A Review of Methods Used to Estimate Pediatric Utility Values in Health Technology Appraisals across Different Agencies

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Background

- Estimating utility values to inform the evaluation of technologies for children and adolescents presents methodological challenges.
- Currently, several validated generic health-related quality of life (HRQoL) instruments exist for use in children.
- The National Institute for Health and Care Excellence (NICE) in the UK expresses a preference for the EQ-5D-3L, which is an adult measure for HRQoL and not intended for use in children.
- A previous systematic literature review (SLR) identified several limitations in the assessment of pediatric utilities in NICE appraisals. Our review sought to compare the use of pediatric utilities across NICE and other health technology assessment (HTA) bodies.[1]

Objective

To assess the methods used to estimate utilities in children and adolescents (1 to 18 years of age) between technology appraisals (TA) across different geographies and whether they align with the methodological requirements of the relevant HTA agency.

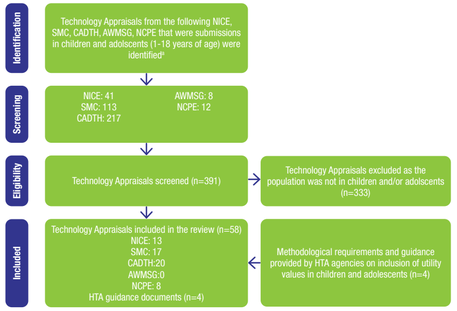
Methods

- The TA documents, including highly specialised technology (HST) evaluations published across five HTAs—NICE,[2] Scottish Medicines Consortium (SMC)[3], All Wales Medicines Strategy Group (AWMSG)[4], National Centre for Pharmacoeconomics (NCPE)[5] and Canadian Agency for Drugs and Technologies in Health (CADTH)[6] reporting on pediatric utility values and published in the last three years (June 2018 to June 2021), were included in this review.
- The HTA websites were accessed between June and July 2021 and publicly available TAs were retrieved and reviewed for indications in children and adolescents (1 to 18 years) and were included in the analyses.
- The included TA documents were reviewed on approaches used to estimate utilities in children and adolescents.
- Specifically, TAs were reviewed for submission type (single TA, multiple TA, HST), indication, intervention type, publication date, population indicated for, HRQoL tool used, population that reported HRQoL, tariff used (population used to estimate utility weights e.g., representative of UK general population), methods used to estimate utility values in the manufacturers cost-utility analyses, review group and committee comments on the appropriateness of the utility values used in the models.
- The methodological requirements and guidance provided by HTA agencies on inclusion of utility values in children and adolescents were identified and reviewed.

Results

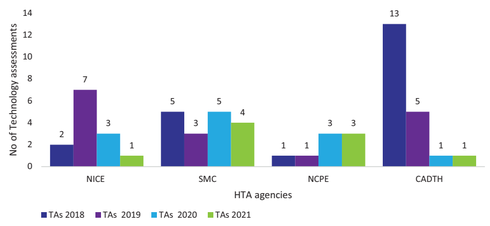
- A total of 391 TAs were retrieved and screened for inclusion from HTA websites; 333 (85%) of these were excluded because the submission was not in children and/or adolescents (**Figure 1**).
- Fifty-eight TAs (14%) that included pediatric-related cost-utility analyses were published in the last three years (NICE=13; SMC=17; AWSMG=0; NCPE=8; and CADTH=20).
- CADTH had the highest number of TAs (n=20) included, with a majority published in 2018 (n=13) (**Figure 2**).

Figure 1. PRISMA Diagram



[a] First pass or title screening included screening of summaries of TAs provided in the HTA websites. Subsequently, relevant TA documents of included first pass screen were reviewed to assess relevance and inclusion in the review.

Figure 2. TAs by Year Published



- Cancer, x-linked hypophosphataemia, hereditary angioedema, epilepsy, retinal dystrophy and spinal muscular atrophy were some of the common indications for submissions in populations with children and adolescents across HTAs (**Figure 3**).
- Most (40/58; 69%) of the TAs were for indications in mixed adult (≥18 years of age) and pediatric populations; only 21% (12/58) were exclusively in children and adolescents alone. (**Figure 4**).

Figure 3. TA Indications across HTAs

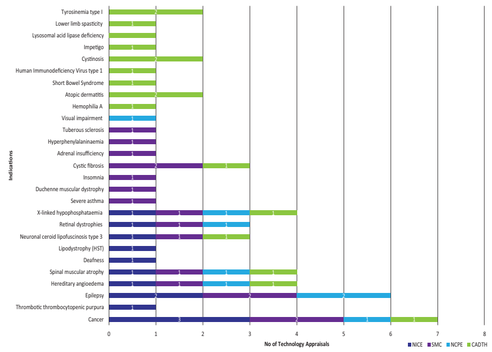
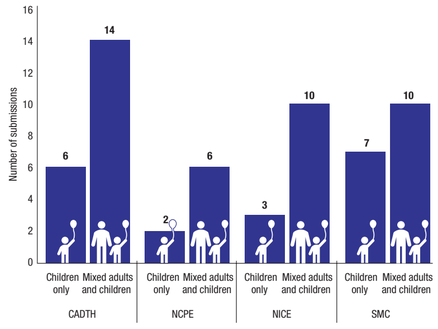


Figure 4. Population Assessed across TAs



Results (Cont'd)

- Across TAs, only 9% (5/58) generated utilities using a pediatric HRQoL measure. Three TAs used utility values mapped to the EQ-5D from Pediatric Quality of Life Inventory (PedsQL) and two used utilities mapped to the EQ-5D-Y from PedsQL.
- The most frequent HRQoL measure was EQ-5D in 57% of TAs (n=33). EQ-5D-5L was used in 17% of TAs (n=10), which were mapped to the ED-5D-3L in half of the TAs using a published algorithm and valued using the adult value set. The child-friendly version of the EQ-5D-Y was used in two TAs and valued using the adult EQ-5D value set.
- Overall, 41% (n=24) of TAs used observational data, 34% (n=20) used vignette studies, 28% (n=16) used trial data to estimate utility values across HTAs (**Figure 5**).
  - Most vignette studies used clinician elicitation of health state as proxy for patients (n=16); patients and caregivers elicitations were limited (n=4).
- Age adjustment of utility values were not clearly reported across all TAs. Regression analyses and adjustments for age were used to extrapolate pediatric utility values in three TAs.
- Methodological guidance on inclusion of child-specific utilities across HTA agencies was limited.

Figure 5. Data Sources across TAs

Although the use of validated generic quality-of-life (QoL) instruments specific to children was encouraged by agencies such as NICE, there was lack of clear guidance on the estimation and inclusion of utilities specific to children.

NICE

- Thirteen NICE submissions (nine TAs and four HSTAs) across 12 different indications reported on indications in children and adolescents (1 to 18 years of age).
- Seven TAs sourced utility data from trials alone.
  - Six were in mixed populations of adults and children and only one was conducted exclusively in children.
- Seven TAs used mixed data sources such as trial data and vignette studies or published observational data.
- One TA used data from an observational study and discrete choice experiments.
- Six TAs relied on vignette studies to generate utilities. The vignettes described the modelled health states and were scored by clinician proxy elicitation in four TAs, and by patients with the condition and their carers in two TAs.
- Most TAs used the adult tariff EQ-5D measure (n=11).
  - Three TAs used ED-5D-3L and three used ED-5D-5L.
  - Two TAs used visual analogue scales.
  - Two TAs used the Health Utility Index 3 (HUI3); HST11 used HUI3 alongside EQ-5D.
  - Four TAs mapped other QoL instruments such as the 36-item Short Form health survey (SF-36; TA667, TA630) and PedsQL (TA588, HST12) to EQ-5D.

NICE (Cont'd)

- Some TAs used various methods of estimating utilities. For example, TA588 generated utilities by three different utility sources:
  - Mapping PedsQL data collected from the trial to the EQ-5D via a published algorithm
  - From a vignette study of the child version the EQ-5D-Y completed by clinicians and scored using the adult version of the EQ-5D-3L
  - Alternative utilities from published observational studies

However, the evidence review group (ERG) commented that the utilities had poor face validity and none of the utilities were ideal; therefore, it preferred the vignette study.

- Across TAs, the ERG questioned the robustness of the vignettes compared to trial data, not using a preference-based method to value health states, poor face validity, and obtaining utilities from experts rather than patients or parents.
- Age adjustment of utility values for estimation of child and adolescent utilities showed increase in age associated with decline in HRQoL. TA538 estimated utilities by applying decrements to an age-specific EQ-5D general population and TA606 applied a regression coefficient per 10 years of age to show older age.

NCPE

- Eight NCPE submissions in children and adolescents were found across seven different indications for the last three years.
- Two NCPE TAs used bespoke vignette studies conducted by the manufacturer to derive utilities, two used trial data, and two used observational data.
- Most TAs did not provide information on the HRQoL measure used to generate utilities (n=6).
  - TA for burosumab (Crysvita®) used EQ-5D 3L to generate utility values, elicited using EQ-5D 5L by UK based clinicians which was then mapped to UK EQ-5D 3L values.
  - TA for idebenone (Raxone®) used direct elicitation of utilities using the standard gamble and time trade-off methods.
- There was limited information on how utilities were adjusted for age across all TAs. In the TA for burosumab (Crysvita®) utility values were elicited separately (clinician proxy) for children and patients at 18 years, 40 years and 60 years of age.
- Overall, there were concerns about the approaches and assumptions used across manufacturers' vignette studies. In the TAs exclusively in children (Zolgensma®, Crysvita®) there were concerns about the sources and methods used to estimate utilities and the variation in the population from which utilities were generated (e.g., patients, or parent/clinician proxies).

CADTH

- Twenty CADTH TAs were included across 16 indications including two each on atopic dermatitis, cystinosis and hereditary tyrosinemia type 1.
- Fourteen TAs were indicated in a population of mixed adults and children; only six submissions were exclusively in children.
- Six were from vignette studies (n=6).
  - All reported the use of proxy values from clinical experts.
- Only three TAs estimated utilities from trial data:
  - One TA in mixed population of adults and children used trial data from a subgroup of older patients aged 18 to 25 years as a proxy for adolescent patients aged 14 to 18 years and stratified by treatment.
- Most CADTH submissions reported using utility values estimated using EQ-5D (n=13).
  - One EQ-5D-5L and EQ-5D-3L used in two TAs each, EQ-5D-Y child-friendly version was used in two TAs, seven TAs stated the HRQoL measure as EQ-5D without mention of levels.
  - Three TAs used HUI3 alongside EQ-5D and one TA used the HUI2 measure.
  - One TA used direct elicitation of utilities using time trade off.
  - Two TAs that were indicated in children-only population mapped PedsQL to EQ-5D and EQ-5D-Y questionnaires.
  - Five assessments did not report the QoL tool used to generate utilities.
- While the majority of TAs did not clearly report how age-adjustment of utility values were estimated, one TA for lanadelumab used a regression coefficient of -0.02205 per 10 years of age to show older age was associated with reduced health utility scores.
- The CADTH Common Drug Review noted that the use of patient proxies is not ideal and fails to accurately reflect the QoL of the patient. The TA for cerliponase-alfa indicated for patients with CLN2 disease was criticised for the use of clinician proxy as opposed to caregiver or family member proxy.

SMC

- Seventeen SMC submissions were included across 16 indications including two in cystic fibrosis.
- Most data were from observational studies (n=7), followed by a substantial number of vignette studies (n=7).
  - Vignettes for health states were assessed by clinicians as proxy for patients experiencing the health state in four submissions; the remainder used patient proxies.
- Trial data used to estimate utilities were limited (four submissions).
  - Only one submission used trial data exclusively in children, and three submissions used trial data from mixed populations of adults and children.
  - Only EQ-5D-3L questionnaires were used in five TAs, of which four were mapped from EQ-5D-5L.
  - Four TAs reported HRQoL as EQ-5D, without any reference to levels, of which one was mapped from the PedsQL.
  - Four TAs used HUI3 and one TA used HUI2.
  - One TA used HUI3 alongside EQ-5D, another TA used HUI3 alongside HUI2.
  - Two TAs provided utility estimates by direct elicitation using visual analogue scale and standard gamble.
  - Most TAs used adult tariffs EQ-5D to value utilities in the pediatric population. One TA that used EQ-5D estimated by clinicians who assigned different utilities for children (EQ-5D Y) and adults.

Discussion

- Previous research has highlighted issues with the estimation of utility values in children and adolescents to inform the evaluation of technologies for NICE.[1] Our research suggests that these issues extend to other HTA agencies across different geographies.
- In this current review, most submissions identified in children and adolescent populations were in rare diseases and genetic disorders.
- Few clinical trials directly measured HRQoL in children.
- TAs exclusively in children did not provide clear details on who completed the questionnaire and if parent/caregiver/clinician proxies were used. Therefore, although the trial was exclusively in children, it may not reflect pediatric HRQoL.
- Across mixed pediatric and adult populations, there was a lack of clarity regarding who completed the questionnaire children/adolescents/adults.
- Several TAs elicited utilities using proxies and most utility values were elicited indirectly using proxy responses of clinicians rather than patients themselves or their parents; utilities estimated this way may not fully reflect the impact of the condition on a patient's day-to-day QoL.
- Many assessments that used published observational data derived utilities from patients with proxy conditions and were based on assumptions that the utility values may be representative of the disease indicated.

Conclusions

Methodological guidance on utility estimation in children is limited across HTA agencies. Guidance across different HTA agencies does not explicitly recommend the use of utilities specific to children, except for NICE. Based on the current review, TAs have not consistently adopted the use of pediatric utilities in cost-utility analyses for children or combined child/adult populations. The evidence suggests scarcity of patient reported values either due to the challenges of deriving utility values in children or rarity of the disease. EQ-5D utility data intended for use in adults has been widely used across economic evaluations to represent child and adolescent HRQoL. All current approaches adopted for modelling pediatric HRQoL including using adult versions of HRQoL measures, using clinician/parent/caregiver proxies and mapping pediatric QoL measures to adult QoL instruments have been reported to have substantial uncertainties. Therefore, there is need for clearer guidance on estimation and valuation of utilities in children across HTA agencies.

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