REACH-ASD Health Economic Analysis Plan

Trial: A Randomised Controlled Trial of Psychoeducation and Acceptance & Commitment Therapy for Parents of Children recently diagnosed with ASD (REACH-ASD)

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Roles and responsibilities

This HEAP was prepared by Aleix Rowlandson and Gemma Shields. The trial health economists are responsible for conducting and reporting the economic evaluation in accordance with the HEAP.

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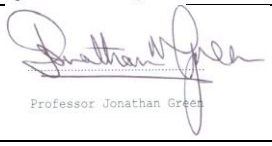
Jonathan Green	Chief Investigator		06 November 2023

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Abbreviations

ACT	Acceptance and Commitment Therapy
ASD	Autism spectrum disorder
CEA	Cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CHU-9D	Child Health Utility 9D Index
CUA	Cost-utility analysis
DSU	Decision Support Unit
GHQ-30	General Health Questionnaire- 30
HEAP	Health Economics Analysis Plan
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
NHS	National health service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute of Health Research
NMB	Net monetary benefit
NS-SEC	National Statistics Socio-economic
QALYS	Quality-Adjusted Life Years
RCT	Randomised controlled trial
SATQ	Subthreshold Autism Trait Questionnaire
SUI	Service-Use Interview
TAU	Treatment as usual
UK	United Kingdom
WTP	Willingness-to-pay
WEMWBS	The Warwick-Edinburgh Mental Wellbeing Scale

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Trial overview

The following sections reproduce text and summarise key details from the research proposal (submitted as part of the grant application) and the REACH-ASD trial protocol [1].

Trial background

Autism Spectrum Disorder (ASD; hereafter autism) affects around 1.5% of children in the developed world [2]. Whilst there are many diverse presentations of autism, the Diagnostic and Statistical Manual of Mental Disorders (DSM)-V states they show persistent 'deficits' in social communication and repetitive pattern of behaviour, interests or activities [3]. Although often diagnosed in childhood, it is a lifelong condition and many require continuing support and are unable to enter into fulltime employment [4]. The personal and societal impact of autism is significant; e.g., with autistic individuals reporting reduced mental health, lower levels of qualifications and employment [5–7]. The impact on immediate family members is also increasingly recognised [8]. Parents of children with an autism diagnosis are reported to have three key areas of need; emotional, informational and relational [9]. Furthermore, there is a considerable economic impact; with autism being related to increased healthcare service use, childcare costs, education costs, accommodation costs and costs related to productivity losses (for autistic adults and parents/caregivers) [10].

Guidelines from the National Institute for Health and Care Excellence (NICE) recommend provision of timely post-diagnostic family support [11,12]. However, the evidence base for intervention is lacking. Subsequently, there is a need for an evidenced programme of post-diagnostic support for parents/primary caregivers, focussed on the caregivers mental health, wellbeing and adaptation. Prior theory, evidence, and caregiver consultation during the development of this trial application indicated that such support should combine autism psychoeducation along with psychological strategies focused on caregiver adjustment and wellbeing. Alongside evidence for effectiveness, demonstrating that interventions are cost-effective is becoming more of a priority due to growing demand, resource scarcity and finite budgets, which are becoming more prominent across health care systems.

Further details on trial procedures and methods can be found in the trial protocol [1], a brief overview is provided below.

Aim of the trial

The trial aims to evaluate the clinical and cost-effectiveness of the Empower-Autism intervention plus treatment as usual (TAU), in comparison to TAU alone.

Objectives of the trial

Objectives of the trial include:

1. To test intervention effectiveness over TAU on caregiver mental health, wellbeing, knowledge, adjustment, stress, and self-efficacy.

2. To test intervention effectiveness over TAU on family wellbeing, (c) child wellbeing, behaviour, and adaptive functioning.
3. To assess its cost-effectiveness whether, when compared to TAU, the intervention is cost-effective from the perspective of the NHS and social care (economic evaluation component).
4. To identify perceptions of the intervention and barriers to implementation within routine service provision (process evaluation).

Objective 3 is the focus of this health economics analysis plan.

Trial population

Parents/primary caregivers of children aged 2-15 years with a recent autism diagnosis, recruited from Greater Manchester/North West UK NHS and local authority centres. The inclusion and exclusion criteria are reported in Table 1.

Table 1 Trial inclusion and exclusion criteria

	Inclusion	**Exclusion**
Child	• Child aged between 2 years 0 months and 15 years 11 months at consent • Child received a diagnosis of autism from an NHS professional within the last 12 months • Child diagnosed with autism is a patient/service user of one of the trials collaborating centres	• Child aged <2 years 0 months or >15 years 11 months at consent • Child received a diagnosis of autism from a non-NHS professional or beyond the last >12 months
Parent/ primary caregiver	• One "index" adult per child (child's parent/primary caregiver; must be aged 18 years or over), nominated by family	• Adults with insufficient English language • Adult with significant learning disability or significant hearing/visual impairment • Adults with current severe psychiatric condition • Significant current safeguarding concerns within family (identified by referring clinician)

Intervention and comparator

Intervention: The Empower-Autism intervention is a caregiver group-based manualised post-diagnostic programme that combines autism psychoeducation and a brief Acceptance and Commitment Therapy (ACT). The autism psychoeducation includes: an introduction to autism; strategies to support understanding and communication; understanding and managing emotions, behaviour, and sensory needs, and navigating the education system. The ACT elements provide psychological input to caregivers to support their mental health, stress management and adjustment to their child's diagnosis. The intervention will be delivered by trial-specific NHS practitioners alongside local specialist clinicians.

Comparator: Treatment as usual (usual local post-diagnostic offers and more general treatment-as-usual are variable across collaborating centres and will be specified through health economic data).

Trial design

A multi-centre two parallel group single (researcher)-blinded randomised controlled trial of the Empower-Autism intervention plus TAU versus TAU alone, for parents/primary caregivers of children aged 2-15 years who have received an autism diagnosis within the previous 12 months. Caregivers in the trial intervention arm will access the Empower-Autism programme in place of their standard usual local post-diagnostic workshop offer. Caregivers in the TAU arm will receive the usual post-diagnostic offer of their local area. Caregivers in both trial arms can access all other services and intervention therapies on offer in their locality, as per usual care.

Individual randomisation will be completed by child, with one “index” parent/caregiver per child, and stratification by centre, using 2:1 randomisation ratio (groups of randomisation ranged between 7-17 participants15). Randomisation will be completed using an online randomisation service. Initial feasibility phase and internal pilot to test recruitment, both with pre-specified progression criteria. A total of 380 parents/primary caregivers from centres will be recruited to the trial (estimate 256 intervention/124 TAU).

Caregiver mental health (measured using the General Health Questionnaire- 30) at 52-week follow-up will be used as the primary outcome, with key caregiver, family and child secondary outcomes, cost-effectiveness analysis and a nested process evaluation.

Trial start and end date

The trial start date refers to the date on which first patient consented to participate within the trial, and the end date refers to the date on which the last patient follow-up was completed for the final participant. Details of these are provided below:

- Start date: 16/09/2020
- End date: 18/05/2023

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Health Economic Analysis Plan

Purpose of the HEAP

This document outlines the methods for economic evaluation conducted as part of the REACH-ASD trial, including how data will be collected, analysed, and reported. The HEAP has been written following a review of the trial protocol and Statistical Analysis Plan (SAP) to ensure there is consistency. Note the contents of the HEAP follows the recommendations made by Thorn et al., 2021 [13].

Aim of the economic evaluation

The aim of the economic evaluation component of the REACH-ASD trial will be to estimate the cost-effectiveness of the addition of the Empower-Autism intervention plus treatment as usual (TAU) versus TAU for parents/primary caregivers of children recently diagnosed with autism, from the perspective of the NHS and social care in a UK setting.

Objectives of the economic evaluation

The primary objectives for the trial cost-effectiveness analysis will be to:

- Estimate the costs of health and social care service use in the intervention and usual care groups, and assess whether there are differences between groups
- Estimate the quality adjusted-life years (QALYs) of patients in the intervention and usual care groups, and assess whether there are differences between groups
- Assess whether any additional benefit is worth any additional cost

Overview of the economic analysis

The within trial economic analysis will be performed using patient-level data collected from the trial during baseline and follow-up study time points.

The economic analysis will use a within-trial, intention-to-treat (ITT) approach, and include all participants randomised to the two trial arms. The primary analysis will use the NHS and Social care (costs) perspective, as recommended by NICE, with a 12 month time horizon. In addition, a parents/primary caregivers (health benefits) perspective will be used.

The analytical approaches will take the form of a cost-utility analysis (a subset of cost-effectiveness analysis), with QALYs (EQ-5D-5L and published utility tariffs recommended by NICE at the time of the analysis) used as the measure of health benefit for the primary analysis. Regression analysis, adjusted for key covariates, will estimate the net costs and QALYs of the intervention. The estimates of net costs and QALYs from the regression analyses will be bootstrapped to simulate 10,000 pairs of incremental cost and QALY outcomes. Outcome pairs will be plotted on a cost-effectiveness plane, with a cost-effectiveness acceptability curve generated to estimate whether outcomes are acceptable to decision makers, with the probability of cost-effectiveness also estimated, alongside a net benefit statistic.

Sensitivity analyses will explore the intervention's cost-effectiveness by changing key methods and assumptions. For example, key sensitivity analyses include using alternative measures of health (the GHQ-30 and WEMWBS [parental/primary caregiver mental health]), focusing on child outcomes (the CHU-9D [child wellbeing], and using a wider societal perspective (including indirect costs of lost productivity).

Jurisdiction

The trial will be conducted in England, UK, which has a national health service (NHS) and social care, providing publicly funded healthcare, primarily free of charge at the point of use.

Perspective

The primary cost-effectiveness analysis will take an NHS and social care perspective, in line with the NICE reference case (NHS and personal social services) [14]. A secondary analysis will include a broader societal perspective, inclusive of costs associated with caregivers' absenteeism from work (productivity losses).

Time horizon

The primary economic analysis will compare the costs and health benefits (consequences) of each arm over the follow-up period of 52-weeks.

Statistical software

Descriptive analysis and data manipulation will be conducted using SPSS V.25 and the main statistical analyses will be conducted using Stata V.14. or higher.

Identification of resources

The following items of healthcare resource use (for caregiver and child) that may differ between study arms will be collected in the trial, this includes primary, secondary, and community-based health and social care services. In addition, caregivers will be asked to report on any autism-specific group-based services accessed, and any time absent from work (productivity losses) due to their own ill health or their child's ill health or care needs. Staff training and delivery of the intervention will also be measured to assess the cost of the intervention.

Measurement of resource use data

Resource/service use data will be collected from caregivers via Health and Social Care Service-Use Interview (SUI), completed by research staff at baseline, 26- and 52-week follow-up. The SUI was developed from existing autism-related SUIs held by the co-applicants and through discussion with the PPI representative, caregiver advisory group and clinical members of the study team. The SUI will obtain data on any services used (i.e., inpatient, outpatient, A&E, primary, community and social care use). Note the SUI also includes medication, but this will not be used in the cost-effectiveness analysis. Two copies of the SUI are included in the questionnaire pack; one pertaining to the caregivers service use and another to identify service use related to the child diagnosed with autism. The SUI collects data on the type of service, reason for use (planned or unplanned), and unit measure (e.g., number of visits). An overview is provided in Table 2. The SUI will be collected at baseline (capturing 6 months pre assessment) and 26- and 52-week follow up (capturing the time since last assessment).

A separate form collected at the same time points (Parent Group-based Interventions Questionnaire) will ask caregivers about autism-specific group-based interventions accessed. Combining this form with the SUI data will provide a picture of the range of services used by both caregivers and children. This will be collected separately to the main service use form, as the Empower-Autism intervention may be mentioned which would result in unblinding research assistants.

Table 2 Service use collection

Service type	**Unit measure**
Caregiver and child service use (collected by a self-report economic questionnaire)	
Hospital inpatient	Days per stay
Hospital day	Number of visits

Hospital outpatient	Number of visits
Accident and emergency	Number of visits
Primary care[a]	Number of visits
Community care[b]	Number of visits
Treatment as usual (collected by a self-report parent/primary caregiver group questionnaire)[c]	
Parental/primary caregiver groups/workshops	Number of sessions
Empower-Autism therapy (collected by the trial team)	
Staff time	Number of hours
Notes: [a] examples include general practitioner; [b] examples include community-based mental health care and social support; [c] treatment as usual refers to any parental/primary caregiver groups/workshops that parents/primary caregivers may access outside of the trial's intervention Empower-Autism.	

The Service Use Interview will also collect data from parents/primary caregivers related to their productivity. This includes:

- Absences from work due to child's Autism (including appointments, behavior, etc.)
- Absences from work due to child's ill-health and social care (excluding the above)
- Absences related to their own health (physical and mental)

Valuation of resource use data

For the reported health and social care use, unit costs for services will be derived from national average unit cost data [15,16].

The price year for costs will reflect the most recent unit costs available at the time of analysis (2022). The total direct health and social care costs of service use for each trial arm will be estimated by summing the costs of each resource by the reported use to provide health and social care.

Productivity losses will be calculated using the human capital approach, which involves multiplying time off work by wage/salary. The trial demographics questionnaire collects participant job titles and household income. Whilst both could be used to indicate salary, until the data are available, the completeness and ease of estimating more specific salaries by participant is unknown. This data will be reviewed when available and appropriate unit costs will be agreed with the research team. If specific salary costs by participant are unfeasible or potentially inaccurate, a general wage rate based on national data will be used to value productivity changes (this also alleviates equity concerns related to incorporating wages) [26].

Intervention costing

Intervention session delivery will be costed based on the salary of the Empower-Autism therapists and any other assistance required. Unit costs including wages, salary oncosts, overhead and capital will be used, taken from the latest Personal Social Services Research Unit (PSSRU) unit costs publication. Both direct (session delivery) and indirect time (supervision, training, preparation, etc.) will be estimated by trial therapists. The intervention cost per participant will reflect group sizes and the number of sessions attended.

Identification of outcome(s)Parent outcomes: Health benefit for the primary economic analysis will be Quality-Adjusted Life Years (QALYs) derived from utility scores, obtained using the EQ-5D-5L quality of life instrument and published utility tariffs, as recommended by NICE

at the time of the analysis. QALYs and the EQ-5D are used here, as this is the preferred measure of health-related quality of life in adults, according to the NICE reference case[17]. However, while the EQ-5D is a commonly used generic measure of health, evidence on its responsiveness to change in mental health is more limited and sometimes contradictory. Some evidence suggests that the EQ-5D is limited in capturing mental health outcomes[18], while other evidence suggests a good response to mental health changes[19,20]. Therefore, sensitivity analysis will include additional outcomes relating to caregivers' mental health and wellbeing. The General Health Questionnaire-30 (GHQ-30) and the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)[21,22].

Child outcomes: While the intervention is aimed at improving caregiver wellbeing, as caregiver wellbeing/mental health has previously been found to influence parent-child relationships (with an ultimate impact on child wellbeing) [23], child wellbeing is being explored using the adapted Child Health Utility 9D Index (CHU-9D). This measure also allows for the estimation of utilities to calculate QALYs for children. This measure is specifically designed for use in children and adolescents, and contains nine items (Worried, Sad, Pain, Tired, Annoyed, Schoolwork/homework, Sleep, Daily routine, and Activities). The CHU-9D is well-validated for use in young people [23–26], and is reported as the preferred method of valuation over the EQ-5D-Y, an alternative youth specific measures of health related quality of life [27]. The CHU-9D is also validated for completion by proxy (caregiver completion on behalf of the child), the method used within the REACH-ASD trial [26,28].

Measurement of outcome(s)

Caregivers' measurements (including the ED-5D-5L, GHQ-30 and WEMWBS will be collected at baseline, 12-, 26- and 52- weeks post randomisation. Child outcomes (CHU-9D) will be completed by parent/caregiver proxy, with measures collected at baseline, 12-, 26- 52-weeks. Due to the COVID-19 pandemic, some research activities (including interviews) will be remote. Researchers will help participants with completion over the phone or via videoconference to assist with understanding and to minimise missing data.

Valuation of outcome(s)

Utility scores will be derived from responses to the EQ-5D-5L. UK utility values will be derived using the approach recommended by NICE, which is currently using the validated mapping function from the existing EQ-5D-3L. In line with current NICE recommendations, the mapping function developed by the Decision Support Unit (DSU) using the 'EEPRU dataset' will be used for reference case analyses [17].

Total QALYs will be estimated as follows:

$$QALY = \Sigma[(U_i + U_{i+1}) /2] \times (t_{i+1} – t_i)$$

Here, U = utility value and t = time between assessments. The time between assessments is the time from baseline data collection to follow-up.

Analysis population

Analysis will follow intention-to-treat principles, with the full analysis set to include all randomised participants.

Timing of analyses

The analysis will be conducted once all participants have completed 52-weeks follow-up and data has been entered. The within-trial primary analysis will take a 52-week time horizon and only use data obtained directly for participants.

Discount rate for costs and benefits

As the analysis will be conducted using a 52-week time horizon, discounting will not be required for either costs or benefits.

Impact of COVID-19

Note this section is not included in the recommendations made by Thorn et al., 2021 [13]. It has been added to clarify the impact of COVID-19 on the trial and the cost-effectiveness analysis.

Note that the trial collects from participants, at each time point, a COVID-19 questionnaire which asks whether in the last two weeks:

- The participant (or their household) has been affected with regards to their employment due to the COVID-19 pandemic
- The participant has been unable to access care for their child (not including nursery/school)
- The participant (or their household) has been affected with regards to their wellbeing due to the COVID-19 pandemic
- The participant (or their household) has been unwell with COVID-19 or experienced a bereavement due to COVID-19
- The household income has been affected due to COVID-19

A major change to the trial, resulting from COVID-19, was the move from face-to-face to virtual delivery of sessions. This has affected the cost of intervention delivery by removing some costs of delivery (e.g., room hire).

Key economic outcomes are likely to be greatly impacted by COVID-19, for instance; total costs are anticipated to be lower during the pandemic as services had reduced availability or in extreme cases were completely shut [29–32] and health status may be lower as it will reflect ill-health related to COVID-19 infections [33].

Whilst COVID-19 is likely to have affected the data, it is anticipated that it will have affected the trial arms equally. Summarised responses to the COVID-19 questionnaire will be reviewed by the health economics team to assess the potential impact and to decide whether any additional sensitivity analyses are required to address the impact of the pandemic.

Cost-effectiveness threshold(s)

The willingness-to-pay (WTP) threshold in the UK commonly reported by NICE is currently between £20,000 and £30,000 per QALY [17]. However, while a previous review of NICE decisions suggested a WTP range of between £0 and £35,000 per QALY, more recent evidence has suggested that WTP thresholds closer to between £6,000 and £15,000 per QALY may be more appropriate [34–36]. Based on this evidence, the estimated mean QALYs and costs associated with each treatment option (Empower-Autism plus TAU; TAU alone) will be compared against a range of values (£0 per QALY to £30,000 per QALY) for decision makers willingness-to-pay.

Statistical decision rule(s)

Mean differences in costs, QALYs and net benefits between the groups (Empower-Autism plus TAU versus TAU alone) will be estimated with associated 95% confidence intervals.

Analysis of resource use

Differences in the use of services used between randomised groups will be described but not compared statistically. Use of categories between groups will be compared individually (e.g., primary care, secondary care, etc.) and as total costs (at each assessment point). This will enable us to identify whether there are any notable differences in particular areas of service use between the groups.

Analysis of costs

Differences in overall mean costs between the arms will be analysed using a generalised linear model with gamma family, log distribution (to account for the skewed distribution of cost data). Minimisation variables of the randomisation process and key covariates will be included in the regression model to control for baseline factors that may influence costs.

Analysis of outcomes

An appropriate regression model (e.g., ordinary least squares) will be used to adjust for any imbalance in baseline utility and the minimisation variables of the randomisation process. Minimisation variables of the randomisation process and key covariates will be included in the regression model to control for baseline factors that may influence QALYs.

Data cleaning for analysis

Plausibility checks will be conducted on relevant data fields to check for any values which may be considered implausible (i.e., triple digit inpatient admissions since the SUI). Where problems are identified and timeframe permitting, data will be cross checked with original copies of recorded data from the SUIs. In addition, manual checks will be conducted of the reported services used to identify any reported services which do not align to the stated perspective of the analysis. Where such services are identified, this data will be excluded. Checks will be conducted on the data (e.g., to identify minor errors in data entry) and any corrections will be accounted for in the Stata code. To aid analysis, 'other' service use descriptions will be cleaned and recoded. Where participants entered descriptions as free text, categories will be collapsed by the research team to simplify analysis (e.g., "CBT" and "cognitive behaviour therapy" will be collapsed into CBT). This will allow key types of 'other' service use to be categorised and appropriate unit costs identified.

Missing data

It is highly likely that data will be missing, either from loss to follow-up or incomplete data collection, the level of missing data for economic outcomes will be reported (costs and QALYs). Missing data will be accounted for in the analyses of net costs, net QALYs and cost effectiveness acceptability. The methods used to deal with missing follow-up data will be determined according to the extent and pattern of missing data (e.g., multiple imputation, missing indicator or propensity score methods) [37–39]. Models used to impute missing data will likely be based on key covariates associated with costs or health benefits.

Analysis of cost-effectiveness

Cost and QALY data will be synthesised within an incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB) statistic from the NHS and PSS perspective.

The ICER is calculated as:

$$\text{ICER} = \frac{\text{Cost}_{\text{intervention plus TAU}} - \text{Cost}_{\text{TAU}}}{\text{QALYs}_{\text{intervention plus TAU}} - \text{QALYs}_{\text{TAU}}}$$

The ICER represents the additional cost of an intervention per additional QALY gained. Note that if the intervention is cost saving and produces more QALYs when compared to TAU, an ICER will not be presented as an intervention is dominant in such a scenario. Likewise, if the intervention is dominated it will be described in this way rather than calculated and presented numerically.

The NMB is calculated as:

NMB = (incremental QALYs * WTPT) – incremental cost

Sampling uncertainty

Nonparametric bootstrapping will be used to investigate sampling uncertainty. Net cost and QALY estimates from the regression analyses will be bootstrapped to simulate 10,000 pairs of costs and QALY outcomes. The distribution of the bootstrap iterations will be plotted on a cost-effectiveness plane to assess parameter uncertainty (the spread and location of the data points will provide a visualisation of uncertainty). The bootstrap resampling estimates will also be used to construct a cost-effectiveness acceptability curve (CEAC), which will provide a visual representation of the probability of the Empower-Autism intervention being cost-effective at different willingness-to-pay threshold values.

Subgroup analysis/analysis of heterogeneity

Analyses may be conducted in the final data set to investigate whether cost-effectiveness varies between different patient subgroups. It should be noted that if this is conducted, it will be significantly limited by sample size and is only explorative. Potential subgroup analyses are included with rationale in Table 3.

Table 3 Potential subgroup analyses

Subgroup	**Rationale**
Parental adjustment to diagnosis	Aligned to the SAP and using baseline Reaction to Diagnosis Questionnaire (RDQ) data.
National Statistics Socio-economic (NS-SEC) subgroup	Aligned to the SAP and defined using presence/absence of adult in household in professional or administrative occupation using NSEC levels 1 / 2 vs 3 – 8.
Subthreshold Autism Trait Questionnaire (SATQ) subgroup	Aligned to the SAP and using tertiles.
Parental/primary caregiver stress baseline mental health	Aligned to the SAP and as defined by the baseline GHQ-30 (cut off score of 5+ to distinguish between low vs high mental health difficulties). This will investigate whether cost-effectiveness differs in groups with lower or higher mental health needs.

Sensitivity analysis

Sensitivity analyses will be conducted if data are sufficient to explore uncertainties surrounding key parameters in the economic evaluation (Table 4).

Table 4 Planned sensitivity analysis

Analysis	Changes	Rationale
Using child reported service use and CHU-9D values	Use of child service use data and outcomes	The wellbeing of parents/caregivers of children with autism has previously been found to influence parent-child relationships, with an ultimate impact on child wellbeing [23]. Subsequently, an analysis will be conducted using the service use and outcomes reported for the children included in the trial.
Complete case analysis	Removal of participants with incomplete/missing data	Using only the observed data will provide insight to the result for the group of participants with complete follow up and complete data (evaluable cohort). The results of the complete case analysis will be compared to the primary analysis (using multiple imputation) to give an indication of how robust the cost-effectiveness estimate is to the assumptions around missing data.
Measure of benefit	Using the GHQ-30 in a cost-effectiveness analysis	Utilities may not be sensitive to all important changes. The cost-effectiveness of MCT intervention using a condition-specific measure of effectiveness, rather than the generic QALY, will be explored. This will likely look at the cost per point change in the GHQ-30 (the primary trial outcome). However if a clinically meaningful change is available at the time of analysis, the cost-effectiveness analysis will focus on this.
	Using the WEMWBS scores in a cost-effectiveness analysis	Utilities may not be sensitive to all important changes. As parental wellbeing is one of the main goals of treatment, cost-effectiveness will be explored using the WEMWBS. This will likely look at the cost per unit improvement in WEMWBS score. However if a clinically meaningful change is available at the time of analysis, the cost-effectiveness analysis will focus on this.
Utility value set to estimate QALYs	Using the crosswalk algorithm1	The crosswalk algorithm (previously recommended by NICE) will be used to provide alternative utility values. This will assess the impact of the different methods that can be used to estimate utility.
Cost of intervention	Assuming both larger and smaller group sizes	When delivering an intervention, group sizes may differ due to various reasons (i.e., changes in demand, eligibility, enrolment etc.). As the resources required for intervention delivery are relatively stable (irrespective of group size), group size influences the cost per participant (i.e., if groups are larger, cost per participant is lower). As group sizes are also likely to differ with real-world delivery, it is important

		to assess the impact of group size on cost-effectiveness outcomes as this will be useful to decision makers when planning provisions.
Time horizon	26-week time horizon	The final trial follow-up is 52-weeks. This analysis will consider the 26-week follow-up, to assess the impact of different follow-up periods on cost-effectiveness results.
Perspective	Inclusion of productivity losses	Sectors other than the health service may incur costs or benefits from healthcare interventions. Adopting a societal perspective helps to account for any wider costs or benefits associated with an intervention [40]. This analysis will incorporate the productivity data collected within the trial.
Notes: [1] The crosswalk algorithm was recommended by NICE until February 2022.		

Further, in the event of participants with high service costs, we may choose to exclude cost outliers. Accurately estimating healthcare costs can be challenging due to skewing, whereby small numbers of patients use disproportionately more services than others.[41] Patients with extreme data values can disproportionately influence cost-effectiveness outcomes, especially when there is a limited sample size. Therefore, identifying and excluding participants with 'extreme' values (e.g., values above the 95th/99th centile) will be useful for determining the influence these values have on cost-effectiveness conclusions. The exclusion rule will be applied to both arms of the trial.

Decision analytic modelling

In the original protocol, it was detailed that a simple decision model will explore the potential cost-effectiveness of the intervention over a longer time horizon. Note, this will only be likely to be useful if the intervention is demonstrated to be effective within the trial timeframe. Further, the model is supplementary to the within-trial analysis described above which is the focus of the cost-effectiveness component of the work. Subsequently, any economic modelling will be detailed in a separate protocol once it is determined (from the trial results) whether it will have value.

Cost-consequence analysis

The potential benefits of the intervention are multifaceted and likely to not only impact the caregivers, but may also have downstream effects on the child with autism. Different decision makers may be more or less interest in specific outcomes or costs of the economic evaluation. Therefore, a cost-consequence analysis will be presented. A cost-consequence analysis presents all of the categories of cost (direct and indirect) and a number of outcomes separately for the intervention and the comparator, rather than synthesising costs with outcomes. Presenting costs and outcomes in a disaggregated form will enable decision makers to choose which costs and effects are most relevant to their local decision making context and viewpoint. Furthermore, it is unclear how the intervention may impact on resource use and subsequent costs. The cost-consequence will clearly report costs by category and will allow us to reflect on changing service use. Whilst it is often assumed positive changes in health will reduce service use, this is potentially unlikely to be the case for this intervention. For example, a lack of information about were to seek help has previously been cited by parents as a key barrier to accessing services for their child's mental health[42]. As the intervention is not only intended to improve the mental health/wellbeing of caregivers, but also supply them with

information on local, national, and online sources of information and support [43], it is possible that wider healthcare service use among the treatment arm may increase post-intervention (as caregivers' knowledge of appropriate services/where to seek help increases). Therefore, it is important to consider service use at a more granular level (i.e., category of service used), as this will not only enable us to compare differences but also identify whether any observed changes may be indicative of more positive/appropriate service use.

Planned dissemination

Findings will be published within the final NIHR report. The within-trial cost-effectiveness analysis will be published as a standalone journal publication. Furthermore, it may be presented at relevant academic conferences.

Reporting standards

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement was created to ensure health economic evaluations are identifiable, interpretable, and useful for decision making, and is also broadly applicable to any form of intervention intended to improve the health of individuals or the population[44]. The updated CHEERS 2022 28-item checklist will be followed when reporting the components of the health economic evaluation. The completed CHEERS checklist will be made available within the supplementary materials.

Reporting deviations from the HEAP

Any deviation from HEAP will be described and justified in the final published NIHR report and any associated manuscripts.

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