A REVIEW OF THE METHODS USED TO ESTIMATE AND MODEL UTILITY VALUES IN NICE TECHNOLOGY APPRAISALS FOR PAEDIATRIC POPULATIONS

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EXECUTIVE SUMMARY

Introduction

The evaluation of technologies for children and adolescents presents particular methodological challenges, and one key challenge is in the assessment of health-related quality of life (HRQoL). Children and adolescents may be less able to report or assess their own health or the impact of their condition on aspects of their health-related quality of life, and this may require a mixture of proxy-report and self-report of their health according to what is appropriate for their age and cognition. In addition, their health status may in turn have substantial impacts on health and the quality of life of their parents, siblings and wider family members. This raises the issue of what can and should be done to measure and value benefits of technologies for children and adolescents for economic evaluation.

The purpose of this review was to examine previous National Institute of Health and Care Excellence (NICE appraisals and methods used to generate health state utilities for child and adolescent health states in different patient groups. This will enable a better understanding of how utility values have been generated to reflect the HRQoL of children and adolescents to generate QALYs for health technology assessment. It may provide a basis for NICE's future considerations about recommendations for estimating child and adolescent health utilities.

Methods

We searched for all NICE Technology Appraisal (TA) and NICE Highly Specialised Technology (HST) appraisals where the licensed indication for the technology included people under 18 years. The review includes 31 nice appraisals. We assessed publicly available documents: the Evidence Review Group or Assessment Group reports, committee guidance documents and, where required, the company submission. The utility values in these reports related to the main health effect of the condition, treatment, adverse events, complications and the health utility of others (such as carers or other family members).

Results

Most appraisals generated utility values using EQ-5D scored using the adult version of the EQ-5D exclusively (n=14), thirteen included other utility measures and direct elicitation methods of patient own utility alongside EQ-5D, and four did not use the EQ-5D. Seven appraisals used both adult and child and adolescent population-specific measures: Health Utilities Index Mark

2 (n=4); a paediatric-specific preference-based measure for atopic dermatitis (n=1); the youth version of the EQ-5D (EQ-5D-Y) generated using mapping and valued using the UK EQ-5D adult tariff (n=2). All of the appraisals that used a child and adolescent-specific population specific measure also used at least one other method to generate utility values.

The most common method used to generate utility values was the EQ-5D scored using the UK value set for adults (n=27 appraisals included utility values generated using EQ-5D). Other adult generic preference-based measures were also used, including HUI3, as well as direct elicitation methods of patient own utility using standard gamble and time trade-off elicitation methods, though typically these were used to generate only a subset of health states in the economic model, with the EQ-5D also used to generate utility values for other health states.

Over half of the appraisals (n=17, 55%) applied some form of adjustment to utility values to estimate utility values in the child, adolescent and adult populations. The most common form of adjustment of utility values was age adjustment (n=12, 39%) and although the approaches varied considerably most used a published formula in the literature estimated using adult responses to health-related quality of life measures. For example, in five cases linear algebraic extrapolation was used to extrapolate from the utility values in UK adult population to ages under 16. Other forms of adjustment were used to account for the characteristics of the patient population in the dataset of interest using regression analysis.

The cost-effectiveness analyses used a wide range of utility values to reflect general population health for children and adolescents, varying from 0.85 to 1. In the absence of data, the authors assumed these values or derived them by extrapolating from adult responses.

Information on the ages of those completing the preference-based measured used to estimate utility values of the child and adolescent population was rarely reported.

Committees rarely commented on the limitation of the use of adult utilities as reflective of child utilities. Committees accepted values used in previous models or those retrieved from systematic searches of literature because the choice of values was justified by the absence of specific data for children and adolescents. In cases where the committees did comment on the limitations of the approaches used to establish utility values for children and adolescents, it was to highlight the use of secondary sources to generate utility values rather than evidence from the clinical studies of the health technology in question. Specifically mentioned were the trade-offs in the relevance of the sample population to the model population, requirements of the NICE Methods Guide (e.g., preference-based measure) and the size and quality of the studies (e.g., levels of missing data).

Discussion

The generation and use of utility values for economic models for child and adolescent populations is an area that would benefit from both further research and clearer recommendations from institutions such as NICE around best practice in the area.

Our review demonstrates that, in submissions made to NICE, there is substantial variation in the approaches that have been taken in this area. There is widespread use of approaches that are generally considered appropriate for adults, but it remains unclear if this is an appropriate approach to the estimation of utility values for children and adolescents. Even within those appraisals that used adult utility values, there are a range of approaches applied. For example some appraisals use EQ-5D, others use EQ-5D-Y but with adult EQ-5D utility values attached. Others use varying methods to try to adjust adult utility values to extrapolate to younger age groups. These different approaches will all generate different estimates of health gain, and consequently cost-effectiveness but, to date, few of these issues have been investigated thoroughly.

Suggested points for consideration by NICE:

The NICE Methods Guide refers to the existence of alternative validated measures for children and adolescents, but it does not recommend any particular approach, nor rule out using the adult version of the EQ-5D. Subsequent updates of the Methods Guide may wish to consider the following issues:

- At a minimum, committees should be provided with information about the ages and distribution of age of those completing the preference-based measured used to estimate utility values of the child and adolescent population. This is particularly the case if utility values are retrieved from the literature searches rather than a main trial.
- Should NICE recommend the use of child and adolescent specific measures? This may encourage more companies to administer such instruments in their clinical studies.

  - If so, which measure(s)?
  - What should be done when such data are not available?
  - How should the measure(s) be valued? This will include selection of the value set to generate utilities, or if appropriate selection of appropriate methodology used to generate utility values including population, elicitation technique, and perspective
  - Should the adult reference case measure - EQ-5D - be used to represent child and adolescent health in cost-effectiveness analyses, and if so under which circumstances?
- How should any potential transition between self-report and proxy-report utility values be managed?
- How should any potential transition between measures in cost-effectiveness analyses be managed? Different measures may be used as the patient ages
- Should utility values be age-adjusted for the child and adolescent population? If so, how?
- How should general population health be estimated for the child and adolescent population aged 0 to 18 years?

Recommendations for future research:

- Evidence of the content validity and wider psychometric performance of child and adolescent preference-based measures to determine whether (and under which circumstances) they are appropriate for use in economic models. This can include content validation in all age groups that the measure is used in (since this may differ to the age group that the measure was developed for) and across a range of conditions
- Generation and validation of appropriate scoring systems to generate utility values from existing child and adolescent population preference-based measures, for example via mapping from widely used child profile measures as well as value sets for child and adolescent population preference-based measures
- Comparison of utility values and ICERs generated using child and adolescent population preference-based measures, EQ-5D and mapped utility values for the same patients where possible
- Potential generation of an exchange rate between adult EQ-5D utilities and child utilities, to enable committees to consider the equivalent HRQoL impact and ICER if

the utilities were generated using child self-report health-related quality of life data rather than adult EQ-5D data, potentially using preference-based mapping

- Examine whether differences in adult and paediatric general population utility values can substantially influence results in models with long time horizons (e.g. decades or a lifetime) and a proportionally small duration where the simulated subjects are a part of the child and adolescent population
- Review and critical assessment of potential methods that can be used to model utility data for child and adolescent populations, including:
    - Transition between self-report and proxy-report utility values
    - Transition between measures in cost-effectiveness analyses as the patient ages
    - Age-adjustment of utility values for the child and adolescent population
    - Estimation of disease free health for the child and adolescent population aged 0 to 18 years

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ABBREVIATIONS AND DEFINITIONS

AG: Technology Assessment Group

CUA: Cost-utility analysis

DCE: Discrete Choice Experiment

EQ-5D: EuroQol- 5 Dimension

ERG: Evidence Review Group

HRQoL: Health-related quality of life

HST: Highly Specialised Technologies

HSUV: Health state utility value

HTA: Health Technological Appraisal

HUI: Health Utilities Index

ICER: The incremental cost-effectiveness ratio

MTA: Multiple Technology Appraisal

QALY: Quality-adjusted life year

ScHARR: School of Health and Related Research

SF-36: 36-Item Short Form Survey

STA: Single Technology Appraisal

VAS: Visual Analogue Scale

1. INTRODUCTION

1.1. BACKGROUND

Economic evaluation is now an important component of decision-making in health care systems across the world. Methods for these analyses must be appropriate for decisions relevant to many different populations including children, adolescents, working age adults and retired people. The evaluation of technologies for children and adolescents presents particular methodological challenges, one of which is in the assessment of health-related quality of life. Resource allocation decisions are important for all economies with budget constraints, and health presents particular challenges where resources are allocated across health and social care sectors and also across different populations including children, adolescents, working age adults and retired people. The allocation of resources across different populations presents methodological challenges, as different information or different methods may be most appropriate. The evaluation of technologies for children and adolescents presents particular methodological challenges, and one key challenge is in the assessment of health-related quality of life (HRQoL). For example, children and adolescents may be less able to accurately report their own health, and this may require a mixture of proxy-report and self-report of their health according to what is appropriate for their age and cognition. This raises the issue of what is and should be done to measure and value benefits of technologies for children and adolescents for economic evaluation.

Cost-utility analysis (CUA) is commonly used in the appraisal of interventions and technologies, and is required by NICE for health technology assessment[1]. CUA describes the relationship between costs and health benefits measured using quality-adjusted life years (QALYs). The QALY requires data that express HRQoL in the form of a single value, known as a health state utility value (HSUV), which is anchored on a 1-0 scale where 1 represents full health and 0 is equivalent to dead, with negative values representing health states worse than being dead.

The NICE Guide to the methods of technology appraisal 2013 (“Methods Guide”) includes a reference case which specifies the methods considered by NICE to be the most appropriate for the Appraisal Committee's purpose for technology appraisals for both paediatric and adult populations[1]. The reference case in the Methods Guide is the recommendation of the use of EQ-5D to generate QALYs for adult populations. The Methods Guide further states that

HRQoL should be self-reported directly from patients, or, if that is implausible, their carers[1]. However, the Methods Guide is not as prescriptive for children and adolescents:

"When necessary, consideration should be given to alternative standardised and validated preference-based measures of health-related quality of life that have been designed specifically for use in children. The standard version of the EQ-5D has not been designed for use in children. An alternative version for children aged 7–12 years is available, but a validated UK valuation set is not yet available". (page 42)

The NICE Methods Guide therefore allows a range of different preference-based measures to be used to generate utility values for the assessment of technologies for use in child and adolescent populations. There is a large body of literature reporting that different measures generate different utility values when used on the same patients (for an overview see[2]), meaning that using different measures to assess interventions for child and adolescent populations may not be compatible with the requirement to make decisions in a consistent manner. This raises issues of how best to estimate utility values reflecting the health of children and adolescents and incorporate the child-to-adult transition in models. The appropriate estimation of utility values involves multiple considerations:

- which dimensions of health-related quality of life to include (and the basis of the selection);
- whether the dimensions of health-related quality of life vary by age (for example different dimensions for adolescents and infants);
- whether the health state of the child is self-reported by the child or proxy-reported by their carer (which will differ by age and cognition);
- valuation of the health state classification system including which technique (for example time trade-off),
- whose values (for example representative sample of the UK population), and
- from which perspective (adult perspective – imagining what it would be like for you now to experience the health states, or child perspective – for example imagining what it would be like for a 10 year old child to experience the health states).

One option to generate utility values for children and adolescents is to generate utility values for adults, using self-report EQ-5D, and assume that those estimates would be the same for children and adolescents living with the same condition. Whilst this maintains comparability between appraisals for children, adolescents and adults, it may not be appropriate to expect that children and adolescents experience the condition in the same way as adults. Another option is to use child and adolescent measures that enable children and adolescents to self-report their health where possible and to use proxy-report where this is not possible. Whilst this potentially ensures a more accurate representation of the child's and adolescent's experience, it raises issues of comparability between appraisals and methodological issues around the combination of self-report, proxy-report and adult measures once the child progresses into adulthood. Both approaches also require a decision to be made on normative valuation issues raised earlier, including, whose values are used for the health states and using which perspective.

Aims and objectives

The purpose of this project is to examine NICE technology appraisals to identify the methods used to estimate and model utility values for child and adolescent health states in different patient groups to enable a better understanding of how utility values have been generated for use in health technology assessment. This may provide a basis for NICE's future recommendations relating to the estimation of child health utilities within the technology appraisal and scientific advice programmes.

The objectives are:

1. How have previous NICE technology appraisals estimated child and adolescent health utilities?
2. When the cost effectiveness analysis requires the tracking of patients through childhood and into adulthood, how have the health utilities been estimated and modelled?
3. What limitations in the methods used to generate utility values for children and adolescents have been reported by committees?

2. SUMMARY OF GENERIC PREFERENCE-BASED MEASURES

This section provides a summary of some of the available generic preference-based measures for adults and for children and adolescents. The summary is not exhaustive of all measures (for a recent overview see [2]).

EQ-5D

The EQ-5D is the most commonly used generic preference-based measure for adults[3]. The descriptive system is measured in five dimensions: mobility; self-care; usual activities; pain/discomfort; and anxiety/depression. The original version, the EQ-5D-3L, has 3 levels of severity for each dimension (no problems, some problems, extreme problems/unable). EQ-5D has a large number of value sets including a UK value set elicited using the time trade-off technique with adults[4 5]. The newer version of the EQ-5D, the EQ-5D-5L, has 5 levels for each of the 5 dimensions (no problems, slight problems, moderate problems, severe problems and extreme problems). and though there is a value set for England the EQ-5D-3L value set can also be used via mapping functions[6 7]. If EQ-5D-5L is used in technology appraisal submissions NICE currently recommends use of a cross-walk to the EQ-5D-3L valuation set[8 9].

HUI2 and HUI3

The Health Utilities Index (HUI) is a preference-based measure originally developed for use with children with cancer, although it is more widely regarded and used as a generic preference-based measure. The HUI currently consists of two systems, HUI2 and HUI3, both of which can be used for children and adolescents.

The HUI2 descriptive system comprises the following seven dimensions: sensation; mobility; emotion; cognition; self-care; pain; and fertility[10]. Each dimension has between three and five levels, although the fertility dimension is rarely used. The HUI3 has eight dimensions: vision; hearing; speech; ambulation; dexterity; emotion; cognition; pain. Each dimension has between five and six levels[11]. HUI2 has a UK value set[12] alongside a Canadian value set[10], whilst the HUI3 has a Canadian value set[11]. Both HUI2 value sets were elicited using standard gamble and visual analogue scale elicitation techniques of the adult general population using a child perspective, where the Canadian sample was made up of parents of children. The HUI3 value set was elicited using standard gamble and visual analogue scale elicitation techniques of the adult general population using their own perspective.

EQ-5D-Y

The EQ-5D-Y is the child-friendly version of the EQ-5D. The EQ-5D-Y descriptive system is almost identical to the adult version, comprising of five dimensions: mobility; looking after myself; doing usual activities; having pain or discomfort; feeling worried, sad or unhappy[13]. These are the same dimensions of the EQ-5D, reworded to ensure relevance and clarity for children and adolescents. Each dimension has 3 levels: no problems, some problems and a lot of problems[14]. It is answerable by a proxy (e.g. parent or carer) for those aged 4–7 years and self-report for those aged 8–11 years. Between ages 12–16 the youth or adult versions can be used and from 16 onwards the adult version is generally preferred[14]. There is no EQ-5D-Y UK value set and though it is possible to use the EQ-5D value set by applying the tariff to the analogous domains and levels[4], there are limitations associated with this approach[15].

CHU9D

The CHU9D has 9 dimensions, with 5 levels each, developed with children to assess the child/adolescent’s functioning across the health domains of worry, sadness, pain, tiredness, annoyance, school, sleep, daily routine and activities[16 17 18]. It was designed for use in children aged 7–11 years, but can be completed via parent/guardian proxy for children aged 4-7 years. Value sets exists for the UK[19], Australia[20 21] and The Netherlands[22]. The value sets were generated using standard gamble with adult general population values for the UK and a using a discrete choice experiment with adult members of the Netherlands general population. Discrete-choice experiment, time trade-off and standard gamble methods were used with adolescent general population to generate values for Australia.

3. METHODS

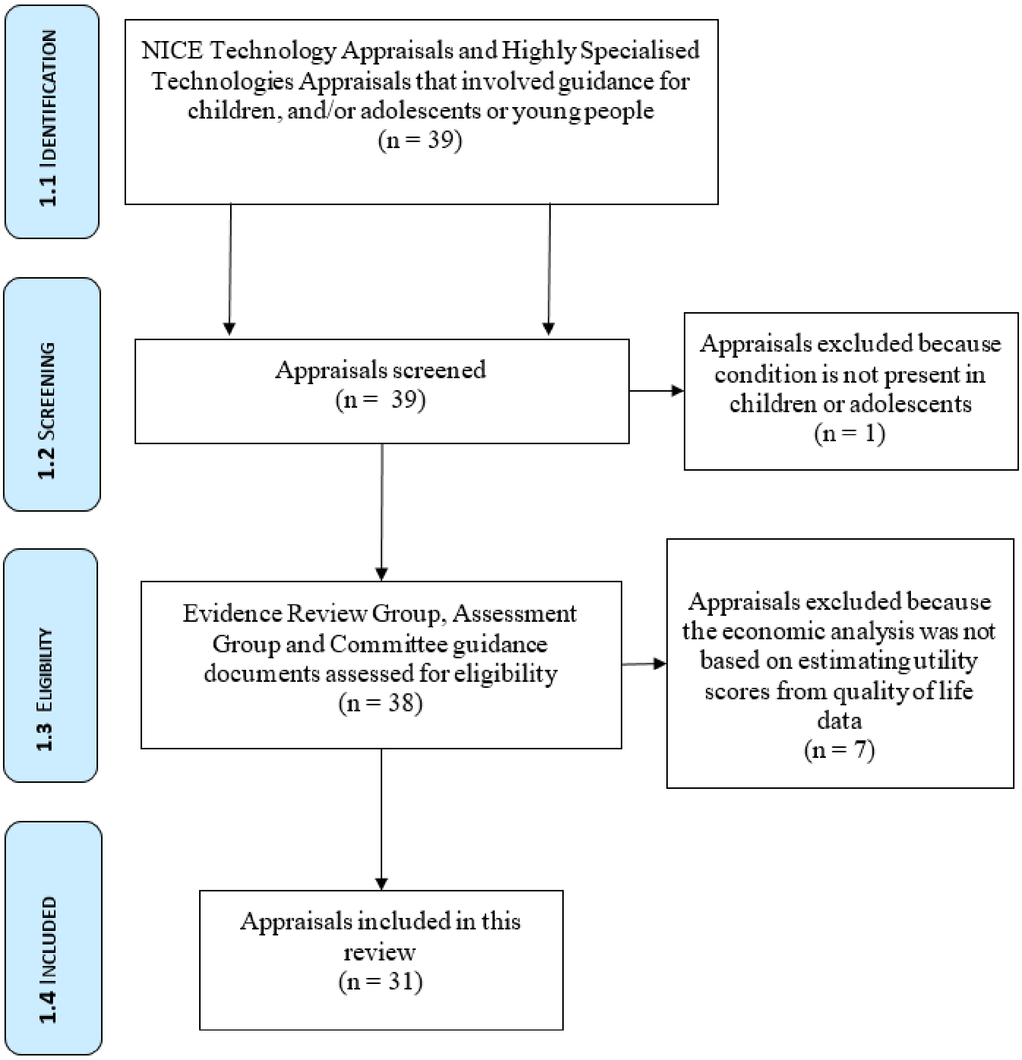
3.1. SEARCH STRATEGY

The NICE Guidance and advice list website was accessed on 12th April 2018. The search strategy for this cross-sectional review comprises We searched for all NICE Technology Appraisal (TA) and NICE Highly Specialised Technology (HST) appraisals documents and reports publicly available (on NICE website) and where the licensed indication for the technology included use in children and/or adolescents or young people (under 18 years). This review is based on the publicly available Evidence Review Group (ERG) or Assessment Group (AG) report, and committee final appraisal and final evaluation determination on how the technology should be used in the NHS in England. Company submission documents that are available on NICE's website were retrieved and reviewed when more detail was required on the methods of assigning child utility values in the company's models.

3.2. INCLUDED STUDIES

A total of 33 NICE Technology Appraisals (TAs) and 6 NICE Highly Specialised Technologies (HST) reports were identified. One report was excluded from this review because the treatment (pacemaker) is not typically introduced in child or adolescent populations. Seven were excluded because the economic analysis was not based on a cos-utility analysis. Appraisals where the committee guidance covered both adult and children and adolescents were included, even in cases where the economic models simulated only adults, since the choice of estimating cost effectiveness only for adults may have been reached after a review and discussion of alternative approaches including generating utility values for children and adolescents. We intended to identify and record any such deliberation. Therefore, 31 appraisals were included in this review. Seventeen were single technology appraisals, eight were multiple technology appraisal and 6 were highly specialised technology appraisals. We examined all submitted models in these appraisals.

Figure 1: PRISMA flow diagram



In Single Technology Appraisals (STAs) and Highly specialised technology (HST) information reported on the company's model was extracted. In Multiple Technology Appraisals (MTAs), information reported on the AG model was extracted. Information from the company's models was extracted in cases where aspects of the model were relevant to the committee's discussion around child utilities. All data reported relate to the base case analysis for company or AG model. Electronic versions of the cost-effectiveness models were not available for review. Often the company and review group reports summarised and appraised existing models in the wider economic literature, but those models are not covered in the scope of this review.

3.3. Data extraction

Information was extracted, both regarding the utility values included in the cost-effectiveness model and any commentary by the company, independent review groups (ERG or AG) and committees about the utility values. If a utility value reported in a submission referenced a published source, the original article was sought, and any further details extracted from there. Data were extracted by a single experienced systematic reviewer with an appropriate background in health economics.

3.3.1. Submission information

Submission information included: the appraisal process used (STA, MTA or HST), the date of publication of the guidance, the health condition, health technology, details of the evidence provider (e.g., an economic model from the company or an independent assessment group), and whether the submission included a cost-utility analysis.

3.3.2. Source of utility data

Data were extracted about the source of the utility data (e.g. sample size, population, setting), the value set (e.g. representative sample of the UK population) and the valuation method (e.g. time trade-off, standard gamble) and any adjustments made to values (e.g. for age and gender profiles), the methods of mapping to a utility score (where data were not directly obtained with a preference-based health related quality of life measure) and any other approaches to estimate utility values in absence of data or reported values in the wider literature.

3.3.3. Economic modelling

A summary of the economic model included health states, type of economic model (e.g. Markov, Decision Tree or Discrete Event Simulation), cycle length, the ages of the population upon entry into the model, the time horizon of the model and utility values used for children and adolescents at baseline, disease free, healthy state and key disease states.

3.3.4. Committee discussion of utility values

Any written text on the topic of estimating values for children and adolescents in the committee discussion section of the guidance and assessment reports was extracted.

4. RESULTS

Table 1 shows the health conditions that are covered in the 31 included appraisals, with the most common being asthma (three appraisals), influenza (two appraisals), juvenile arthritis (two appraisals) and osteosarcoma (two appraisals). It should be noted that multiple appraisals on the same health conditions are due to reviews and updates of older appraisals. The identified appraisals covered a varied range of health conditions including cystic fibrosis, arthritis, deafness and eczema.

Table 1: Included technology appraisals.

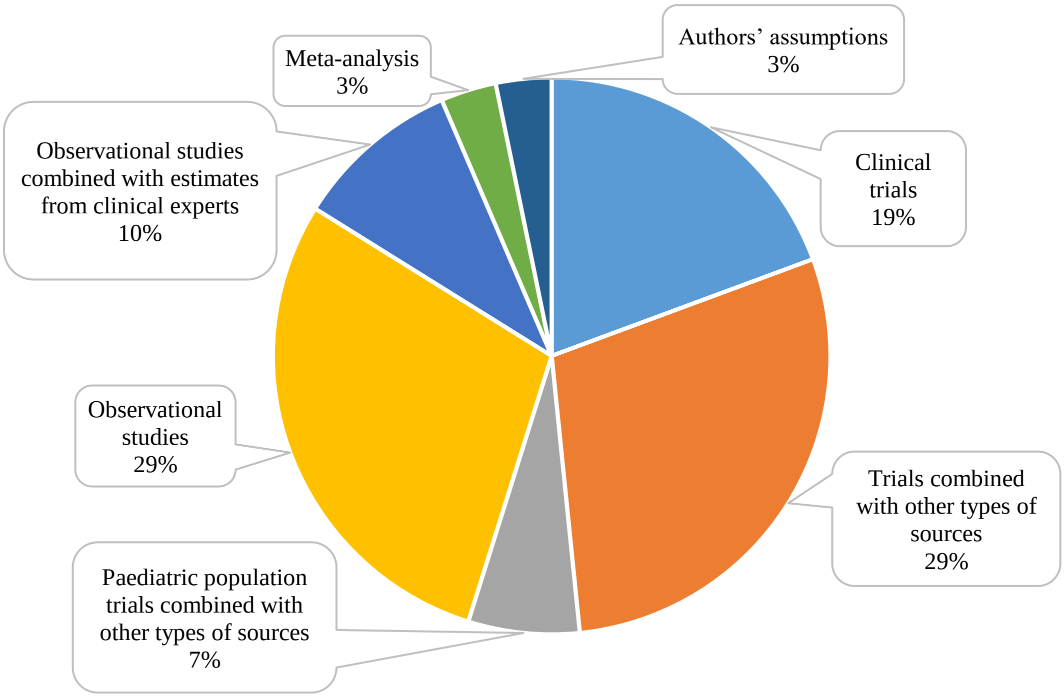
Health condition	Reference
Abdominal aortic aneurysms	TA167
Acute Lymphoblastic leukaemia	TA408
Adenosine deaminase deficiency	HST7
Asthma	TA131& TA138 & TA278
Atopic eczema	TA82
Atypical haemolytic uraemic syndrome	HST1
Bee and wasp allergy	TA246
Bipolar I disorder	TA292
Brain tumours	TA23
Chronic hepatitis C	TA300
Cystic fibrosis	TA398
Deafness	TA166
Diabetes mellitus	TA 151
Fabry disease	HST4
Hypophosphatasia	HST6
Immunosuppressive therapy for kidney transplant	TA482
Influenza	TA168 & TA158
Juvenile arthritis	TA238 & TA373
Lung infection in cystic fibrosis	TA276
Mucopolysaccharidosis type IVa	HST2
Muscular dystrophy	HST3
Osteosarcoma	TA235 & TA188
Psoriasis	TA 455
Renal disease	TA165
Ulcerative colitis	TA329
Urticaria	TA339

4.1. Sources of utility data

Seven appraisals estimated economic models only for the adult population, though guidance was provided for both paediatric and adult populations (TA23, TA329, TA165, TA167, TA151, HST4, HST1).

Figure 2 shows the data sources of utility values used in appraisals. The 3 appraisals that used observational studies combined with estimates from clinical experts had the experts complete the EQ-5D for illustrative vignettes (HST6, HST2) or estimate a utility value between zero and one (HST3). Two appraisals relied on data from paediatric population trials that were conducted exclusively in children and adolescents and other types of sources (TA455, TA292). However, these trials did not measure HRQoL using a preference-based measure. Thus, to generate child and adolescent utility values both appraisals retrieved information from observational studies. In one case with a published mapping formula to generate EQ-5D-Y utility values from the condition specific measure used in child and adolescent trials (TA455) and the other appraisal used EQ-5D scores of adult patients with the health condition (TA292).

Figure 2: Data sources of utility values in appraisals



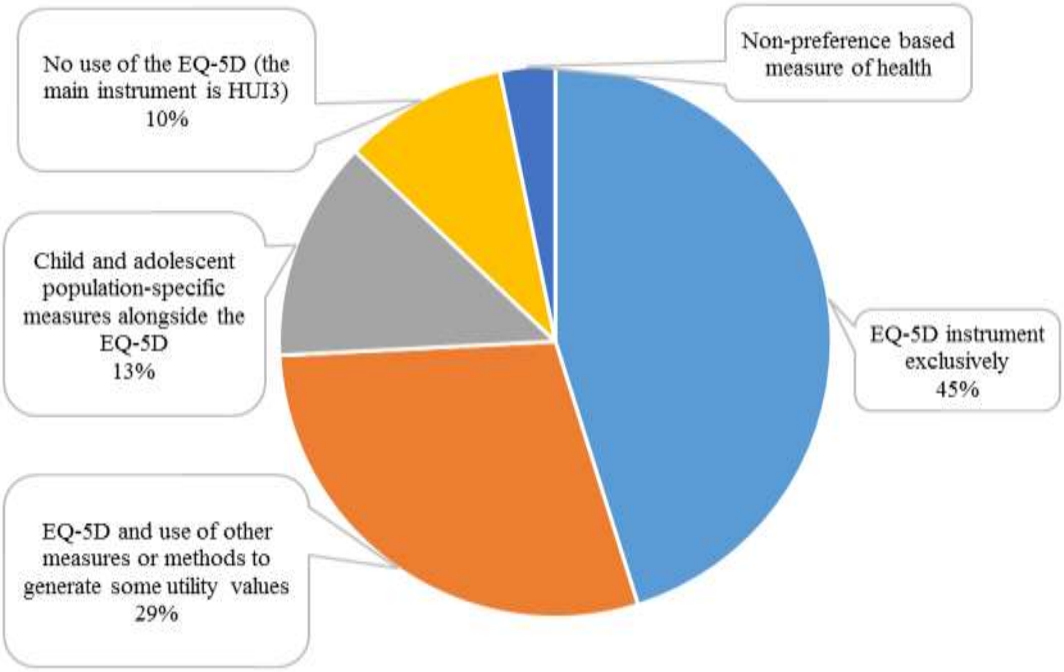
4.2. HEALTH RELATED QUALITY OF LIFE MEASURES

Figure 3 shows the HRQoL measures used to generate utility values in appraisals. The majority of appraisals used the adult version of the EQ-5D to generate utility values (n=27) (TA82, TA131, TA138, TA151, TA158, TA165, TA167, TA168, TA188, TA235, TA238, TA246, TA276, TA278, TA292, TA300, TA329, TA339, TA398, TA408, TA455, TA482, HST1, HST2, HST4, HST6, HST7). Fourteen appraisals used more than one HRQoL measure to generate utility values for all health states in the economic model (TA82, TA151, TA158, TA165, TA168, TA188, TA235, TA276, TA329, TA373, TA408, TA455, HST3, HST7). Utility values were mainly based on the EQ-5D but the economic models also had utility values calculated using the Health Utilities Index Mark 2 (HUI2) and Mark 3 (HUI3) (TA158, TA166, TA168, TA235, TA373, TA408, HST3), the SF 36 (TA 188) or calculated from direct elicitation using vignettes such as SG, TTO, or rating scale (TA151, TA165, TA235, TA329, HST7). Four (TA82, TA158, TA168, TA455) out of nine appraisals that used only children and adolescents in the economic model (no adults) applied different HRQoL measures across different health states and age ranges while the other five appraisals used only the EQ-5D (TA131, TA138, TA238, TA292, TA482).

One appraisal used only the HUI3 (TA166), another used HUI3 in combination with clinical advice on the disutility for a health state, and another appraisal used only HUI2 and HUI3, but estimated utility values for different health states with alternative versions (HUI2 and HUI3) (TA373). One appraisal did not use a preference-based measure to generate utility values and used one item from a cancer-specific patient reported outcome measure, the EORTC QLQ-C30. The item asks patients “how would you rate your overall quality of life during the past week?”, with anchors of “very poor” to “excellent” that were converted to a scale of zero to one. This scale was treated as a utility index with the worst possible response equivalent to dead at 0 and the best was equivalent to full health at 1 (TA23).

The majority of appraisals used only adult responses to HRQoL measures (n=22). Four appraisals used responses from children, adolescents and adults, four appraisals used responses from adults for some utility values and responses from children and adolescents for other utility values, and one appraisal used responses from adolescents and adults.

Figure 3: Health related quality of life measures used to generate utility values



4.2.1. EQ-5D

Table 2 describes the methodology used to generate utility values. The most common approach was to use the EQ-5D instrument exclusively, which was the approach taken in around half (n=15, 48%) of the 31 appraisals (TA138, TA167, TA238, TA246, TA278, TA292, TA300, TA131, TA339, TA398, TA482, HST1, HST2, HST4, HST6). These appraisals were for a technology indicated for use in children, adolescents and adults with two appraisals (TA238, TA292) for the population of children and young people only.

Twelve appraisals included an economic model with utility values based on the EQ-5D, with some health states or treatment effects generated using another generic measure of health (TA455, TA276, TA82, TA408, TA329, TA235, TA188, TA168, TA165, TA158, TA151, HST7).

Table 2: Summary of methods used to generate utility values per appraisal (n=31)

Condition	TA	HRQoL Measure	Respondents to HRQoL	Mapping (from health or HRQoL to generate utilities)	Age-adjustment to utilities	Data sources for utility values	Children transition to adults in the model	Committee guidance for adults, children and adolescents (all) or children and adolescents
Abdominal aortic aneurysms	167	EQ-5D	Adults	No	No	Trials	Enter as adults	All
Acute Lymphoblastic leukaemia	408	EQ-5D, HUI2, HUI3	Adults	No	Yes	Observational studies	Yes	All
Adenosine deaminase deficiency	HST7	EQ-5D, TTO, VAS, SG	Adults	No	Yes	Observational studies	Yes	All
Asthma	131 & 138	EQ-5D	Adults	Yes	No	Trial, observational studies	No	All
Asthma	278	EQ-5D	Adults	Yes	No	Trials, observational studies	Yes	All
Atopic eczema	82	EQ-5D, preference-based measure for use in children with atopic dermatitis	Adults; child responses to preference-based measure	No	No	Observational studies, clinical experts	No	All
Bee and wasp allergy	246	EQ-5D	Adults	No	Yes	Observational studies	No	Children and adolescents
Bipolar I disorder	292	EQ-5D	Adults	No	Yes	Child and adolescent trial, observational studies	No	Children and adolescents
Brain tumours	23	EORTC QLQ-C30, assumed to be a utility index	Adults	No	Yes	Trials	Enter as adults	All
Chronic hepatitis	300	EQ-5D	Adults	No	Yes	Observational studies	Yes	All
Cystic fibrosis	398	EQ-5D	Children, adolescents and adults	No	Yes	Trials	Yes	All

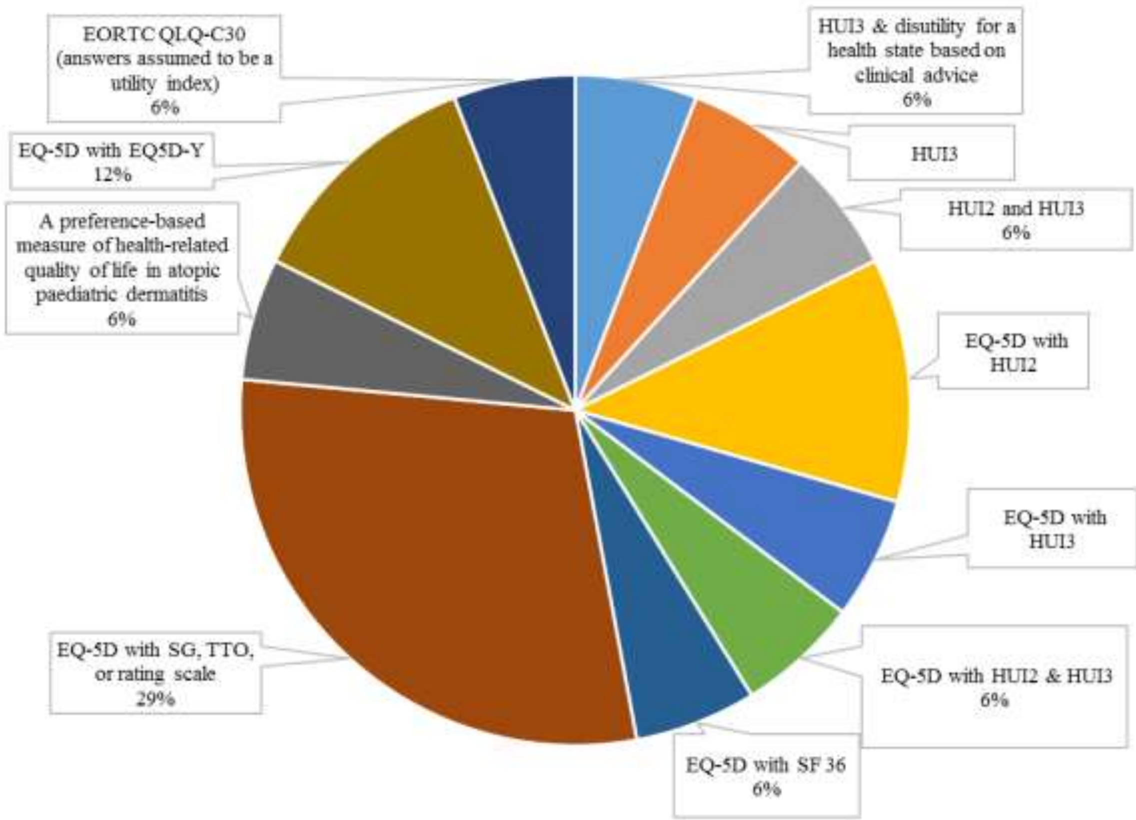
Condition	TA	HRQoL Measure	Respondents to HRQoL	Mapping (from health or HRQoL to generate utilities)	Age-adjustment to utilities	Data sources for utility values	Children transition to adults in the model	Committee guidance for adults, children and adolescents (all) or children and adolescents
Deafness	166	HUI3	Adults	Yes	Yes	Observational studies	Yes	All
Diabetes mellitus	151	EQ-5D, direct elicitation (SG, TTO, rating scale)	Adults	No	No	Observational studies	Enter as adults	All
Fabry disease	HST4	EQ-5D, discrete choice experiment	Adults	No	Yes	Observational studies	Enter as adults	Age over 16 years
Haemolytic uraemic syndrome	HST1	EQ-5D	Adults	No	No	Trial	Enter as adults	All
Hypophosphatasia	HST6	EQ-5D	Adults	No	No	Clinical experts	Yes	All
Immunosuppressive therapy	482	EQ-5D	Adults	No	Yes	Meta-analysis	No	All
Influenza	158& 168	EQ-5D, TTO, VAS, HUI2	Adults; adults, children and adolescents responded to VAS	No	Yes	Trials, observational studies	Yes (company) No (AG)	All
Juvenile arthritis	373	HUI2, HUI3	Children, adolescents and young adults	No	No	Observational study	Yes	All
Juvenile idiopathic arthritis	238	EQ-5D	Adults	Yes	No	Trials	No	Children and adolescents
Lung infection in cystic fibrosis	276	EQ-5D, EQ5D-Y	Adolescents and adults	Yes	No	Trials, observational studies	Yes	All
Mucopolysaccharidosis type IVa	HST2	EQ-5D	Adults	No	Yes	Observational studies and clinical experts	Yes	All
Muscular dystrophy	HST3	HUI3, disutility for a health state based on clinical advice	Adults, children and adolescents responded to HUI3	No	No	Observational studies. clinical experts	Yes	All

Condition	TA	HRQoL Measure	Respondents to HRQoL	Mapping (from health or HRQoL to generate utilities)	Age-adjustment to utilities	Data sources for utility values	Children transition to adults in the model	Committee guidance for adults, children and adolescents (all) or children and adolescents
Osteosarcoma	188	EQ-5D, SF-36 (two methods[23 24] to translate SF-36 into utilities based on rating scales)	Adults	Yes	Yes	Trials, observational studies	Yes	Children and adolescents
Osteosarcoma	235	EQ-5D, average utility by health state from six NICE HTA appraisals using EQ-5D, HUI3, SG	Adults	No	Yes	Trials, observational studies	Yes	Children, adolescents and young adults
Psoriasis	455	EQ-5D-Y, EQ-5D	Adults; child responses to EQ-5D-Y	Yes	No	Child and adolescent trials, observational studies	No	Children and adolescents
Renal disease	165	EQ-5D, TTO, VAS	Adults	No	No	Observational studies	Enter as adults	All
Ulcerative colitis	329	EQ-5D, weighted averages from other instruments (e.g. TTO, VAS)	Adults	No	Yes	Trials, observational studies	Enter as adults	All
Urticaria	339	EQ-5D	Children, adolescents and adults	No	Yes	Trials	Yes	All

4.2.2. *Alternative approaches to applying the EQ-5D exclusively*

Figure 4 shows the alternative approaches that were used that did not involve the exclusive use of EQ-5D. These are discussed in greater detail below.

Figure 4: Alternative approaches to applying the EQ-5D exclusively (n=17)



4.2.3. *Other generic preference-based health related quality of life measures, direct utility elicitation and other approaches*

Other measures of health-related quality of life based on a standardised and validated generic quality of life instrument were: the HUI3 (TA166, TA373, TA408, HST3) and SF-36 (TA188), though note that this was not scored using the SF-6D. Utility values from direct elicitation using vignettes such as SG, TTO, or rating scale (TA151, TA165, TA235, TA329, HST7).

In one appraisal the manufacturer estimated HRQoL utility values from an expert panel discussion and questionnaire session, in accordance with the Delphi technique (TA82). The elicitation methods for utility values were not detailed in the appraisal. In another case utility decrements for the paediatric and adult population for types of infusion were based on the results of a discrete choice experiment to estimate how many years of additional life the respondents would consider equivalent to receiving treatment by infusion for the rest of their life (HST4). One appraisal assumed that children aged 6-11 years experienced the same improvement in HRQoL from treatment as that found from adults and adolescents (based on EQ-5D data) collected in a trial (TA278). One appraisal used a question on the cancer-specifc EORTC QLQ-C30 and converts responses onto a scale of zero to one, and treats this as a utility index (TA23).

4.2.4. Child and adolescent population-specific quality of life measures

Eight of the 31 appraisals (25%) appraisals included child and adolescent population-specific measures to estimate utility values for health states in the models. One submission used a preference-based measure of quality of life in atopic paediatric dermatitis (TA82) alongside EQ-5D. Two appraisals included mapping to EQ-5D-Y values, with utilities generated from the EQ-5D-Y responses using the EQ-5D adult value set (TA455, TA276). Four submissions used the HUI2 (TA408, TA158, TA168 and TA373), though each also used at least one other method to generate utility values.

There is no clear pattern in the use of alternative generic HRQoL instruments to generate values for the main health states in HTAs (TA151, TA158, TA166, TA168, TA373, TA408, HST3). They are used as a main health state in a wide range of economic models and patient populations including models where children and adolescents do not progress into adulthood (TA158, TA168), children and adolescents progress to adulthood (TA166, TA373, TA408, HST3), the entry age is adult but the committee guidance is for an adult and child and adolescent populations (TA151), and where adults are the respondents to the measure (TA166, TA408, HST3).

4.3. MAPPING METHODS TO A HEALTH RELATED QUALITY OF LIFE MEASURE

In 8 appraisals mapping was used to convert other measures to utility values. Mapping functions are estimated using regression analyses and can be used to estimate utility values for a required preference-based measure when this evidence is otherwise unavailable, or where modelled values are required, for example to control for age[7]. Table 3 shows appraisals that used mapping to generate utility values. Table 7 to 9 in the Appendix summarises whether there was mapping to establish utility values in appraisals and provides details on the approach taken.

Table 3: Summary of the appraisals with mapping methods to HRQoL measures (to generate utility values)

Measures	Number of appraisals with mapping
Source instrument	
Childhood Health Assessment Questionnaire	1
Height	1
Speech recognition scores	1
Asthma Quality of Life Questionnaire	3
Cystic Fibrosis Questionnaire	1
Dermatology Quality of Life Index	1
Utility measure mapped to	
EQ-5D values	5
EQ-5D-Y	2
HUI3	1

The most common measure mapped to was the EQ-5D. The mapping approaches including mapping functions estimating EQ-5D utility values from a condition-specific measure (TA131, TA138, TA188, TA238, TA278) and to the EQ-5D-Y (TA276, TA455).

In two appraisals mapping was between HRQoL data from the child patient, Dermatology Quality of Life Index (TA455) and the Cystic Fibrosis Questionnaire (TA276), to utility values from a population-specific measure in a child and adolescent population (EQ-5D-Y). The EQ-5D-Y was valued using the EQ-5D tariff for the UK adult general population. One study mapped speech recognition scores onto HUI3 utility values not using an validated algorithm. Four of the appraisals estimated their own mapping model (TA188, TA238, TA278, TA166), two were based on an unpublished model (TA131, TA138), one was based on a published study (TA455) and another relied on assumptions about the relationship between the measures that was not evidence based (TA238).

4.4. CHILD AND ADOLESCENT VALUES USED FOR GENERAL POPULATION HEALTH STATES.

The choice of general population health state values directly affects the HRQoL gain attributable to a treatment intervention in models, and this impacts on the cost-effectiveness of treatment. Therefore it is important to understand the range of baseline paediatric utility values and how they were established in the absence of child and adolescent HRQoL data. Table 4 shows a sample of utility values chosen for general population and disease free health states and mild conditions to illustrate the wide range of values reported.

Table 4: Sample of child and adolescent general population full health utility values reported in appraisals

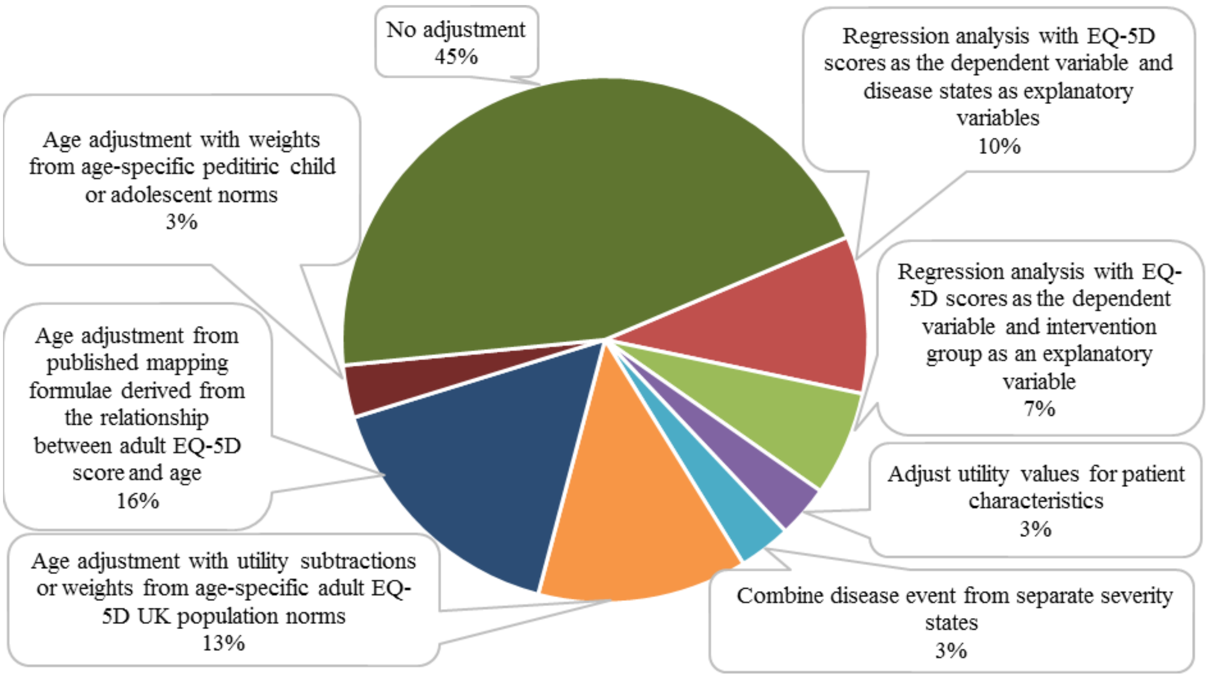
HTA	Condition	Health state measure	Health state	Utility value
82	Atopic eczema	Authors assumption	Non-recurrence of eczema	1
HST2	Mucopolysaccharidosis type IVa	EQ-5D	Asymptomatic state	Utility = 1 - 0.0003 × Age. For example, a utility score age of 15 of 0.996
HST7	Adenosine deaminase deficiency	EQ-5D	Utility value of surviving patients	Health Utility = 0.968 + 0.023 × Male – 0.002 × Age – 0.00001 × Age^2 For example, a utility score age of 15 of 0.97 (male), 0.936 (female)
482	Immunosuppressive therapy for kidney transplant in children and young people	EQ-5D	Disease free	Health Utility = 0.968 + 0.023 × Male – 0.002 × Age – 0.00001 × Age^2 For example, a utility score age of 15 of 0.97 (male), 0.936 (female)
292	Moderate to severe manic episodes in adolescents with bipolar I disorder	EQ-5D	Disease free	Health Utility = 0.946 – 0.0002 × Age – 0.00003 × Age^2 + 0.026 × Male) For example, a utility score age of 15 of 0.962 (male), 0.936 (female)
300	Chronic hepatitis C in children and young people	Authors assumption	Disease free (for people younger than 17 years)	0.95 (company model) Utility (AG model) = 1.0138 - 0.0033 × Age. For example, a utility score age of 15 of 0.964
138 & 131	Chronic asthma in adults and in children	EQ-5D	'symptom-free' health state	0.97
HST7	Adenosine deaminase deficiency–severe combined immunodeficiency	EQ-5D	Disease free (under 25)	0.96
158	Preventing flu	EQ-5D	Disease free (under 25)	0.94
168	Preventing flu	EQ-5D	Healthy children (1-12 years)	0.87
HST6	Paediatric-onset hypophosphatasia	EQ-5D	Lowest severity (level 1)	0.86
235	Osteosarcoma	EQ-5D	Disease free post recurrence	0.85
238	Juvenile idiopathic arthritis	EQ-5D	"Controlled" (Health State)	0.77

The range of utility values used for child and adolescent with no disease incidence history ranged from 0.87 (TA168) to 1.0 (TA82). In the absence of data, the authors assumed these values (TA82) or extrapolated to children and adolescents from the relationship between age and HRQoL in the adult general population (TA292, TA300, TA482, HST2, HST7).

4.5. ADJUSTMENTS TO UTILITIES

Tables 7 to 9 in the Appendix summarise whether there were adjustments to utilities in appraisals and provides detail on the approach taken. Figure 5 shows the main type of adjustment to utility values used in the appraisals.

Figure 5: Main type of adjustment to utility values used in appraisals



Adjustments to utility values in models included applying utility decrements or weights from the existing literature or a dataset (for example to estimate the adverse effects from treatment) (TA300, TA131, TA138**,** TA158, TA 246, TA329, TA408, TA482, HST7). Another approach was to estimate the EQ-5D utility scores of health state descriptions (TA339, TA398, HST4) or the treatment effect (TA131, TA138) in regression analysis by having EQ-5D scores as the dependent variable and control/treatment group status or disease states as explanatory variables. Regression approaches have been used to estimate the HSUV of a health condition by severity level (TA339), establish the independent effects on EQ-5D scores of separate states of health functioning (lung function and pulmonary exacerbations)

(TA398) , adjust utility values for patient characteristics (e.g. age, body weight, sex, social class and long-standing illness) (TA188) and adjust individual patient trial data collected in multinational settings for UK analysis (TA138). In other cases, it was to account for the characteristics of the patient population in the dataset of interest (TA235) or combine disease event from separate severity states (TA329). In one appraisal utility decrements were adjusted for the expected duration of an acute and chronic disease episode based on expert advice (HST7).

Age and gender specific adult and child utility values were calculated from available data (TA408), published formulae (TA292, TA300, TA482, HST2, HST7) or utility weights based on the mean or median of adult age groups published in the literature (TA158, TA166, TA168, TA246, TA300, TA339, TA408, HST2). Where age adjustments were used it was used to reflect the natural decline in quality of life associated with older age. All age-adjustments in the appraisals increased the health utility of children and adolescents compared to adults. For example, a utility score of 0.61 was adjusted to 0.66 for the recurrence/relapse state of osteosarcoma patients to reflect children and adolescents (TA235).

In five appraisals the utility value for children and adolescents in full health aged under 16 years were extrapolated from published mapping formulae derived from the relationship between adult HRQoL (measured by the EQ-5D) and age (TA292, TA300, TA482, HST2, HST7). These were estimated in samples of adults using an adult instrument, and were used to extrapolate beyond the data to children and adolescents. The utility values for general population full health for children and adolescents were generated using a utility multiplier applied to utility values of disease states (established using HRQoL measures with adults) to find the age-adjusted HSUV for disease states in the child and adolescent population. This is known as the multiplicative utility approach to age adjustment[25].

Ten appraisals were based on utility subtractions or weights from age-specific adult EQ-5D UK population norms (TA158, TA166, TA168, TA235, TA246, TA292, TA300, TA408, HST2, HST7) while one appraisal was based on child and adolescent weights from the HUI3 (TA235). In six of these appraisals children and adolescents under 16 were given the same value (TA158, TA166, TA168, TA235, TA246, TA408). Consequently, the utility values for adults were adjusted for age more often in appraisals than utility values for children and adolescents. For example, one appraisal on treatment for influenza applied a utility score of

0.85 to healthy children (1-12 years) and in the same model had adult utility values decline with age (TA 168).

Just one appraisal reported using ‘child weights’ (TA235) for the age adjustment. The child weights were taken from a population-based (in Italy) Childhood Cancer Registry of Piedmont, and the measure of HRQoL was the HUI3. The utility values obtained for different child ages were applied to the child and adolescent patient (cancer) population in the model.

4.6. APPROACHES TAKEN TO INCORPORATE THE CHILD-TO-ADULT TRANSITION

Figure 6: Appraisals that incorporated the child-to-adult transition

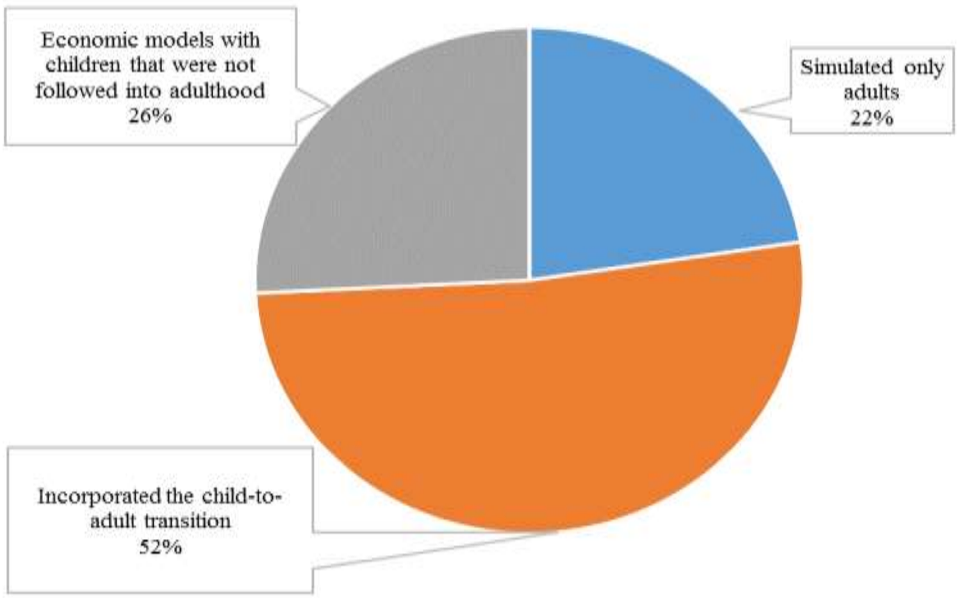


Figure 6 shows the proportion of appraisals that incorporated the child-to-adult transition as the patient ages. Most of the appraisals had a child and adolescent population that progressed into adulthood (TA158, TA166, TA168, TA188, TA235, TA276, TA278, TA300, TA339, TA373, TA398, TA408, HST2, HST3, HST6, HST7). These types of models typically had a lifetime time horizon (TA158, TA166, TA168, TA188, TA276, TA278, TA300, TA398, HST2, HST7, HST6) and wide variation in the methods chosen to estimate utility in the child, adolescent and adult stages. The models most often estimated utility values for child, adolescent and adult populations with the EQ-5D completed by adults (TA158, TA168, TA188, TA276, TA278, TA300, TA408, HST7, HST6) although other measures were considered such as the HUI (TA373, TA408, HST3), SF 36 (TA188), VAS/TTO (TA151, TA158, TA168, HST7), SG (HST7), and a clinical measure mapped to adult EQ-5D values (TA188, TA278) or the HUI (TA166).

In the majority of appraisals that incorporated the child-to-adult transition, children had the same utility values for event states as adults (TA188, TA235, TA276, TA300, TA339, TA398, TA373, TA408, HST6, HST7). Two appraisals had different HSUVs for adults and children to represent the progressive nature of an disease that started in early childhood (HST2, HST3). Four appraisals had different HSUVs for adults and children but there no change in utility as children transitioned to adults because age subgroups were modelled separately. (TA158, TA166, TA168, TA 278).

Seven appraisals included economic models that simulated only adults (TA23, TA151, TA165, TA167, TA329, HST4, HST1) when the committee guidance covered the entire patient population (adults and children and adolescents). The committees did not justify their recommendation for children and adolescents when the cost-effectiveness evidence presented was based on adults. These appraisals concerned treatment for conditions that are more prevalent in adults including brain tumours, ulcerative colitis, abdominal aortic aneurysms, diabetes and first-episode psychosis.

Eight of the appraisals were with economic models with children and adolescents that were not followed into adulthood, beyond the age of 18 years (TA82, TA131, TA138, TA238, TA246, TA292, TA455, TA482). These appraisals included treatment in the child and adolescent population for immunosuppressive therapy after kidney transplantation, idiopathic arthritis, psoriasis, Bipolar disorder and influenza. The models mainly estimated child utilities from adult EQ-5D scores (TA131, TA138, TA238, TA292, TA482, HST6) although other approaches included mapping condition-specific measures to the EQ-5D (TA82), the Dermatology Quality of Life score to the EQ-5D-Y (TA455) and estimating utility values from the EQ-5D supplemented with information for some health states from other preference based approaches such as the TTO and HUI (TA158, TA168).

5. COMMITTEE DISCUSSIONS ON UTILITY VALUES

All committees assessed the models to check if appropriate utility values were used in the economic models. Some committees noted the advice of clinical experts when considering the utility gain from treatment for children and adolescents (HST2, HST4, TA278) or utility value of a disease condition (TA166). Committees' opinions of appropriate values varied depending on the exact specification of the model in terms of the health states and population, but attention was frequently paid to the requirements in the NICE methods guide. For example, one committee commented that the methods used to derive the utility values should meet NICE's reference case (TA235), another noted the limitation of not using any generic preference-based instrument to measure health-related quality of life (TA276). In one case, utility values generated from trial data were considered preferable to data from the literature (HST3). Other committees stated that they favoured direct estimates from a preference-based measure (TA278, TA398) particularly in comparison to the limitations from mapping a condition-specific measure to a generic preference-based measure although specific limitations with mapping methods were not mentioned (TA276, TA455). One committee considered whether the HRQoL measure (EQ-5D) captured all important domains of the condition (growth failure in height of children and adolescents) (TA188) and another committee was concerned with establishing the appropriate value for the disutility of carers for children (HST4).

In cases where the committees did comment on the limitations of the approaches used to establish child and adolescent utility values it was to highlight the uncertainty in the model findings introduced by the trade-offs in the relevance of the sample population to the model population, requirements of NICE Methods Guide (e.g., preference-based measure) and the size and quality of the studies (e.g., levels of missing data) (TA166, TA482). The lack of data was recognised to cause bias that could lead to over-estimation or under-estimation of the utility gain from treatment (TA188, HST1, HST2) or the utility decrement from disease complications (TA166, HST6). Committees accepted the use of values in previous models (e.g. the AG using the values on the company submission or a company from a previous HTA submission) or those retrieved from systematic searches of literature because the choice of values were justified by the absence of child and adolescent data. However, one committee did comment that the utility values from a previous HTA had not been updated, or revalidated to assess their appropriateness for an appraisal of treatments in a younger population (TA300). There was no evidence in comments by the committees that the absence of child and adolescent utility data and associated uncertainties in the model findings made a contribution to a negative or restricted recommendation.

Committees did discuss utility values of health states (TA235, HST1, HST2, HST3, HST4, HST6) but rarely compared the appropriateness of HSUV in the children or adolescents with those for young people or adults (TA238, HST7). A few committees commented on the limitation of the use of adult utilities as reflective of child utilities (TA166, TA188, TA238, TA276, TA278, TA300, TA482). When they did, it was most often to express concern that the utility estimates reflected the benefits of treatment in adulthood and may not capture the potential utility gain during childhood (TA166, TA188, TA300). However, two committees explicitly agreed that it was reasonable to use utility values estimated from adults given the lack of available child and adolescent data for patient groups (TA455, TA482), and another committee preferred the AG economic model in which the same utility gain was assumed for adults, adolescents and children to the company model where there was no health-related quality of life improvement from treatment in children (TA278). Only in one appraisal did a committee discuss age-adjustment of utility values, agreeing that age-adjusted utility values should be used in the model (TA235).

6. DISCUSSION

The most common method used to generate utility values for children and adolescents was the EQ-5D adult version, scored using the UK value set (n=27 of 31 appraisals). Other adult generic preference-based measures were used, including HUI3, as well as direct elicitation methods of SG and TTO, though typically these were used to generate only a subset of health states in the economic model, with the EQ-5D also used to generate utility values for other health states. Out of all appraisals, only 7 (22.6%) used child and adolescent population-specific measures to report the health of a child. Four appraisals used the HUI2, a measure that cannot be self-completed by younger children aged below 12, but its value sets were elicited from adults imagining a child in the health state. One appraisal involved using a paediatric condition-specific preference-based measure in a child population, and two appraisals generated EQ-5D-Y values that were mapped from condition-specific profile measures and scored using the EQ-5D adult value set to generate the utility values. All 7 appraisals also used at least one other method to generate utility values for some health states in the economic model.

In the majority of appraisals it was not possible to identify the ages of the respondents to the health-related quality of life measure used as the source for utility estimates, or easily distinguish whether the instrument had been completed by the child and adolescent population, the combined child, adolescent and adult population or proxy (e.g. parents, carers or clinicians answering on behalf of the child) with the information provided. However, EQ-5D and HUI3 are adult measures not intended for use in children, and the HUI2 can be used both in children and adults. This suggests that most of the utility values used in the economic models to reflect child and adolescent HRQoL were based on adolescent or adult self-report health for the same condition. In the majority of appraisals utility values were based on only adult responses (n=22), but it is not always clear whether they are reporting their own health (they could be proxy-reporting health).

The child and adolescent population-specific measure CHU-9D was not used to generate utility values in any submission, despite use in over 180 studies to date. EQ-5D-Y was used in 2 appraisals, yet it should be noted that there is no UK value set for the EQ-5D-Y which may have influenced the decision not to use it in clinical studies.

The findings raise the question of whether adult self-reported health, scored using a value set generated for adult health states valued by adults using an adult perspective, with no age adjustment to account for differences, is appropriate for generating the utility values used to reflect child and adolescent health states. The appropriateness of use of adult self-reported health, scored using the standard value set appropriate for adults relies on several assumptions:

1) adults, children and adolescents are affected in the same way by conditions, that is according to the same dimensions with the same impact on severity of problems in those dimensions;
2) the same dimensions of HRQoL are equally relevant for children, adolescents and adults;
3) the value sets for adult health states are applicable to adults, adolescents and children, that is the adult general population (not children or adolescents) valuing adult health states (not child health states) from an adult perspective (typically imagining themselves in the health state) will capture the HRQoL of child health states.

There is evidence that each of these assumptions could be challenged. A systematic review published in 2014 challenges assumption 1) where it was concluded that adults, children and adolescents perceive and value health differently[26] and the review recommended further development of child- and adolescent-specific measures. Assumption 2) could be challenged by the fact that adult and child and adolescent measures often have different dimensions, for example anxiety and depression in an adult measure in comparison to worry for a child and adolescent measure. However, it could be argued that the underlying dimension – mental health – is constant across the two and that the same underlying dimensions are equally relevant for children, adolescents and adults. Regardless, even if there are a core set of dimensions that are equally relevant for children, adolescents and adults, the wording of dimensions would need adaptation for children to be able to self-report their own health. Equally whilst the content of measures differs, this is due to the process used to develop a measure. The CHU9D differs in its dimensions to the EQ-5D and also differs to the EQ-5D-Y in the process used to develop the measure. The EQ-5D-Y was generated by adapting the adult EQ-5D content for children[20], whereas the CHU-9D was developed from interviews with children aged 7 to 11 years to generate the dimensions of the classification system[17 18]. Thus, CHU-9D should be seen as an entirely de novo child-specific instrument that has no aspect of consistency with other measures except potentially in regard to its valuation method, whereas EQ-5D-Y is an adaptation of an adult instrument for use in children. Recent research has challenged assumption 3), finding that health states are valued differently when described for an adult or a child, implying that adult EQ-5D-3L value sets are different to the child and adolescent population[27].

A further consideration is the distinct developmental stages in child and adolescent populations. Children and adolescents are not a single population but present a spectrum of developmental stages in cognitive and linguistic capacities within and across ages. Full health at each stage can be defined by the absence of problems in any dimensions of health on a health-related quality of life measure. However, important domains of health could be categorized differently at each stage, and respondents/proxy-responders could respond differently at each stage despite no underlying change in health. For example, there are different norms for speech-language development at different child ages although failure to meet this standard does not imply a cognitive illness.

The widespread use of adult EQ-5D utility values in NICE appraisals may be driven by practical and pragmatic concerns. There are significant challenges in collecting self-report or carer-report health data for child and adolescent patients, in particular for rare conditions, and there is much larger availability of adult EQ-5D data. This may explain why just two appraisals were based on trials with only child and adolescent patients and these trials did not collect health related quality of life information with a preference-based measure that could be used to generate utility values. The age of the population may also be a factor. The EQ-5D could be self-reported by older adolescents (or proxy-report if this is not possible) where arguably the dimensions may be both understood and appropriate, and this may achieve consistency with trial data collected with adults. The use of utility values established from adult responses to the EQ-5D may also be due to children and adolescents progressing into adulthood (e.g. to 60 years and older) in the economic models, since a large majority of models had time horizons of 60 years and over.

There was generally reliance in the appraisals on secondary data sources, mapping functions and published formulae of age adjustments to inform the child utility values of appraisals, rather than trial or primary data collection. The absence of information based on direct observation of the impact of treatment in children and adolescents may limit how generalizable the data in the appraisals are to children and adolescents.

Utility values were commonly adjusted was to allow the HRQoL values of disease states or treatment impact from a different set of patients (another country or health condition) to be used in the UK patient population of interest, or to account for adverse events of treatment. Forms of age adjustment in the adult populations, for example by simple linear extrapolation from the utility values in older UK populations, in some cases were continued to ages under 16 although most often all ages under 16 were given the same baseline HRQoL. This may be because the onset of age-related decline in health-related quality of life is considered to occur after reaching adulthood. The methods used to establish the mapping functions and age adjustments varied considerably, although in most cases these relied on published studies established from adult responses to HRQoL measures and did not perform analyses specific to the appraisal.

We found no clear pattern in the selection of preference-based measure used in economic models based on the date of the NICE documents submission. This is likely because the large majority of submission were after 2008 when NICE had developed prescriptive methodological guidelines, which include some stipulation on the use of preference-based measures to generate utility values in assessments.

The cost-effectiveness analyses used a wide range of values to reflect general population health and disease free states across children and adolescents, varying from 0.85 to 1. In the absence of data, the authors assumed these values or derived them by extrapolating from adult responses.

This report has a number of strengths and weaknesses. A previous review in 2016 considered the approaches to generate utility values in child populations in NICE appraisals over time[26]. As in this review they ‘found that most had used adult utilities to inform the model, due to the unavailability of suitable child derived utilities; furthermore, it was clear that here was no trend away from this over time’ (p. 349). Their findings were demonstrated using three illustrative case studies. This review extends that enquiry by updating the included appraisal to 2018 and provides detail on the health related quality of life measures and value sets used to establish child and adolescent utility values, the different approaches taken to establish child and adolescent utility values in the absence of data, approaches taken to incorporate the child-to-adult transition and linking those approaches to the corresponding response from Appraisal Committees.

A potential limitation of the discussion of NICE Appraisal Committee views about the utility values is that it was rare for NICE Appraisal Committees to comment on child and adult utilities specifically. Instead committees often commented on the uncertainty in the utility values in the submission, due to concerns about the absence of data to inform values. These committees may not have needed to present further clarifying comments because the independent academic groups discussed the topic in detail. The independent academic groups view is beyond the scope of this report and may have differed from the final guidance by the committee. In addition, the level of reported detail on the modelling approaches to establishing child utilities varied by submission. This report uses submission documents that are available to the public, but in some cases data and analyses were designated as confidential in the company submission meaning we could not report those values or methods.

7. CONCLUSION

The generation of utility values for economic models for children and adolescents is an area that would benefit from both further research and clearer recommendations from institutions such as NICE around best practice in the area.

There have been inconsistencies in the methods used to generate utility values for economic models for child and adolescent populations. There is widespread use of approaches that are generally considered appropriate for adults, but what isn't clear is whether these approaches are appropriate for use to generate utility values for children and adolescents. Even within the approaches used that follow guidance for adult utility values there are inconsistencies in the approaches used, for example some technology appraisals use EQ-5D, others use EQ-5D-Y with adult EQ-5D utility values, and others adjust utility values to account for age. To date many of these issues have not been investigated thoroughly.

It is expected that clearer recommendations in the NICE Methods Guide around utilities for children and adolescents would reduce variability in the methods used to generate utility values for children and adolescents, and increase consistency in the evidence considered across different technology appraisals.

Suggested points for consideration by NICE:

- At a minimum, committees should be provided with information about the ages and distribution of age of those completing the preference-based measured used to estimate utility values of the child and adolescent population. This is particularly the case if utility values are retrieved from the literature searches rather than a main trial.
- Should NICE recommend the use of child and adolescent specific measures? This may encourage more companies to administer such instruments in their clinical studies.
  - If so, which measure(s)?
  - What should be done when such data are not available?
  - How should the measure(s) be valued? This will include selection of the value set to generate utilities, or if appropriate selection of appropriate methodology used to generate utility values including population, elicitation technique, and perspective

    - Should the adult reference case measure - EQ-5D - be used to represent child and adolescent health in cost-effectiveness analyses, and if so under which circumstances?
- How should any potential transition between self-report and proxy-report utility values be managed?
- How should any potential transition between measures in cost-effectiveness analyses be managed? Different measures may be used as the patient ages
- Should utility values be age-adjusted for the child and adolescent population? If so, how?
- How should general population health be estimated for the child and adolescent population aged 0 to 18 years?

Recommendations for future research:

- Evidence of the content validity and wider psychometric performance of child and adolescent preference-based measures to determine whether (and under which circumstances) they are appropriate for use in economic models. This can include content validation in all age groups that the measure is used in (since this may differ to the age group that the measure was developed for) and across a range of conditions
- Generation and validation of appropriate scoring systems to generate utility values from existing child and adolescent population preference-based measures, for example via mapping from widely used child profile measures as well as value sets for child and adolescent population preference-based measures
- Comparison of utility values and ICERs generated using child and adolescent population preference-based measures, EQ-5D and mapped utility values for the same patients where possible
- Potential generation of an exchange rate between adult EQ-5D utilities and child utilities, to enable committees to consider the equivalent HRQoL impact and ICER if the utilities were generated using child self-report health-related quality of life data rather than adult EQ-5D data, potentially using preference-based mapping
- Examine whether differences in adult and paediatric general population utility values can substantially influence results in models with long time horizons (e.g. decades or a lifetime) and a proportionally small duration where the simulated subjects are a part of the child and adolescent population

- Review and critical assessment of potential methods that can be used to model utility data for child and adolescent populations, including:
    - Transition between self-report and proxy-report utility values
    - Transition between measures in cost-effectiveness analyses as the patient ages
    - Age-adjustment of utility values for the child and adolescent population
    - Estimation of disease free health for the child and adolescent population aged 0 to 18 years

REFERENCES

1. National Institute for Clinical Excellence. Guide to the methods of technology appraisal. London: NICE, 2013
2. Brazier, J., Ratcliffe, J., Saloman, J. and Tsuchiya, A., 2017. *Measuring and valuing health benefits for economic evaluation*. OXFORD university press.
3. Richardson J, McKie J, Bariola E. Multiattribute utility instruments and their use. In: Culyer AJ, editor. Encyclopaedia of Health Economics. Vol. 2. San Diego: Elsevier; 2014. p. 341-57.
4. Dolan, P.Modeling valuations for EuroQol health states. *Medical care.* 1997. 1095-1108
5. Oppe, M. and Devlin, N.J. eds., 2007. *EQ-5D value sets: inventory, comparative review and user guide*. Berlin, Germany: Springer.
6. Hernandez Alava M, Wailoo A, Pudney S. Methods for mapping between the EQ-5D-5L and the 3L for technology appraisal. NICE DSU Report. 2017
7. Ara, R., Rowen, D. and Mukuria, C. The use of mapping to estimate health state utility values. *PharmacoEconomics.* 2017. 35(1), pp.57-66.
8. Van Hout B, Janssen M, Feng Y et al. Interim scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value in Health*, 2012. 15: 708-15.
9. NICE, Position statement on use of the EQ-5D-5L valuation set for England (updated November 2018). Accessed 15 January 2019. Available at: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l
10. Torrance, G.W., Feeny, D.H., Furlong, W.J., Barr, R.D., Zhang, Y. and Wang, Q. Multiattribute utility function for a comprehensive health status classification system: Health Utilities Index Mark 2. *Medical care.* 1996. 702-722.
11. Feeny, D., Furlong, W., Torrance, G.W., Goldsmith, C.H., Zhu, Z., DePauw, S., Denton, M. and Boyle, M. Multiattribute and single-attribute utility functions for the health utilities index mark 3 system. *Medical care*. 2002. 40(2), 113-128.
12. McCabe, C., Stevens, K., Roberts, J. and Brazier, J. Health state values for the HUI 2 descriptive system: results from a UK survey. *Health economics*, 2005. 14(3), 231-244
13. Ravens-Sieberer, U., Wille, N., Badia, X., Bonsel, G., Burström, K., Cavrini, G., Devlin, N., Egmar, A.C., Gusi, N., Herdman, M. and Jelsma, J. Feasibility, reliability,

and validity of the EQ-5D-Y: results from a multinational study. *Quality of life research.* 2010. 19(6), 887-897

14. Wille, N., Badia, X., Bonsel, G., Burström, K., Cavrini, G., Devlin, N., Egmar, A.C., Greiner, W., Gusi, N., Herdman, M. and Jelsma, J. Development of the EQ-5D-Y: a child-friendly version of the EQ-5D. *Quality of life research.* 2010. 19(6), 875-886
15. Kind P, Klose K, Gusi N, Olivares PR, Greiner W. Can adult weights be used to value child health states? Testing the influence of perspective in valuing EQ-5D-Y. Quality of Life Research, 2015; 24:2519-2539
16. Stevens, K. Developing a descriptive system for a new preference-based measure of health-related quality of life for children. *Quality of Life Research,* 2009. 18(8), 1105-1113.
17. Stevens, K.J. Working with children to develop dimensions for a preference-based, generic, pediatric, health-related quality-of-life measure. *Qualitative Health Research*, 2010. 20(3), 340-351.
18. Stevens, K. Assessing the performance of a new generic measure of health-related quality of life for children and refining it for use in health state valuation. *Applied health economics and health policy*, 2011. 9(3), 157-169.
19. Stevens, K. Valuation of the child health utility 9D index. *Pharmacoeconomics,* 2012. 30(8), 729-747.
20. Ratcliffe, J., Huynh, E., Stevens, K., Brazier, J., Sawyer, M. and Flynn, T., 2016. Nothing About Us Without Us? A Comparison of Adolescent and Adult Health-State Values for the Child Health Utility-9D Using Profile Case Best–Worst Scaling. *Health economics*. 2016. 25(4), 486-496.
21. Ratcliffe, J., Couzner, L., Flynn, T., Sawyer, M., Stevens, K., Brazier, J. and Burgess, L., 2011. Valuing child health utility 9D health states with a young adolescent sample. *Applied health economics and health policy*. 2011. 9(1), 15-27.
22. Rowen, D., Mulhern, B., Stevens, K. and Vermaire, J.H. Estimating a Dutch Value Set for the Paediatric Preference-Based CHU9D Using a Discrete Choice Experiment with Duration. *Value in Health*. 2018
23. Fryback DG, Lawrence WF, Martin PA, Klein R, Klein BE. Predicting Quality of Well-being scores from the SF-36: results from the Beaver Dam Health Outcomes Study. *Medical Decision Making*. 1997.17:1-9.

24. Shmueli A. The SF-36 profile and health-related quality of life: an interpretative analysis. *Quality of Life Research*. 1998. 7, 187-95

25. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value in health*. 2010. 13(5), 509-18.

26. Montgomery, S.M. and Kusel, J. The prevalence of child-specific utilities in NICE appraisals for paediatric indications: rise of the economic orphans?. *Expert review of pharmacoeconomics & outcomes research*, 2016. 16(3), 347-350

27. Thorrington D, Eames K. Measuring health utilities in children and adolescents: a systematic review of the literature. *PloS one*. 2015 Aug 14. 10(8):e0135672

28. Deriving preference-based single indices from non-preference based condition-specific instruments: Converting AQLQ into EQ5D indices. 2002. Sheffield: ScHARR

29. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D Scores for the United Kingdom. *Medical Decision Making*. 2011. 31(6), 800-804.

APPENDIX

Table 5: NICE Technology Appraisals referenced in this report

Reference	Title	Published	Last Updated	Met the inclusion criteria in this review
TA482	Immunosuppressive therapy for kidney transplant in children and young people	Oct-17	Oct-17	Yes
TA455	Adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people	Jul-17	Jul-17	Yes
TA408	Pegaspargase for treating acute lymphoblastic leukaemia	Sep-16	Sep-16	Yes
TA398	Lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation	Jul-16	Jul-16	Yes
TA373	Abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis	Dec-15	Dec-15	Yes
TA339	Omalizumab for previously treated chronic spontaneous urticaria	Jun-15	Jun-15	Yes
TA329	Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy	Feb-15	Feb-15	Yes
TA300	Peginterferon alfa and ribavirin for treating chronic hepatitis C in children and young people	Nov-13	Nov-13	Yes
TA292	Aripiprazole for treating moderate to severe manic episodes in adolescents with bipolar I disorder	Jul-13	Jul-13	Yes
TA278	Omalizumab for treating severe persistent allergic asthma	Apr-13	Apr-13	Yes
TA276	Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis	Mar-13	Mar-13	Yes
TA246	Pharmalgen for the treatment of bee and wasp venom allergy	Feb-12	Feb-12	Yes
TA238	Tocilizumab for the treatment of systemic juvenile idiopathic arthritis	Dec-11	Dec-11	Yes
TA235	Mifamurtide for the treatment of osteosarcoma	Oct-11	Oct-11	Yes
TA188	Human growth hormone (somatropin) for the treatment of growth failure in children	May-10	May-10	Yes
TA168	Amantadine, oseltamivir and zanamivir for the treatment of influenza	Feb-09	Feb-09	Yes
TA167	Endovascular stent–grafts for the treatment of abdominal aortic aneurysms	Feb-09	Feb-09	Yes
TA166	Cochlear implants for children and adults with severe to profound deafness	Jan-09	Jan-09	Yes
TA165	Machine perfusion systems and cold static storage of kidneys from deceased donors	Jan-09	Jan-09	Yes
TA158	Oseltamivir, amantadine (review) and zanamivir for the prophylaxis of influenza	Sep-08	Sep-08	Yes
TA151	Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus	Jul-08	Jul-08	Yes

TA138	Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over	Mar-08	Mar-08	Yes
TA136	Structural neuroimaging in first-episode psychosis	Feb-08	Feb-08	No
TA131	Inhaled corticosteroids for the treatment of chronic asthma in children under the age of 12 years	Nov-07	Nov-07	Yes
TA92	HealOzone for the treatment of tooth decay (occlusal pit and fissure caries and root caries)	Jul-05	Jul-05	No
TA88	Dual-chamber pacemakers for symptomatic bradycardia due to sick sinus syndrome and/or atrioventricular block	Feb-05	Nov-14	No
TA81	Frequency of application of topical corticosteroids for atopic eczema	Aug-04	Aug-04	No
TA82	Tacrolimus and pimecrolimus for atopic eczema	Aug-04	Aug-04	Yes
TA74	Pre-hospital initiation of fluid replacement therapy in trauma	Jan-04	Jan-04	No
TA49	Guidance on the use of ultrasound locating devices for placing central venous catheters	Oct-02	Oct-02	No
TA38	Inhaler devices for routine treatment of chronic asthma in older children (aged 5–15 years)	Mar-02	Mar-02	No
TA23	Guidance on the use of temozolomide for the treatment of recurrent malignant glioma (brain cancer)	Apr-01	Mar-16	Yes
TA10	Guidance on the use of inhaler systems (devices) in children under the age of 5 years with chronic asthma	Aug-00	Aug-00	No

Table 6: NICE Highly Specialised Technologies referenced in this report

Reference	Title	Published	Last Updated	Met the inclusion criteria in this review
HST7	Strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency	Feb-18	Feb-18	Yes
HST6	Asfotase alfa for treating paediatric-onset hypophosphatasia	Aug-17	Aug-17	Yes
HST4	Migalastat for treating Fabry disease	Feb-17	Feb-17	Yes
HST3	Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene	Jul-16	Jul-16	Yes
HST2	Elosulfase alfa for treating mucopolysaccharidosis type IVa	Dec-15	Dec-15	Yes
HST1	Eculizumab for treating atypical haemolytic uraemic syndrome	Jan-15	Jan-15	Yes

Table 7: Summary of mapping methods and adjustment to utilities in appraisals that base utility values for child health states on the EQ-5D exclusively

Condition	TA	Mapping	Mapping details	Adjustment to utilities	Adjustment details
Abdominal aortic aneurysms	167	No	None	No	None
Asthma	131 & 138	Yes	Unpublished mapping algorithm to map Asthma Quality of Life Questionnaire to EQ-5D.	None	Utilities based on a study that used regression models of individual patient trial data to enable 'adjustment for the UK analysis using the full GOAL [trial] dataset'
Asthma	278	Yes	Asthma quality of life questionnaire to EQ-5D[28]	No	None
Bee and wasp allergy	246	No	None	Yes	The model estimates the number of deaths and life years under each treatment arm over the time horizon chosen. The life years are adjusted to calculate QALYs by using age dependent EQ-5D Weighted Heath Status Index population norm
Bipolar I disorder	292	No	None	Yes	A multiplicative utility approach: the utility values in adult populations with bipolar disorder converted into multiplicative decrements (relative to the age-gender matched adult general population). These were then applied to utility values for the age-gender matched paediatric general population, which were calculated from a published formula[25]
Chronic hepatitis	300	No	None	Yes	A multiplicative utility approach: 1. Baseline utilities for the general population were estimated. Utility = 1.0138 - 0.0033 × Age. 2. A utility multiplier was derived by comparing the health state utility from the literature to the utility of the general population with the same age and gender composition. 3. Utility multipliers (from step 2) were applied to baseline utilities (from step 1) corresponding to the model cohort age and gender composition

Cystic fibrosis	398	No	None	Yes	Utility values estimated from regression to model the relationship between EQ-5D utility values, lung function and pulmonary exacerbations reported in two trials
Fabry disease	HST4	No	None	Yes	Infusion-related utility decrements were based on a discrete choice experiment (DCE). The ratio of any two DCE coefficients can be used to estimate the marginal rate of substitution, how many years of additional life the respondents would consider equivalent to receiving treatment by infusion for the rest of their life.
Haemolytic uraemic syndrome	HST1	No	None	No	None
Hypophosphatasia	HST6	No	None	No	None
Immunosuppressive therapy	482	No	None	Yes	Age-dependent utility estimated from published formula[25] to take account of differences in ages less than 18 years. This formula was $\text{Utility} = 0.967981 - 0.001807 \times \text{Age} - 0.000010 \times \text{Age}^2 + 0.023289 \times \text{Male}$ Health state-specific utility decrements (EQ-5D) from general population utility (EQ-5D)
Juvenile idiopathic arthritis	238	Yes	Childhood Health Assessment Questionnaire (CHAQ) to EQ-5D. The mapping was taken from a mapping formula derived in an adult RA population that maps the (adult) Health Assessment Questionnaire onto EQ-5D utilities	No	None
Mucopolysaccharidosis type IVa	HST2	No	None	Yes	Utility value for asymptomatic paediatric health states (e.g. 0-9 years) were taken from published mapping formulae[29] derived from around 80,000 American adults. A decrement of 0.0003 was subtracted from a utility score of 1 (i.e. perfect health) per year from birth.

Urticaria	339	No	None	Yes	Utility values estimated from regression to model the relationship between EQ-5D utility values and urticaria Activity Score

Table 8: Summary of mapping methods and adjustment to utilities in appraisals that include non-EQ-5D adult utility values for paediatric health states

Condition	TA	Mapping	Mapping details	Adjustment to utilities	Adjustment details
Acute Lymphoblastic leukaemia	408	No	None	Yes	HSUV estimated from a comparison of condition utility values to the UK and international general population Utility value estimates were obtained by using Health Utility Index (HUI2 and HUI3) data obtained from a study based on US and Canadian acute lymphoblastic leukemia (ALL) patients for different treatment phases. To find the impact of different treatment phases on UK people the following approach was taken. The relative difference in quality of life estimates between the UK people with ALL and the ALL patients in the US and Canada was found. This decrement was applied to published EQ-5D estimates for the general population. Health state-specific utility decrements (EQ-5D) from general population utility (EQ-5D)
Adenosine deaminase deficiency	HST 7	Yes	VAS converted to SG values.	Yes	Age-specific utility values estimated from published formulae[25]. Health Utility = $0.968 + 0.023 \times \text{Male} - 0.002 \times \text{Age} - 0.00001 \times \text{Age}^2$ Utility decrements from literature adjusted to account for the duration of a chronic episode based on expert clinical advice.
Deafness	166	Yes	Speech recognition scores mapped to HUI3 (company)	Yes	Age based utility weights from the literature. In the company model, to reflect a documented inverse relationship between duration of deafness prior to implantation and utility gain from implantation, a utility decrement (of 0.002) was subtracted from the utility gain for each year of deafness.
Diabetes mellitus	151	No	None	No	None
Influenza	158 & 168	Yes	VAS converted into TTO utilities	Yes	The QALYs lost through influenza-related mortality were derived for patients by weighting the average life years lost by the EQ-5D data representing UK population norms
Juvenile arthritis	373	No	None	No	None

Muscular dystrophy	HST 3	No	None	No	None
Osteosarcoma	188	Yes	Published height to EQ-5D mapping (company)	Yes	The mapping (height standard deviation score and EQ-5D scores) adjusted in regression analysis for age, body weight, sex, social class and long-standing illness.
Osteosarcoma	235	No	None	Yes	Age-adjusted utility values done by HUI weights reported by published[29] child utility weights for cancer patients
Renal disease	165	No	None	None	Renal disease
Ulcerative colitis	329	No	None	Yes	Utility of disease events based on separate severity states found in the literature. For example, the assessment group averaged the utility values for 'moderate' and 'severe' disease to derive a value for moderately to severely active disease. To establish complications the company model produced a weighted mean utility from studies which use different elicitation methods

Table 9: Summary of mapping methods and adjustment to utilities in appraisals that include paediatric measures to generate utility values

Condition	TA	Mapping	Mapping details	Adjustment to utilities	Adjustment details
Atopic eczema	82	No	None	No	None
Brain tumours	23	No	None	Yes	Global quality of life question converted to a scale of zero to one and treated as a utility index.
Lung infection in cystic fibrosis	276	Yes (company)	Health utilities were derived from a mapping study to translate the Cystic Fibrosis Questionnaire to the EQ5D-Y	No	None
Psoriasis	455	Yes	Dermatology Quality of Life Index mapped to EQ-5D-Y Age-gender matched healthy paediatric	No	None

			general population weights		