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| protocol |
| **Quality of Little Lives Study (QuoLL) - Usability of EQ-5D-Y adapted for use in children aged 2-4 years**  **Short title:** QuoLL – Usability of adapted EQ-5D-Y |
| **Lay title:** Quality of Kids’ Lives Study – Finding the best way to measure kids’ health  HREC 71963  **Protocol cover note:** This study will collect data concurrently with another similar project *(HREC #71872 ‘QUality Of Life in Kids: Key evidence to strengthen decisions in Australia (QUOKKA) –Paediatric Quality of Life Multi-instrument Comparison Study’)* so as to reduce the burden on recruiting departments as well as potential participants.  Version: 3  Date: 14 April 2021   | **Version Number and Date** | **Summary of changes** | | --- | --- | | **V1, 22/02/2021** | **Initial ethics application** | | **V2, 24/03/2021** | **Resubmission 1 addressing ethics queries** | | **V3, 14/04/2021** | **Resubmission 2 addressing ethics queries** | |
| **CONFIDENTIAL**  This document is confidential and is the property of Murdoch Children’s Research Institute. No part of it may be transmitted, reproduced, published, or used without prior written authorisation from the institution.  **Statement of Compliance**  This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research (2007 and all updates), applicable national and local regulations and in the spirit of the Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016 annotated with TGA comments. |

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# PROTOCOL SYNOPSIS

|  |  |
| --- | --- |
| ***TITLE*** | Quality of Little Lives Study (QuoLL) - Usability of EQ-5D-Y adapted for use in children aged 2-4 years |
| ***STUDY DESCRIPTION*** | This study is to test the administration of the EQ-5D-Y proxy survey adapted for children aged 2-4 years who are well through to those that are very sick. The feasibility, sensitivity, acceptability and responsiveness of the adapted EQ-5D-Y survey will be assessed through repeated measurement of the adapted EQ-5D-Y up to 8 weeks following the initial survey. The performance of the adapted survey will be compared to the Global Health Measure, Child Health Utility (CHU9D), Paediatric Quality of Life Inventory (PedsQL), Toddler and Infant (TANDI) and Health Utilities Index (HUI2). Performance will be analysed and compared at summary, dimension and item levels using psychometric analyses. Additionally, the feasibility, acceptability and responsiveness of the various instruments will be compared. |
| ***OBJECTIVES*** | The primary objective is to compare the performance of an adapted version of the EQ-5D-Y on currently available paediatric QoL instruments among Australian children in terms of consistency, acceptability, feasibility, reliability, validity, sensitivity and responsiveness. |
| ***OUTCOMES AND OUTCOME MEASURES*** | The outcome and outcome measures of the study are:   * **Consistency** measured by comparing the consistency of summary and dimension specific responses on each instrument. * **Validity**   + Content validity measured qualitatively during pilot testing stage   + Construct validity     - Within-scale analysis measured using factor analysis     - Known group differences measured by descriptively comparing a priori assumptions regarding expected differences between disease groups and healthy children.     - Convergent validity measured by analysing the correlation of similar constructs from different instruments hypothesised to measure similar constructs.     - Discriminant validity measured by analysing whether dimension responses are independent of child age. * **Reliability**   + Test-retest reliability measured by measured by agreement on dimension-level responses between the initial survey to the re-test survey up to 8 weeks later. * **Responsiveness** will be assessed using dimension level responses from children whose proxy respondents reported a change in general status from the initial survey to the re-test survey up to 8 weeks later in comparison to those not showing a change. This will be assessed to determine the extent to which instruments are responsive to change in general status. * **Feasibility and acceptability** measured by the completeness of data, time to complete instruments and self-reported difficulty. * **Sensitivity** measured by sensitivity to known changes in HRQoL. |
| ***POTENTIAL CONFOUNDING FACTORS (SUB-GROUP ANALYSIS)*** | Due to the study design there are no confounding factors to consider, however, we will be performing several sub-group analysis to understand how the validity, reliability, feasibility, acceptability and responsiveness of instruments varies according to participant sociodemographic characteristics (e.g. child sex, child age, parent education and family socioeconomic status (SES)). |
| ***STUDY POPULATION*** | Survey data will be collected from parents of children aged 2-4 years. Data will be collected on approximately 400 Australian children who are well through to those that are very sick. |
| ***DESCRIPTION OF SITES ENROLLING PARTICIPANTS*** | Survey data will be collected through The Royal Children's Hospital (RCH) and via online survey panels. |
| ***STUDY DURATION*** | This study is estimated to be completed in 24 months, with recruitment planned to begin in March 2021. |
| ***PARTICIPANT DURATION*** | Participants will be required to complete an initial 15-30 minute survey followed by a second 5-minute survey up to 8 weeks after they complete the initial survey. Total estimated participation is 20-35 minutes. |

# GLOSSARY OF ABBREVIATIONS

|  |  |
| --- | --- |
| **ABBREVIATION** | **TERM** |
| AE | Adverse Event |
| CHU9D | Child Health Utility (QoL instrument) |
| HUI2 | Health Utilities Index 2 |
| HREA | Human Research Ethics Application |
| HREC | Human Research Ethics Committee |
| HRQoL | Health Related Quality of Life |
| NHMRC | National Health and Medical Research Council |
| ICC | Intraclass Correlation Coefficient |
| MCRI | Murdoch Children’s Research Institute |
| PedsQL | Paediatric Quality of Life Inventory (QoL instrument) |
| PI / CPI | Principal Investigator / Coordinating Principal Investigator |
| QoL | Quality of Life |
| QALY | Quality Adjusted Life Year |
| RCH | The Royal Children’s Hospital (Melbourne) |
| SES | Socioeconomic Status |
| SDQ | Strengths and Difficulties Questionnaire |
| TANDI | Toddler and Infant (QoL instrument) |

# ADMINISTRATIVE INFORMATION

# Sponsor

On behalf of the sponsor, the EuroQol group, the Study Principal Investigator (Study PI) will undertake and/or oversee those Sponsor responsibilities delegated by the Sponsor.

| **Study Sponsor** | EuroQol Group |
| --- | --- |
| **Contact name** | *Elly Stolk* |
| **Address** | Marten Meesweg 107, Rotterdam, 3068 AV, Netherlands |

# Expected duration of study

This study is estimated to be completed in 24 months. Recruitment is planned to begin in March 2021 and be completed by January 2023. Once enrolled participants will be required to complete an initial 15-30 minute survey (completed at time of recruitment) followed by a second 5 minute survey up to 8 weeks after they complete the initial survey. Total participation is estimated to take 20-35 minutes over an 8 week period per participant.

# Contributorship

| **Name** | **Email** | **Affiliation/role** | **Study Role** | **Summary of contribution** |
| --- | --- | --- | --- | --- |
| A/Prof Kim Dalziel | kim.dalziel@unimelb.edu.au | Head, Health Economics Unit, The University of Melbourne  Team Leader, Health Services Research, The Royal Children’s Hospital Melbourne | Principal Investigator | Budget and timeline management, oversee staff and workplan, overall study design, oversee study design execution, data analysis, stakeholder engagement, write up and dissemination. |
| Prof Harriet Hiscock | Harriet.hiscock@rch.org.au | Paediatrician, Centre for Community Child Health, The Royal Children’s Hospital, Melbourne  Group Leader, Health Services, Murdoch Children’s Research Institute  Director, Health Services Research Unit, The Royal Children’s Hospital  Professorial Fellow, Department of Paediatrics, University of Melbourne | Co-investigator | Budget and timeline management, oversee staff and workplan, overall study design, oversee study design execution, data analysis, stakeholder engagement, write up and dissemination. Survey development, recruitment planning, stakeholder engagement, study design planning, write up and dissemination |
| Nancy Devlin | nancy.devlin@unimelb.edu.au | Professor of Health Economics, Centre for Health Policy, University of Melbourne. | Co-investigator | Expert input in health related quality of life measurement, survey development, data analysis, write up and dissemination |
| A/Prof Oliver Rivero-Arias | oliver.rivero@npeu.ox.ac.uk | Associate Professor of Health Economics, Nuffield Department of Population Health, Oxford University | Co-investigator | Survey development, statistical analysis planning, expert input in methodology and analysis, write up and dissemination |
| Michael Herdman | mherdman@ohe.org | Head of Health Outcomes, Office of Health Economics, London. | Co-investigator | Expert input in health related quality of life measurement, survey development, data analysis, write up and dissemination |
| Dr Li Huang | li.huang@unimelb.edu.au | Research Fellow, Health Economics Unit, The University of Melbourne | Co-investigator | Study design participation, statistical analysis planning, data analysis, write up and dissemination |
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# INTRODUCTION AND BACKGROUND

# Background and rationale

There are few health-related quality of life (HRQoL) measures available to estimate Quality Adjusted Life Years (QALYs) as part of economic evaluation for children, particularly for younger children [1][2][3]. And there is currently no preference-based generic multi-attribute utility instrument that is designed for children under 4 years of age aside from two very recent measures which are only suitable for children aged 0-1 year [4] and 1-3 years [5][6], and none recommended by authorities for the estimate of QALYs. This compromises the ability to inform efficient allocation of health care resources across age groups [7], which is critical considering that younger children are large consumers of health care services [6]. For example, children aged 0-4 comprise the greatest absolute number of emergency department presentations in Victoria compared to every other age group [8]. Gaps in evidence about utilities (single index scores derived from HRQoL measures for the estimation of QALYs) for paediatric outcomes have been noted by Health Technology Assessment bodies. For example, in Australia the Pharmaceutical Benefits Advisory Committee (PBAC) and Medical Services Advisory Committee (MSAC) have noted that they want to facilitate and promote greater use of paediatric patient reported outcomes (PROs) in cost effectiveness evidence to assist resource allocation decisions [9]. In the UK, the National Institute for Health and Care Excellence (NICE) has established a working group to address the same issue [10]. Literature reviews have identified the very weak evidence upon which paediatric utilities are currently based [11].

One of the most common HRQoL measures used to generate utility scores and QALYs for children is the EQ-5D-Y [12] [13], and the CHU9D is another commonly used utility instrument [14]. Neither measures were designed for children under 4 years. However, the CHU9D have provided guidance notes to extend use of the instrument to child populations under 5 years. This means the CHU9D with guidance notes is currently able to be used for children 2-5 years. We note, however, that the CHU9D guidance notes do not appear to have been informed by a foundation of empirical investigation to check whether they yield appropriate means of administering the instrument for children under 5 (i.e. as far as we can tell, there is no accompanying paper setting out the basis for the adaptation of the CHU9D instrument for children <5 years).

Despite that the EQ-5D-Y was not recommended for children under 4 years of age, validated non-preference-based instruments for children aged 2-4 years such as the PedsQL have dimensions that are similar to the current EQ-5D-Y such as walking/running, bath/showering, sports/activities, hurt/ache and sad/worried [15]. Likewise, mapping has shown a good relationship between EQ-5D-Y dimensions and the non-preference-based PedsQL [16]. In the United States, the PedsQL instrument is being explored in terms of its potential for preference-based scoring to enable the calculation of utilities for younger children and inclusion in economic evaluation (PhRMA Foundation grant 2019100004, PI Prosser).

Being one of the most common utility instruments for children, the EQ-5D-Y [12] is recommended for children aged 4-7 years using the proxy (typically parent) version, with the self-reported version recommended for children aged 7- 15 years [13]. Earlier research [17] suggests that EQ-5D-Y in its current format would not be suitable as a proxy version for use in children under 4 years, which is problematic for paediatric clinical research. For example, at present a clinical trial of asthma/wheezing would exclude children aged 2-4 from data collection using the EQ-5D-Y resulting in missing data for these children. However, it may be possible to adapt EQ-5D-Y for use in children between the ages of 2 and 4 years, without substantially altering the content or integrity of the instrument [16] [17]. Below the age of 2 years, substantial changes to the content would likely be needed [18].

Focus groups were previously used understand how the EQ-5D-Y could be adapted for children aged 2-4. Parents and carers of children aged 2-4 attended focus groups to inform these adaptations (see Section 6.2.1.1 and 6.2.2.1 of Appendix A). The adapted EQ-5D-Y now needs test administration for children aged 2-4 years who are well through to those that are very sick and compared based on psychometric performance to other QoL measures.

# Study aim (s)

This study aims:

* assess the validity and reliability of the adapted EQ-5D-Y and compare it to the PedsQL, CHU9D, HUI2 and TANDI.
* assess the acceptance, version preference, convergent validity and known group validity of the adapted EQ-5D-Y.
* assess reliability and responsiveness through repeated measurement with EQ-5D-Y up to 8 weeks following the initial survey.
* compare acceptance and validity of the adapted and original EQ-5D-Y for measurement of HR-QoL.
* assess the psychometric performance of the adapted EQ-5D-Y to other quality of life instruments currently available for this age group (PedsQL, CHU9D, HUI2 and TANDI).

# STUDY OBJECTIVES AND OUTCOMES

# Primary objective

The primary objective is to compare the performance of an adapted version of the EQ-5D-Y on currently available paediatric QoL instruments among Australian children in terms of acceptability, feasibility, reliability, validity, sensitivity and responsiveness.

# Secondary objectives

The secondary objectives are:

* To evaluate how different paediatric QoL instruments compare by child age and condition
* To evaluate how the convergence/divergence of the different paediatric QoL instruments compare by age/condition
* To compare the performance of general QoL instrument and relative disease specific QoL instruments including their ability to discriminate between groups with known conditions
* To provide a validated EQ-5D-Y version for young children that is ‘fit for purpose’ in judging the effectiveness and cost effectiveness of paediatric interventions.

# Outcomes

* + 1. **Primary Outcomes:**

The study will compare the QoL instruments according to the following measures of instrument performance:

* **Validity**: the degree to which the QoL instrument measures the construct(s) it purports to measure.
  + Content validity: the degree to which the content of the adapted EQ-5D-Y is an adequate reflection of the construct to be measured.
  + Construct validity: the degree to which the scores of a QoL instrument is consistent with hypotheses based on the assumption that the instrument validly measures the construct to be measured.
* **Reliability**: The stability of a measuring instrument.
  + Test-retest reliability: the reliability over time.
* **Feasibility and acceptability**: the ease at which the patient is able to complete the instrument.
* **Responsiveness**: the ability of an instrument to detect change in the construct to be measured.
  + 1. **Secondary Outcomes:**

How the above list of outcomes compare by child age, parent vs proxy report and disease group.

# STUDY DESIGN

# Overall design

This study involves the prospective collection of several paediatric QoL instruments via two surveys, an initial 15-30 minute survey and a retest follow-up 5 minute survey up to 8 weeks later. A small subset of participants from the study being run in parallel (HREC #71872) will be randomized to a 2-day follow up, however, it is not expected the n=400 children used for this study will be part of that small subset. Collecting these paediatric QoL instruments concurrently across a range of age and disease groups will allow the performance of the adapted EQ-5D-Y (for children aged 2-4yrs) to be assessed.

This study will involve the primary data collection of paediatric QoL instruments as well as the adapted proxy EQ-5D-Y survey in populations of children with a variety of health conditions as well as healthy children. We aim to collect survey data on n=400 Australian children aged 2-4 years (inclusive) recruited through RCH and online survey panels. An iterative approach will be adopted, with a soft launch allowing for concomitant statistical analysis to inform adjustments in selection criteria to maximise informativity where most needed. By collecting survey data through the RCH we aim to collect data from children who have a wide range of health conditions. Importantly, collecting data from children at RCH will allow us to capture children with more severe and less common health conditions.

The initial survey will include several paediatric QoL instruments: Global Health Measure, CHU9D, PedsQL, TANDI, adapted EQ-5D-Y (3L and 5L), carer QoL (EQ-HWB) and sociodemographic questions (including the Strengths and Difficulties Questionnaire (SDQ) (Appendix A). The HUI2 will be included as an additional instrument at random in the initial survey for some participants. We will pilot the percentage of participants randomised to also receive the HUI2 (75% of the first 100 participants of children aged 2-4 will be randomised to receive the HUI2). After this we may increase or decrease the percentage randomised to receive the HUI2 based on information gained from piloting. The initial survey is expected to take approximately 15-30-minutes to complete.

Parents of children with the following condition will be recruited via an online survey panel and will be asked to complete an additional disease specific measure (listed below): ADHD, anxiety or depression, ASD, asthma, dental decay or sleep problems. This strategy will primarily be used to recruit participants for the study being run in parallel (HREC #71872), however, this will include the recruitment of parents/caregivers of children aged 2-4years old who will be asked to also take part in this study.

* Asthma: PedsQL asthma module
* ASD: KIDSCREEN
* Sleep problem: Sleep Disturbance Scale for Children (SDSC)
* Dental decay: Child Perceptions Questionnaire (CPQ 11-14)
* Anxiety and depression: The Revised Children’s Anxiety and Depression Scale, Short form (RCADS-25)
* ADHD: Strengths and Weaknesses of Attention-Deficit/Hyperactivity Disorder Symptoms and Normal Behavior Scale (SWAN)

The follow-up survey will be a paired back version of the initial survey to maximise participation. This follow-up survey will be sent out up to 8 weeks after completion of the initial survey. The follow-up survey will include fewer QoL instruments: adapted EQ-5D-Y (3L and 5L), TANDI, Global Health Measure, CHU9D (Appendix A). No sociodemographic questions will be included in the follow-up survey.

Caregivers/parents will be asked to provide consent and complete the sociodemographic questions. The caregiver/parent will be asked to complete the QoL questions using proxy report related to their child. The order that the different QoL instruments are presented will be randomised for each participant. The consent and sociodemographic questions will always remain as the first two blocks of questions in the initial survey.

Survey data will be collected online using the secure REDCap database system.

The performance of the various paediatric QoL instruments will be analysed and compared using psychometric analyses. Additionally, the feasibility, acceptability and responsiveness of the various instruments will be compared.

# Study population

Parents/caregivers of Australian children aged 2-4 years.

# Inclusion Criteria

Participants need to meet to following criteria to be included in the study:

* Parent/caregiver of a child(ren) aged of 2-4 years at enrolment.

# Exclusion Criteria

Participants meeting any of the following criteria will be excluded from this study:

* Is unable to communicate in written English. Language will be simplified as much as possible to allow inclusion of caregivers who might have limited English proficiency
* Reside outside of Australia
* Unable to answer or comprehend questions

# Screening questions for online panel

# Online panel screening questions

Are you the parent, caregiver or guardian of a child aged 2 to 18 years?

\*Please note that although the age range for this study is 2-4years the screening question is 2-18 years as this study will collect data concurrently with another similar project *(HREC #71872*) which will collect data on children up to the age of 18 and hence the screening question captures the age range for both studies. Parents/caregivers will be filtered be part of this study if they enter that they are the parent/caregiver of a child aged 2-4years. Parents/caregivers are made aware of this in the PICF.

# Online panel disease groups

**Anxiety and/or depression**

As per SDQ cut off for ‘abnormal’ internalising (anxiety and depression) behaviour problems. See Appendix A for SDQ wording.

**Attention deficit hyperactivity disorder (ADHD)**

Has your child been diagnosed with Attention deficit hyperactivity disorder (ADHD) by a doctor?

Yes 🡪 inclusion

No 🡪 exclusion

**Autism Spectrum Disorder (ASD)**

Has your child been diagnosed with Autism Spectrum Disorder (ASD) by a doctor?

Yes 🡪 inclusion

No 🡪 exclusion

**Dental Decay**

Has your child had tooth decay in the last 2 years (excluding preventative care)?

* Yes🡪 inclusion
* No🡪 exclusion

**Asthma**

Has your child been diagnosed with Asthma by a doctor?

Yes 🡪 inclusion

No 🡪 exclusion

**Sleep problems**

How much is (study child)’s sleeping pattern or habits a problem for you?

Not a problem at all🡪 exclusion

A small problem🡪 exclusion

A moderate problem🡪 inclusion

A large problem 🡪 inclusion

# Recruitment of potential participants

Potential participants will be recruited through the following multi-pronged approach, strategy:

* **Telehealth (TH):** RCH TH appointments will be used to advertise the study. We will advertise in the virtual waiting room and at the end of all TH appointments. The advert will include a short description of the study and will have a link to the PICF and survey (Appendix B).
* **Face-to-face in clinic method:** a research assistant (RA) with an iPad will approach parents in the waiting rooms across RCH. The RA will approach families in the following RCH departments after notifying the clinic/reception staff of that day about their presence and why they will be approaching families: Short stay unit (SSU), Neurology, Neurodevelopment and Disability, Centre for Community Child Health (CCCH), General Medicine, Colorectal surgery, Day surgery, and Endocrinology and Diabetes. To ensure only appropriate families are approached and care is not being disrupted the RA will approach families in the following RCH departments after being provided a list of families approved for approaching from the department staff of that day: Short Stay Unit (SSU). Given the current COVID-19 global pandemic, face-to-face recruitment will not begin until the recruiting RCH departments allow this to occur. Please see Section 7.1 for details on the COVID-19 safe practices for this study.
* **Face-to-face in playground:** an RA will attend the local RCH playground (east side) (likely in the morning to avoid nap times) where they will approach parents with a handout which describes the study and what is involved (Appendix B).
* **Contacting via another study:** Participants from the study ‘*Validation of a single screening question tool to assess the mental health of children with chronic illness admitted to the Day Medical Unit at The Royal Children’s Hospital, Melbourne’ (HREC: 67053)* were asked if they would like to be contacted for future research about children’s health and wellbeing. Families who ticked they would like to hear about this type of research will be contacted by the research team to invite them to this study (Appendix E). Participants will be followed up regarding their invitation to take part in the study as per the contact management plan (Appendix D).
* **Clinician send short link:** Clinicians will email, text or electronically send (inc RCH portal) a link to survey with a short description of the study (Appendix F). A link to the survey will be sent by clinicians from the following RCH departments: Neurology, Neurodevelopment and Disability, Centre for Community Child Health (CCCH), General Medicine, Colorectal surgery, Day surgery, and Endocrinology and Diabetes.
* **Advertisement:** Posters in high traffic areas with a QR code linked to the PICF and online survey (Appendix G). These posters will be placed in the following RCH departments: SSU, Neurology, Neurodevelopment and Disability, Centre for Community Child Health (CCCH), General Medicine, Endocrinology and Diabetes, Colorectal surgery, and Day Surgery.
* Childcare centre: The RCH onsite childcare will email out a short description of the study with a link to the survey to parents/caregivers who have children aged 2-4 years (Appendix H).
* **Social media:** We will advertise the study on the MCRI Facebook and Twitter (Appendix B). The Facebook advert will target families of children aged 2-4 years. This advert has been designed in collaboration with the MCRI digital communications team and will have a link to the survey.
* **Recruitment via Intensive Care Unit (ICU)**: We will recruit potential participants via the ICU. Elective admissions to ICU will be actively recruited. ICU research staff will approach potential participants for consent prior to the child’s admission to ICU (e.g. pre-operative clinic visit or while in hospital). ICU families expressing an interest in research studies will also be eligible to participate, however, only elective admissions will be actively recruited. Elective admissions were chosen as the focus of active recruitment after consultation with the ICU research team, they feel that approaching families for consent before the child is admitted to ICU is the most ethical approach as we will be able to discuss the study with families before the child is admitted to ICU, when the family has capacity to understand what taking part in the study involves. This approach will also allow us to avoid the active recruitment of families in cases where recruitment would be considered inappropriate for this study, for example, where the child is unlikely to survive or where the child has had an unplanned admission to ICU and the stress of the family is very high. Additionally, the ICU research team will be the staff approaching these families about the study for consent. This is the most appropriate approach as the ICU research staff work within the ICU department and will be familiar to the families as well as having the training and experience to ensure they are only approaching appropriate families (i.e. families who are not currently in a high state of stress) for the study.

Parents/caregivers will also be identified using an online panel managed and maintained by Pureprofile Australia (PPA). Participants will be randomly selected from those in the panel eligible to take part in this study. Before taking part in the survey potential participants will need to complete relevant screening questions (see Section 4.2.3). This strategy will primarily be used to recruit participants for the study being run in parallel (HREC #71872), however, this will include the recruitment of parents/caregivers of children aged 2-4years old who will be asked to also take part in this study. A group of potential participants registered with the panel will be consented to complete the survey. All existing members of the panel have completed a double opt-in process to join the panel and have consented to complete online surveys over the course of their membership of the panel. They are provided the opportunity to accept or not accept any offer to participate in a new survey. PPA will provide the link to the survey panel members via the REDCap link. Further detail regarding the Panel survey company methods is provided in a separate attachment (Pureprofile Panel Quality Document). PPA is approved by MCRI Legal.

Participants recruited via the ICU will be consented in person by the ICU research team (Appendix L), this will allow the ICU research team to discuss the study and what is involved with potential participants as well as to ensure only appropriate families are being approached to take part.

# Consent

Informed written consent will be obtained from parent/caregivers prior to survey commencement. Consent will be obtained online. All participants will be required to read the Participant Information and Consent Form (PICF) prior to providing consent (Appendix I- RCH PICF and Appendix J- Online panel PICF).

# STUDY VISITS AND PROCEDURES

# Study timeline

There will be an initial survey (Appendix A) followed by a second shorter survey up to 8 weeks after the completion of the first survey (Appendix A).

# Schedule of assessments

The initial survey will mark the beginning point of the participants involvement. Participants can enter the study at any point and are not required to be on the same schedule as another participant. Participants will be sent a reminder 2-8 weeks after initial survey to complete a follow-up survey.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Measures collected** | **Assessment** | **RCH Sample (n=400)** | | **Online panel- disease specific groups\*** | | **Online panel- healthy children\*** | |
| **Initial survey** | **Follow-up survey**  **(up to 8 weeks)** | **Initial survey** | **Follow-up survey**  **(up to 8 weeks)** | **Initial survey** | **Follow-up survey**  **(up to 8 weeks or 2 days)** |
| **CORE MEASURES (if ‘x’ each participant will receive)** | | | | | | |
| **Informed Consent** | **x** |  | **x** |  | **x** |  |
| **Demographic Information** | **x** |  | **x** |  | **x** |  |
| **Carer QoL (EQ-HWB)** | **x** |  | **x** |  | **x** |  |
| **SDQ** | **x** |  | **x** |  | **x** |  |
| **PedsQL** | **x** | **x** | **x** | **x** | **x** | **x** |
| **TANDI (if <4yrs)** | **x** | **x** | **x** | **x** | **x** | **x** |
| **EQ5DY (3L, 5L and VAS) adapted** | **x** | **x** | **x** | **x** | **x** | **x** |
| **CHU9D with guidance notes** | **x** | **x** | **x** | **x** | **x** | **x** |
| **Global Health Measure** | **x** | **x** | **x** | **x** | **x** | **x** |
| **Disease specific QoL measure (if applicable)**   * Asthma: PedsQL asthma module * ASD: KIDSCREEN * Sleep problems: SDSC * Dental decay: CPQ * Anxiety and depression: RCADS-25 * ADHD: SWAN |  |  | **x** |  |  |  |
| **ADDITIONAL MEASURE (if ‘x’ participants will be randomised to receive one of the following measure blocks)** | | | | | | |
| **HUI2 (if >=2yrs)** | **x\*\*** |  |  |  | **x** |  |

\* These study groups will primarily form part of the participants for study being run in parallel (HREC #71872), however, these groups may also include the parents/caregivers of children aged 2-4years old who will also form part of this study.

\*\*For participants from the RCH sample, the HUI2 will be included as an additional instrument at random to some parents of children aged 2-4years in the initial survey. See Section 4.1 for further detail.

# PROCEDURES

# Description of procedures

Participants will be identified through a number of methods outlined in Section 4.3. To ensure the only eligible participants complete the survey, we will have screening questions prior to entry to entry to the PICF and survey. Screening questions will be the same for all children recruited through RCH and social media (Appendix A). The online survey panel screening questions will also include questions that specify the condition/health status being targeted, please see Section 4.2.3 for a breakdown of which groups will be asked which screening questions.

Participants will be followed up for the follow-up survey as per the contact management plan (Appendix D). There will be 3 follow-ups over the period of a month to encourage completion of the second survey. The majority of participants will be followed up by the research team, however, participants recruited via Pureprofile with be followed up by Pureprofile as the research team will not hold the contact details for these participants.

This study will collect data concurrently with another similar project *(HREC #71872 ‘QUality Of Life in Kids: Key evidence to strengthen decisions in Australia (QUOKKA) –Paediatric Quality of Life Multi-instrument Comparison Study’)* so as to reduce the burden on recruiting departments as well as potential participants by joining these surveys together. This way we would only approach a family once and based on the child’s age they would be filtered through to slightly different survey questions based on their child’s age. The PICF explains to participants that if they will be taking part in a study comparing quality of life measures and if they have a child aged 2-4 they will also be asked to take part in testing a new tool (the aim of this study).

We will perform statistical analysis as data is collected to monitor the groups of participants completing the survey, this analysis will inform adjustments in recruitment to maximise informativity where most needed.

All data will be collected via surveys. Surveys will be completed by parents/caregivers. The survey will be completed online via REDCap. In most cases the potential participant will be provided a link to the survey via one of the recruitment strategies and will complete the survey on their own device. For recruitment that is face-to-face a RA will provide the potential participant with the option to complete the survey on their own device or on an iPad the RA can provide. To ensure safe practice with COVID-19, face-to-face recruitment will not begin until approval from the head of each department involved in recruitment has been provided. COVID safe practices will occur when recruiting in person and details on the safety procedure are provided in Section 7.1.

**Procedure for participants recruited via ICU**

Potential participants from ICU will be approached and consented by ICU research staff, in most cases this consent will be completed prior to the child’s admission to ICU, however, in rare cases where families show an interest in taking part while in ICU they will be consented by ICU research staff while their child is in ICU. The ICU research staff will notify the study team once a participant has been recruited to the study and will again notify the study team once the child has been admitted to ICU. The study team will then text or email a link to the online survey to the parent/caregiver with the aim of having the participant complete the initial survey whilst the child is in ICU. The study team and ICU research team will work closely together to follow-up participants to complete the initial survey. If the consented participant has been sent a link to the initial survey and has not yet completed the ICU research team will approach the family and provide a gentle reminder to complete the survey, they will also offer an iPad to assist with completing the survey. Before the study team contacts these participants to prompt them to complete the follow-up survey, they will check in with the ICU research team to ensure the child has been discharged from ICU and to ensure the child has not died. In the rare event the child has died the family will not be contacted to complete the follow-up survey.

# Participant withdrawals and losses to follow up

# Withdrawal of consent

Participants are free to withdraw from the study at any time upon their request or the request of their legally acceptable representative. Withdrawing from the study will not affect their relationship with, or care by, the hospital and affiliated health care professionals. Participants will be notified in the PICF that they are free to withdraw at any time (Appendix I- RCH PICF and Appendix J- Online panel PICF).

# Losses to follow-up

To minimise loss to follow-up for the second survey we will be use the following multi-pronged approach:

* Notify parent/caregiver when they sign up to the study that participation involves the completion of another survey in 2-8 weeks’ time
* Keep the second survey very short (5 minutes)
* Have the second survey at a close interval to the first survey so the study is still front and center of their mind
* Contact families multiple times as per the contact management plan to remind them to complete the survey (Appendix D)

A participant is considered lost to follow-up if the maximum number of contacts has been reached and they have not completed the second survey. If participants are lost to follow-up their responses to the initial survey can still be used in several of the analyses.

# Study Closure

The end of the study for a given participant is defined as completion of both the initial and follow-up survey or if the maximum number of contacts has been reached for the follow-up survey.

# POTENTIAL RISKS RELATED TO STUDY CONDUCT

This study offers low or negligible risks as all participants are either caregivers who have provided informed consent to take part in the survey. Completing the survey may be an inconvenience for families, however, they can complete the survey at a time that best suits them. Questions related to the child’s own general health will be asked, and this may be sensitive for some participants, although health questions are very generic. The health questions that will be used are generic and are based on items that have been included in other surveys that elicit general health related quality of life from participants. Participants will be informed that they will answer questions about their child’s general health and wellbeing prior to taking part; therefore, if this is something that concerns them they will be able to make an informed decision not to take part or to cease survey part way through if they wish.

To ensure the psychological safety of participants recruited via ICU, these families will have access to the ICU psychologist. The ICU research team will be able to connect the family with the ICU psychologist if needed.

* 1. **COVID-19 Safety Plan**

As this study involves face-to-face recruitment as part of the recruitment strategy, COVID-19 safety plans have been developed to ensure participant facing recruitment is safe and in accordance with both MCRI and RCH policies and procedures (Appendix K). Face-to-face recruitment will only occur under ‘COVID normal’ restrictions and in the event face-to-face recruitment is required to be paused due to changes in COVID restrictions we will switch to one of the many other recruitment strategies we have in place. At every stage we will be guided and abide by both MCRI and RCH guidance regarding COVID-19.

# POTENTIAL BENEFITS

The findings of this study will inform whether a proxy survey is suitable for children aged 2-4 to measure health status of children in this age group. This research will provide the EuroQoL Group information on the performance and validity of the EQ-5D-Y for proxy use for children aged 2-4 years. This will enable economic evaluation to include patients of younger ages which will mean they can be more fully considered in government decision making and clinical evaluation.

# DATA AND INFORMATION MANAGEMENT

# Overview

The Principal Investigator is responsible for storing essential study documents relevant to data management.

The Principal Investigator is responsible for maintaining adequate and accurate source documents that include all key observations on all participants. Source data will be attributable, legible (including any changes or corrections), contemporaneous, original, accurate, complete, consistent, enduring and available. Changes to source data (hardcopy and electronic) must be traceable, must not obscure the original entry, and must be explained where this is necessary.

The Principal Investigator and research team will also maintain accurate data collection and be responsible for ensuring that the collected and reported data is accurate, legible, complete, entered in a timely manner and enduring. To maintain the integrity of the data, any changes to data (hardcopy and electronic) must be traceable, must not obscure the original entry, and must be explained where this is necessary.

Any person delegated to collect data, perform data entry or sign for data completeness will be recorded on the delegation log and will be trained to perform these study-related duties and functions.

# Data management

The source documents for this study include online questionnaires completed by the participant and the consent forms which are also completed online via REDCap. Source data for this study will include:

* Appendix A: Initial survey
* Appendix A: Follow-up survey

# Data capture methods and data use, storage, access and disclosure during the study

All data will be captured electronically via REDCap. Electronic data will be securely stored in MCRI's REDCap database system and in files stored in MCRI's network file servers, which are backed up nightly. Additionally, data will be de-identified for analysis and stored in a restricted access folder on the University of Melbourne network drive on a password protected computer. Files containing private or confidential data will be stored only in locations accessible only by appropriate designated members of the research team. Data on the MCRI network drive is backed up nightly to a local backup server, with a monthly backup taken to tape and stored offsite. No data will be sent off-campus. All data analysts will be required to become an MCRI honorary to access data. Overseas investigators will not require access to individual level data (they will only see aggregate data such as non-identifiable summary tables that would be displayed in a journal article) and hence no data will be sent overseas.

Purepofile will identify potential participants and will provide the REDCap link to these participants to complete. Pureprofile maintains a secure data storage operation where all client and Account Holder details are backed up on multiple, mirrored and redundant server systems within a private security facility. Pureprofile stores multiple sets of data from client projects on both local server networks and web based project management systems. In any given survey a respondent’s data is collected anonymously with data only tagged to a random identification number. The project team will only use anonymised data collected as part of this study, and will not have access to any personal information held by Pureprofile. Pureprofile has been reviewed and approved by MCRI legal. Importantly, Pureprofile already has rightful access to personal information on potential participants and thus the research team will not be providing any personal information to Pureprofile and Pureprofile will not be providing the research team with any personal information of the participants. All individual level data received from participants recruited via Pureprofile will be provided by the participants themselves. To ensure a good distribution of participants is recruited by Pureprofile we will regularly monitor the types of participants recruited by Pureprofile. Pureprofile may provide aggregate data to the research team on participant demographics (e.g. distribution of participant age). Additionally, the research team may provide Pureprofile with aggregate data on the participants recruited via Pureprofile (e.g. distribution of income ranges). Aggregate data will be presented in such a way that individuals will not be identifiable.

REDCap is hosted on MCRI infrastructure and is subject to the same security and backup regimen as other systems (e.g. the network file servers). Data is backed up nightly to a local backup server, with a monthly backup taken to tape and stored offsite. REDCap maintains an audit trail of data create/update/delete events that is accessible to project users who are granted permission to view it. Access to REDCap will be provided via an MCRI user account or (for external collaborators) via a REDCap user account created by the MCRI system administrator. The permissions granted to each user within each REDCap project will be controlled by, and will be the responsibility of, the study team delegated this task by the Principal Investigator. REDCap has functionality that makes adding and removing users and managing user permissions straightforward. All data transmissions between users and the REDCap server are encrypted. The instructions for data entry to REDCap must be read and the training log signed prior to personnel commencing data entry on REDCap.

Authorised representatives of the sponsoring institution as well as representatives from the HREC, Research Governance Office and regulatory agencies may inspect all documents and records required to be maintained by the Investigator for the participants in this study. The study site will permit access to such records.

The data will be used for the analyses specified in the protocol. Following the completion and analysis of the study, the data will be retained long-term following the mandatory archive period for use in future research projects.

The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorised third party, without prior approval. Additionally, minimal clinical information (self-reported child condition if applicable) will be collected.

# Data confidentiality

Participant confidentiality is strictly held in trust by the Principal Investigator, participating investigators, research staff, and the sponsoring institution and their agents.

To preserve confidentiality and reduce the risk of identification during collection, analysis and storage of data and information, the following will be undertaken:

* The number of private/confidential variables collected for each individual has been minimised. The data collected will be limited to that required to address the primary and secondary objectives.
* Participant identifiers will be stored securely in REDCap which has permission control functionality.
* Participant data will be identified through use of a unique participant study number/code assigned to the study participant and these will be securely stored on REDCap. A master-file of identifiable data and the participant ID will be restricted to the study team and authorised persons.
* Separation of the roles responsible for management of identifiers and those responsible for analysing content. Data will be stored securely in REDCap which has the functionality to provide users with different levels of access. Only the level of access required to complete their role will be provided to the research team members. For example, data analysts will only be provided access to variables not labelled as ‘identifiers’.

# Quality assurance

To maximise the quality and consistency of processes, data collection and documentation, all research procedures will be carried out by the research team as per the procedures outlined in the protocol. The study coordinator and PI Dalziel will review REDCap database on a weekly basis to correct errors in data entry and evaluate for accuracy and completion.

# Archiving - Data and document retention

Information will be kept for at least 5 years after the publication of the study as per The Australia Code for Responsible Conduct of Research, after which time it will either be destroyed or kept indefinitely, according to MCRI policy.

# Data sharing

The data (or parts of it) may also be used in related research projects by other researchers in collaboration with the project team for purposes of comparing analyses or applying different statistical techniques in a rapidly evolving methodological field. Only anonymised data will be used for this, and all analyses will be agreed with the project team.

Beginning 12 months following analysis and article publication, the following will be made available long-term for use by future researchers from a recognised research institution whose proposed use of the data has been ethically reviewed and approved by an independent committee and who accept MCRI’s conditions for access:

* Individual participant data that underlie the results reported in this article after de-identification (text, tables, figures and appendices)
* Study protocol, Statistical Analysis Plan, PICF

# STUDY OVERSIGHT

# Site Study Management Group (SMG)

The project team lead by PI Dalziel will provide expert advice and overall supervision, and ensure that the study is conducted to the required standards. The project will meet at least monthly, with more frequent meetings as needed. This EuorQoL project will work closely with a related MRFF project to ensure consistent methods and a shared recruitment strategy.

## Consumer involvement

To inform the adaptations in the adapted version of the EQ-5D-Y, focus groups with parents and carers were used (HREC project # 69836). These parents and carers will also be used to pilot the survey prior to testing.

# STATISTICAL METHODS

# Sample Size Estimation

Sample size calculation has not been performed due to a lack of data available to inform how expected responses are likely to be distributed or compare to other QoL measures. We considered it more important to ensure a heterogenous sample in child/family characteristics and in child health-related quality of life. This diversity in the sample is important to determine the validity and applicability of the HRQoL instruments to groups of children. We had considered a smaller sample size which would have allowed for shorter study period and smaller budget, however we settled on 400 participants to ensure the rigor needed for the analyses. This results in a 12-month recruitment window and most of the budget which is needed to obtain participation of 400 families.

# Statistical Analysis Plan

Data will primarily be displayed as dimension-level responses and analysed based on international consensus.[19,20]

| Outcome [19,20] | Definition [19] | Analysis [20] |
| --- | --- | --- |
| 1. Feasibility and acceptability | The ease at which the patient is able to complete the instrument. | Measured by the completeness of data, time to complete and self-reported difficulty. |
| 1. Validity | The degree to which the QoL instrument measures the construct(s) it purports to measure. |  |
| * 1. Content validity | The degree to which the content of the EQ-5D-Y (A) is an adequate reflection of the construct to be measured. | Measured qualitatively from pilot data, using expert opinion and literature review. |
| * 1. Construct validity | The degree to which a QoL instrument is consistent with hypotheses based on the assumption that the instrument validly measures the construct to be measured. |  |
| * + 1. Known group differences | The ability of an instrument to differentiate known groups. | Known group differences measured by descriptively comparing a priori assumptions regarding expected differences between disease groups and healthy children. |
| * + 1. Convergent validity | Evidence that the scale is correlated with other measures of similar constructs. | Convergent validity measured by analysing the correlation of similar constructs from different instruments. We also check the size and the direction the change. |
| * + 1. Discriminant validity | Evidence that the scale is not correlated with measures on different constructs. | Discriminant validity measured by analysing whether dimension responses are independent of child age. |
| 1. Reliability | The degree to which the responses for children who have not changed are the same for repeated measurement under certain conditions. |  |
| * 1. Test-retest reliability | The stability of a measuring instrument. | Test-retest reliability measured by agreement on dimension-level responses between the initial survey to the re-test survey up to 8 weeks later. |
| 1. Responsiveness | The ability of an instrument to detect change in the construct to be measured. | This will be assessed to determine the extent to which instruments are responsive to change in general status. |

# Subgroup analysis

We will investigate how the key outcomes described above vary by child age, sex, SES, disease group/health status and parent proxy vs self-report.

# Data transformation

We will generate value set scores from raw scores.

# Methods to account for missing, unused or spurious data

To manage missing, unused or spurious data we will:

* Describe missingness and follow guidelines from each instrument authors if available
* Consider or explore imputation if more than 5% missing
* Create reminders for missed questions but allow participants to continue with no answer (if possible in REDCap)
* Ask participants why they didn’t respond to certain questions or report the difficulty of answering more generally
* Working with panel company to put rules about minimum acceptable data (if possible with REDCap and Pureprofile)

# Population to be analysed

All participants with complete data will be included in analysis. Participants with some missing data may be included following guidelines if available.

# ETHICS AND DISSEMINATION

# Research Ethics Approval & Local Governance Authorisation

This protocol and the informed consent document and any subsequent amendments will be reviewed and approved by the human research ethics committee (HREC) prior to commencing the research. A letter of protocol approval by HREC will be obtained prior to the commencement of the study, as well as approval for other study documents requiring HREC review.

# Amendments to the protocol

This study will be conducted in compliance with the current version of the protocol. Any change to the protocol document or Informed Consent Form that affects the scientific intent, study design, participant safety, or may affect a participants willingness to continue participation in the study is considered an amendment, and therefore will be written and filed as an amendment to this protocol and/or informed consent form. All such amendments will be submitted to the HREC, for approval prior to being implemented.

# Protocol deviations and serious breaches

All protocol deviations will be recorded and reported to the Study PI, who will assess for significance. Those deviations deemed to affect to a significant degree rights of a study participant or the reliability and robustness of the data generated in the clinical study will be reported as serious breaches. Reporting will be done in a timely manner. The Study PI will assess the event within 72 hours and report to the approving HREC within 7 days

Where non-compliance significantly affects human participant protection or reliability of results, a root cause analysis will be undertaken and a corrective and preventative action plan prepared.

Where protocol deviations or serious breaches identify protocol-related issues, the protocol will be reviewed and, where indicated, amended.

# PARTICIPANT REIMBURSEMENT

Participants will be offered a small token of appreciation for their time.

Participants who are recruited via the RCH recruitment methods will be offered a small token of appreciation for their time. These participants will receive a $15 family online gift pay gift voucher for completing both the initial and follow-up survey. The token of appreciation will be provided on completion of the follow-up survey. The amount reimbursed compensates participants for some of their time but is not seen as high enough to unduly coerce.

Participants who participate via the online survey panel will receive a small token of appreciation. This takes the form of money deposited to their bank accounts or reward cards that are allocated by PureProfile Australia (PPA) dependent on the questionnaire length. Using this system online is seen as a neutral system that does not skew the participation of certain demographic groups. Each respondent will receive approximately $3 to $4 depending on survey completion which can be redeemed once every 2 months on balances over $25 up to a total of $50. The amount reimbursed compensates participants for some of their time but is not seen as high enough to unduly coerce. Participants also receive small amounts (10 cents) for answering questions to determine eligibility for a survey.

# FINANCIAL DISCLOSURE AND CONFLICTS OF INTEREST

There are no financial and other competing interests for investigators for the overall study.

# DISSEMINATION AND TRANSLATION PLAN

The results of the study will be reported in peer-reviewed publications and presented at conferences. The findings will be disseminated directly to key stakeholders to inform the evaluation of child quality of life in Australia and across the world. The results of this study will also inform future work being completed by the wider EuroQoL working group as well as the wider QUOKKA working group and thus will be disseminated to these two stakeholder groups as a priority.

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# APPENDICES

|  |  |
| --- | --- |
| Appendix A | Survey |
| Appendix B | Short Written Advert |
|  |  |
| Appendix D | Contact Management Plan |
| Appendix E | Similar Study Invitation |
| Appendix F | Study Blurb |
| Appendix G | QR Poster advert |
| Appendix H | Childcare email invitation |
| Appendix I | PICF RCH |
| Appendix J | PICF Online Panel |
| Appendix K | COVID sub plan |
| Appendix L | ICU RCH PICF |