# Evaluation of Parent Intervention for Challenging Behaviour in Children with Intellectual Disabilities (EPICC-ID)

## Health Economics Analysis Plan

### Version History

| Version | Date | Changes |
|---|---|---|
| 1.0 | 23/01/2019 | |
| 1.1 | 1/02/2019 | Review and amendments by Rachael Hunter |
| 1.2 | 27/03/2019 | Minor edits |
| 1.3 | 15/04/2019 | Update by Rachael Hunter for DMEC comments |
| 1.4 | 5/11/2019 | Moved and formatted sign-off page; formatted page numbering |
| 1.5 | 20/01/2020 | Addressed DMC comments |
| 1.6 | 15/03/2021 | Changes to account for COVID-19 pandemic |

**Contents**

# Health Economics Analysis Plan

## 1. Purpose of health economics analysis plan

The purpose of this health economics analysis plan is to set out in detail the analysis and reporting procedure intended for the economic analyses to be undertaken in the EPICC-ID trial.
While the intentions outlined in this plan will be followed as closely as possible, the plan also describes the circumstances under which amendments are permitted and the documentation of such changes; any deviations from this plan will be justified in the final report. The analysis plan is designed to ensure that there is no conflict with the protocol and the statistical analysis plan (SAP) and should be read in conjunction with them.

## 2. Economic analysis background

### 2.1 Aim

The aim of the economic evaluation is to assess the cost-effectiveness of delivering the level 4 Stepping Stones Triple P (SSTP) intervention. The intervention is designed to reduce challenging behaviour in children with moderate to severe intellectual disabilities, compared with treatment as usual.

### 2.2 Perspective

The primary analysis will be conducted from the NHS and personal social services (PSS) perspective.

A secondary analysis from the perspective of parents/caregivers will be conducted.

### 2.3 Time horizon

The economic analysis will compare the costs and benefits of each arm over 12 months of follow-up.

## 3. Economic measurements

### 3.1 Identification of outcomes

The primary economic outcome measure will be Quality Adjusted Life Years (QALYs) derived from utility scores, obtained using the Pediatric Quality of Life (PedsQL) General Core Scales (GCS), mapped into EQ-5D-Y quality of life instrument for children [1]. For parents/caregivers QALYs will be derived from utility scores, obtained using EQ-5D-5L quality of life instrument.

### 3.2 Measurement of outcomes

- Health related quality of life of the child (Pediatric Quality of Life, PedsQL™ GCS; [2]). The measure covers Physical, Emotional, Social, School Functioning domains. It contains a parent proxy report for children aged 2 years and over. Measurements will be recorded at baseline, 4 months and 12 months post-intervention.
- Health related quality of life of the parent/caregiver (EQ-5D-5L; [3]). Self-completed questionnaire will capture parent/caregiver perspective on his/her health status, which will be used in the economic evaluation. Measurements will be recorded at baseline, 4 months and 12 months post-intervention.

### 3.3 Valuation of outcomes

- Child: The Pediatric Quality of Life Inventory™ (PedsQL™) General Core Scales (GCS) was designed to provide a modular approach to measuring health-related quality of life in healthy children, as well as those with acute and chronic health conditions, across the broadest, empirically feasible, age groups (2-18 years). Currently, it is not possible to estimate health utilities based on the PedsQL™ GCS, either directly or indirectly. Mapping algorithms [1] will be used to provide an empirical basis for estimating health utilities (and form QALYs) in childhood when EQ-5D data are not available.

- Parent/Caregiver: Utility scores will be derived from responses to the EQ-5D-5L using valuations obtained from an English population [4]. These will be used to form QALYs over the 12-month period, adjusting for any imbalances in baseline scores [5].

### 3.4 Identification of relevant resource use

Data will be collected for resource use consumption. For the NHS and PSS perspective, data will be collected on use of health services in primary and community care, investigations and prescribed medication, hospital admission and outpatient attendance, ambulance use, and social care.

For the analysis from the parent/caregiver perspective, we will additionally collect data on out-of-pocket expenses (private therapies and treatments).

### 3.5 Measurement of resource use

#### *3.5.1 Set up costs*

Study records of the number of therapists attending training sessions will be used to track resources used in the delivery of the training programmes including trainee and trainer time (and preparation time), travel costs, attendance incentives and course materials to calculate the fixed cost of training.

#### *3.5.2 Delivery of the intervention*

For the delivery of the intervention, the number of sessions delivered and the time each therapist spent with a family will be recorded; also, any materials provided to parents.

#### *3.5.3 Health and social care utilisation*

NHS community care, care from social services and participant personal resource use during the 12 month follow-up will be captured using a modified version of the Child and Adolescent Service Use Schedule (CA-SUS) [6]. The measure is administered by a research assistant as an interview and has been developed and used in a number of evaluations of interventions in children including preschool age e.g. PACT, TIME-A, Healthy Start Happy Start trials. Data on accommodation, health and social care resource use will be collected at baseline (for the past 6 months) and 4 months (for the past 4 months) and 12 months (for the past 6 months) post-intervention.

#### *3.5.4 Personal expenditure on healthcare*

Expenditure on private use of treatments and therapies (out-of-pocket) will be captured in the CA-SUS.

### 3.6 Valuation of resource use

- Unit costs for therapists to train for and deliver the intervention will be based on the most recently available national estimates. Actual expenses incurred for training materials, refreshments and therapists travel will be recorded.
- Health and social care resource use will be costed using unit costs from the most recent Unit Costs of Health and Social Care published by the Personal Social Services Research Unit (PSSRU) [7] and NHS reference costs [8] supplemented by micro-costing or local estimates if necessary. The costs of medications will be estimated from the British National Formulary [9]. We will ask about health and social care resource use utilisation in the past 6 months at baseline and at 12 month follow-up and in the past 4 months at 4 month follow-up. The primary analysis will include only health and social care data collected as part of the trial and hence cover only 10 months of the trial (missing months 4 to 6). We will project costs from 4 month and 12 month follow-up to estimate the 12 month health and social care resource use as part of sensitivity analyses.

Resource use will be combined with unit costs to estimate the incremental cost or savings of the intervention. All costs will be reported in 2017/2018 pounds sterling, adjusted for inflation if necessary. No discounts will be applied, as trial follow-up does not exceed 12 months.

The cost of each resource item will be calculated by multiplying the number of resource units used by the unit cost. The total cost for each participant will then be estimated as the sum of the cost of resource use items consumed.

**4. The overall economic evaluation**

All analyses will be conducted using intention-to-treat (ITT) principles, comparing the two groups as randomised and including all participants in the analysis. Analyses will conform to accepted economic evaluation methods [10].

- Cost-effectiveness analysis: mean incremental cost from the NHS and PSS perspective per change in Child Behaviour Check List (CBCL). Incremental cost-effectiveness ratios will be reported and uncertainty explored using cost-effectiveness acceptability curves [11, 12].
- Exploratory analysis of quality of life using PedsQL™ to predict utility scores: the use of Health-Related Quality of Life instruments in children is increasingly adopted in clinical trials and permits standardised measurement and comparison between studies [11]. There is no single, valid, preference-based measure for health state valuation in children under the age of 5 or children with intellectual disability and therefore it is not currently possible to calculate QALYs for use in cost-utility analysis [13]. PedsQL™ showed feasibility, reliability and validity in children with learning and developmental disabilities [14]. As a result, we shall use the PedsQL™ GCS and the mapped EQ-5D-Y utility scores algorithm [1, 15] to calculate QALYs. Mean cost per participant for the intervention and treatment as usual will be reported by type of service use. We will calculate the mean cost per QALY using the mapped EQ-5D-Y. Mean QALY per participant will be calculated as area under the curve for the duration of the trial, adjusting for baseline values.
- Cost-benefit analysis of the impact on the parents/caregivers: Responses to EQ-5D-5L will be used to calculate QALYs in a standard format and valued as willingness-to-pay (WTP) for a QALY gained. We will calculate the mean cost per QALYs using the EQ-5D-5L and the associated algorithms [16, 17] mapping [18] the 5L descriptive system data onto the 3L valuation set as recommended by NICE [19]. Mean QALY per participant will be calculated as area under the curve for the duration of the trial, adjusting for baseline values. As caring responsibilities of caregivers are complementary to state funded caring we shall also calculate the societal value of caring provided by family/caregivers.

### 4.1 Data cleaning and missing costs and outcomes

Data cleaning will be undertaken prior to unblinding by the health economic researcher. Data cleaning will include correction of obvious 'free text' response errors (e.g. misspelling), group coding of similar resource items (e.g. 'orthopaedics' and 'trauma & orthopaedics' clinics) to enable unit costing, and simple imputation of data missing minor details (e.g. missing drug dose) based on reasonable assumptions (e.g. the most commonly prescribed dose). Researchers and the clinical expert will discuss any areas of uncertainty.

Missing data will be explored to determine its patterns, extent and association with any participant characteristics.

The primary analysis will include all participants using multiple imputation to predict missing costs and outcomes [20].

### 4.2 Analysis of QALYs

We will report the incremental mean difference in QALYs between the two arms of the trial and 95% confidence intervals adjusting for therapist clustering in the intervention arm only (random coefficient model). This model will also adjust for baseline CBCL score and randomization stratification factors (centre, level of ID) using fixed effects.

### 4.3 Analysis of costs

Overall, mean costs and standard deviations for both arms of the trial will be calculated. We will estimate the incremental mean difference in total costs between the two arms of the trial and 95% confidence intervals adjusting for therapist clustering in the intervention arm only (random coefficient model). This model will also adjust for baseline CBCL score and randomization stratification factors (centre, level of ID) using fixed effects

Bootstrapping techniques will be used to derive bias corrected confidence intervals [21].

### 4.4 Analysis of relative costs and outcomes

Cost and QALY data will be combined to calculate an incremental cost-effectiveness ratio (ICER). Uncertainty in the point estimate of cost per QALY will be quantified using bootstrapping methods to calculate confidence intervals around the ICER.

The results of the non-parametric bootstrap will be presented on a cost-effectiveness plane (CEP). Cost-effectiveness acceptability curves (CEACs), showing the percentage of cases that the intervention is cost-effective, over a range of values of WTP for a QALY gained, will be constructed using the bootstrap data from a range of values of WTP for a QALY gained for each different costing perspective and for the different methods of calculating QALYs. The probability that the intervention is cost-effective compared to treatment as usual at a WTP for a QALY gained of £20,000 and £30,000, and £13,000 as a measure of opportunity cost [22] will be reported.

## 5. Further economic analyses

### 5.1 Sensitivity analyses

One-way sensitivity analyses will be used to judge the potential impact of sources of uncertainty:

- Complete case analysis
- If there is an imbalance between arms in the number of different variables, additional sensitivity analyses will be conducted adjusting for these variables. This will be in line with the sensitivity analyses described in the SAP.
- Analysis including the assumption that participants attended all group/individual sessions
- It is possible that other algorithms for mapping the PedsQoL to preference-based utilities that can be used in economic evaluations will be available. Sensitivity analyses will explore the impact of using these alternative algorithms on the results.
- Given that training costs may differ between the trial and implementation of the intervention due to learning or being delivered to a larger patient group, we will test the impact of varying training costs (particularly as a result of larger patient numbers per staff member trained) on the mean incremental cost per QALY gained.

## 6. Accounting for COVID-19 pandemic

COVID-19 pandemic affected the trial from the 26$^{th}$ of March 2020, when the lockdown rules were imposed.

Research visits have moved to an online format and are proceeding, and researchers complete all assessments over the telephone. Therefore, an increase in missing data during the COVID-19 period is not expected.

Study follow-ups continued throughout this period, but child-parent observations and cognitive neuropsychological assessments that required face-to-face contact were omitted from the study. This may affect the cost of the intervention.

The CA-SUS questionnaires at 4 and 12 months were completed by parents during research visits and then handed over to the Trial Manager for data entry before the pandemic. As this is no longer possible, researchers are completing the CA-SUS questionnaires over the telephone removing the question about attendance of parenting groups that will unblind them.

COVID-19 may have had an impact on children and carers' mental health and HRQoL during this period.

We will report outcome descriptive statistics by intervention arm and data collection before and after 26 of March 2020. This will include summaries of missing data.

## 7. Updating the economic analysis plan

### 7.1 Changes to existing analyses

Dated changes to the analysis plan will be documented in this section. Circumstances under which changes will be permitted are as follows.

- Development of EQ-5D-Y value sets for use in children and adolescents (research is currently ongoing)
- Preliminary data cleaning or analysis (conducted prior to unblinding) suggesting that planned analyses are sub-optimal.

### 7.2 Post hoc analyses

Any suitable analyses that are identified after unblinding will be listed in this section, dated and the source will be identified. Such analyses will be identified clearly as post hoc analyses in trial reports.

## 8. References


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## 9. Sign Off

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