carers instead of one increased the probability of Rotarix being cost-effective from 81% to 97%.	Utility estimates were from Brisson et al. (2010).(44) Carers completed the HUI:2 on behalf of the patient, and the EQ-5D questionnaire to evaluate their own utility loss over a two-week period.
Christensen et al(17)	2014	Meningitis	Base case scenario	Family member QALY losses included in a scenario analysis (excluded in the base case)	NR	By including family QALYs, the vaccination cost-effective price increased from £8 to £11 per dose.	QALYs on the family (closest 4 family members of the patient) was estimated to be 48% of the patient QALY gains from vaccination. (Estimated from Al-Janabi et al.)(45) QALY loss to bereaved family

Author	Date	Indication / population	Type of analysis in which Carer HRQL is included.	Method for including carer HRQL and for combining patient and carer QALYs	Size of carer HRQL effect	Impact on ICER (where available in the study)	Source of carer HRQL data and carer QALY information
							members estimated to be 9% of the QALY losses to the child who died, also included in the analysis.
Creswell et al(18)	2015	Anxiety disorder	Base case	Child QALYs only included in cost utility analysis (children experienced spillover of the interventions administered to the mother). QALYs of the mothers who directly received the interventions were excluded.	No statistically significant improvements in carer health utility from baseline to 12 month follow up.	NR	Children and mother EQ-5D scores were elicited at the start and the end of the trial, with around 70 mothers and children in each treatment arm.
Fisman et al(19)	2012	Rotavirus	Base case	Loss of quality-adjusted life days in a parent–child dyad used to generate cost-utility estimates.	Not stated or explored	NR	Utility estimates were from Brisson et al. (2010).(44) Carers completed the HUI:2 on behalf of the patient, and the EQ-5D questionnaire to evaluate their own utility loss over a two-week period.
Flood et al(20)	2005	Frail older patients	Not included in the synthesis of costs and benefits.	Although carer QALYs were measured, it appears that they were not included in the synthesis of benefits.	There was no statistically significant difference in EQ-5D scores between the intervention and comparator arms of the trial, for both patients (p=0.29), and for carers (p=0.194).	NR	321 patients were included in the analysis. Only 113 carers were included in the analysis, due to missing data for carers at baseline and follow-up.
Gani et al(21)	2008	Multiple Sclerosis	Base case, scenario analysis	In the base-case analysis the utility of carers was included. In an alternative scenario analysis, the utility of carers was excluded.	NR	Excluding carer disutility in the scenario analysis led to a small increase in the ICER from £2300 to £2500 per QALY.	Utility for carers from a study of Alzheimer's disease carers. A scale was extrapolated from this study to represent carer disutility according to the

Author	Date	Indication / population	Type of analysis in which Carer HRQL is included.	Method for including carer HRQL and for combining patient and carer QALYs	Size of carer HRQL effect	Impact on ICER (where available in the study)	Source of carer HRQL data and carer QALY information
							severity of patient MS (ranging from 0.00 for patients with low-level MS to 0.14 for patients with the most severe MS).
Getsios et al(22)	2010	Alzheimer's	Base case (in both health care and societal perspectives)	Two perspectives used: health care payer and societal perspective. In health care payer perspective – health care (mainly NHS) costs, sum of patient and carer QALYs In societal perspective – health care costs plus carer productivity costs , sum of patient and carer QALYs	Carer QALY gains estimated to be approximately 10% of patient QALY gains. Including carer productivity losses was a more influential parameter; the reduction in costs to carers was estimated to be approximately equivalent to the reduction in costs to the health care provider, from administering donepezil.	NR	Patient and carer QALYs estimated using data from several donepezil trials. The regression model for patient QALYs came from an external study; a new regression model for carer QALYs was developed using data from 3 donepezil trials.
Getsios et al(23)	2012	Alzheimer's	Appears to be included in both base case analyses	Two perspectives used: health care payer and societal perspective. In health care payer perspective – NHS costs and QALYs (although unclear whether QALYs were aggregated to include carers under this perspective) In societal perspective – NHS costs plus carer productivity costs , and patient + carer QALYs (summed).	NR	Societal perspective - including carer QALYs reduced the ICER of the early assessment intervention by 12-15% (depending on the comparator that was used). Including carer productivity losses had a more substantial effect on the ICER in the societal perspective. The inclusion of these productivity losses effectively more than halved the ICERs for both interventions. It should be noted that the societal perspective may have changed the costs that are included as well as the QALYs included.	Patient and carer QALYs estimated using data from several donepezil trials. The regression model for patient QALYs came from an external study; a new regression model for carer QALYs was developed using data from 3 donepezil trials.

Author	Date	Indication / population	Type of analysis in which Carer HRQL is included.	Method for including carer HRQL and for combining patient and carer QALYs	Size of carer HRQL effect	Impact on ICER (where available in the study)	Source of carer HRQL data and carer QALY information
Greer et al(24)	2011	Pertusiss	Base case	Not stated	Not stated or explored.	NR	Utilities estimated for two parents and children. For parents a utility decrement applied if the child died, a larger utility decrement applied if child survived with a neurologic disability. Utility decrements taken from Little et al. Model took into account proportion of single-parent households in population (15%)
Hartz et al(25)	2012	Alzheimer's	Base case (in both health care and societal perspectives)	Two perspectives used: health care payer and societal perspective. In health care payer perspective – health care costs, sum of patient and carer QALYs In societal perspective – health care costs plus carer productivity costs , sum of patient and carer QALYs	Carer QALY gains estimated to be approximately 10% of patient QALY gains. Including carer productivity losses was an influential parameter. The reduction in costs to carers was estimated to be approximately 40% of the reduction in costs to the health care provider, from the administration of donepezil.	Dominated	Patient and carer QALYs estimated using data from several donepezil trials. The regression model for patient QALYs came from an external study; a new regression model for carer QALYs was developed using data from 3 donepezil trials.
Hornberger et al(46)	2012	Cancer (leukemia)	Base case societal perspective	Utility decrements summed for patient and spouse in each of the 3 states of the Markov model. These 3 states were progression free survival (estimated decrement to spouse=0.18, progressive	Intervention - 1.15 more QALYs than comparator for patient QALYs. Combined QALYs, for intervention produced only 1.03 more QALYs than comparator. - Overall impact of	NR	Utility values of spouses of patients from Basu et al. that estimated utility losses for spouses of patients with prostate cancer, depending on how

Author	Date	Indication / population	Type of analysis in which Carer HRQL is included.	Method for including carer HRQL and for combining patient and carer QALYs	Size of carer HRQL effect	Impact on ICER (where available in the study)	Source of carer HRQL data and carer QALY information
				illness (0.40) and death (0.60). A 1-year bereavement period was assumed for the spouse of a patient that died.	intervention in extending patient's life expectancy compared to comparator estimated to result in an overall negative impact on spouse as a result of longer duration of spillover.		much the cancer progressed, and disutility resulting from the patient dying.
Itzler et al(26)	2011	Rotavirus	Base case	Two perspectives adopted: health care and societal. Health care perspective: Health care costs, patient and carer QALYs. Societal perspective: Health care and carer costs, patient and carer QALYs	Estimate for patient QALYs in this study - much higher than other rotavirus evaluations included here, as they used the VAS estimate for patient QALYs rather HUI:2. (VAS 3-fold higher than the HUI:2 estimate).	Carer QALYs likely to be of relatively less influence in this economic evaluation compared to many of the other studies that were included in this review.	Utility estimates were from Brisson et al. (2010).(44) Carers completed the HUI:2 and VAS on behalf of the patient, and the EQ-5D questionnaire to evaluate their own utility loss over a two-week period.
Jit et al(27)	2009	Rotavirus	Base case (health care perspective)	Base case analysis (health care perspective): one carer QALYs included, carer costs excluded, makes 'realistic' adjustment to child and carer QALYs (50% reduction for the home-treated cases) Scenario analysis 1: (health care perspective): carer costs and QALYs excluded Scenario analysis 2 (societal perspective): one carer included, carer costs included Scenario analysis 3 (using most favourable assumptions for vaccinating): two carers included, no reduction	NR	Scenario analysis: Excluding carer approximately doubles ICER from the base case analysis. Including a second carer approximately halves ICER from base case.	Utility estimates were from Brisson et al. (2010).(44) Carers completed the HUI:2 on behalf of the patient, and the EQ-5D questionnaire to evaluate their own utility loss over a two-week period.

Author	Date	Indication / population	Type of analysis in which Carer HRQL is included.	Method for including carer HRQL and for combining patient and carer QALYs	Size of carer HRQL effect	Impact on ICER (where available in the study)	Source of carer HRQL data and carer QALY information
				adjustment of the QALY losses for home-treated cases.			
Jit et al(28)	2007	Rotavirus	Base case	Base case: summed QALY losses for patients and their two carers. Excluded carer productivity losses Scenario analysis 1: Included carer QALYs and also included carer productivity losses.	NR	A sensitivity analysis was carried out across the 95% confidence interval for carer QALYs. It was found that the ICER is particularly sensitive to carer QALYs when they are varied across the full 95% confidence interval. It should be highlighted that the 95% confidence interval for carer QALYs exhibited much more uncertainty (greater width) than the patient QALYs.	Utility estimates were from Brisson et al. (2010).(44) Carers completed the HUI:2 on behalf of the patient, and the EQ-5D questionnaire to evaluate their own utility loss over a two-week period.
Little et al	2005	Herpes Simplex	Base case	QALYs for the mother and child were summed.	Mother and child QALYs were not presented in a disaggregated form so this could not be ascertained	NR	Maternal utility decrement when a child had either moderate or severe neurologic impairment was applied of 0.17, using an estimate from the literature for the mother from having a child with Down syndrome. A maternal utility decrement of 0.07 was also applied when the child died.
Meeuwsen et al(29)	2013	Dementia	Base case and scenario	Patient and carer QALYs summed Scenario analysis 1: Patient and carer costs. Only patient QALYs. Scenario analysis 2: Cost and QALY of patient only. Scenario analysis 3: Cost and QALY of carer only	There was no difference in QALYs for both patients and carers between intervention and comparator arms of trial. Therefore including/excluding carer QALYs did not have much	NR	N=175 patients and their primary carer. In final analysis n=160 pairs evaluated.

Author	Date	Indication / population	Type of analysis in which Carer HRQL is included.	Method for including carer HRQL and for combining patient and carer QALYs	Size of carer HRQL effect	Impact on ICER (where available in the study)	Source of carer HRQL data and carer QALY information
					impact to results in the base case and scenario analyses.		
Melliez et al(30)	2008	Rotavirus	Base case	Unclear how patient and carer QALYs were combined.	Not explored explicitly.	NR	Utility estimates were from Brisson et al. (2010).(44) Carers completed the HUI:2 on behalf of the patient, and the EQ-5D questionnaire to evaluate their own utility loss over a two-week period.
Milne et al	2009	Rotavirus	Base case and scenario	Several scenario analyses which undertook alternative perspectives for costs (from health care or government perspective) In another scenario analysis, the disutility of two caregiving parents was included instead of one carer.	NR	Scenario analysis : 2 carers disutility instead of one carer. Including this second carer reduces ICER by 45%.	Utility estimates were from Brisson et al. (2010).(44) Carers completed the HUI:2 on behalf of the patient, and the EQ-5D questionnaire to evaluate their own utility loss over a two-week period.
Neumann et al(31)	1999	Alzheimer's	Scenario	In the base case analysis only patient QALYs were considered. In a scenario analysis carer QALYs were added.	QALYs for carers were generally invariant to severity of patient illness and setting of patient treatment,	Little impact on the cost effectiveness ratio when applied in the scenario analysis.	Carer QALYs were measured in a cross-sectional study using the HUI:2 in a sample of 528 carers of people with Alzheimer's disease, stratified by disease severity (201 mild, 175 moderate and 142 severe) and care setting (354 community and 164 nursing home). Carers both proxy reported the

Author	Date	Indication / population	Type of analysis in which Carer HRQL is included.	Method for including carer HRQL and for combining patient and carer QALYs	Size of carer HRQL effect	Impact on ICER (where available in the study)	Source of carer HRQL data and carer QALY information
							health of the patients, and also their own health utility.
Newall et al(32)	2007	Rotavirus	Base case	Base case analysis (health care perspective): QALYs for the child and the primary carer. Societal perspective: Included productivity losses for the carers; but only QALYs for the child included (carer QALYs excluded to prevent double counting). Further scenario analysis: The inclusion of QALY gains from two carers, rather than one.	Societal perspective: Under this perspective, vaccination was a dominant strategy (reduced total costs, increased QALYs).	Further scenario analysis: Substantially improved the cost-effectiveness of the two vaccinations. Including two carers instead of one reduced the ICER of Rotarix from $60000 to $40000.	Utility estimates were from Brisson et al. (2010).(44) Carers completed the HUI:2 on behalf of the patient, and the EQ-5D questionnaire to evaluate their own utility loss over a two-week period.
Perez-Rubio et al(33)	2011	Rotavirus	Base case	Base case: Patient and QALY losses for two parents were included.	NR	QALY losses for two carers (i.e. both parents) effectively will reduce the ICER for rotavirus vaccination by around 70%.	Utility estimates were from Brisson et al. (2010).(44) Carers completed the HUI:2 on behalf of the patient, and the EQ-5D questionnaire to evaluate their own utility loss over a two-week period.
Pham et al(34)	2014	Terminally ill	Base case	Three QALY decrements were applied to family members: from experiencing bereavement, from caregiving, and from having a break from caregiving.	Interventions estimated to produce small gains on QALDs of carers (<10% of patient QALD gains).	NR	QALY values using elicitations from 921 carers, who were then compared with matched population based QALY scores, to calculate a QALY loss. Regression analysis was also performed to establish the magnitude of QALY loss for carers.

Author	Date	Indication / population	Type of analysis in which Carer HRQL is included.	Method for including carer HRQL and for combining patient and carer QALYs	Size of carer HRQL effect	Impact on ICER (where available in the study)	Source of carer HRQL data and carer QALY information
Poirier et al(35)	2009	Pneumococcal	Base case	Not stated	NR	Scenario analysis- child only (excluded the carer). This adjustment resulted in a small increase in the ICER from 18000 dollars to 20000 dollars.	Disutility during the acute phase was assumed to be the same for the patient and one carer. This assumption is based on an unpublished study.
Salize et al(36)	2013	Alcoholism	Base case	N/A. Only QALYs of family members assessed (patient QALYs not measured and excluded in analysis	Intervention cost per QALY for outpatient treatment = 5470 euros < 30 000 euros (threshold) Intervention cost per QALY for inpatient treatment = 37601 euros > 30 000 euros (threshold)	NR	48 carers and relatives, n=24 family members of inpatients, n=24 family members of outpatients, using the WHO-BREF.
Schawo et al(37)	2015	ADHD	Base case	Base case: Includes carer costs, includes carer utility. Scenario 1: Costs of carers excluded Scenario 2: Utility of carers excluded	The study by Al-Janabi(45) estimated total family spillover to be 48% of the utility loss incurred by children with developmental problems. Therefore, the authors multiplied patient QALYs by 1.48 to estimate total QALYs for the base case analysis.	NR	QALYs on the family (closest 4 family members of the patient) estimated as 48% of the patient QALY gains from vaccination. (Estimate from previous study by Al-Janabi et al(45) of family members of meningitis survivors). A regression model was used to determine the magnitude of the association between family member health and patient health.
Shim et al	2009	Rotavirus	Base case	Base case - vaccination was cost-effective when considering QALYs for the child and one carer (but not cost-effective	NR	Including one carer approximately halves the ICER in both health care and societal perspectives.	Utility estimates were from Brisson et al. (2010).(44) Carers completed the HUI:2

Author	Date	Indication / population	Type of analysis in which Carer HRQL is included.	Method for including carer HRQL and for combining patient and carer QALYs	Size of carer HRQL effect	Impact on ICER (where available in the study)	Source of carer HRQL data and carer QALY information
				when considering QALYs for child only).			on behalf of the patient, and the EQ-5D questionnaire to evaluate their own utility loss over a two-week period.
Sturkenboom et al(38)	2015	Parkinson's	Not stated	Three analyses performed: Overall method unclear. May have used the same perspective for both costs and outcomes (e.g. carer only perspective calculated a NMB using carer costs and carer outcomes only). 1) Patient only. Experiences EQ-5D gain of 0.02 from intervention 2) Carer only. Experiences EQ-5D gain of 0.04 from intervention 3) Patient-carer pairs. This was a complete case analysis in which only patient-carer dyads were included. Patient and carer QALYs appear to be aggregated (utility gain of 0.05 from intervention).	The gains to the carer from occupational therapy were estimated to be larger (+0.04) than the gains to the patient (+0.02); however neither of these gains were statistically significant when assessed separately (or when aggregated across patient-carer dyads).	NR	Utility values from 189 patients and 178 carers.
Tilson et al	2011	Rotavirus	Scenario	Base case analysis uses a health care perspective and utilities for the child only. Scenario analysis 1. Including the QALYs lost by one carer. Scenario analysis 2. For the societal perspective, the informal carer work losses were included, carer utility losses excluded.	NR	Scenario analysis 1. Reduces ICER from base case analysis by 45%. Scenario analysis 2. For the societal perspective, Scenario analysis 3. Reduces ICER from scenario analysis 2 by 45%.	Utility estimates were from Brisson et al. (2010).(44) Carers completed the HUI:2 on behalf of the patient, and the EQ-5D questionnaire to evaluate their own utility loss over a two-week period.

Author	Date	Indication / population	Type of analysis in which Carer HRQL is included.	Method for including carer HRQL and for combining patient and carer QALYs	Size of carer HRQL effect	Impact on ICER (where available in the study)	Source of carer HRQL data and carer QALY information
				Scenario analysis 3. Societal perspective. Work losses, as well as one carer utility losses included.			
Tu et al(39)	2012	Rotavirus	Scenario	Base case: child only. Scenario 1: including QALYs of one carer. Scenario 2: including QALYs of two carers.	Small impact of spillover - rotavirus causes far more deaths in developing country setting (1660 in a birth cohort), so QALY losses for patients far outweigh the carer spillover QALY losses.	Base case: Probability of vaccination being cost effective is 67% Scenario 1: QALYs of one carer increase probability of cost-effectiveness to 70% Scenario 2: QALYs of two carers increase probability of cost-effectiveness to 74%.	Utility estimates were from Brisson et al. (2010).(44) Carers completed the HUI:2 on behalf of the patient, and the EQ-5D questionnaire to evaluate their own utility loss over a two-week period.

EQ-5D: EuroQol-Five Dimension, SF-6D: Short Form 36, HUI:2: Health Utilities Index ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life year, CI – confidence interval, NR – not reported.

Study characteristics

Included studies were published between 1999 and 2019, although one study(46) used family member data that had been collected between 1986 and 1994(47), and one study did not fully report the family member data collection dates (9). In a number of studies the rationale for including carer QALYs was an acknowledgment of the impact / burden on them, in some it appeared to be simply because the data were available, and in others no rationale was provided.

Figure 2 shows the countries where the studies were conducted. Of the 38 included studies, 11 were conducted within the UK, and one in Ireland, a further ten studies were conducted in other European countries and, one study was conducted across 5 European countries(27). Six studies were conducted in the USA, four in Canada, two in Australia, and one in New Zealand. One study was conducted in Vietnam, and one in Taiwan.

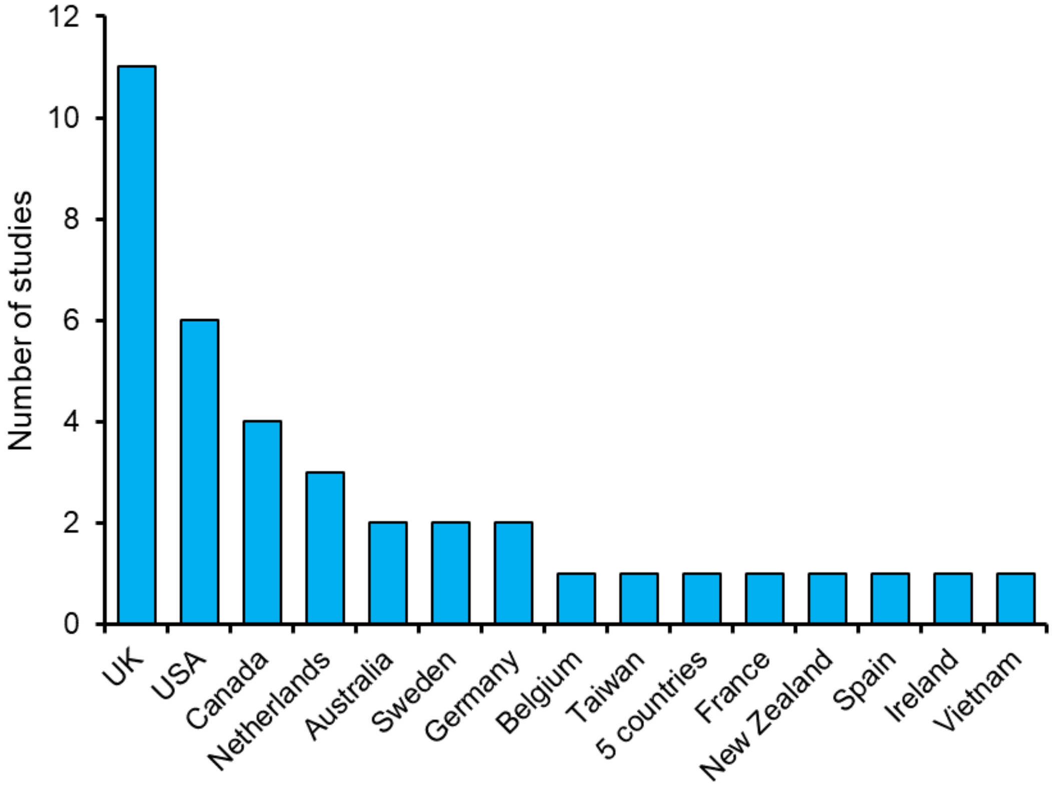


Figure 2: Study countries

Figure 3 shows the conditions examined in the studies. Fifteen of the CUAs examined vaccination in children, (16, 19, 26-28, 30, 32, 33, 39, 48-50) (17)(35)(24). Eleven were interventions for patients with a chronic illness, such as Alzheimer's disease in 4 studies,(22, 23, 25, 31) dementia in three,(11, 12, 29) and Parkinson's disease in two studies.(10, 51) Two studies examined interventions for terminally ill patients (9, 34). Several other conditions were examined in just one studies as can be seen in figure 3. The studies covered a range of interventions, including some complex interventions, psychological interventions, and pharmaceuticals

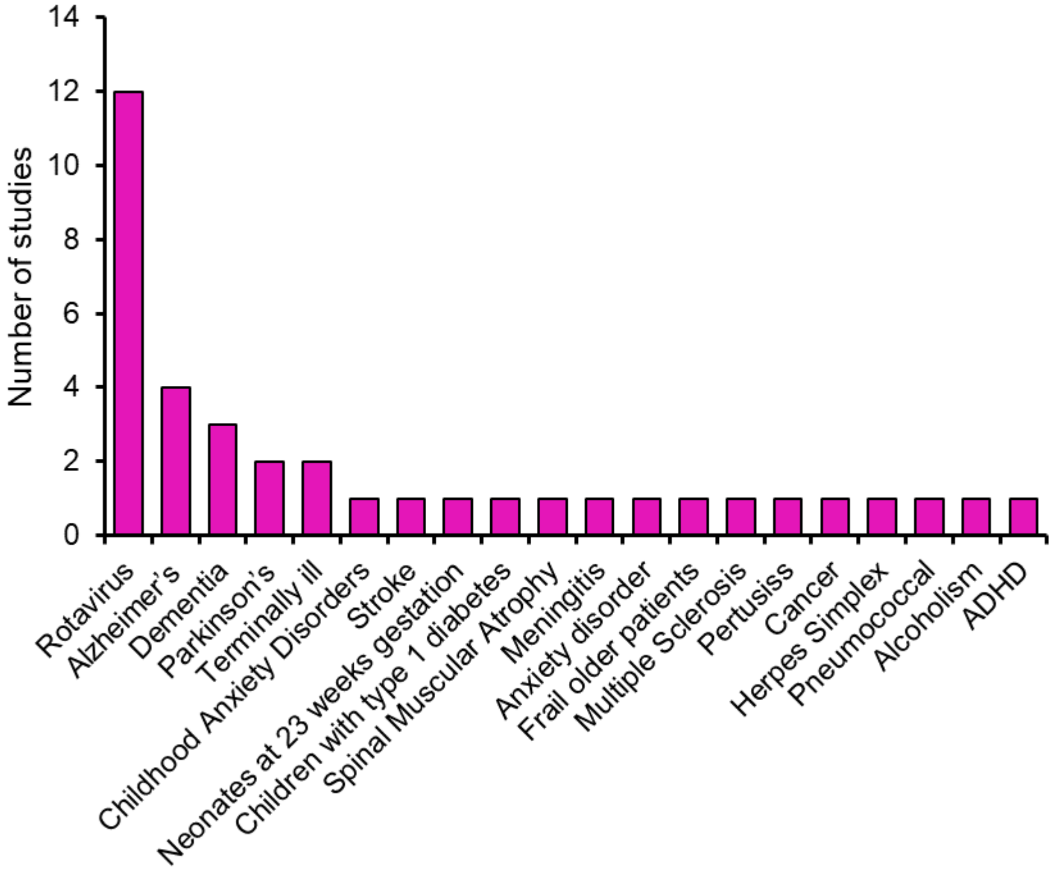


Figure 3: Study conditions

Source of family member utility values, data use, and assumptions made

Across the included studies it was noted that models and trials tend to use different sources.

In eleven studies (7, 8, 11, 12, 14, 18, 20, 29, 31, 36, 38) family member utility values were measured in a trial and incorporated in to the cost utility analysis, within the same study. In four studies, family member QALYs were measured in the intervention and control arms.(7, 20, 29, 38). In two of these studies it was noted that there were significant missing data for carer utilities which could lead to bias; (20, 29) in Flood et al., (2005)(20) full data was available from only 113 carers out of the 321 patients in the study,(20). However, another CUA from the Netherlands was able to obtain carer data from almost all patients recruited into the study(38) .

Twelve model based studies investigated the rotavirus vaccination (16, 19, 26-28, 30, 32, 33, 39, 48-50). In all of these CUAs the family member utility values came from the same cross-sectional study by Brisson et al. (2010) (44), which the authors of the study noted provided the best available data. In Brisson et al (2010) (44) carers completed the EQ-5D for themselves and the HUI:2 on behalf of the child patients, but the data were applied in a variety of ways across the twelve models. Three further cost utility analyses of Alzheimers's disease (22, 23, 25) used the same previous donepezil clinical trials (55-57) to construct an in individual patient data set using baseline information to create simulated patients.

Whilst a number of studies used data from the same source, or trial , ten analyses used estimates of family QALYs from an external study, whilst using a different study or utility instrument to estimate the QALYs of the patients.(9, 10, 15, 17, 21, 24, 34, 37, 46, 52) In five studies, the external study that provided an estimate of carer utility was related to a different condition (13, 21, 37, 46, 52), this raises the issue of how appropriate this is and whether these provided imperfect surrogates. For example, one used a study on the health spillovers of meningitis(45) to estimate family QALYs for ADHD (37).

In was also noted that in studies that used the same data, different assumptions may have been made, for example, in Bilcke et al. (2009)(16) an assumption was made that parents who did not seek professional medical treatment for their child's rotavirus incurred only 50% of the utility decrement compared to parents that did seek medical treatment. It was unclear, in Fisman et al. (2012)(19) whether QALYs for one parent, or for both parents were included. In Itzler et al. (2011) carers completed the HUI:2 and the VAS on behalf of the patient (26) (and used the VAS elicitations for the base case analysis), and the EQ-5D questionnaire to evaluate their own utility loss over a two-week period (using Brisson et al., 2010 data) (44).

Outcome measurement technique

Figure 4 shows how the family member health status was generated in the studies. Of the 38 CUAs, 32 CUAs used indirect measures; of which 23 used the EQ-5D, and four used the SF-6D,(22, 23, 25). One used a value generated from the City of Hope Quality of Life family measure (9). Direct measures of family member health status (including standard gamble and time trade-off techniques) were used in four CUAs which referred to external studies for these estimates (13, 24, 46, 52).

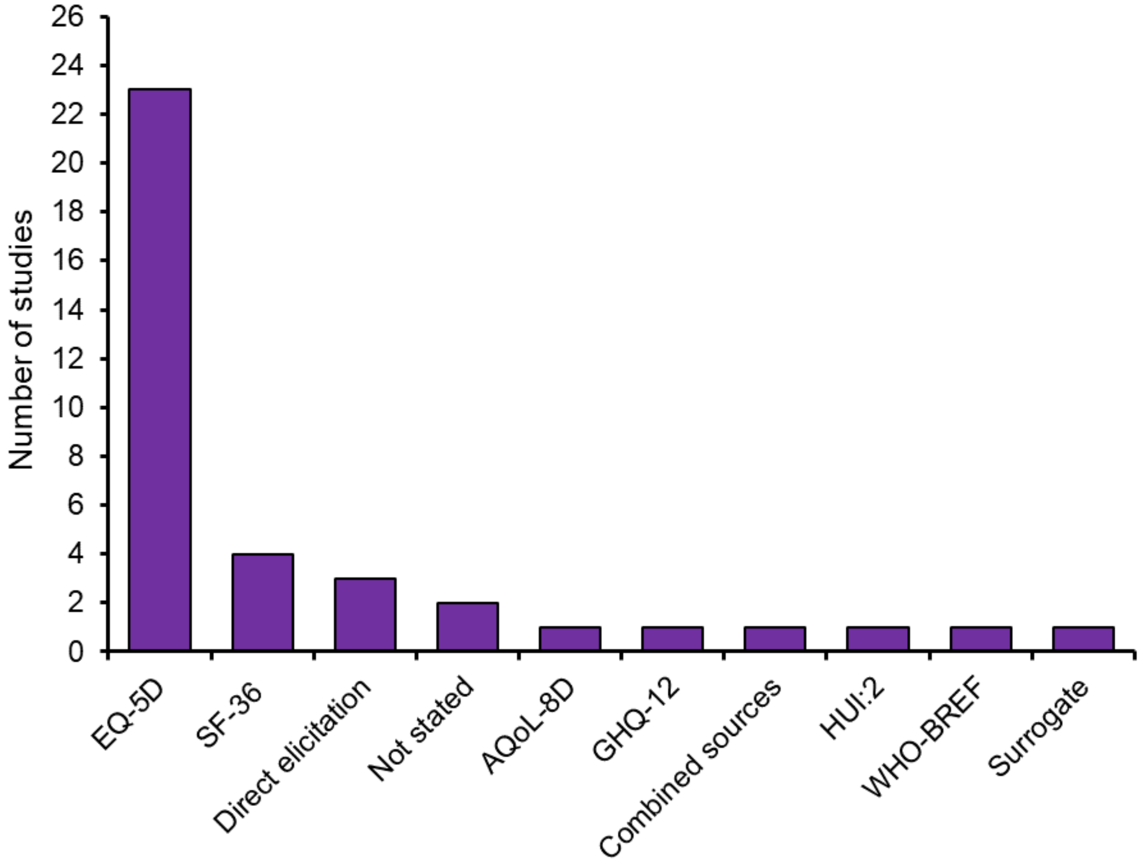


Figure 4: Study outcome measures

Individuals included in analysis

Most CUAs incorporated health utilities from one carer, most often the primary carer or one parent. Two CUAs included QALYs across the four closest family members of the patient.(17, 37) In 5 CUAs of childhood illness, QALYs for both parents were included in the analysis,(14, 24, 28, 33) whilst two CUAs included both parents but also appeared to adjust for presence of single-parent families(24, 26). One CUA included 2.5 carers per patient, based on previous literature on family size (10). Two CUAs did not state the number of carers that were included.(19, 20) Four CUAs that included health spillovers additionally included QALYs for bereaved family members (17, 34, 46, 52).

Impact of including health spillovers in the analysis

In eleven studies it was not possible to assess the impact of including health spillovers. This was because, in four studies, QALYs for patients and carers were not presented in a disaggregated form,(8, 19, 24, 52) and in one, how they were combined was unclear (30). In one study patient utility values were examined but not used to generate QALYs (12) and in one study although carer QALYs were measured, they were not included in the analyses (20). In one study(7) QALYs were not combined, and carer QALYs reported to be improved in both trial arms.

In three studies patient utility values were not included, with these studies only looking at carer utility (14, 18, 36). These studies were on alcoholism (36) with carer utilities examined, on anxiety disorder in mothers (18) measuring child utilities, and on childhood type 1 diabetes (14) where carer utilities were measured. Arguably these conditions have a large impact on family member utility and were studied separately for this reason.

Size of family QoL effect

In the 27 studies where it was possible to assess the impact of including health spillovers there was considerable variation in the impact they had on cost-effectiveness of interventions, and how the impact was reported, for example in some cases QALYs were not reported, and in others the ICER was not reported. Only four studies provided information on both the impact of including family member QALY s and how this changed the ICER.

Impact on QALYs

Ten studies reported data on patient and family member QALYs in the analysis (see Table X). Across all ten studies carers were reported to experience QALY gains as a result of the intervention. The significance of family member QALYs was highlighted in three studies where QALY gains for the carer were reported to be similar to or exceeded patient QALY gains as a result of the intervention(9, 11, 38).

Table 5 Studies presenting data on family member QALYs and a summary of the results.

Author	Date	Condition	QALY finding	Carer QALYS similar to or exceeded patient QALY gains
Isenberg (9)	2017	Palliative care patients	Intervention potential to save 3.06 QALYs for carers. Combing the QALYs generated from patient encounters (0.05 QALY) and carers (3.06 QALYs), the intervention could yield 3.11 QALYs.	Yes
Kalabina(10)	2019	Advanced Parkinson's disease (aPD)	Carer utility decrement ranged from 0.00 to -0.12. QALY gain for patients 1.26	
Lamb(11)	2018	Dementia (mild to moderate)	Incremental QALYS base case -0.0220; adjusted for carer QALYs -0.00665	Yes
Partridge(13)	2009	Neonates at 23 weeks gestation	Carer (parent) utilities range from 1 - 0.75 depending on neonatal outcome. (intact survival, death, impairment).	
Zuluaga-Sanchez(15)	2019	Infantile-Onset and Later-Onset Spinal Muscular Atrophy	Health-state carer disutility values (based on disease severity) ranged from -0.160, to - 0.00. QALY gains for patients - infantile-onset 3.86; Later-onset 9.54. QALY gains for carers- infantile-onset 0.02; Later-onset 2.39.	
Getsios et al(22)	2010	Alzheimer's	Carer QALY gains estimated to be approximately 10% of patient QALY gains.	
Hartz et al(25)	2012	Alzheimer's	Carer QALY gains estimated to be approximately 10% of patient QALY gains.	
Pham et al(34)	2014	Terminally ill	Interventions estimated to produce small gains on QALDs of carers (<10% of patient QALD gains).	
Sturkenboom et al(38)	2015	Parkinson's	The gains to the carer from occupational therapy were estimated to be larger (+0.04) than the gains to the patient (+0.02).	Yes

A further twelve studies on the rotavirus vaccination using the same data to estimate QALYs(44) reported that average carer QALYs lost to rotavirus were similar to the average patient QALYs lost. In a study that only assessed family member QALYs the intervention was cost effective by applying carer QALYs alone (36).

Conversely, one CUA used an external study to predict that carer QALYs would be lost as the patient's health and life expectancy improved due to a longer duration of care burden.(46). This study showed that the intervention produced 1.15 more QALYs than comparator for patients, but the combined QALYs for the patient and carer, produced only 1.03 more QALYs than comparator. Demonstrating that the overall impact of intervention in extending patient's life expectancy compared to comparator was estimated to result in an overall negative impact on spouse as a result of longer duration of spillover.

Impact on the ICER

Seventeen studies reported the impact of including family member QALYs on the ICER. Table 6 and figure 5 show the impact on the ICER of including family member QALYs in the analysis

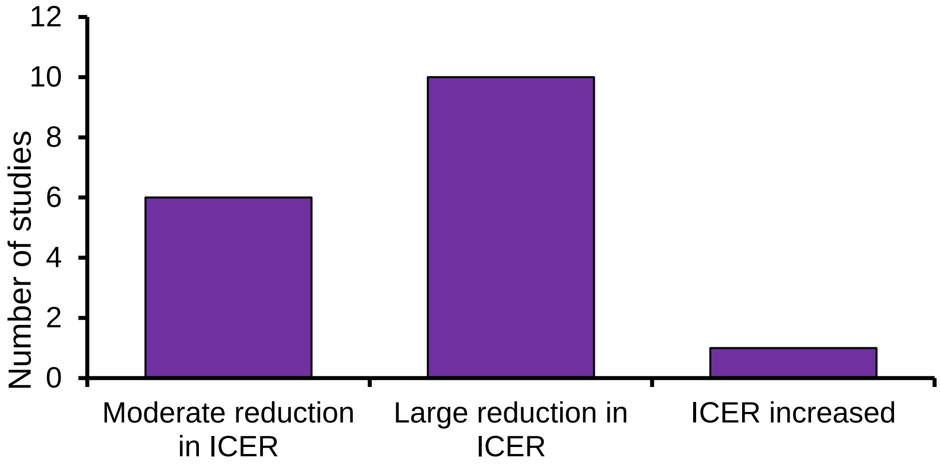


Figure 5. The impact of including family member QALYS on the ICER

Table 6 Impact of including family member QALYs on the ICER

Author	Date	Condition	Impact on ICER
Kalabina(10)	2019	Advanced Parkinson's disease (aPD)	Base case ICER £52,110. When carer disutility included as a scenario analysis the ICER was reduced to £47,266
Lamb(11)	2018	Dementia (mild to moderate)	ICER was dominated with and without carer QALYs.
Partridge(13)	2009	Neonates at 23 weeks gestation	From the neonatal perspective universal and selective resuscitation are cost-effective at $55713 or $55844 per nQALY. Combined maternal neonatal perspective ICER for universal resuscitation $88537 (when probability of neonatal death is <0.95).
Christensen et al(17)	2014	Meningitis	By including family QALYs, the vaccination cost-effective price increased from £8 to £11 per dose.
Gani et al(21)	2008	Multiple Sclerosis	Excluding carer disutility in the scenario analysis led to a small increase in the ICER from £2300 to £2500 per QALY.
Getsios et al(23)	2012	Alzheimer's	Societal perspective - including carer QALYs reduced the ICER of the early assessment intervention by 12-15% (depending on the comparator that was used).
Hartz et al(25)	2012	Alzheimer's	ICER Dominated
Jit et al(27)	2009	Rotavirus	Scenario analysis: Excluding carer approximately doubles ICER from the base case analysis. Including a second carer approximately halves ICER from base case.
Jit et al(28)	2007	Rotavirus	Scenario analysis: Excluding carer approximately doubles ICER from the base case analysis. Including a second carer approximately halves ICER from base case.
Milne et al	2009	Rotavirus	Scenario analysis : 2 carers disutility instead of one carer. Including this second carer reduces ICER by 45%.
Neumann et al(31)	1999	Alzheimer's	Little impact on the cost effectiveness ratio when applied in the scenario analysis.
Newall et al(32)	2007	Rotavirus	Further scenario analysis: Substantially improved the cost-effectiveness of the two vaccinations. Including two carers instead of one reduced the ICER of Rotarix from $60000 to $40000.

Author	Date	Condition	Impact on ICER
Perez-Rubio et al(33)	2011	Rotavirus	QALY losses for two carers (i.e. both parents) effectively will reduce the ICER for rotavirus vaccination by around 70%.
Poirier et al(35)	2009	Pneumococcal	Scenario analysis- child only (excluded the carer). This adjustment resulted in a small increase in the ICER from 18000 dollars to 20000 dollars.
Shim et al	2009	Rotavirus	Including one carer approximately halves the ICER in both health care and societal perspectives.
Tilson et al	2011	Rotavirus	Scenario analysis 1. Reduces ICER from base case analysis by 45%. Scenario analysis 2. For the societal perspective, Scenario analysis 3. Reduces ICER from scenario analysis 2 by 45%.
Tu et al(39)	2012	Rotavirus	Base case: Probability of vaccination being cost effective is 67% Scenario 1: QALYs of one carer increase probability of cost-effectiveness to 70% Scenario 2: QALYs of two carers increase probability of cost-effectiveness to 74%.

Six studies on the rotavirus vaccination, which all used the same data (44), all included at least one carer in the base case analysis (Jit et al., 2008; Jit et al., 2009; Newall et al 2007; Perez-Rubio et al., 2011; Milne et al., 2009; Bilcke et al 2009), all reported that the ICER was dominated and where a second carer was added the ICER was reduced. One of these studies specifically reported that excluding carer QALYs approximately doubled the ICER from the base case, and that including a second carer approximately halved the ICER from base case (27).

In six studies, carer QALY gains were small in magnitude compared to patient QALY gains and the impact of including carer QALYs on cost-effectiveness was therefore small (10, 11, 21, 25, 31, 35).

In Partridge et al. (2015)(13) on neonatal resuscitation at 23 weeks gestation, resuscitation was not cost-effective from a carer (maternal) perspective but was cost effective from a combined patient (neonatal) carer (maternal) perspective. Although it should be noted that this study may represent an unusual scenario where the carer could be seen as the patient, and would explain why the patient (neonatal) QALYs were initially excluded from the analysis.

4. DISCUSSION

This review highlights similar issues to the previous review of NICE appraisals(3) – very few economic evaluations have included carer QALYs (only 38 of all published cost utility analyses), the methods for doing so are not consistent. That so few CUAs have included carer QALYs is consistent with previous research (4, 5). As we excluded studies which did not include carer QALYs we cannot examine why they are commonly excluded. Furthermore, the rationale for why carer QALYs were included in our included studies was not always clear or consistent, with many studies not reporting any rationale. It is therefore difficult to understand how analysts determine whether carer QALYs should be included, and whether there are general rules that can be made for specific conditions, populations or interventions. It was not always possible to determine the methods by which carer QALYs were included in the analyses reported here, as these were not always clearly described, which may be due to word space limitations in journal articles. This was more possible in the review of NICE appraisals due to the level of detail provided in the committee papers.

There were some similarities in terms of the interventions, populations and conditions included in this review and the review of NICE appraisals (3). Eleven of the studies were from a UK setting, so it is likely that their perspective and methods were influenced by the NICE Methods for Technology Appraisal guidance. Given the international importance of NICE methods for CUA, it is plausible that NICE methods guidance influenced studies conducted in other jurisdictions. Fifteen of the CUAs included here evaluated a vaccination – while these would be assessed by the Joint Committee for Vaccines and Immunisation (JCVI) (53), JCVI recommend that evaluations are consistent with the perspective adopted by NICE. Many of the studies we identified considered chronic conditions, such as Alzheimer’s disease, which were common conditions for inclusion of carer QALYs in the NICE review. Additionally, some of the included studies here focussed on a paediatric population, which was also a finding of the NICE review. This may suggest that there are some conditions and populations where the inclusion of carer QALYs is particularly common, where there is a clear carer burden, but it is not clear to what extent these are influenced by precedents set and data availability in these conditions or populations. Although, the CUAs identified in this review covered a broader range of interventions compared to those included in the NICE TA review, such as complex interventions, psychological interventions, and also included a broader range of conditions and patients, such as neonates.

A key difference between the studies reviewed here and those included in the NICE review is that this review included within-trial CUAs, whereas all the CUAs in the

NICE review used models (3). This is because almost all CUAs for NICE require models to extrapolate outcomes to consider a sufficiently long time horizon and need to include multiple comparators. The trial-based analyses included here used carer utility data collected within the study, whereas the model-based evaluations relied on external sources. When relying on external data, the models included here faced similar challenges to those observed in the NICE review, with multiple studies using the same source but interpreting the data differently (as in the rotavirus examples), or in relying on source data from a different disease area. Furthermore, a lot of the model based estimates appear to be based on cross-sectional data, which presents a weakness, as trial based analyses are likely to be more valid, depending on how the data are used. Although it was noted in this review that of four studies that measured family member QALYs in the intervention and control arms, two had significant missing data for carer utilities, such missing data could lead to bias in the reporting of the results. Also, some of the studies relied on assumption, rather than empirical estimation. With one study using an assumption of 50% in one study, whilst in another a preference based measure was not used and therefore this could require an assumption to produce utilities. In future CUAs it would be helpful if details on the source data used for carer utility, including justification for using sources from other disease areas if appropriate were reported.

The studies included here used a range of family member health status measures. Unlike NICE appraisals where the EQ-5D is specified as a preferred measures,(2) these studies were not necessarily following guidance, so we cannot comment on whether different measures were appropriate. The majority of studies included here did use the EQ-5D and a benefit of using a generic instrument is that it does allow comparison between populations with different health profiles and conditions. However, in measuring quality of life of informal carers of people with dementia, generic instruments have been criticised for lacking validity (58). The dimensions of generic instruments have also been criticised as insensitive to the psychological consequences and the positive aspects of providing care (59). These scores may include the impact of spillover but also the underlying health of the individual. This does raise issues regarding the comparability of carer QALYs across appraisals, and also the separate issue of whether the same utility measures should be used for patients and carers. For example, in one rotavirus evaluation included here (Itzler et al) the estimate for patient QALYs was much higher than similar evaluations included here, as they used the VAS estimate for patient QALYs rather HUI:2. (VAS 3-fold higher than the HUI:2 estimate).

Furthermore, some studies used direct utility elicitation methods which have been suggested to more likely to lead to overestimates of health spillovers, and potentially double counting in a cost-utility analysis (54). This is because it may be difficult for family members to disentangle spillover of the patient’s illness on their health, with the disutility the patients experience from their own illness. Also, not all family members will have the same spillover, and will differ between those who are the carers and those who are not, the relevance of the two could also be argued as different.

As in the NICE review, we found inconsistency with the number of carers included, ranging from one carer to the whole family. The justification for the number of carers was not always clear, and inconsistencies were observed in seemingly comparable scenarios such as the number of parents included for a childhood illness. Four CUAs included in this review incorporated QALY losses for family members due to bereavement, compared to one CUA in the review of NICE appraisals (2). If future CUAs include HRQoL of bereaved family members they should report their role or relationship to the patient, and a clear rationale for their inclusion. Future CUAs should also provide clear details of the method used to measure carer utility, including justification for this measure, and a rational for which carer perspectives are included, the primary carer, or for other carers and family members as well. This may include a rational for if a carer HRQoL decrement is modified to reflect their relationship to the patient (e.g. parent-child, child-parent, spouse). In this review it seems particularly relevant for cases where children are the patients, and the effects are felt by more than one parent and extends to siblings, yet to differing degrees. The nature of intensity of caregiving and bereavement effects and how to deal with this for the wider family in still unclear when the existing literature is still focused on the primary caregiver.

Unlike the review of NICE appraisals, it was difficult to examine the impact of including carer QALYs on cost-effectiveness, as QALYs and ICERs were not routinely reported including and excluding carer QALYs. Generally, including carer QALYs appeared to increase the difference in QALYS between the intervention and comparator, consistent with the findings from the review of NICE appraisals. In future CUAs it would be helpful if authors explicitly specify whether carer QALYs were included or excluded, and the rationale for doing this, report the method used to include carer QALYs, report total and incremental QALYs separately for patients and carers and report separate ICERs including and excluding carer QALYs.

This review adds to the growing body of literature regarding the inclusion of health spillovers in economic evaluation. It provides a comprehensive, systematic review of CUAs across countries, conditions and interventions, and identifies a number of issues which are pertinent for both analysts conducting CUAs and decision-makers appraising them. A key limitation of the review lies within the level of information available. Within a NICE appraisal, a greater level of detail is available for both describing the methods and reporting results, and this is reviewed and critiqued by an independent assessment group. This level of detail is valuable in understanding how carer QALYs have been included, and the impact they have on the results. Developers of future guidance for the reporting of economic evaluations may wish to consider specifying that justification for including or excluding carer QALYs should be provided, the methods for doing so should be described, and results should be reported separately for patients and carers.

Unlike NICE appraisals, CUAs reported in journal papers do not necessarily link to a policy decision about the intervention. It is therefore not possible in this review to know how the results were used in decision-making, and whether the inclusion of carer QALYs was considered relevant, or whether decision makers considered cost-effectiveness thresholds lower than the standard in evaluating CUAs incorporating health spillovers(54).

Some limitations around the methods of this review should also be noted. Only one systematic reviewer conducted study selection and data extraction. English language studies were excluded, and although we are aware that very little evidence is published in languages other than English, we acknowledge that there is a possibility that data may have been missed. Studies were also excluded if population terms such as family carer or informal care were not mentioned in the abstract, again we acknowledge that there is a possibility that potentially relevant evidence may be available that did not fit this criteria. It should also be noted that this is a descriptive review, with no critical appraisal, and no judgement is made about the use of non-preference based measures, the use of cross-sectional data, and the validity of regression models used in the CUAs included in this review.

5. CONCLUSION

Relatively few CUAs at present have attempted to include carer or family member health-related QALYs generated from health spillover. Of those that have it appears that family and carer utilty, and QALYs are an important factor in CUAs and have the potential to impact the ICER in cost effectiveness analyses. Generally, including carer QALYs appeared to increase the difference in QALYS between the intervention and comparator, and where data were available, including carer QALYs appeared to reduce the ICER. A number of methodological factors have been identified as potentially significantly influencing the impact family member utilities have in cost utility analyses, and these should be considered in situations where health spillovers are included. Many of the issues raised here were previously identified in reviewing NICE appraisals,(3) and their identification in published CUAs too heightens the need for guidance in these areas.

Particularly, the rationale for why carer QALYs were included in our included studies was not always clear or consistent, and it was not always possible to determine the methods by which carer QALYs were included in the analyses reported here. It was noted here that there are some conditions and populations where the inclusion of carer QALYs is particularly common, particularly for chronic illnesses where carer burden is great.

This review included within-trial CUAs, which used carer utility data collected within the study, whereas the model-based evaluations relied on external sources. Weaknesses were noted in both types of evaluation. In some trial based evaluations significant missing data were noted, whilst for some of the model based CUAs relying on external data, it was noted that multiple studies using the same source but interpreting the data differently (as in the rotavirus examples), or relied on source data from a different disease area. It was also noted that some of these appeared to be based on cross-sectional data, which presents a weakness. Some studies relied on assumption, rather than empirical estimation. In future CUAs it would be helpful if details on the source data used for carer HRQoL were clearer.

It was also noted that different measures and measurement techniques were used across studies raising the issue of comparability across studies. Furthermore, different measures were used for patients and carers incorporated into the analysis and the implications of this are also unclear. Inconsistency in the number of carers included was also noted, ranging from one carer to the whole family, and some incorporated QALY losses for family members due to bereavement, clear rationale for their inclusion was rarely given.

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6. APPENDICES

APPENDIX 1 - SEARCH STRATEGIES

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to March 14, 2019

420 results

15th March 2019

#	Searches	Results
1	(cost effective* or cost benefit or cost utility or economic evaluation).tw.	132747
2	(QALY* or quality adjusted life year* or quality of life or DALY* or healthy life year* or healthy years equivalent*).tw.	246681
3	(euroqol or euro qol or eq5d or eq 5d or eq-5d or (euro adj qol) or (eur adj qual) or (eq adj 5d)).tw.	9174
4	(hui3 or hui 3 or health utilities index mark 3 or health utilities mark three or hui III or huiIII).tw.	466
5	(sf6D or sf 6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form sixD or sf-6d or 6d or 6-d or 6 dimension).tw.	7755
6	2 or 3 or 4 or 5	255853
7	(((family or families or network member* or household) adj5 member*) or relatives or caregiver* or carer* or informal care* or unpaid care* or parent* or spouse* or spillover*).tw.	653568
8	1 and 6 and 7	987
9	limit 8 to yr="2015 -Current"	420

Database(s): Embase 1974 to 2019 March 14

697 results

15th March 2019

#	Searches	Results
1	exp economic evaluation/	284724
2	exp "cost utility analysis"/	8746
3	exp "cost effectiveness analysis"/	139139
4	exp "cost benefit analysis"/	79988
5	or/1-4	284724
6	exp quality adjusted life year/	23128
7	exp "quality of life"/	450801
8	DALY$.ti,ab.	3346
9	healthy life year$.ti,ab.	178
10	healthy years equivalent$.ti,ab.	28
11	(euroqol or euro qol or eq5d or eq 5d or eq-5d or (euro adj qol) or (eur adj qual) or (eq adj 5d)).ti,ab.	17136
12	(hui3 or hui 3 or health utilities index mark 3 or health utilities mark three or hui III or huiIII).ti,ab.	664
13	(sf6D or sf 6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form sixD or sf-6d or 6d or 6-d or 6 dimension).ti,ab.	9150
14	or/6-13	464848
15	5 and 14	41689
16	(family adj5 member$).ti,ab.	199284

17	network member$.ti,ab.	1187
18	(household adj5 member$).ti,ab.	3566
19	relatives.ti,ab.	69620
20	exp caregiver/	69799
21	informal care$.ti,ab.	5707
22	unpaid care$.ti,ab.	437
23	carer$.ti,ab.	19370
24	caregiver$.ti,ab.	75841
25	spouse$.ti,ab.	20422
26	exp parent/	223766
27	spillover$.ti,ab.	3907
28	or/16-27	588059
29	15 and 28	2003
30	limit 29 to yr="2015 -Current"	697

Database(s): Econlit 1886 to March 07, 2019
4 results
15th March 2019

#	Searches	Results
1	(cost effective* or cost benefit or cost utility or economic evaluation).mp.	14325
2	(QALY* or quality adjusted life year* or quality of life or DALY* or healthy life year* or healthy years equivalent*).mp.	3503
3	(euroqol or euro qol or eq5d or eq 5d or eq-5d or (euro adj qol) or (eur adj qual) or (eq adj 5d)).mp.	164
4	(hui3 or hui 3 or health utilities index mark 3 or health utilities mark three or hui III or huiIII).mp.	19
5	(sf6D or sf 6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form sixD or sf-6d or 6d or 6-d or 6 dimension).mp.	50
6	2 or 3 or 4 or 5	3601
7	(((family or families or network member* or household) adj5 member*) or relatives or caregiver* or carer* or informal care* or unpaid care* or parent* or spouse* or spillover*).mp.	28206
8	1 and 6 and 7	11
9	limit 8 to yr="2015 -Current"	4

CRD
1 result
15th March 2019

Line	Search	Hits
1	((cost effective* or cost benefit or cost utility or economic evaluation))	22514
2	((QALY* OR quality adjusted life year* OR quality of life OR DALY* OR healthy life year* OR healthy years equivalent*))	11802
3	((euroqol or euro qol or eq5d or eq 5d or eq-5d))	790
4	(euro NEAR qol) OR (eur NEAR qual) OR (eq NEAR 5d)	654
5	((hui3 or hui 3 or health utilities index mark 3 or health utilities mark three or hui III or huiIII))	42
6	((sf6D or sf 6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form sixD or sf-6d or 6d or 6-d or 6 dimension))	72
7	((family OR families OR network member*)) OR ((household NEAR/5 member*)) OR ((relatives OR caregiver* OR carer* OR informal care* OR unpaid care* OR parent* or spouse* or spillover*))	5475

8	#2 OR #3 OR #4 OR #5 OR #6	11835
9	#1 AND #7 AND #8	1094
10	(#9) IN NHSEED	943
11	(#9) IN NHSEED FROM 2015 TO 2019	1