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Health state utility values among children and adolescents with disabilities: protocol for a systematic review

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Health state utility values among children and adolescents with disabilities: protocol for a systematic review

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Abstract

Introduction: Increasingly, assessment of health care technologies and interventions requires the assessment of both costs and utilities. Health state utility values (HSUVs) are measured using a range of generic and condition-specific measures. While adult-specific instruments are often used to capture HSUVs among children and adolescents, there is evidence to show that they are not appropriate for this population. Further, generic measures may not be appropriate for use in people with disabilities. The objectives of this systematic review are to describe the methods used to obtain HSUVs, including mode of administration and psychometric properties, and provide summary statistics for HSUVs among children and adolescents with disabilities.

Methods and analysis: The following databases will be searched from inception for English-language studies of any design: PubMed; PsychInfo; Medline; Scopus; CINAHL Plus; Econlit and EMBASE databases. Two reviewers will independently screen titles, abstracts and full text articles for studies reporting HSUVs for children and adolescents with disabilities aged up to 19 years of age. One reviewer will extract data items including descriptors of the study methods and sample, instruments used to capture HSUVs, summary statistics for HSUVs, and items relating to the quality of reporting. A second reviewer will extract data for 10% of included studies. A narrative summary of results from included studies and summary statistics for HSUVs will be presented. If sufficient data is identified we will pool summary statistics for HSUVs according to the method used to obtain the HSUV using a random effects model. In addition, we will explore the determinants of the HSUVs using a meta-regression.

Ethics and dissemination: Ethical approval will not be required as no original data will be collected as part of this review. The completed review will be submitted for publication in a peer-reviewed journal and presentation at conferences.

Systematic review registration number: This protocol will be registered with the International Prospective Register of Systematic Reviews following peer review.

Strengths and limitations of this study:

- This review will provide a comprehensive review of how health state utility values (HSUVs) are obtained from children and adolescents with disabilities, which will identify gaps in the research and improve consistency in reporting of HSUVs in this population
- A strength of this study is that it will include studies of children and adolescents with a range of disabilities. Where possible results will be presented according to disability type.
- A limitation of this study is that publications that are not peer-reviewed such as unpublished theses and conference presentations will not be included.

Background

Economic evaluations are increasingly used to inform the evidence base in decisions regarding the adoption of health care interventions. A cost-utility analysis (CUA), which compares the costs and health benefits (using quality of life), is commonly used in the appraisal of interventions and technologies. The strength of the CUA is the fact that costs are compared with quality adjusted life years (QALYs), a measure which incorporates both the quantity and quality of life. By using QALYs, various disparate outcomes can be combined into a single composite summary outcome which allows broad comparisons across different disease areas in the health sector. When calculating QALYs, quantity is captured using life years while the quality is captured using health state utility values (HSUVs). To enhance the transparency and hence reliability of evidence from CUA, it is key that the process of collecting data for the CUA is robust, transparent and systematic [1,2]. Health state utility values are ranked on a scale anchored at 1 (full health) and 0 (a health state of equivalent value to being dead). HSUVs can be elicited using methods such as the Time Trade Off methods (TTO) or the Standard Gamble (SG). Often generic measures, such as the EuroQol EQ-5D, are recommended to be used in economic evaluations because they allow comparison across health care interventions and sectors [2].

Disability is “a difficulty in functioning at the body, person, or societal levels, in one or more life domains, as experienced by an individual with a health condition in interaction with contextual factors” [3]. Disability refers to the negative aspects of the interaction between individuals with a health condition (such as cerebral palsy, cardiovascular disease, depression) and personal and environmental factors (such as negative attitudes, inaccessible transportation and public buildings, and limited social supports) [4]. Although the prevalence of disability varies between countries and within countries, depending on how disability is conceptualised and assessed [4], the global prevalence among adults is approximately 15.6% [4]. Research into the health needs, health outcomes, and effectiveness of interventions, particularly rehabilitation interventions, is a priority

for improving health care among people with disabilities [4]. Encompassed in this is the need to evaluate the cost-effectiveness of health care interventions.

Condition-specific measures of quality of life are often used when assessing the effectiveness of interventions in children and adults with disability [5-7]. However, traditionally, it is generic preference based measures such as the EQ-5D that have been employed in CUA analyses, and not condition-specific measures [2]. The validity of applying these generic measures, which have been developed in the general population, to groups with certain specific conditions has been debated [8,9,10].

Several reviews have identified that generic measures of HSUVs may lack validity in people with conditions resulting in physical disability [10-13]. However, there is a lack of information regarding the utility and psychometric properties of measures used to obtain HSUVs in children and adolescents with disabilities. Many studies of children use methods that have been developed for adults to obtain HSUVs [14]. Adult-specific methods may not be appropriate for capturing HSUVs among children and adolescents [15]. Some methods have been developed exclusively for use in capturing child and adolescent HSUVs while some of the existing adult specific tools have been modified to make them child-friendly [15]. However, the utility weights obtained from these have not been adapted to incorporate the possibly different child and adolescent preferences [14,16]. Further, there is variation in the mode of administering methods to children (i.e. by proxy or self-reported) [14]. The combination of the issues with obtaining HSUVs in children and potential problems with administering generic measures to people with disabilities may result in large variation in how HSUVs are assessed in studies of children with disabilities and potentially inaccurate measurement of QALYs. As a result, CUA, comparing the costs and health benefits of health care interventions may be inaccurate and lead to poorly informed decisions regarding the adoption of new interventions.

Objectives

This review will address the following objectives:

1. Describe the methods used to obtain HSUVs from children and adolescents with disabilities.
2. Describe how these methods are administered.
3. Describe the psychometric properties of the methods used to obtain HSUVs from children and adolescents with disabilities.
4. Report summary statistics for HSUVs among children and adolescents with disabilities obtained from each method identified.

Methods

The methods used for this systematic review will be in line with available recommendations on reviews of health state utility values [17-21]. In addition, a scoping review was conducted to inform the methods of this review. Reporting of the review will adhere to recommendations of the PRISMA statement [22]. The protocol will be registered with the International Prospective Register of Systematic Reviews following peer review.

Study eligibility

Study designs

We will include studies presenting HSUVs derived from both direct (such as standard gamble, time trade off, visual analogue scale) and indirect methods (such as EuroQol EQ-5D and all its variants, CHU-9D, AQoL-6D, PALQLQ, PAHOM, HUI-2, Quality of Well-Being Scale and 16D-questionnaire) of capturing HSUVs. There will be no restriction on the type of studies to be included. Examples of types of studies to be included in the review are:

- studies that compare existing or new measures of HSUVs;
- studies that validate measures of HSUVs;
- randomised clinical trials that incorporate cost utility assessments

Participants

The review will include studies reporting HSUVs for children and adolescents with disabilities aged up to 19 years of age. We will include studies reporting HSUVs for the general population if they report HSUVs for children and adolescents with disabilities separately. Children and adolescents with the following broad forms of disabilities will be included:

a) Intellectual impairment (e.g. learning difficulties) or intellectual disability
b) Physical impairment (e.g. mobility impairment, poliomyelitis)
c) Developmental disability (e.g. ASD or cerebral palsy)
d) Sensory impairments (e.g. visual impairment, speech impairment)
e) Multiple impairment – at least two of the above

Language

We will include articles reported in the English languages only.

Exclusion criteria

We will exclude studies reporting HSUVs in adults with disabilities or in children or adults without disabilities. We will also exclude reviews, commentaries, unpublished theses, conference abstracts, and any unobtainable texts.

Search strategy

A systematic search will be conducted to capture HSUVs used in children and adolescents with disabilities. The following databases will be searched from inception: PubMed; PsychInfo; Medline; Scopus; CINAHL Plus; Econlit and EMBASE. We will also search for studies on the EQ-5D, HUI, NHS Economic Evaluation Database (NHS EED), and Health Technology Assessment (HTA) websites. Reference lists of key papers will be reviewed for additional references.

Search terms

The development of the search terms was informed by a scoping review of the literature [14,23-28]. Specific search terms include different variants of child and adolescent terms (infant, newborn, child and adolescent), health utility terms (EQ-5D, Time trade off, Standard Gamble) and disability. A sample search strategy is provided in Appendix 1.

Data management

Literature search results will be managed using Mendley reference management software.

Study selection

Two reviewers will review the titles and abstracts for inclusion. If a study appears to meet the inclusion criteria or if there is any doubt regarding the inclusion of the study the full text of the article will be retrieved. Full text articles will be reviewed independently by both reviewers and disagreements resolved through discussions with a third reviewer. Reasons for exclusions will be documented for all full text articles. The PRISMA flow diagram [22] will be used to summarize the number of articles identified, retrieved, screened, assessed, included, and excluded as well as the reasons for exclusions.

Data extraction

Data extraction will be conducted by one reviewer. A second reviewer will extract data from 10% of the included papers which will be determined through a random selection process. If HSUVs are not available from the study report we will contact the authors.

Data items

Details of the data extraction items are provided in Appendix 2. The data extraction form has been piloted by two reviewers (LK, JR). Data extraction items include a description of the study methods, sample and results as well as items relating to the quality of reporting. The ISOQOL minimum standards for patient-reported outcome measures [29] and the CREATE checklist [30] informed the list of data extraction items. The items extracted will include:

- A description of the study background, aims and methods: funding sources; conflicts of interest; statement of ethical approval; aim of study; study design; duration of study; duration of participation; study setting; method of recruitment; sample size; sampling method; number randomised to each group, and description of intervention and comparator (if study is a trial)
- A description of the participant (and respondent, if different) characteristics: age; sex; race; socioeconomic status; diagnosis; type of disability; years in present disability; disability severity; other medical conditions; years in this condition
- A description of the methods used to obtain HSUVs: instrument used (e.g. CHU-9D); mode of administration (e.g. self-reported or proxy); relationship between participant and respondent if administered by proxy; time points measured and reported; length of time to complete the instrument
- A description of the psychometric properties of the instrument: a statement of validity, reliability and responsiveness (if longitudinal study); methods used to determine psychometric properties and similarities and statement of differences between participants and target population if study is examining psychometric properties of the instrument
- A description of the results of the study: response rates; reasons for missing data; reasons for exclusion of respondents or observations; summary statistics for HSUVs.

Data synthesis

Qualitative analyses

A summary of the results from the included studies will be presented according to disability type (intellectual impairment or disability, physical impairment, developmental disability, sensory impairments, multiple impairments) and instrument used to obtain HSUVs if a sufficient number of studies for each type is identified. In addition, all identified HSUVs and the relevant attributes of their associated studies will be tabulated.

Quantitative analyses

If we identify sufficient data for a meta-analysis we will pool summary statistics for HSUVs according to the method used to obtain the HSUV using a random effects model. Random effects models take into account between-study heterogeneity. Heterogeneity between the findings of the reviewed studies will be assessed using the I^2 statistic. In addition, we will explore the determinants of the HSUVs using a meta-regression. Statistical analyses will be performed using STATA software (StataCorp. 2015).

Ethics and dissemination

Ethical approval will not be required as no original data will be collected as part of this review. If a quantitative analysis is conducted it will rely entirely on data extracted from published studies. The completed review will be submitted for publication in a peer-reviewed journal and presentation at conferences.

Discussion

The principal objectives of the planned systematic review are to evaluate how HSUVs are obtained in children and adolescents with disabilities, identify if the HSUVs currently used are appropriate for use in this population, and provide summary statistics for HSUVs in this population. We will collate this data to identify areas that require further research regarding the measurement of HSUVs in children and adolescents with disabilities.

The intended audience of this review goes beyond health economists working to develop decision models to guideline developers, policy makers, clinicians and researchers. In summarising the instruments which have been validated for use in this population group, we will also highlight those which have not yet been validated. We hope that the identification of these knowledge gaps will encourage and direct future instruments validation work.

Author contributions: LK, NA, and JR developed the idea for the review. LK wrote the first draft. NA and JR revised the protocol. JR will act as guarantor of the review.

Competing interests: The authors declare no conflicts of interest.

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Appendix 1: Sample Medline search strategy

1 exp Disabled Persons/

2 ((physical* or intellectual* or psychiatric* or sensory or motor or neuromotor or cognitive or mental* or developmental or communication or learning) adj2 (disabilit* or disabl* or handicap*)).mp.

3 exp Intellectual Disability/

4 ((cognitive* or learning or mobility or sensory or visual* or vision or sight or hearing or physical* or mental* or intellectual*) adj2 impair*).mp.

5 (mental* adj1 retard*).mp.

6 ((mental* or emotional* or psychiatric* or neurologic*) adj2 (disorder* or ill or illness*)).mp.

7 (deaf or deafness or blind or blindness).mp.

8 1 or 2 or 3 or 4 or 5 or 6 or 7

9 (infant* or infanc* or child* or adolescen*).mp.

10 8 and 9

11 (EQ-5D* or EQ5D* or "time-trade-off" or "time trade off" or TTO or "standard gamble" or "standard-gamble" or SG or "health utilit* or "HUI" or "SF36" or "SF-36" or "CHU-9D" or CHD9D or "Quality of well being" or "Quality of Well-Being" or "Quality of Well Being or "QALY" or Quality of life adjusted years" or "QoL"").mp.

12 "Cost-utility or "cost utility

13 "Cost-effectiveness or "cost effectiveness

14 "Cost-benefit" or "CBA"

15 11 or 12 or 13 or 14

16 10 and 15

Appendix 2: Data extraction items

1. Study ID
2. Year of publication
3. Author contact details
4. Publication type (e.g. full report)

After texts eligibility confirmed

Background information

1. Country
2. Funding sources
3. Conflicts of interest
4. Statement of ethical approval

Study aim and methods

1. Aim of study
2. Study design
3. Duration of study
4. Duration of participation
5. Multicentre or single centre
6. Study setting
7. Inclusion/exclusion criteria
8. Sample origin - Setting participants recruited from (clinical/ community)
9. Method of recruitment
10. Sample size
11. Sampling method

If trial

1. Number randomised to each group
2. Description of intervention including intervention provider and duration of programme
3. Description of comparator

Participant characteristics (for sample recruited and sample included in the analysis if different). Note if participant is not respondent these characteristics should also be described for respondents.

1. Age
2. Sex
3. Race
4. Socioeconomic status

Disability

1. Diagnosis
2. Disability type
    a. Years in present disability
3. Disability severity
4. Other medical condition
    a. Years in this condition

HSUVs determination

1. Instrument used to obtain health utility
2. Attributes of instrument described
3. Mode of administration (e.g. self-reported or proxy)
4. If administered by proxy, relationship between respondent and participant
5. Preference elicitation technique(s) described
6. Time points measured
7. Time points reported

8. Measurement scale
9. Length taken to complete

If study is not examining validity of the instrument

10. Is validity of the instrument in children and adolescents with disabilities reported? If not, is this information published?
11. Is reliability of the instrument in children and adolescents with disabilities reported? If not, is this information published?
12. Is responsiveness of the instrument in children and adolescents with disabilities reported if it is a longitudinal study? If not, is this information published?

If study is examining psychometric properties of the instrument

13. Is evidence of the content validity of the instrument provided?
    a. Are the methods used to solicit and confirm attributes of the instrument relevant to the measurement application?
    b. Do the authors report similarities and differences between the participants included in the evaluation and the target population?
    c. Is the recall period for the measurement application justified?
14. Is evidence of construct validity provided?
    a. What measures were used to demonstrate construct validity?
    b. Do the authors report similarities and differences between the participants included in the evaluation and the target population?
    c. Are predefined hypotheses on the expected associations between measures and the instrument of interest provided?
15. Is evidence of other types of validity provided?
    a. What methods are used to determine other types of validity?

b. Do the authors report similarities and differences between the participants included in the evaluation and the target population?

16. Is evidence of responsiveness provided?

    a. Is empirical evidence of changes in scores consistent with predefined hypotheses regarding changes in the instrument provided?

    b. Do the authors report similarities and differences between the participants included in the evaluation and the target population?

17. Is evidence of reliability provided?

    a. Is the reliability of the method >0.70 for group-level comparisons?

    b. If the reliability is lower than 0.70 is this justified?

    c. What method is used to determine reliability (e.g. test-retest reliability)?

    d. Is this method justified?

Results

1. Study response rate

    a. Overall response rate

    b. Response rate for instrument at each time point

    c. Reasons for missing data

    d. Rate of exclusion of any respondents or observations

    e. Reasons for excluding any respondents or observations provided

2. HSUV score

    a. Summary statistics

Section/topic	Item #	Checklist item	
ADMINISTRATIVE INFORMATION			
Title			Page no.
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number	Awaiting registration
Authors			
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	1
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support			
Sources	5a	Indicate sources of financial or other support for the review	1
Sponsor	5b	Provide name for the review funder and/or sponsor	1
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	1
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
METHODS			
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	15
Study records			
Data	11a	Describe the mechanism(s) that will be used to	6

management		manage records and data throughout the review	
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	6
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	7/16
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	NA
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7
Data			
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	7-8
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	8
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	Not planned
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	NA

Source: (Moher et al, 2015)

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Abstract

Introduction: Increasingly, assessment of health care technologies and interventions requires the assessment of both costs and utilities. Health state utility values (HSUVs) are measured using a range of generic and condition-specific measures. While reviews have identified that generic measures of HSUVs may lack validity in adults with conditions that result in physical disability, there is little information available on the methods used to obtain HSUVs in children and adolescents with disabilities. The objectives of this systematic review are to describe the methods used to obtain HSUVs, including mode of administration and psychometric properties, and provide summary statistics for HSUVs among children and adolescents with disabilities.

Methods and analysis: The following databases will be searched from inception for English-language studies of any design: PubMed; PsychInfo; Medline; Scopus; CINAHL Plus; Econlit and EMBASE databases. Two reviewers will independently screen titles, abstracts and full text articles for studies reporting HSUVs and/or data on the psychometric properties of preference-based measures for children and adolescents with disabilities aged up to 19 years of age. Two reviewers will independently extract data items including descriptors of the study methods and sample, instruments used to capture HSUVs, summary statistics for HSUVs, and items relating to the quality of reporting. A descriptive summary of results from included studies and summary statistics for HSUVs will be presented. If sufficient data is identified we will pool summary statistics for HSUVs according to the method used to obtain the HSUV using a random effects model. In addition, we will explore the determinants of the HSUVs using a meta-regression.

Ethics and dissemination: Ethical approval will not be required as no original data will be collected as part of this review. The completed review will be submitted for publication in a peer-reviewed journal and presentation at conferences.

Systematic review registration number: This protocol will be registered with the International Prospective Register of Systematic Reviews following peer review.

Strengths and limitations of this study:

- A strength of this review is that it will include studies of children and adolescents with a range of disabilities. Where possible results will be presented according to disability type.
- A limitation of this review is that publications that are not peer-reviewed such as unpublished theses and conference presentations will not be included.
- This review will also only include reports written in English and therefore could exclude relevant information.
- It may not be possible to report summary statistics for HSUVs if the methods used to obtain HSUVs are found to be inappropriate for use in this population.

Background

Economic evaluations are increasingly used to inform the evidence base in decisions regarding the adoption of health care interventions. A cost-utility analysis (CUA), which describes the relationship between costs and health benefits (using quality of life), is commonly used in the appraisal of interventions and technologies. The strength of the CUA is the fact that costs are compared with quality adjusted life years (QALYs), a measure which incorporates both the quantity and quality of life. By using QALYs, various disparate outcomes can be combined into a single composite summary outcome which allows broad comparisons across different disease areas in the health sector. When calculating QALYs, quantity is captured using life years while quality is captured using health state utility values (HSUVs). To enhance the transparency and hence reliability of evidence from CUA, it is key that the process of collecting data for the CUA is robust, transparent and systematic [1,2]. Health state utility values are ranked on a scale anchored at 1 (full health) and 0 (a health state of equivalent value to being dead). HSUVs can be elicited using methods such as the Time Trade Off methods (TTO) or the Standard Gamble (SG). Often generic measures, such as the EuroQol five dimensions questionnaire (EQ-5D), are recommended to be used in economic evaluations because they allow comparison across health care interventions and sectors [2].

Disability is “a difficulty in functioning at the body, person, or societal levels, in one or more life domains, as experienced by an individual with a health condition in interaction with contextual factors” [3]. Disability refers to the negative aspects of the interaction between individuals with a health condition (such as cerebral palsy, cardiovascular disease, depression) and personal and environmental factors (such as negative attitudes, inaccessible transportation and public buildings, and limited social supports) [4]. Although the prevalence of disability varies between countries and within countries, depending on how disability is conceptualised and assessed [4], the global prevalence among adults is approximately 15.6% [4]. Approximately 5% of children aged 0 to 14 years worldwide experience a moderate or severe disability [4]. Research into the health needs, health outcomes, and effectiveness of interventions, particularly rehabilitation interventions, is a

priority for improving health care among people with disabilities [4]. Encompassed in this is the need to evaluate the cost-effectiveness of health care interventions.

Condition-specific measures of quality of life are often used when assessing the effectiveness of interventions in children and adults with disability [5-7]. However, traditionally generic preference based measures such as the EQ-5D have been employed in CUA analyses, and not condition-specific measures [2]. The validity of applying these generic measures, which have been developed in the general population, to groups with specific conditions has been debated [8,9,10].

Several reviews have identified that generic measures of HSUVs may lack validity in adults with conditions resulting in physical disability [10-13]. There is a lack of information, however, regarding the utility and psychometric properties of measures used to obtain HSUVs in children and adolescents with disabilities. Understanding how HSUVs are obtained in children and adolescents with disabilities and the psychometric properties of these measures in this population is important for interpreting the findings of CUA of health interventions.

Objectives

This review will address the following objectives:

1. Describe the methods used to obtain HSUVs from children and adolescents with disabilities.
2. Describe how these methods are administered.
3. Describe the psychometric properties of the methods used to obtain HSUVs from children and adolescents with disabilities in this population.
4. Report summary statistics for HSUVs among children and adolescents with disabilities obtained from each method identified.

Methods

The methods used for this systematic review will be in line with available recommendations on reviews of health state utility values [14-18]. In addition, a scoping review was conducted to inform

the methods of this review. Reporting of the review will adhere to recommendations of the PRISMA statement [19]. The protocol will be registered with the International Prospective Register of Systematic Reviews following peer review.

Study eligibility

Study designs

We will include: 1) studies reporting HSUVs among children and adolescents with disabilities derived from both direct (such as standard gamble, time trade off, visual analogue scale) and indirect methods (such as EuroQol EQ-5D and all its variants, Child Health Utility 9D [CHU-9D], Assessment of Quality of Life 6D [AQoL-6D], Pediatric Asthma Health Outcome Measure (PAHOM), Health Utilities Index Mark 2 [HUI-2], Quality of Well-Being Scale and 16D-questionnaire); and 2) studies reporting the utility and/or psychometric properties of measures used to obtain HSUVs in children and adolescents with disabilities.

There will be no restriction on the type of studies to be included. Examples of types of studies to be included in the review are:

- studies that compare existing or new measures of HSUVs;
- studies that validate measures of HSUVs;
- randomised clinical trials that incorporate cost utility assessments

Participants

The review will include studies reporting HSUVs for children and adolescents with disabilities aged 0 to 19 years of age. We will include studies reporting HSUVs for the general population if they report HSUVs for children and adolescents with disabilities separately. Studies of children and adolescents aged 0 to 19 years with the following broad forms of disabilities will be included:

a) Intellectual impairment (e.g. learning difficulties) or intellectual disability

b) Physical impairment (e.g. mobility impairment, poliomyelitis)

c) Developmental disability (e.g. autism spectrum disorder [ASD] or cerebral palsy)

d) Sensory impairments (e.g. visual impairment, speech impairment)

e) Multiple impairment – at least two of the above

Where studies include children, adolescents and adults, e.g. participants aged 5 to 20 years, or adolescents and adults, e.g. participants aged 15 to 20 years, we will extract data on children and adolescents separately if possible. If this is not possible we will include the study in the descriptive analysis but not in the quantitative analysis. Where studies include adults with disabilities we will interpret the results of these studies in the context of the proportion of children and/or adolescents included in the study.

Language

We will include articles reported in the English languages only.

Exclusion criteria

We will exclude studies reporting HSUVs in adults with disabilities only or in children or adults without disabilities. We will also exclude reviews, commentaries, unpublished theses, conference abstracts, and any unobtainable texts.

Search strategy

A systematic search will be conducted to capture HSUVs used in children and adolescents with disabilities. The following databases will be searched from inception: PubMed; PsychInfo; Medline; Scopus; CINAHL Plus; Econlit and EMBASE. We will also search for studies on the EQ-5D, Health Utilities Inc [HUInc], National Health Service Economic Evaluation Database (NHS EED), and Health Technology Assessment (HTA) websites. Reference lists of key papers will be reviewed for additional references.

Search terms

The development of the search terms was informed by a scoping review of the literature [20-26]. Specific search terms include different variants of child and adolescent terms (infant, newborn, child and adolescent), health utility terms (EQ-5D, Time trade off, Standard Gamble) and disability. A sample search strategy is provided in Appendix 1.

Data management

Literature search results will be managed using Mendeley reference management software.

Study selection

Two reviewers will review the titles and abstracts for inclusion. If a study appears to meet the inclusion criteria or if there is any doubt regarding the inclusion of the study the full text of the article will be retrieved. Full text articles will be reviewed independently by both reviewers and disagreements resolved through discussions with a third reviewer. Reasons for exclusions will be documented for all full text articles. The PRISMA flow diagram [19] will be used to summarize the number of articles identified, retrieved, screened, assessed, included, and excluded as well as the reasons for exclusions.

Data extraction

Data extraction will be conducted independently by two reviewers. Disagreements between the two reviewers will be resolved primarily through discussions and where necessary a third reviewer will be involved. If HSUVs are not available from the study report we will contact the authors. A period of two months from the request date will be allowed for the author to respond.

Data items

Details of the data extraction items are provided in Appendix 2. The data extraction form has been piloted by two reviewers (LK, JR). Data extraction items include a description of the study methods, sample and results as well as items relating to the quality of reporting. As this review will identify patient-reported outcome measures used to obtain HSUVs in children and adolescents with

disabilities, the International Society for Quality of Life Research (ISOQOL) minimum standards for patient-reported outcome measures [27] was used to inform data extraction items. These items include information on the reliability, validity and burden of the patient-reported outcome measure, which will aid identification of suitable outcome measures as well as highlight improvements in reporting and additional research that are required in the field. Further, the CREATE checklist (Checklist for REporting VAluaTion StudiEs) [28] was consulted when developing the data extraction items. As the objectives of this review are broad, all items on the CREATE checklist may not be applicable to all included studies and therefore the checklist as a whole will not be used. Instead items from the CREATE checklist informed the data to be extracted such as a description of the attributes of the instrument, the sampling method, the response rate, and reasons for excluding any respondents or observations. The items extracted will include:

- A description of the study background, aims and methods: funding sources; conflicts of interest; statement of ethical approval; aim of study; study design; duration of study; duration of participation; study setting; method of recruitment; sample size; sampling method; number randomised to each group; and description of intervention and comparator (if study is a trial)
- A description of the participant (and respondent, if different) characteristics: age; sex; race; socioeconomic status; diagnosis; type of disability; years in present disability; disability severity; other medical conditions; years in this condition. As there is not a standard method of categorising severity across all disability types the method used to categorise severity will be extracted from each article.
- A description of the methods used to obtain HSUVs: instrument (e.g. CHU-9D) or direct elicitation technique (e.g. TTO) used; mode of administration (e.g. telephone, face-to-face); data source (e.g. self-reported or proxy); relationship between participant and respondent if administered by proxy; time points measured and reported; length of time to complete the instrument or administer the method to elicit HSUVs.

- A description of the psychometric properties of the instrument in children and adolescents with disabilities: a statement of validity, reliability and responsiveness (if longitudinal study); methods used to determine psychometric properties and statement of differences between participants and target population if study is examining psychometric properties of the instrument
- A description of the results of the study: response rates; reasons for missing data; reasons for exclusion of respondents or observations; summary statistics for HSUVs.

Data synthesis

Descriptive analyses

A summary of the results from the included studies will be presented according to disability type (intellectual impairment or disability, physical impairment, developmental disability, sensory impairments, multiple impairments) and instrument used to obtain HSUVs if a sufficient number of studies for each type is identified. In addition, all identified methods of obtaining HSUVs and the relevant attributes of their associated studies will be tabulated. We will also report the number of studies where data extraction items were not available in order to provide an overview of the quality of reporting by study authors.

Quantitative analyses

If we identify sufficient data of sufficient quality for a meta-analysis we will pool summary statistics for HSUVs according to the method used to obtain the HSUV using a random effects model. We will only include data obtained using methods that are identified as having adequate validity and reliability among children and adolescents with disabilities. Heterogeneity between the findings of the reviewed studies will be assessed using the I-squared (I^2) statistic. In addition, we will explore the determinants of the HSUVs, including disability type, using a meta-regression. Statistical analyses will be performed using STATA software version 14 (StataCorp. 2015).

Ethics and dissemination

Ethical approval will not be required as no original data will be collected as part of this review. If a quantitative analysis is conducted it will rely entirely on data extracted from published studies. The completed review will be submitted for publication in a peer-reviewed journal and presented at conferences.

Discussion

The principal objectives of the planned systematic review are to evaluate how HSUVs are obtained in children and adolescents with disabilities, report the psychometric properties of measures used to obtain HSUVs among children and adolescents with disabilities and if appropriate, provide summary statistics for HSUVs in this population. We will collate this data to identify areas that require further research regarding the measurement of HSUVs in children and adolescents with disabilities.

Previous literature suggests that adult-specific methods of obtaining HSUVs are used in studies of children [20,29,30], even though the utility weights obtained from these methods have not been adapted to incorporate the possibly different child and adolescent preferences [29,30]. These issues may be compounded by potential problems with administering generic measures to people with disabilities [10-13] resulting in inaccurate CUA among children and adolescents with disabilities and poorly informed decisions regarding the adoption of new interventions in this population.

The intended audience of this review therefore goes beyond health economists to guideline developers, policy makers, clinicians and researchers. In summarising the instruments which have been validated for use in this population group, we will also highlight those which have not yet been validated. We hope that the identification of these knowledge gaps will encourage and direct future instruments validation work.

While it is anticipated that this review will provide useful information on measures used to obtain HSUVs in children and adolescents with disabilities there are a number of limitations with the proposed review. Firstly, as reports that are not peer-reviewed and are not written in English will be

excluded from the review, relevant information may not be included. This may also reduce the generalisability of the findings to specific populations of children and adolescents. Further, it may not be possible to report summary statistics for HSUVs if the methods used to obtain HSUVs are found not to have adequate validity and reliability among children and adolescents with disabilities. It may also not be possible to determine if disability type predicts HSUVs if insufficient data for each disability type is identified.

Author contributions: LK, NA, and JR developed the idea for the review. LK wrote the first draft. NA and JR revised the protocol. JR will act as guarantor of the review.

Competing interests: The authors declare no conflicts of interest.

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Appendix 1: Sample Medline search strategy

1 exp Disabled Persons/

2 ((physical* or intellectual* or psychiatric* or sensory or motor or neuromotor or cognitive or mental* or developmental or communication or learning) adj2 (disabilit* or disabl* or handicap*)).mp.

3 exp Intellectual Disability/

4 ((cognitive* or learning or mobility or sensory or visual* or vision or sight or hearing or physical* or mental* or intellectual*) adj2 impair*).mp.

5 (mental* adj1 retard*).mp.

6 ((mental* or emotional* or psychiatric* or neurologic*) adj2 (disorder* or ill or illness*)).mp.

7 (deaf or deafness or blind or blindness).mp.

8 1 or 2 or 3 or 4 or 5 or 6 or 7

9 (infant* or infanc* or child* or adolescen*).mp.

10 8 and 9

11 (EQ-5D* or EQ5D* or "time-trade-off" or "time trade off" or TTO or "standard gamble" or "standard-gamble" or SG or "health utilit* or "HUI" or "SF36" or "SF-36" or "CHU-9D" or CHD9D or SF-6D* or SF6D* or PALQLQ* or PAHOM* or "Quality of well being" or "Quality of well-being" or "QALY" or Quality of life adjusted years" or "QoL"").mp.

12 "Cost-utility or "cost utility

13 "Cost-effectiveness or "cost effectiveness

14 "Cost-benefit" or "CBA"

15 11 or 12 or 13 or 14

16 10 and 15

Appendix 2: Data extraction items

1. Study ID
2. Year of publication
3. Author contact details
4. Publication type (e.g. full report)

After texts eligibility confirmed

Background information

1. Country
2. Funding sources
3. Conflicts of interest
4. Statement of ethical approval

Study aim and methods

1. Aim of study
2. Study design
3. Duration of study
4. Duration of participation
5. Multicentre or single centre
6. Study setting
7. Inclusion/exclusion criteria
8. Sample origin - Setting participants recruited from (clinical/ community)
9. Method of recruitment
10. Sample size
11. Sampling method

If trial

1. Number randomised to each group
2. Description of intervention including intervention provider and duration of programme
3. Description of comparator

Participant characteristics (for sample recruited and sample included in the analysis if different). Note if participant is not respondent these characteristics should also be described for respondents.

1. Age
2. Sex
3. Race
4. Socioeconomic status

Disability

1. Diagnosis
2. Disability type
    a. Years in present disability
3. Disability severity
4. Other medical condition
    a. Years in this condition

HSUVs determination

1. Method used to obtain health utility
2. Attributes of method described
3. Mode of administration (e.g. telephone, face-to-face)
4. Data source (e.g. self-reported or proxy)
5. If administered by proxy, relationship between respondent and participant
6. Preference elicitation technique(s) described
7. Time points measured

8. Time points reported
9. Measurement scale
10. Length taken to complete

If study is not examining validity of the instrument

11. Is validity of the instrument in children and adolescents with disabilities reported? If not, is this information published?
12. Is reliability of the instrument in children and adolescents with disabilities reported? If not, is this information published?
13. Is responsiveness of the instrument in children and adolescents with disabilities reported if it is a longitudinal study? If not, is this information published?

If study is examining psychometric properties of the instrument

14. Is evidence of the content validity of the instrument provided?
    a. Are the methods used to solicit and confirm attributes of the instrument relevant to the measurement application?
    b. What is the evidence of content validity?
    c. Do the authors report similarities and differences between the participants included in the evaluation and the target population?
    d. Is the recall period for the measurement application justified?
15. Is evidence of construct validity provided?
    a. What measures were used to demonstrate construct validity?
    b. Do the authors report similarities and differences between the participants included in the evaluation and the target population?
    c. Are predefined hypotheses on the expected associations between other measures and the instrument of interest provided?

d. What is the empirical evidence to support predefined hypotheses on the expected associations between other measures and the instrument?

16. Is evidence of other types of validity provided?
    a. What methods are used to determine other types of validity?
    b. Do the authors report similarities and differences between the participants included in the evaluation and the target population?
    c. What is the empirical evidence of other types of validity?
17. Is evidence of responsiveness provided?
    a. Is empirical evidence of changes in scores consistent with predefined hypotheses regarding changes in the instrument provided?
    b. Do the authors report similarities and differences between the participants included in the evaluation and the target population?
18. Is evidence of reliability provided?
    a. What method is used to determine reliability (e.g. test-retest reliability)?
    b. Is this method justified?
    c. What is the empirical evidence for each type of reliability investigated?
    d. Is the reliability of the method >0.70 for group-level comparisons?
    e. If the reliability is lower than 0.70 is this justified?

Results

1. Study response rate
    a. Overall response rate
    b. Response rate for instrument at each time point
    c. Reasons for missing data
    d. Rate of exclusion of any respondents or observations
    e. Reasons for excluding any respondents or observations provided

2. HSUV score

    a. Summary statistics

Section/topic	Item #	Checklist item	
ADMINISTRATIVE INFORMATION			
Title			Page no.
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number	Awaiting registration
Authors			
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	1
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support			
Sources	5a	Indicate sources of financial or other support for the review	1
Sponsor	5b	Provide name for the review funder and/or sponsor	1
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	1
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
METHODS			
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	15
Study records			
Data	11a	Describe the mechanism(s) that will be used to	6

management		manage records and data throughout the review	
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	6
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	7/16
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	NA
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7
Data			
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	7-8
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	8
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	Not planned
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	NA

Source: (Moher et al, 2015)