Systematic Review of Cost-Utility Analyses That Have Included Carer and Family Member Health-Related Quality of Life.

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ABSTRACT

Objectives: Health interventions for patients can also affect the health of their informal carers and family members. These changes in carer or family member health could be reflected in cost-utility analyses (CUAs) through inclusion of their quality-adjusted life years (QALYs). We conducted a systematic review to identify and describe all CUAs that have included family member health-related QALYs.

Methods: Four bibliographic databases were searched from inception to July 2021. A two-stage sifting process for inclusion of studies was undertaken. We performed data extraction using a standardised data extraction form, and performed a narrative synthesis of the evidence.

Results: 40 CUAs published between 1999 and 2021 were identified. CUAs were conducted in 15 different countries. CUAs examined thirteen different conditions including fifteen CUAs on vaccination, five on Alzheimer's disease, two on Parkinson's disease, three on dementia and two on terminal illness. The EQ-5D was the most commonly used measure of family member health. Generally, including carer QALYs resulted in lower incremental cost-effectiveness ratios.

Conclusions: When considering the total number of economic evaluations published, few have included family member QALYs and the methods for doing so are often inconsistent and data sources often limited. Estimation of family member QALYs in patient CUAs were regularly uncertain, and often substantial in magnitude. The findings highlight the variation among methods, and call for greater consistency in methods for incorporating family member QALYs in patient CUAs.

HIGHLIGHTS

- To date, cost-utility analyses have rarely included family member QALYs.
- Including family QALYs generally resulted in lower ICERs.
- Methods for including family QALYs have varied, consistency is important.

INTRODUCTION

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. 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). 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).

Previous research suggests relatively few CUAs have included family QALYs. A 2012 systematic review found only six published economic evaluations that included carer QALYs (3), 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. There may be particular conditions where the inclusion of carer QALYs is more common, particularly where there is a clear carer burden. However, a review by Lin et al (2019) found only nine of 63 published economic evaluations in Alzheimer's disease or dementia included carer HRQoL(4), whilst in a review of paediatric CUAs, Lavelle et al (2019) found that only 15 out of 142 CUAs included health outcomes for family members(5). Furthermore, a recent review (6)of published NICE Technology Appraisals (TAs) and Highly Specialised Technologies (HSTs) showed that twelve of 414 TAs (3%) and four of eight HSTs (50%) included carer health-related quality of life (HRQoL) in CUAs. Including carer HRQL increased the incremental QALYs and decreased incremental cost-effectiveness ratios

(ICERs) in all cases. The authors concluded that the inclusion of carer HRQL in NICE appraisals is relatively uncommon and has been limited by data availability. Whilst few CUAs have included carer HRQoL it has been suggested that ignoring the potentially large impacts to carers may be inequitable and inefficient(7). This is because, some health conditions, as well as having a significant impact on the quality of life of patients, also have a significant impact on the quality of life of those that are involved in the care of those patients. By ignoring the impacts on carers we are not valuing certain treatments and interventions that have a substantial impact on carers highly enough, and ultimately the impact of that may be that these treatments are withheld. However, variation in how costs and outcomes are included in CUAs and the extent to which decision makers value the importance of including family member HRQoL cause inconsistency in comparisons between different CUAs. For example, the National Institute for Health and Care Excellence (NICE) suggest that economic evaluations should include direct health effects for patients and carers where relevant(8), with The Second Panel on Cost-Effectiveness in Health and Medicine in the USA similarly recommending that health effects should be those accruing to patients and other affected parties including caregivers(9). Whilst, Guidelines for submissions to the Pharmaceutical Benefits and Advisory Committee in Australia (10) 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 refer to carers at all (11).

The first objective of the systematic review was to identify all CUAs of patient interventions that have included QALYs of informal carers and family members published up to 2021. The second objective was to determine and outline the methods that have been used in these studies to measure health spillovers and to include them in the CUA, and to report the results with and

without family member or carer QALYs, where available. This will provide a comprehensive overview of the existing CUAs that have included health spillovers to date.

METHODS

SEARCHES

We performed searches in four bibliographic databases (MEDLINE via Ovid, 1946 to 2021; Embase via Ovid, 1974 to 2021; EconLit via Ovid, 1986 to 2021; and NHS EED via CRD 1995-2021) to retrieve studies where CUAs have included health spillover effects. Searches were performed by AB in 2015, updated in March 2019, then in July 2021 using the same search strategies. (For search strategies see Appendix 1 supplementary materials).

SCREENING AND ELIGIBILITY

We performed a two-stage sifting process for inclusion of studies, (title/abstract then full paper sift), with studies scrutinised according to the inclusion and exclusion criteria in Table 1. 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.

(Table 1 Inclusion and exclusion criteria – about here)

DATA EXTRACTION STRATEGY

Data were extracted into a standardised data extraction form. Data extracted included: condition, intervention, population, country, perspective, number and 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.

METHODS OF DATA SYNTHESIS

We performed a narrative synthesis of the evidence. The key areas documented were the number of CUAs 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.

RESULTS

40 CUAs met the eligibility criteria for this review (Figure 1). The key characteristics of the included studies are provided in **Error! Reference source not found.** (Further characteristics are provided in Table S1 supplementary materials).

(Figure 1 PRISMA flow diagram – about here)

STUDY CHARACTERISTICS

Included studies were published between 1999 and 2021, although one study (12) used family member data that had been collected between 1986 and 1994(13), and one study did not fully report the family member data collection dates. 13 CUAs were conducted in the UK, 10 in other European countries, 6 in the USA, 4 in Canada and 2 in Australia.

(**Table 2** – about here)

Fifteen CUAs examined vaccination in children with the majority of these focusing on rotavirus vaccination (15, 17, 20, 26, 29-31, 36, 37, 39, 42, 44, 47, 50, 51). Five studies examined Alzheimer's disease (18, 24, 25, 27, 38), 3 examined dementia (33, 35, 53), 2 examined Parkinson's disease (32, 54), and two examined interventions for patients with a terminal illness (28, 43). The included CUAs covered a wide variety of interventions, including pharmaceutical drugs, complex interventions and psychological interventions.

Most CUAs included QALYs for one carer, most often the primary carer or one parent. Two CUAs included QALYs of the four closest family members of the patient (17, 46). QALYs for both parents were included in 5 CUAs of childhood illness (26, 29, 31, 42, 49) . In two of these CUAs, a further adjustment to account for the proportion of single-parent families was made (26, 29). One CUA included 2.5 carers per patient, based on previous literature on family size (28). Two CUAs did not state the number of carers that were included (20, 21). Four CUAs that included health spillovers additionally included QALYs for bereaved family members (12, 17, 28, 43).

SOURCES OF FAMILY MEMBER UTILITIES

A summary of findings of the included studies are provided in Table S2 supplementary materials.

The source of the family member utility values differed across the included CUAs. Some were generated via direct elicitation through a clinical trial, some via an external study of the same disease, some via an external study of a different disease and some used arbitrary adjustments.

Thirteen CUAs (14, 16, 18, 19, 21, 22, 33, 35, 38, 40, 45, 48, 49) used estimates of family member utilities from a clinical trial. In four of these CUAs, data from family members in the intervention and control arms of a randomised controlled trial (RCT) was collected to enable between-group differences in family member QALYs to be estimated (16, 21, 35, 48). In two of these studies, significant missing data for carer utilities was noted (21, 35); for instance in Flood et al(21), full data was available from only 113 carers out of the 321 patients in the study. In contrast, in another CUA, carer data was obtained from almost all (180 out of 191) of the patients in the trial (48).

In twelve model-based CUAs rotavirus vaccination was examined (15, 17, 20, 26, 29-31, 36, 37, 39, 42, 44, 47, 50, 51) , with all obtaining their estimate of family member QALYs from the same external study of the same disease with a cross-sectional design (55).

In five CUAs, family member QALYs were estimated from an external study of a different disease (12, 23, 34, 41, 46). For example, one CUA of an intervention for ADHD (46) estimated family member QALYs from an external study of the family members of meningitis survivors.

Arbitrary adjustments were made in some model-based CUAs. For instance in Bilcke et al (2009)(15), it was assumed that parents who did not seek professional medical treatment for their child's rotavirus incurred only 50% of the utility decrement of the parents who did seek medical treatment.

UTILITY ELICITATION TECHNIQUE

34 CUAs used indirect measures of family member utility; of which 25 used the EQ-5D and 4 used the SF-6D (24, 25, 27). Direct measures of family member utility (including standard

gamble and time trade-off techniques) were used in four CUAs which referred to external studies for these estimates (12, 26, 34, 41).

IMPACT ON COST-EFFECTIVENESS

Each of the included CUAs was assessed to identify if the inclusion of family member QALYs increased the ICER, decreased the ICER, or if it was not possible to assess. In 29 CUAs, it was possible to assess the impact of including health spillovers on cost-effectiveness. In these CUAs, there was variation in how the impact was reported. In 19 of the 27 CUAs, separate ICERs which included and excluded family member QALYs were reported, and in 10 CUAs disaggregated estimates of patient and family member QALYs were reported. Only 4 of the 27 CUAs reported disaggregated patient and family member QALYs, as well as separate ICERs including and excluding family member QALYs.

Twelve CUAs reported data on patient and carer QALYs in the analysis, with 10 reporting that carer incremental QALYs were positive (Table 3). In 3 CUAs, family member incremental QALYs were similar in magnitude to patient incremental QALYs (28, 30, 48).

(Table 3**.** Studies presenting data on family member QALYs and a summary of the results. – about here)

The twelve CUAs which evaluated rotavirus vaccination used the same external study to estimate patient and family member QALYs (55). The external study reported that average carer QALYs lost to rotavirus were similar to average patient QALYs lost to rotavirus. One patient CUA only included carer QALYs and omitted patient QALYs, and on this basis found

the intervention was cost-effective (45). Conversely, one CUA estimated that carer QALYs would be lost as the patient's health and life expectancy improved due to a longer duration of care burden (12).

Eighteen CUAs reported the impact of including family member QALYs on the ICER (see Table 4.). One CUA of rotavirus vaccination reported that relative to not including carer QALYs at all, including the QALYs of one carer per patient reduced the ICER by 50%, and two carers per patient reduced the ICER by 75% (18). In seven CUAs, 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 (23, 24, 33, 38, 43, 44, 52).

(Table 4. Impact of including family member QALYs on the ICER – about here)

In eleven CUAs it was not possible to assess the impact of including health spillovers on cost-effectiveness. There were various reasons for this. In 4 of the CUAs, QALYs for patients and carers were not presented in a disaggregated form (20, 22, 26, 34) and in one CUA, how they were combined was unclear (36). In one CUA patient utility values were estimated but not used to generate QALYs (40)and in one CUA carer QALYs were measured but not included in the ICER calculation (21). In three of the patient CUAs, only family member QALYs were included and patient QALYs were excluded (19, 45, 49). These CUAs estimated carer QALYs generated from treatment of alcoholism (45), treatment of childhood type 1 diabetes (49), and child QALYs generated from treatment of anxiety disorder in mothers (19).

DISCUSSION

We identified only 40 CUAs of patient interventions which have been carried out have included family member QALYs. The paucity of such CUAs has also been noted in previous studies (3, 56). This is surprising given the importance attributed to the inclusion of family member QALYs by previous authors that have asserted that a patient's health may directly influence the wellbeing of others who care about them as well as those who care for them (2). In this review we found including family member QALYs generally led to reduced ICERs, these were often substantial reductions (although in some cases inadequate reporting limited our ability to assess the impact in terms of magnitude or direction on the ICER). Therefore, this is important as ignoring the potentially large impacts to carers may be inequitable and inefficient (7).

Methods used in the analyses

Given that a number of the studies were from a UK or a US setting, the methods are likely to have been influenced by NICE Methods for Technology Appraisal guidance (8) and The Second Panel on Cost-Effectiveness in Health and Medicine in the US, respectively, with both recommending the inclusion of family member HRQoL(9). Whilst studies from Canadian, Dutch and Australian settings, will use guidance that differs from the UK and US settings, guidelines for submissions to the Pharmaceutical Benefits and Advisory Committee in Australia (10) 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 (11), and the guidance for the Netherlands (57) do not refer to carers at all. This illustrates that comparisons across settings will be inconsistent due to differing guidance, but that decisions within settings may also be inconsistent. Our findings have illustrated that even in settings that do recommend the inclusion of carer QALYs few CUAs

did include carer QALYs. Furthermore, variation in how costs and outcomes are included in CUAs and the extent to which decision makers value the importance of including family member HRQoL cause inconsistency in comparisons between different CUAs.

Conditions included in the analyses

Consistent with Wittenberg et al's 2019 (58) systematic literature review of family and carer HRQoL that found 15 (of 80) studies reported carer HRQL in Alzheimer's disease, and a previous analysis of NICE appraisals (6), many of the studies we identified considered chronic conditions, such as Alzheimer's disease, and some of the included studies here focussed on a paediatric population. Furthermore, there were a small number of CUAs in which patient utility values were not included, and only looked at family member utility (19, 45, 49). Arguably, the conditions studied in these CUAs (alcoholism (45), anxiety disorder in mothers (19), and childhood type 1 diabetes (49), have a large impact on family member utility and were studied separately for this reason. 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. Although, Lin et al (2019) found only nine of 63 published economic evaluations in Alzheimer's disease or dementia included carer HRQL (4), and Lavelle et al (2019) in a review of paediatric CUAs, found that only 15 studies out of 142 CUAs included health outcomes for family members (5). Thus demonstrating that the inclusion of carer HRQL is not routine even in these disease areas. It is not clear to what extent these are influenced by precedents set and data availability in these conditions or populations.

Data collection methods

The trial-based CUAs we identified undertook carer data collection in parallel with patient data collection in the trial, whereas the model-based CUAs relied on external sources. Obtaining cost effectiveness evidence alongside evidence of effectiveness in randomised controlled trials has been suggested to maximise the information available for analysis, and data collection in this manner is often requested by funders. When relying on external data, the models faced challenges, 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, estimates of family member QALYs used in the model-based CUAs were often based on cross-sectional data which may lack validity. However, the alternative approach of collecting data from family members in clinical trials of patient interventions may be less feasible; it was observed that substantial missing data from family members in several trial-based CUAs included in this review was generated. Also, some of the models relied on assumption, rather than empirical estimation.

HRQoL Measures used in the analyses

The majority of studies used the EQ-5D to measure family member health. This is consistent with the systematic review by Wittenberg et al (2019) which found that the EQ-5D was the most common instrument used to measure carer utility (used in 69% of cases) (58). The advantage of using the EQ-5D is that it is the recommended measure of patient health in CUA by a number of guidance bodies (e.g. Netherlands (57), NICE (8)), and using the same instrument for patients and family members may allow for more straightforward aggregation of patient and family member QALYs. A disadvantage of using generic HRQoL measures such as the EQ-5D for measuring family member health is that it has been suggested that such measures may be insensitive in detecting the psychological stress resulting from a family member caring about and for a patient (59). Although as has been shown in a number

of studies reported here the EQ-5D has been able to detect spillover effects and may indicate it is quite useful in detecting such effects. Therefore, there is mixed evidence on the responsiveness of the EQ-5D-5L for measuring the changes in health of informal carers, and further research is needed on this.

Carer QALYs are also measurable through the CarerQoL questionnaire. Although the CarerQoL questionnaire measures care-related quality of life but not health-related quality of life, this questionnaire may be a potential measure for spillover effects among carers which could be included in a standard cost-utility analysis provided that appropriate conversion techniques are implemented to enable them to be subsequently aggregated to patient QALYs (60, 61).

Some studies used direct utility elicitation methods which have been suggested to be more likely to lead to overestimates of health spillovers, and potentially double counting in a CUA (62). This is because it may be difficult for family members to disentangle the effect on their own health, from 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.

Family members included

We found inconsistency in the number of family members included, ranging from one to four family members per patient. The justification for this was not always clear, and inconsistencies were observed in seemingly comparable scenarios such as the number of parents included for a childhood illness, and whether or not family member QALY decrements resulting from bereavement are additionally included in CUAs of interventions

impacting patient survival. Canaway et al (2019) found that care at the end of life impacted a median of eight close individuals to the patient, and suggested that economists should include QALYs of the three closest individuals to the patient (63).

Where patient and family member QALYs were reported, including carer QALYs consistently showed carers experienced QALY gains as a result of the intervention, increased incremental QALYs, and so interventions appeared more cost-effective where carer HRQL was included. This is consistent with previous studies where including carer health outcomes/costs led to less favourable cost-effectiveness results in pairwise ICER comparisons for only two of 43 paediatric studies (64) and two of 33 Alzheimer's disease/dementia studies (4). However, we found that in a number of CUAs it was not possible to assess the impact of including health spillovers, either because QALYs for patients and carers were not presented in a disaggregated form, or how they were combined was unclear, or they simply were not included. This emphasises the need to report estimates of patient and carer QALYs both separately as well as combined in CUAs. Further, there was variation in whether carer QALYs were included in the base case or secondary analyses, and raises the question of how to implement consistent methods in future CUAs.

Limitations of this review are that only one systematic reviewer conducted study selection and data extraction. Whilst we acknowledge this is a significant limitation, the methods were conducted robustly and we have checked the final list of included studies for missing eligible studies. We are also confident that if any eligible papers had been missed they would not substantially change the conclusions from this work. Further, only English language studies were included; therefore studies published in other languages may have been missed. Studies were also excluded if population terms such as family member or informal carer were not

mentioned in the abstract. As a result we may not have captured CUAs which included family member QALYs without mentioning having done this in the abstract. Another limitation is that we did not include every type of familial relationship explicitly in the search strategy, in order to prevent our search strategy from being over-sensitive. Typically studies only include a few family members (63). Instead, our search strategy adopted a focus at the title/abstract level to include CUAs which included spillovers experienced by the 'household members' of patients (who may be non-caregivers), as well as the 'carers/caregivers' of patients which is likely to have captured most CUAs of elderly patients (e.g. with dementia) who in many cases will receive informal care from the their adult children.

It should also be noted that this is a descriptive review with no critical appraisal.

CONCLUSION

Relatively few CUAs of interventions for patients to date have included carer or family member health-related QALYs. Family member QALY estimates, in many cases were substantial in magnitude, and therefore resulted in lower ICERs when included. This review raises several methodological issues including the overall approaches available for including health spillover effects in an economic evaluation. Estimations of family member QALYs in patient CUAs were regularly uncertain, and often substantial in magnitude. The findings highlight the variation among methods. There is a conspicuous need for standardisation of methodologies for including family member QALYs in patient CUAs. We recommend that future CUAs of patient intervention which include family member QALYs, present estimates of QALYs and ICERs both with and without family member QALYs.and call for greater consistency in methods for incorporating family member QALYs in patient CUAs.

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