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| protocol |
| **QUality Of Life in Kids: Key evidence to strengthen decisions in Australia (QUOKKA) –Paediatric Quality of Life Multi-instrument Comparison Study (P-MIC)**  **Short title:** QUOKKA - Comparing measures used in kids  **Lay title:** Quality of Kids Lives Study – Finding the best way to measure kids’ health |
| HREC 71872  **Protocol cover note:** This study will collect data concurrently with another similar project *(HREC #71963 ‘Quality of Little Lives Study (QuoLL) - Usability of EQ-5D-Y adapted for use in children aged 2-4 years’)* so as to reduce the burden on recruiting departments as well as potential participants  Version: 6  Date: 19 October 2021   | **Version Number and Date** | **Summary of changes** | | --- | --- | | **v1 22/02/2021** | **Initial ethics submission** | | **v2 23/03/2021** | **Re-submission 1 to address ethics queries** | | **v3 14/04/2021** | **Re-submission 2 to address ethics queries** | | **v4 29/06/2021** | **Amendment** | | **V5 23/09/2021** | **Amendment (EuroQol extension)** | | **V6 19/10/2021** | **Re-submission to address ethics queries** | |
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# PROTOCOL SYNOPSIS

|  |  |
| --- | --- |
| ***TITLE*** | QUality Of Life in Kids: Key evidence to strengthen decisions in Australia (QUOKKA) –Paediatric Quality of Life Multi-instrument Comparison Study (P-MIC) |
| ***STUDY DESCRIPTION*** | This is a multi-instrument comparison study involving the concurrent collection of several paediatric Quality of Life (QoL) instruments: Global Health Measure, Child Health Utility (CHU9D), Paediatric Quality of Life Inventory (PedsQL), EQ-5D-Y (3L and 5L), EQ-5D-5L,Toddler and Infant (TANDI), Assessment of Quality of Life (AQoL), Patient-Reported Outcome Measurement Information System 25 (PROMIS-25), Health Utilities Index 2/3 (HUI2) and disease specific QoL measures. The performance of the various paediatric QoL measures 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. We will also look at a subset of disease groups to see how generic QoL measures perform compared with disease-specific measures. |
| ***OBJECTIVES*** | The objectives of the study are to:   * Understand how available pediatric QoL instruments compare in terms of acceptability, feasibility, reliability, responsiveness, validity and sensitivity * Provide decision makers and researchers with a practical set of tools that are ‘fit for purpose’ in judging the effectiveness and cost effectivenes of paediatric interventions |
| ***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 will primarily be measured by agreement on dimension-level responses between the initial survey to the re-test survey 2 days later. Only a small subset of n=200 participants will have a 2-day follow-up. * **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 patient sociodemographic characteristics (e.g. child sex, child age, parent education and family socioeconomic status (SES)). |
| ***STUDY POPULATION*** | Survey data will be collected on approximately 6,100 Australian children. Data will be collected on children who are well through to those that are very sick in order to test the instruments across the full range of children included in policy decisions and research studies. |
| ***DESCRIPTION OF SITES ENROLLING PARTICIPANTS*** | Survey data for the primary study will be collected through The Royal Children's Hospital (RCH) (n=1,000) and The Royal Women’s Hospital (RWH)(n=30-50) and via online survey panels (n=5,100). Additionally, survey data for a sub-study, a caregiver/child dyad sample, will be collected via online survey panels (n=500). |
| ***STUDY DURATION*** | The data collection and primary analysis 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. A subset will complete a second 5 minute survey up to 8 weeks after they complete the initial survey (or 2-days for those allocated to the shorter follow-up group). Total estimated participation is 20-35 minutes. |

# GLOSSARY OF ABBREVIATIONS

|  |  |
| --- | --- |
| **ABBREVIATION** | **TERM** |
| AE | Adverse Event |
| AQoL | Assessment of Quality of Life (QoL instrument) |
| CHU9D | Child Health Utility 9 Dimension (QoL instrument) |
| HUI | Health Utilities Index |
| HREA | Human Research Ethics Application |
| HREC | Human Research Ethics Committee |
| HRQoL | Health Related Quality of Life |
| 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 |
| PROMIS | Patient-Reported Outcome Measurement Information System (QoL instruments) |
| QoL | Quality of Life |
| QALY | Quality Adjusted Life Year |
| QUOKKA | QUality Of Life in Kids: Key evidence to strengthen decisions in Australia (Study Title) |
| RCH | The Royal Children’s Hospital (Melbourne) |
| SDQ | Strengths and Difficulties Questionnaire |
| SES | Socioeconomic Status |
| TANDI | Toddler and Infant (QoL instrument) |

# ADMINISTRATIVE INFORMATION

# Registration of observational research

Australian New Zealand Clinical Trials Registry (ANZCTR) registration number: ACTRN12621000657820

# Sponsor

The MCRI are the sponsor for this study. They will work collaboratively with the University of Melbourne who is the lead site for the MRFF and EuroQol grant to conduct this study in accordance with the National Statement, the Australian Code, GCP and relevant regulatory requirements. The study Coordinating investigator is Kim Dalziel (University of Melbourne, Honorary MCRI) The Coordinating Principal Investigator will oversee those Sponsor responsibilities delegated by the Sponsor*.*

| **Study Sponsor** | MCRI |
| --- | --- |
| **Contact name** | *Coordinating Principal Investigator: Kim Dalziel* |
| **Address** | Royal Children’s Hospital, Flemington |

# Study sites

**Primary site:**

The Royal Children’s Hospital

50 Flemington Road

Parkville, Victoria 3052

**Additional site to supplement recruitment of specific subgroup:**

The Royal Women’s Hospital

20 Flemington Road

Parkville, Victoria 3052

# Expected duration of study

The data collection and primary analysis is estimated to be completed in 24 months. Recruitment is planned to begin in March 2021 and be completed by December 2021. 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 30-35 minutes over an eight week period per participant.

# Contributorship

| **Name** | **Email** | **Affiliation/role** | **Study Role** | **Summary of contribution** |
| --- | --- | --- | --- | --- |
| A/Prof Kim Dalziel | kim.dalziel@unimelb.edu.au | Associate Professor  Health Economics Unit, Centre for Health Policy, Melbourne School of Global and Population Health  Honorary Team Leader, Health Services, MCRI | Coordinating 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 | Group Leader, Health Services, Centre for Community Child Health, Murdoch Children's Research Institute  Director, Health Services Research Unit, The Royal Children's Hospital  Professorial Fellow, Department of Paediatrics, The University of Melbourne | Chief Investigator | Survey development, recruitment planning, stakeholder engagement, study design planning, write up and dissemination |
| A/Prof Brendan Mulhern | Brendan.mulhern@chere.uts.edu.au | Associate Professor, Centre for Health Economics Research and Evaluation  Core Member, CHERE - Centre for Health Economics Research and Evaluation, University Technology Sydney | Chief Investigator | Survey development, statistical analysis planning, data analysis, write up and dissemination |
| Dr Li Huang | li.huang@unimelb.edu.au | Senior Research Fellow, Centre for Health Policy, Melbourne School of Global and Population Health | Health economist | Study design participation, statistical analysis planning, data analysis, write up and dissemination |
| Rachel O’Laughlin | [rachel.oloughlin@student.unimelb.edu.au](mailto:rachel.oloughlin@student.unimelb.edu.au) | PhD Candidate, Health Economics Unit, Centre for Health Policy, Melbourne School of Population and Global Health | PhD student | Study design participation, statistical analysis planning, data analysis, write up and dissemination |
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| Prof Julie Ratcliffe | julie.ratcliffe@flinders.edu.au | Health and Social Care Economics Theme Lead, Caring Futures Institute, College of Nursing and Health Sciences Flinders University | Health economist | Oversee study design, statistical analysis planning, data analysis, write up and dissemination of Sample 4, caregiver/child dyad sample. |
| Dr Christine Mpundu-Kaambwa | christine.mpundu-kaambwa@flinders.edu.au | Research Fellow, College of Nursing and Health Sciences, Flinders University | Health economist | Study design, statistical analysis planning, data analysis, write up and dissemination of Sample 4, caregiver/child dyad sample |
| Diana Khanna | khan0420@flinders.edu.au | PhD student, College of Nursing and Health Sciences, Flinders University | PhD student | Study design, statistical analysis planning, data analysis, write up and dissemination of Sample 4, caregiver/child dyad sample |

# INTRODUCTION AND BACKGROUND

# Background and rationale

Decisions about the best use of health system resources by bodies such as Pharmaceutical Benefits Advisory Committee (PBAC) and Medical Services Advisory Committee (MSAC) rely on good evidence about efficacy and cost effectiveness. There is significant potential for better methods to positively impact decision-making: Australia spends around $12 billion per annum through the Pharmaceutical Benefits Schedule (PBS), and $20 billion through the Medical Benefits Schedule (MBS). Addressing this very clear evidence deficit will yield long term benefits and improved value for money across the health care system, resulting in improved population health outcomes.

Economic evaluation, where the cost effectiveness of interventions is assessed using Quality Adjusted Life Years (QALYs), is central to this decision-making process and is widely used around the world to make decisions about health care funding. For example in Australia the Pharmaceutical Benefits Scheme and the Medical Benefits Schedule both formally use cost-effectiveness evidence including the generation of QALYs to make decisions about public funding for pharmaceuticals and technologies. QALYs combine health-related quality of life (HRQoL) and survival (lifespan following intervention) in a single metric, allowing comparisons across health problems, interventions and populations. QALYs are based on patients’ health-related quality of life which is usually self-reported using HRQoL questionnaires. These questionnaires comprise a *descriptive system,* covering different quality-of-life aspects, and a preference-based scoring system that summarises HRQoL via QALY weights derived from the general population (or *utility values*).

There are established methods for *measuring* and *valuing* HRQoL. However, considerable challenges arise in applying these methods to children, in particular very young children.[1-4] For instance, the developmental range of children precludes a ‘one size fits all’ approach to measuring and valuing paediatric HRQoL. The role of proxy completion (usually by parents) for very young or other children who cannot self-report their HRQoL, is also crucial. Currently, there is a lack of sound evidence on this in Australia to guide decision making.

This study will generate new evidence on the peformance of available paediatric HRQoL questionaires. To do that, we will compare the performancee of currently available questionnaires accross a range of age and disease groups.

These data will be used to test the properties and relative merits of paediatric HRQoL questionnaires; similarities and differences in what they measure; and their performance across different ages and diseases. This evidence will improve and inform users’ choice of HRQoL instrument in Australia and around the world, as well as providing information about ways of linking (‘mapping’) between them.

# Study aim (s)

This study aims:

* To compare the performance of currently available pediatric QoL instrument in terms of acceptability, feasibility, reliability, validity and sensitivity across different age and disease groups within the Australian context
* To provide decision makers with a practical set of HRQoL tools that are ‘fit for purpose’ in judging the effectiveness and cost effectivenes of paediatric interventions

# STUDY OBJECTIVES AND OUTCOMES

# Primary objective

The primary objective is to compare the performance of currently available pediatric QoL instruments among Australian children in terms of acceptability, feasibility, reliability, responsiveness, validity and sensitivity.

# Secondary objectives

The secondary objectives are:

* To evaluate how different pediatric QoL instruments compare by child age and disease area
* To evaluate the convergence/divergence of different pediatric QoL instruments by age/condition
* To compare the performance of general QoL instrument relative disease specific QoL instruments including their ability to discriminate between groups with known conditions
* To provide decision makers with a practical set of HRQoL tools that are ‘fit for purpose’ in judging the effectiveness and cost effectivenes of paediatric interventions

# Outcomes

* + 1. **Primary Outcomes:**

The study will compare the following outcomes between QoL instruments [5]:

* **Consistency:** the degree to which the summary and dimension specific responses on each instrument are consistent with dimension and summary responses of other similar instruments.
* **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 QoL instrument is an adequate reflection of the construct to be measured.
  + Construct validity: the degree to which the scores of a QoL instrument are consistent with hypotheses based on the assumption that the instrument validly measures the construct to be measured.
  + Dimension structure: understanding the domains of QoL that each instrument or set of instruments is measuring, and the validity of each item within each domain
* **Reliability**: The stability of a measuring instrument.
  + Internal consistency: the degree of the interrelatedness among the items.
  + Test-retest reliability: the reliability over time.
* **Responsiveness**: the ability of an instrument to detect change in the construct to be measured.
* **Feasibility and acceptability**: the ease and completeness with which the patient is able to complete the instrument.
  + 1. **Secondary Outcomes:**

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

# STUDY DESIGN

# Overall design

This is a multi-instrument comparison study involving 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 (or 2 days later if allocated to shorter follow-up group). Collecting these paediatric QoL instruments concurrently across a range of age and disease groups will allow the performance of these instruments in Australian children to be assessed.

This study will involve the primary data collection of paediatric QoL instruments in populations of children with a variety of health conditions as well as healthy children via an online REDCap survey (Appendix A). We aim to collect survey data on n=6,100 Australian children aged 2-18 years (inclusive) using three samples. Sample 1 will include n=1,000 recruited through RCH, Sample 2 and Sample 3 will include n=3,600 and n=1,500 respectively, recruited through 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. We will also collect data on 500 caregiver/child dyads (Sample 4) recruited through online survey panels

Sample 1 will enable the study to collect survey data on n=1,000 through the RCH with an aim to collect data from children who have a wide range of health conditions.

There will be quota targets within Sample 1 including:

* 30-50 children with rare genetic conditions
* 30-50 children with serious sequalae arising across childhood following birth at an extremely low birthweight recruited via The Royal Women’s Hospital site.
* 30-50 children recruited from the emergency short stay unit

Importantly, collecting data from children at RCH will allow us to capture children with more severe and less common health conditions.

Sample 2 will enable us to collect survey data on disease-specific groups sample: 3,600 parents/caregivers of children with one of nine health conditions through the online survey panel. Disease groups were chosen that had sufficient prevalence to allow for recruitment of groups and with a focus on conditions with larger expected HRQoL decrements. We plan to use the online survey panel to recruit x10 groups of children with the following health status/common conditions:

* General population sample (‘healthy panel’) (n=1,500)
* Attention deficit hyperactivity disorder (ADHD )(N=400)
* Mental health- anxiety and depression (N=400)
* Autism Spectrum Disorder (ASD) (N=400)
* Asthma (N=400)
* Dental decay (N=400)
* Sleep problems (behavioral and clinical) (N=400)
* Epilepsy (N=400)
* Recurrent abdominal pain (N=400)
* Eating disorders (N=400)

Sample 3 will enable us to collect survey data on n=1,500 children through the online survey panels with a hope to capture large numbers of population representative children and children with the same common conditions.

Sample 3 will be further divided into two groups:

* Online panel population sample, normal follow-up: 1,300 parent/caregivers will be followed-up in line with the rest of the cohort, two to eight weeks after initial survey complete.
* Online panel population sample, short follow-up: to assess reliability, 200 parents/caregiver will be followed up at a shorter interval, two days after initial survey complete.

Sample 4 will enable us to collect HRQoL survey data on caregiver/child dyads. The sample will include 500 caregiver/child dyads, with 100 children at each year of age specified (6,7,8,9,10) where both the caregiver and child complete the HRQoL instruments. A repeat survey will be administered 2 days later to test reliability. Sample 4 will be used to assess the relationship and performance of paediatric QoL instruments between proxy and self-report, which forms part of the secondary objective of the study: *“How the above list of outcomes compare by child age, disease group and proxy vs self-report.”*.

The initial survey will include several paediatric QoL instruments (Appendix A). To minimize responder burden and reduce the length of the initial survey we will block instruments into core and additional. All participants will get the core instruments (where relevant) and participants from the online healthy panel (n=1,500) will be randomized to receive one additional block of instrument(s). The core set of instruments each participant will complete includes: Global Health Measure, CHU9D, PedsQL, EQ-5D-Y (3L and 5L, adapted and original), TANDI, sociodemographic questions (including the Strengths and Difficulties Questionnaire (SDQ) and disease specific QoL instrument (if part of the online disease groups panel). In addition to the core instruments, each participant from the online healthy panel (n=1,500) will be randomised to also receive one of the following additional instrument blocks: ‘EQ-5D-5L & HUI2’, AQoL-6D or PROMIS-25. The initial survey is expected to take approximately 15-30-minutes to complete.

The disease specific measures (listed below) will be completed by participants recruited via the online panel for one of the following groups (n=3,600): children with ADHD, anxiety or depression, ASD, asthma, dental decay, sleep problems, epilepsy, recurrent abdominal pain or eating disorders. The following criteria were applied to selection as a hierarchy: 1) Well validated for children, 2) Quality of life measure, 3) Symptom measure. Measures were also required to be short, be able to be completed by parent or self-report (i.e. don’t require clinician or interview) and valid.

* Asthma: PedsQL asthma module
* ASD: KIDSCREEN
* Sleep problems: 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)
* Epilepsy: Quality of Life in Childhood Epilepsy Questionnaire (QoLCE-16)
* Recurrent abdominal pain: Pain Visual Analog Scale (VAS) (x2- today and at last pain episode)
* Eating disorders: Eating Disorder Quality of Life Scale (EDQLS)

The follow-up survey will be a paired back version of the initial survey to maximise participation. For the majority of participants this follow-up survey will be sent out up to 8 weeks after completion of the initial survey. For the small sub-set (N=200) of participants allocated to the shorter follow-up group, the follow-up survey will be sent two days after the completion of the initial survey. The shorter follow-up group will be a subset of the healthy online panel group. The n=200 participants who will be allocated to a shorter follow-up will be a subset of the online panel of healthy children and will be selected at random from this larger group. The follow-up survey will include fewer QoL instruments (PedsQL, Global Health Measure, CHU9D, EQ-5D-Y (3L and 5L) and TANDI (if applicable)) (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. With the exception of Sample 4 (caregiver/child dyad sample, n=500), if the child is younger than 7 years of age or not currently able to complete the survey (e.g. not cognitively able to complete or is currently undergoing a procedure in hospital or with health concerns making them not physically present or able to complete the survey), the caregiver/parent will be asked to complete the QoL questions on behalf of the child (proxy report). If the child is aged 7 or older and capable of completing the survey they will be asked to complete the QoL questions (self-report). The survey will prompt the caregiver/parent to pass the survey onto the child if they identify that their child is capable of completing and aged 7 years or older. For consistency, if the caregiver/parent answers the QoL questions on behalf of the child in the initial survey they will be asked to answer the QoL questions in the follow-up survey. If the child answers the QoL questions in the initial survey, we will ask that the child answers the QoL questions again in the follow-up survey. Survey data will be collected online using the secure REDCap database system. For participants in Sample 4 (caregiver/child dyad sample, n=500) both the caregiver and child will answer the HRQoL questions for each instrument in the survey, this will include children aged 6-10.

The order of the different QoL instruments will be randomised to minimise order effects, meaning the order of the QoL instruments will be varied for each participant. EQ-5D-Y-3L, EQ-5D-Y-5L, and, if relevant the EQ-5D-5L, will be presented to participants with another HRQoL instrument separating them, given their similarities. For participants in samples two and three, where the child is four years or younger and is receiving both the EQ-5D-Y (3L or 5L) original and adapted version, the original version will be displayed directly before the adapted version. Participants will be presented the same ordering for their initial and follow up questionnaires. The consent and sociodemographic questions will always remain as the first two blocks of questions in the initial survey. Additionally, participants from samples two and three, will receive the same instrument(s) they were randomized to receive in the initial survey.

Participants will only be asked to complete QoL instruments and versions that are relevant to them. Please see Appendix A for a full list of initial and follow-up survey questions with a breakdown by child age, person reporting (parent-report vs child self-report or parent and self-report for participants Sample 4) and child disease group.

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

# Study population

Parents/ caregivers of Australian children aged 2-18 years.

# Inclusion Criteria

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

* Parent/caregiver of a child(ren) aged of 2-18 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 panels

# Online panel screening questions for Samples 2 and 3:

| Disease | Screening | Child age range *(Pureprofile to filter based on this range, if Pureprofile not able to do this, we will ask as screening question)* |
| --- | --- | --- |
| Anxiety and/or depression | Does your child have anxiety or depression as diagnosed by a health professional?  Yes - inclusion  No - exclusion | 7-18 |
| ADHD | Does your child have Attention deficit hyperactivity disorder (ADHD) as diagnosed by a health professional?  Yes - inclusion  No - exclusion | 4-18 |
| ASD | Does your child have Autism Spectrum Disorder (ASD) as diagnosed by a health professional?  Yes - inclusion  No - exclusion | 5-18 |
| Dental decay | Does your child **currently have** or have they **experienced in the last 3 months,** any of the following **tooth problems**? *This includes problems that have been treated, untreated or are still undergoing treatment.*   * Yes, cavities, dental decay or hole(s) in teeth * Yes, tooth or teeth filled because of dental decay * Yes, teeth pulled because of dental decay * Yes, accident causing breakage or loss of teeth * Yes, crowded teeth * Yes, problems with bite (e.g. crossbite or overbite) * No, my child has not experienced any of the above tooth problems | 5-18 |
| Asthma | Does your child have Asthma as diagnosed by a doctor?  Yes - go to next qx  No – exclusion    Has your child had symptoms of asthma or used an asthma treatment in the last 12 months?  Yes- inclusion  No-exclusion | 5-18 |
| 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 | 3-16 |
| Epilepsy | Does your child have epilepsy or a seizure disorder as diagnosed by a doctor?  Yes - inclusion  No - exclusion | 4-18 |
| Recurrent abdominal pain | Does your child have the ongoing condition ‘recurrent abdominal pain’?  *Recurrent abdominal pain is at least three episodes of pain that occur over at least three months and affect the child's ability to perform normal activities.*  Yes - inclusion  No - exclusion | 5-18 |
| Eating disorder | Does your child have an eating disorder (such as anorexia, bulimia, or avoidant restrictive food intake) as diagnosed by a health professional?  Yes - inclusion  No - exclusion | 14-18 |

# Online panel screening questions for Sample 4:

Are you the parent, caregiver or guardian of a child aged 6 to 10 years?

Is your child currently able to answer some questions about their health and wellbeing?

Yes to both- inclusion

No to one or both-exclusion

# Recruitment of potential participants

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

Sample 1: n=1000 via RCH

* **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, Gynaecology, Centre for Community Child Health (CCCH), General Medicine, Endocrinology and Diabetes, Complex Care Asthma, Colorectal Surgery, Facial Surgery, Day Surgery, Ophthalmology, and Metabolic Medicine. 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:** a 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 (Appendix B) which describes the study and what is involved.
* **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 the study (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 E). A link to the survey will be sent by clinicians from the following RCH departments: Short Stay Unit (SSU), Neurology, Neurodevelopment and Disability, Gynaecology, Centre for Community Child Health (CCCH), General Medicine, Endocrinology and Diabetes, Complex Care Asthma, Colorectal Surgery, Facial Surgery, Day Surgery, Ophthalmology, and Metabolic Medicine.
* **Advertisement:** Posters in high traffic areas with a QR code linked to the PICF and online survey (Appendix F). These posters will be placed in the following RCH departments: Short Stay Unit (SSU), Neurology, Neurodevelopment and Disability, Gynaecology, Centre for Community Child Health (CCCH), General Medicine, Endocrinology and Diabetes, Complex Care Asthma, Colorectal Surgery, Facial Surgery, Day Surgery, Ophthalmology, and Metabolic Medicine.
* **Childcare centre:** The RCH onsite childcare will email out a short description of the study with a link to the survey to its parents (Appendix G).
* **Social media:** We will advertise the study on the MCRI Facebook and Twitter (Appendix B and H). The Facebook advert will target families of children aged 2-18 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.
* **Recruitment via The Royal Women’s Hospital (RWH)** **PLUSS trial** **of children born extremely premature:** Participants from the study ‘Preventing Chronic Lung Disease in Extremely Preterm Infants Using Surfactant + Steroid’ (PLUSS) trial *(HREC 36383A,* ACTRN12617000322336), an interventional trial of children born < 28 weeks’ gestation, will be approached for recruitment this study (if the child is 2 years or older, corrected for prematurity) when they attend the RWH for the developmental clinic/PLUSS study follow-up. Potential participants will be approached by a member of the PLUSS research team who will ask participants if they would like to take part in this study by providing them a study flyer (Appendix F) and the opportunity to complete the initial survey on an iPad after they have completed the follow-up documentation for the PLUSS trial. The PLUSS research team will be the staff approaching and recruiting caregivers of children born extremely premature to the study. This is the most appropriate approach as the PLUSS research staff work within the RWH and are familiar to the families in the PLUSS trial 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.
* **Recruitment via Australian Genomics of children with rare genetic conditions:** Eligible participants (children currently aged 2-18 years old who are still alive) from Australian Genomics study cohorts who consented to be contacted for future research as part of their involvement in a previous study with Australian Genomics will be sent an email from Australian Genomics inviting them to take part in this study (Appendix Q).
* **Snowball sampling**: We will use snowball sampling, whereby, we will encourage the study adverts (Appendix B and H) to be shared to potential participants by interested parties (e.g., participants, members of the research or advisory team, members of interested stakeholder organisations). For example, encouraging the social media advert to be shared to other parents who may be interested in the study. Sharing of the study advert will be voluntary.
* **Relevant newsletters / email subscription lists / notice boards:** The study advert (Appendix B and H) will be shared via newsletter, email subscription lists and notice boards of relevant organisations who are interested in sharing the study information with their subscribers (e.g. Genetic Support Network of Victoria or Syndromes Without A Name (SWAN)). The newsletter adverts and emails will only be sent to people who have opted in to/ subscribed to receive the email/newsletter.
* **Opt-in letter of invitation from RCH clinics:** RCH clinical departmentswill send a letter of invitation to potential eligible participants under their care (Appendix P). The letter will be an opt-in style letter with a short description of the study and a QR code linking to the PICF and survey. A letter may be sent by participating RCH departments (Short Stay Unit (SSU), Neurology, Neurodevelopment and Disability, Gynaecology, Centre for Community Child Health (CCCH), General Medicine, Endocrinology and Diabetes, Complex Care Asthma, Colorectal Surgery, Facial Surgery, Day Surgery, Ophthalmology, or Metabolic Medicine). Letters will first be sent from only one or two departments to assess response rates before continuing with other departments.

Sample 2 (n= 3,600), Sample 3 (n= 1,500), and Sample 4 (n=500) via online survey panel:

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 who fulfil the age/health status/disease specific quotas that are prespecified in Section 4.1. Before taking part in the survey potential participants will need to complete relevant screening questions. A group of potential participants registered with the panel will be consented to complete the survey. To ensure that the response of 5,600, it is envisaged that approximately 22,000 parents/caregivers from the panel will be invited. These estimates are based on the response rate from a past study using the discrete choice experiment in the UK general population [6], and is usual practice for survey companies such as Pureprofile. 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.

# Consent

Informed consent will be obtained from the parent/caregiver 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 Sample 1, Appendix N ICU PICF Sample 1, Appendix J- Online panel PICF Sample 2 and 3, and Appendix O Online panel PICF Sample 4). In circumstances where children will be completing part of the survey (this will be after the parent/caregiver has already consented and answered some questions), children will be asked to consent to take part (Appendix K). As the parent/caregiver has already consented to take part, the child participant information and consent form is very short, this is to make it easy for the child to read and understand.

Participants recruited via the ICU will be consented in person by the ICU research team (Appendix N), 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.

# STUDY VISITS AND PROCEDURES

# Study timeline

There will be an initial survey (Appendix A) followed by a second shorter survey up to 8 weeks (or two days for a small subset) 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. Most participants will be sent a further link via text or email 2-8 weeks after the completion of the initial survey to complete a follow-up survey. A sub-set of the healthy participants from the online survey panel (n=200) and participants from sample 4 (caregiver/child dyad sample, n=500) will have a 2 day follow-up. We will follow-up participants 3 times over the period of 8 weeks to encourage completion of the second survey. Those with a 2 day follow-up will be followed-up up to 3 times over the period of a week to encourage completion of the second survey. Participants will be followed up for the second survey as per the contact management plan (Appendix L).

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Measures collected** | **Assessment** | **SAMPLE 1**  **RCH Sample (n=1,000)** | | **SAMPLE 2**  **Online panel- disease specific groups (n=3,600)** | | **SAMPLE 3**  **Online panel- healthy children (n=1,500)** | | **SAMPLE 4**  **Online panel- caregiver/child dyad (n=500)** | |
| **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 n=1300 and 2 days n=200)** | **Initial survey** | **Follow-up survey**  **(2 days after initial)** |
| **CORE MEASURES (if ‘x’ each participant will receive)** | | | | | | | | |
| **Informed Consent** | **x** |  | **x** |  | **x** |  | **x** |  |
| **Demographic Information** | **x** |  | **x** |  | **x** |  | **x** |  |
| **Carer QoL (EQ-HWB)** | **x** |  | **x** |  | **x** |  | **x** |  |
| **EQ-5D-5L (caregiver)** |  |  |  |  |  |  | **x** |  |
| **SDQ** | **x** |  | **x** |  | **x** |  |  |  |
| **PedsQL** | **x** | **x** | **x** | **x** | **x** | **x** | **x** | **x** |
| **TANDI (if <=3yrs)** | **x** | **x** | **x** | **x** | **x** | **x** |  |  |
| **EQ-5D-Y 3L (inc VAS) and 5L original (if >= 5 years)** | **x** | **x** | **x** | **x** | **x** | **x** | **x** | **x** |
| **EQ-5D-Y 3L (inc VAS) & 5L adapted (if <=4 years)** | **x** | **x** |  |  |  |  |  |  |
| **EQ-5D-Y 3L original (inc VAS) and adapted OR**  **EQ-5D-Y 5L original (inc VAS) and adapted (if <=4 years)** |  |  | **X\*** | **X\*** | **X\*** | **X\*** |  |  |
| **CHU9D** | **x** | **x** | **x** | **x** | **x** | **x** | **x** | **x** |
| **Global Health Measure** | **x** | **x** | **x** | **x** | **x** | **x** | **x** | **x** |
| **Disease specific QoL measure and disease severity qxs (if applicable)**   * Asthma: PedsQL asthma module * ASD: KIDSCREEN * Sleep problems: SDSC * Dental decay: CPQ * Anxiety and depression: RCADS-25 * ADHD: SWAN * Epilepsy: QoLCE-16 * Recurrent abdominal pain: Pain VAS * Eating disorders: EDQLS |  |  | **x** |  |  |  |  |  |
| **(if ‘x’ participants will be randomised to receive one of the following measure blocks if aged 5-18yrs. Children aged 2-4yrs old will always get allocated to the HUI as no other additional instrument is applicable to this age group.)** | | | | | | | | |
| **AQoL-6D (if =>5yrs)** |  |  | **x** | **x** | **x** | **x** |  |  |
| **HUI2 (if >=2yrs)**  **&**  **EQ-5D-5L (if >=12yrs)** |  |  | **x** | **x** | **x** | **x** |  |  |
| **PROMIS-25 (if =>5yrs)** |  |  | **x** | **x** | **x** | **x** |  |  |

\*Participant will only be randomized to receive (1) EQ-5D-Y 3L original and adapted or (2) EQ-5D-Y 5L original and adapted.

# 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). For Samples 2 and 3 the online survey panel screening questions will also include questions that specify the condition/health status being targeted, please see Section 4.2.3.2 for a breakdown of which groups will be asked which screening questions. 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 maximize informativity where most needed.

Participants will be followed up for the follow-up survey as per the contact management plan (Appendix L). If recruited via RCH (Sample 1), 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 #71963 ‘Quality of Little Lives Study (QuoLL) - Usability of EQ-5D-Y adapted for use in children aged 2-4 years’)* 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 have a child aged 2-4 they will also be asked to take part in testing a new tool (the aim of Project 2, HREC #7196).

All data will be collected via surveys. Surveys will be completed by parents/caregivers and where relevant children may will answer some survey questions on health-related quality of life. With the exception of Sample 4 (caregiver/child dyad sample), parents of children under age 7 and those of children deemed by the parent as unable to complete the survey will complete the entire survey themselves. Again with the exception of Sample 4, children aged 7 and above and deemed by the parent to be able to complete the survey the parent will complete the demographic portion of the survey and then asked for permission to include responses from their children directly for the quality of life questions part of the survey. For participants in Sample 4 (caregiver/child dyad sample) both the caregiver and child will answer the HRQoL questions for each instrument in the survey, this will include children aged 6-10.

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.

Additionally, for children recruited via Australian Genomics and who have consented for data on sharing as part of their initial consent to the Australian Genomics study, CHU9D data (including date of CHU9D completion) completed as part of their involvement in the Australian Genomics study will be extracted and used in this study. See Section 9 for further details on data security and management.

**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.

**Procedure for participants recruited via The Royal Women’s Hospital (RWH)** **PLUSS trial** **of children born extremely premature:**

Potential participants from the PLUSS trial RWH site will be approached by a member of the PLUSS research team for recruitment to this study (if the child is 2 years or older, corrected for prematurity) when they attend the RWH for the developmental clinic/PLUSS study follow-up. The potential participant will be asked if they would like to take part in this study, provided a study flyer (Appendix F) and provided an opportunity to complete the initial survey on an iPad after they have completed the follow-up documentation for the PLUSS trial. The MCRI research team will manage the subsequent follow-up of these participants. The PLUSS research team will inform the MCRI research team if they determine that a participant is not appropriate for follow-up.

**Procedure for participants recruited via Australian Genomics of children with rare genetic conditions:** Potential participants (children currently aged 5-18 years old who are still alive) from Australian Genomics study cohorts who consented to be contacted for future research as part of their involvement in a previous study with Australian Genomics will be sent an email from Australian Genomics inviting them to take part in this study (Appendix Q). To ensure the data collected as part of this study and the CHU9D data previously collected via Australian Genomics can be linked for the cohort of children recruited via Australian Genomics while still ensuring appropriate data security measures, the following process will be followed:

Sending the survey invitation:

* MCRI research team will create a separate REDCap invitation and survey for Australian Genomics participants. This invitation and survey will be an exact copy of the RCH hospital sample survey. This means that anyone who enters this REDCap survey will be able to be identified as an Australian Genomics participant.
* Australian Genomics team to identify potential participants from Australian Genomics study cohorts who consented to be contacted for future research.
* Australian Genomics will send an email invitation to potential participants (Appendix Q) and the public REDCap study invitation and survey (REDCap survey outlined in dot point one).
* MCRI research team will re-consent participants and ask them to complete survey (all done via the one link sent in the invitation).

Data linkage:

* MCRI research team will send the Australian Genomics team Australian Genomics participants who completed the initial survey.
* Australian Genomics team will identify which of these participants had consented to data on sharing and extract the CHU9D data (including date of CHU9D completion) for these individuals.
* Australian Genomics team will provide the CHU9D data to the MCRI research team for each participant.

# 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, or the online survey panel they are part of. 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 families when they sign up to the study that participation involves the completion of another survey in 2-8weeks’ time or 2 days for those allocated to the shorter follow-up group
* 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 centre of their mind
* Contact families multiple times as per the contact management plan to remind them to complete the survey (Appendix L)

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 many 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 or if relevant children 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. This research is designed to compare the validity of existing health-related quality of life instruments for children. The health questions that will be used are existing generic questionnaires and the individual questionnaires have been included in previous research eliciting general health-related quality of life from participants. For a small number of common childhood conditions a disease-specific quality of life measure will be added. Once again, these will all be existing measures and the questions whilst applying to disease areas are still generic in nature. 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 mitigate any risk associated with asking about the child’s health, the survey includes phone numbers and advice as to who the parent/caregiver might contact if they were worried about their child’s health.

However, should an adverse event occur a protocol will be followed where the event will be reported to the Principal Investigator for review who will in turn notify the RCH Human Research Ethics Committee of any concerns arising.

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.

For children recruited via Australian Genomics, linking survey data from this study with CHU9D data previously collected as part of their participation in an Australian Genomics study presents a very low risk. Only data from participants who consented to data on sharing when initially taking part in Australian Genomics study and who take part in this study will be linked. Additionally, participants are agreeing to take part in this study, a study regarding the HRQoL of children where they will complete the CHU9D in addition to other instruments, hence it would be very unlikely they would object to their child’s previously collected CHU9D data to be utilised as part of this study.

* 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 M). 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 advance knowledge about how current paediatric QoL instruments compare in terms of acceptability, feasibility, reliability, responsiveness, validity and sensitivity. This study will also provide decision makers and researchers with a practical set of tools that are ‘fit for purpose’ in judging the effectiveness and cost effectiveness of paediatric interventions, improving the way researchers and decision makers assess child quality of life. Improving the way we measure quality of life in children will help us to give better tests, treatments and services to children in future. The benefits of this study will accrue to all children across Australia and thus may benefit participants in future.

# 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.

# Source Data

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

Another data source for this study will include:

* Australian Genomics rare disease CHU9D survey data

# 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. All data will be accessed via MCRI’s secure network files. Data analysts outside of MCRI will be required to become an MCRI honorary to access the securely stored data. 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.

Pureprofile 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. 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.

We are requesting Australian Genomics participant survey data via a data access request as well as the original data custodians re-contacting the same participants to participate in a new study. This is in-line with the Australian Genomics participant consent form. To ensure the data collected as part of this study and the CHU9D data previously collected via Australian Genomics can be linked for the cohort of children recruited via Australian Genomics while still ensuring appropriate data security measures, data separation principals outlined in Section 6.1 will be followed. Furthermore, Australian Genomics follows strict policies regarding data sharing and the secondary use of data (<https://www.australiangenomics.org.au/resources/tools/data-policies/#1556252179143-43f07231-e756>). All Australian Genomics policies will be followed when obtaining and linking CHU9D data already collected by Australian Genomics, including a data access application which is reviewed by the Australian Genomics Data Access Committee.

Authorised representatives of the sponsoring institution, project team and 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

# Study Steering Committee (SSC)

The wider University of Melbourne QUOKKA project has established a SSC to oversee the large body of work that this study forms part of. This SCC will provide expert advice and overall supervision, and ensure that the study is conducted to the required standards. The SSC will meet at least monthly, with more frequent meetings as needed. This project will work closely with a related EuroQoL project to ensure consistent methods and a shared recruitment strategy.

# Decision Makers Panel (DMP)

This study will have access to a DMP set up by the wider University of Melbourne QUOKKA project, this group will provide input and feedback as required.

# Consumer Advisory Group (CAG)

This study will have access to a CAG set up by the wider University of Melbourne QUOKKA project, this group will provide consumer input and feedback as required.

# STATISTICAL METHODS

# Sample Size Estimation

Due to the observational and methodological nature of this study design it is not possible to calculate a sample size a priori. The sample was estimated from a similar adult study and a review of paediatric QoL studies.[7,8] The sample size will allow for assessment of validity of the HRQoL instruments in a variety of childhood conditions both in and out of the hospital setting ranging from acute to chronic and across severities ranging from well children to those that are very sick. This diversity in the sample is important to determine the validity and applicability of the HRQoL instruments to groups of children.

# Statistical Analysis Plan

# Outcomes and outcome measures

Data will primarily be displayed as individual item, total and aggregate scores based on instrument recommendation.[5,9]

| Outcome [5,9] | Definition [5] | Analysis [9] |
| --- | --- | --- |
| 1. Consistency | The degree to which the summary and dimension specific responses on each instrument are consistent with dimension and summary responses of other similar instruments. | Measured by comparing the consistency of summary and dimension specific responses on each instrument. |
| 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 QoL instrument 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 the scores of a QoL instrument is consistent with hypotheses based on the assumption that the instrument validly measures the construct to be measured. |  |
| * + 1. Within-scale analysis |  | Within-scale analysis measured using factor analysis. |
| * + 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. |
| * + 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. Internal consistency | The degree of the interrelatedness among the items. | Internal consistency measured using item-total correlations, Cronbach alpha coefficients for summary scores and analysis of a repeat question. |
| * 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 2 days later. |
| 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. Responsiveness | The ability of an instrument to detect change over time in the construct to be measured. | Measured 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. |
| 1. Modern Test Theory | Understanding the performance of each item in terms of the information provided | Item response theory analysis, assessment of item and model fit, information and discriminance curves, and differential item functioning. |

# Subgroup analysis

We will investigate how the key outcomes described above vary by child age, sex, SES, disease group (including acute vs chronic conditions), and presence of mental health multimorbidity.

# Data transformation

From the raw HRQoL data we will be able perform validity statistics. We will also score the HRQoL instruments using published scoring weights or value sets.[10-14] This will enable further analysis of validity based on utility scores from the HRQoL measures.

# 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 no more than 5% missing (within or between)
* 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 in analysis if the data required for a particular analysis is complete. Analysis of questionnaire feasibility will also report data missingness as a measure of how feasible the questionnaires are.

# ETHICS

# 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 Site RGO and 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

All 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. The results of this study will also inform future work being completed by the wider QUOKKA team and thus these results will inform the next steps in their future studies. A key component of the dissemination is to communicate results about the performance of the HRQoL instruments back to Australian and international decision makers to inform how they use the evidence in regulatory decision making and evidence generation. This will be done via the QUOKKA decision makers panel.

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# APPENDICES

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| --- | --- |
| Appendix A | Survey |
| Appendix B | Short Written Advert |
|  |  |
| Appendix D | Similar Study Invitation |
| Appendix E | Study Blurb |
| Appendix F | QR Poster advert |
| Appendix G | Childcare email invitation |
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| Appendix I | PICF RCH |
| Appendix J | PICF Online Panel (Samples 2 and 3) |
| Appendix K | Child PICF |
| Appendix L | Contact management plan |
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| Appendix N | PICF RCH ICU |
| Appendix O | PICF Online Panel- Sample 4 (dyad sample) |
| Appendix P | Opt-in letter from RCH department |
| Appendix Q | Email of invitation to Australian Genomics cohorts |