MICE - Mental Health Intervention for Children with Epilepsy

A randomised controlled, multi-centre clinical trial evaluating the clinical and cost-effectiveness of MATCH-ADTC in addition to usual care compared to usual care alone for children and young people with common mental health disorders and epilepsy

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ABBREVIATIONS AND GLOSSARY

CA-SUS	Child and Adolescent Service Use Schedule
CAMHS	Child and Adolescent Mental Health Services
CCTU	Comprehensive Clinical Trials Unit
CHU-9D	Child Health Utility 9-dimensions
CI	Chief Investigator
DAWBA	Development and Well-Being Assessment
DMEC	Data Monitoring & Ethics Committee
DoH	Department of Health
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
EQ-5D-5L	EuroQuality of life -5 dimensions- 5 levels
ESQ	Experience of Service Questionnaire
EU	European Union
GAD-7	Generalised Anxiety Disorder Assessment
GCP	Good Clinical Practice
GOSH	Great Ormond Street Hospital
GP	General Practitioner
ICD	International Classification of Diseases
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ISF	Investigator Site File
ITT	Intention to Treat
LTC	Long Term Condition
MATCH-ADTC	Modular Approach to Therapy for Children with Anxiety, Depression, Trauma or Conduct Problems
NHS	National Health Service
NPT	Normalisation Process Theory
PI	Principal Investigator
PIS	Participant Information Sheet
PDSA	Plan-Do-Study-Act
PMG	Programme Management Group
PPI	Patient & Public Involvement
PSC	Programme Steering Committee
QA	Quality Assurance
QALY	Quality Adjusted Life Year
QC	Quality Control
QMMP	Quality Management and Monitoring Plan
PASCET	Primary and Secondary Control Enhancement Training
PedsQL	Paediatric Quality of Life
PDSA	Plan-Do-Study-Act
PHQ-9	Patient Health Questionnaire
PSSRU	Personal Social Service Research Unit
R&D	Research and Development
RAG	Research Advisory Group
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SDQ	Strengths and Difficulties Questionnaire
SDV	Source Data Verification
SOP	Standard Operating Procedure

SSA	Site Specific Approval
TMF	Trial Master File
TMT	Trial Management Team
ToR	Terms of Reference
UCL	University College London

1 INTRODUCTION

1.1 Background and rationale

Mental health disorders in the context of long-term conditions in young people are currently overlooked and undertreated[1] despite their impact on physical health and quality of life and, in adults, increased chance of death[2 3]. An NHS priority is the closer integration of mental and physical healthcare[4]. Evidence-based psychological treatments for common childhood mental health disorders (anxiety, depression and disruptive behaviour disorders) have not been systematically evaluated in young people with epilepsy despite their high prevalence in this population[5-7].

Whilst there are many evidence-based psychological treatments, very few are used in clinical practice partly because they address singular, specific mental health disorders whereas 40% of patients have multiple mental health disorders[8 9]. MATCH-ADTC is a NICE-compliant, psychological intervention to treat multiple common mental health disorders in youth[10 - 12]. It draws from social learning theories to encourage positive behaviours and reduce unhelpful ones and is based on principles of cognitive behaviour therapy (CBT) for managing anxiety and depression in children. The treatment contains therapeutic procedures used in the leading evidence-based psychological treatments that have been evaluated in over 322 randomized controlled trials[13].

MATCH-ADTC is divided into three modules. One is for anxiety disorders and is based on 'Coping Cat'[14]. The second module is for the treatment of depression and is based on 'Primary and Secondary Control Enhancement Training' (PASCET).[15] The third module is for Parent Training for behavioural problems.[16] Both Coping Cat and PASCET have been used successfully in children with physical illnesses.[17]According to the protocol, the therapist focuses on the initial problem area identified by the patient and family together with the information gathered in the clinical and research assessment. It is considered to represent true evidence-based practice in that the protocol combines research evidence, clinical judgement, patient values and preferences.[18] Once a problem area has been selected (e.g., anxiety), an algorithm specifies a default sequence of modules and guides clinical judgement. However, the intervention is also personalised so that if the default sequence cannot be implemented (e.g., due to low mood), then the sequence can be changed to address the immediate issue. Once that issue has been addressed, treatment for the original problem area is resumed. Carers and family members can join the telephone/Skype sessions where appropriate and in the original trial 41% of the sessions included the child/young person plus a family member.[19]

One potential advantage of MATCH-ADTC over existing protocols is that it can be used to treat the significant proportion (approximately 40%) of patients who have multiple mental health problems.[20] Other advantages are that the intervention is designed to be adapted for a diverse range of children, ages and problems and can be delivered in a range of social and healthcare services, including neurological services, by non-mental health specialists. In addition, it can be delivered over the telephone or via Facetime or Skype.

1.2 Objectives

The aim of this programme of research is to transform the treatment of mental health disorders in young people with epilepsy by identifying and treating mental health problems within epilepsy services to enable early detection and intervention.

Specifically, the trial aims to determine the clinical and cost-effectiveness of adding a personalised modular psychological intervention - MATCH-ADTC with epilepsy-relevant content integrated throughout and an additional epilepsy-specific module - to usual care delivered by non-mental health specialists, over the telephone/Skype, within epilepsy services, for young people with epilepsy who meet DSM-5 diagnostic criteria for a mental health disorder.

The purpose of this study is to evaluate the clinical and cost-effectiveness of MATCH-ADTC in addition to usual care, compared to usual care alone for children with common mental health disorders and epilepsy at six months post-randomisation in a multicentre, randomised controlled trial (RCT).

2 STUDY METHODS

2.1 Trial design

MICE is a multi-centre RCT, with quantitative and health economic evaluation. Patients aged 3-18 years within epilepsy services (and their accompanying parent/carer) will be approached for the trial. The process of determining eligibility will involve being asked some brief questions, completing the SDQ and, if above threshold, a full computerised diagnostic assessment. Those meeting diagnostic criteria of a mental health disorder will be invited to take part in the trial. Participants will then be individually randomised to usual care only, or to usual care plus the intervention. Those who receive the intervention will have a clinical assessment before it begins.

2.2 Randomisation

Participants will be randomised 1:1 to receive either usual care alone or MATCH-ADTC in addition to usual care. Randomisation will use a minimisation algorithm incorporating a random element, by the following minimisation factors:

- Primary mental health disorder – anxiety/depression/disruptive behaviour/trauma
- Presence of autistic spectrum disorder or autism – yes/no
- Age - <11/11 or more
- Presence of intellectual disability – yes/no

2.3 Sample size

The sample size is 334 children and young people with epilepsy, and their parents /carers.

Previous effect size estimates for MATCH-ADTC using measures comparable to the SDQ range from 0.51-0.65. [21 22] The effect size (ES) for usual care is estimated to be 0.16-0.2.[23] We have therefore conservatively based our calculation on an ES=0.3 which is modest for a psychological intervention study. Our small pilot study comparing the guided self-help psychological intervention against a waitlist control found a large effect size: pre-treatment SDQ scores were 20.7 (SD=3.1) and 21.6 (SD=4.0) respectively and post treatment scores were 18.8 (SD=3.5) and 19.1 (SD=4.3) respectively, a difference between groups in the mean pre-post SDQ changes of 0.82.

A total sample size of 334 children has been chosen as this could detect an effect size of 0.3 for the SDQ, at the 5% significance level with 80% power, assuming an average of 14 children per therapist, an ICC of 0.01 for therapist effects, a correlation of 0.5 between baseline and follow-up SDQ, and a loss to follow-up rate of 10%. We will take steps to minimise the amount of missing data. A generalized mixed model will be used to analyse the primary outcome adjusting for baseline SDQ and minimisation variables.

2.4 Framework

MICE is a superiority trial. Specifically, the trial aims to determine the clinical and cost-effectiveness of adding a personalised modular psychological intervention - MATCH-ADTC with epilepsy-relevant content integrated throughout and an additional epilepsy-specific module - to usual care delivered by non-mental health specialists, over the telephone/Skype, within epilepsy services, for young people with epilepsy who meet DSM-5 diagnostic criteria for a mental health disorder.

2.5 Statistical interim analyses and stopping guidance

Formal review of the accumulating data will be performed at regular intervals (at least annually) by an independent Data Monitoring and Ethics Committee (DMEC). The DMEC will be asked to advise on whether the accumulated data from the trial (and potentially in the light of results from other relevant trials) justifies continuing recruitment of further patients or further follow-up. A decision to discontinue recruitment, in all patients or in selected subgroups, will be made only if the result is likely to convince a broad range of stakeholders, including participants in the trial and the general clinical community.

No formal interim analysis is planned in this trial.

2.6 Timing of final analysis

It is expected that the last patient's primary endpoint data visit will be in September 2022. All CRFs for primary endpoint data should be available within 7 days of this visit. Data query and cleaning will commence once this CRF is entered in to the database.

The final analysis will start when all data for the primary endpoint is entered into the database and all corresponding queries are resolved.

2.7 Timing of outcome assessments

The timing of outcome assessments is provided in section 5.6 of the protocol.

3 STATISTICAL PRINCIPLES

3.1 Confidence intervals and p-values

All applicable statistical hypothesis tests will be 2-sided and will be performed using a 5% significance level, unless otherwise specified. All confidence intervals presented will be 95% and two-sided.

3.2 Analysis population

The primary analysis will be conducted following the intention to treat (ITT) principle where all randomised patients are analysed in their allocated group whether or not they receive their randomised treatment. All efforts will be made to ensure that the primary outcome data is collected for all patients. Missing baseline data are not anticipated since baseline data must be recorded to allocate treatment. All patients with reported outcome data within the time window defined in the protocol will be included in the analysis. Patients who had booster sessions following main therapy, prior to the six-month timepoint, will also be included in the primary analysis population.

An ITT analysis of all patients with reported outcome data will be performed for all secondary outcomes.

4 TRIAL POPULATION

4.1 Screening, recruitment, withdrawal/follow-up

Patients screened but not enrolled in the trial and reasons for exclusions will be reported, and recruitment will be presented by centre and month.

The number of patients who have been withdrawn or were unwilling to continue follow-up will be reported by treatment arm.

The throughput of patients from those screened to those who are enrolled and assessed for trial endpoints, and included in the analysis, will be summarised in a CONSORT flowchart.[24]

4.2 Eligibility

Eligibility and inclusion/exclusion criteria are provided in the protocol in section 5.3.

4.3 Baseline patient characteristics

The list of baseline characteristics to be summarised is provided in Appendix A at the end of this document.

Baseline characteristics will be summarised for all randomised patients. Summary measures will be mean and standard deviation for continuous (approximate) normally distributed variables, medians and interquartile ranges for non-normally distributed variables, and frequencies and percentages for categorical variables.

Baseline characteristics will include the percentage of patients within each of the categories defined by the minimisation factors: primary mental health disorder (anxiety/depression/disruptive behaviour/trauma), presence of autistic spectrum disorder or autism (yes/no), age (<11/11 or more) and presence of intellectual disability (yes/no).

5 ANALYSIS

5.1 Outcome definitions

5.1.1 Primary outcome

The primary outcome measure is the total difficulties score from the Strengths and Difficulties Questionnaire (SDQ) reported by the parent/carer at six months post-randomisation.

5.1.2 Secondary outcomes

a) SDQ total difficulties score reported by parent/carer at 12 months post randomisation.
b) SDQ impact score from the Strengths and Difficulties Questionnaire reported by the parent/carer at six and twelve months post-randomisation.
c) Revised Child Anxiety and Depression Scale (RCADS) reported by parent/carer at six and 12 months.

d) Paediatric Quality of Life Epilepsy Module (PedsQL) reported by parent/carer at six and 12 months.
e) Depression reported by parent/carer at six and 12 months using the Patient Health Questionnaire (PHQ-9).
f) Generalised anxiety disorder reported by parent/carer at six and 12 months using the Generalised Anxiety Disorder Assessment (GAD-7).
g) Hague Seizure Epilepsy Scale reported by parent/carer at six and 12 months.
h) Number of serious adverse events (SAEs).

5.1.3 Rationale and details for outcome measures

The timing of the primary effectiveness outcome at 6 months is because we expect to see the maximum benefit from treatment at this time point, which corresponds to the end of treatment. However, we will be following up the children and the difference at 12 months is a secondary outcome.

SDQ

The SDQ is a brief behavioural screening questionnaire for 3-16 year olds. The SDQ is a 25 item scale with an impact scale and is widely used nationally. The 25 items are divided between 5 scales (emotional, conduct problems, hyperactivity/inattention, peer relationship problems, prosocial behaviour). [25] A slightly modified informant-rated version is used for the parent/carer of 3-4 year olds compared to that completed by the parent/carer of 4-18 year olds. 22 items are identical, the item on reflectiveness is softened, and 2 items on antisocial behaviour are replaced by items on oppositionality.

Total difficulties score is generated by summing scores from all the scales except the prosocial scale. The total difficulties score ranges from 0 to 40, and is considered missing if one or more of the 4 component scores is missing. Higher total difficulties scores indicate a higher risk of a diagnosis of mental illness.

The impact score is generated by summing up the items on overall distress and impairment. Scores range from 0 to 10 for parent-report. The impact score for 2-4 year olds is calculated in an identical way to the score for 4-17 year olds. The only change is that, the item on 'Classroom learning' for 4- 17 year olds becomes 'Learning' for 2-4 year olds.

RCADS

This is a 47-item questionnaire which is one of the main outcome measures used in the Child and Young People's Improving Access to Psychological Therapies Programme[26]. It is included in this trial to allow comparison with this national initiative, has parent-reported version, and

robust psychometric properties for the assessment of anxiety and depression in outpatient populations.

The questionnaire has six subscales - separation anxiety disorder, social phobia, generalized anxiety disorder, panic disorder, obsessive compulsive disorder, and low mood (major depressive disorder). It yields a Total Anxiety Scale (sum of the five anxiety subscales) and a Total Internalizing Scale (sum of all six subscales). The questionnaire assesses parents' report of the child/young person's symptoms of anxiety and depression across the same six subscales. The questionnaire can be scored using spreadsheets available from the developer (link: https://www.childfirst.ucla.edu/resources/).

PHQ-9

The PHQ-9 is a nine-item questionnaire that measures depression in adults.[27] It consists of the nine criteria upon which the diagnosis of DSM-IV depressive disorders is based. As a severity measure, the PHQ-9 score can range from 0 to 27, since each of the nine items can be scored from 0 (not at all) to 3 (nearly every day). For analysis, the PHQ-9 will be used as a continuous variable. Summary scores at baseline will also be presented by dividing into 5 categories of increasing severity and looking at proportions of patients in each: 0–4 (minimal or none), 5–9 (mild), 10–14 (moderate), 15–19 (moderately severe), and 20 or greater (severe).

GAD-7

The GAD-7 is a seven-item instrument that measures the severity of generalised anxiety disorder (GAD) in adults. The score is calculated by assigning scores of 0, 1, 2, and 3, to the response categories of "not at all," "several days," "more than half the days," and "nearly every day," respectively, and then adding together the scores for the seven questions. GAD-7 total score for the seven items ranges from 0 to 21. For analysis, the GAD-7 will be used as a continuous variable. Summary scores at baseline will also be presented by using cut-points for mild (5-9), moderate (10-14), and severe (15 or over) anxiety, respectively.

HASS

The Hague Seizure Epilepsy Scale is a 13-item, parent/carer reported questionnaire, which rates subjective experiences of the severity of their child's seizures. Items are statements, which are rated on a four-point or five-point scale from most to least severe (e.g. 'always', 'usually', 'sometimes', or 'never'). Total scale score ranges from 13 to 54.[28]

PedsQL

The PedsQL epilepsy module measures the impact of epilepsy on quality of life.[29] The questionnaire uses a 5-point Likert scale from 0 (Never) to 4 (Almost always). Scores are

transformed to a 0 to 100 scale. Items are reversed, scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0. Scale scores are then computed as the mean score (sum of the items in the scale/ number of items answered). If more than 50% of the items in the scale are missing, the scale score will not be computed. Higher scores indicate fewer problems.

The Parent Report for Toddlers (ages 2-4) of the PedsQL™ 3.0 Epilepsy Module is composed of 22 items comprising 5 dimensions - Impact, Cognitive Functioning, Sleep/Rest, Executive functioning and Mood/ Behaviour.

The Child and Parent Reports for Young Children (ages 5-7), Children (ages 8-12), Teens (ages 13-18), and Young Adults (18-25) are composed of 29 items comprising 5 dimensions as above.

5.2 Analysis methods

The results of the analyses will be reported following the principles of the ICH E3 guidelines on the Structure and Content of Clinical Study Reports[30]. Dummy tables are presented in the Appendix.

5.2.1 Adjustment factors

All models will be adjusted for the minimisation factors, unless stated otherwise.

- Primary mental health disorder – anxiety/depression/disruptive behaviour/trauma
- Presence of autistic spectrum disorder or autism – yes/no
- Age - <11/11 or more
- Presence of intellectual disability – yes/no

5.2.2 Primary outcome analysis

A multilevel repeated measures linear regression model will be used to estimate the difference between the intervention groups in total difficulties score of the parent reported SDQ at 6 months post randomisation.

Mixed effects linear regression will be used to determine if there is any difference in the total difficulties score due to intervention. The model will include fixed effects for intervention group, baseline SDQ total difficulties score and the minimisation factors; age (<11 versus 11+), primary mental health disorder (anxiety, depression, disruptive behaviour or trauma), presence of autistic spectrum disorder (yes/no) and presence of intellectual disability (yes/no). A random therapist factor will be included to account for any therapist effects. However, as therapists will be delivering the intervention in MATCH-AD arm only, we will be performing a partially clustered model where the random effect will be applicable to the intervention arm only. We will use heteroscedastic individual level errors to allow for

differences in variation between those in the intervention arm and those in usual care. This model will be fitted using restricted maximum likelihood (REML). The Kenward-Roger correction will be applied to protect against inflation of type I error. We will follow the recommendations that were set out in the publication by Flight et *al,* for this analysis.[31]

Results will be presented as an adjusted treatment effect and the associated 95% CI. If the intervention is effective, we would expect to see a reduction in the total difficulties score.

The model for the SDQ total difficulties at 6 months, $y_{ij,}$ where i indexes the patient and j the therapist, is:

$$y_{ij} = \beta_0 + \beta_1(\text{treatment}_{ij}) + \beta_2(Y_{0i}) + \beta_3(\text{disorder}_i) + \beta_4(\text{autism}_i) + \beta_5(\text{age}_i) + \beta_6(\text{intellectual disability}_i)$$

Where, for treatment = 1 (MATCH-AD with usual care)

$$y_{ij} = \beta_0 + \beta_1 + \beta_2 + \beta_3 + \beta_4 + \beta_5 + \beta_6 + u_j + \varepsilon_{ij}$$

And, for treatment = 0 (Usual care only),

$$y_{ij} = \beta_0 + \beta_2 + \beta_3 + \beta_4 + \beta_5 + \beta_6 + r_{ii}$$

And, $u_j \sim N(0, \sigma_u^2)$
$\varepsilon_{ij} \sim N(0, \sigma^2_\varepsilon)$
$r_{ij} \sim N(0, \sigma^2_r)$

The primary outcome is the mean difference between treatment groups at six months, estimated as β_1.

The model makes assumptions about random effects distributions, correlation structure and residuals, which will all be investigated. If any assumptions are not met then transformation of the SDQ scores may be required.

Sensitivity analysis of primary outcome

We plan to carry out the following sensitivity analyses on the primary outcome to assess the robustness of results:

(i) A small number of participants are expected to respond to the MICE questionnaires outside of the defined window in the protocol (-1 week/ +3 weeks). In such a situation we will carry out additional analyses:

- The primary model including SDQ data of those patients outside of the window by a week.
- The primary model including everyone with an SDQ measure at or around the six-month timepoint.

(ii) The primary outcome model will be refitted adjusting for participants' Covid status (whether they tested positive at least once during the trial), to account for potential effect of the SARS-CoV-2 virus on participants' responses to the SDQ questionnaire.

(iii) We will also carry out additional adjustment of baseline HASS scores to account for variation in seizure severity.

(iv) Some participants on the MATCH-ADTC arm are expected to have one or both of the booster sessions offered within six of months of randomisation. We plan to carry out a further sensitivity analysis that will exclude patients who had at least one booster session before the six-month timepoint.

5.2.3 Secondary outcome analysis

Continuous Secondary Outcomes

Each of the following continuous secondary outcome measures will be analysed using a separate linear mixed effects model:

- SDQ total difficulties reported by parent/carer at 12 months post randomisation.
- SDQ impact reported by parent/carer at six and 12 months post randomisation.
- Revised Child Anxiety and Depression Scale (RCADS) reported by parent/carer at six and 12 months.
- HASS reported by parent at six and 12 months.
- Paediatric Quality of Life Epilepsy Module (PedsQL) reported by parent/carer at six and 12 months.
- Measure of depression of parent/carer as a change from baseline at six and 12 months using the Patient Health Questionnaire (PHQ-9).
- Measure of generalised anxiety disorder in parent/carer as a change from baseline at six and 12 months using the Generalised Anxiety Disorder Assessment (GAD-7).

Serious adverse events

The proportion of patients experiencing at least one serious adverse event will be summarised by treatment arm. The number and percentage of serious adverse events will be presented descriptively by arm. Information on grades of events and whether the events are expected or unexpected, will be presented. If sufficient number of SAE events occur during the course of the trial logistic regression analysis will be carried out to compare proportion of events by arm. The number of participants withdrawing from the trial due to an SAE will be summarised by treatment.

5.2.4 Exploratory Analysis

Analysis of moderators

The regression model for the primary outcome will be extended using interaction terms to investigate the effect of treatment on pre-specified variables to assess for potential moderating effect on treatment. We will include interactions between treatment and comorbidity (number of mental health disorders), presence of autistic spectrum disorder or autism, age, presence of intellectual disability, gender, baseline severity of seizures (HASS), severity of participants' mental health problems (SDQ impact) and severity of parental mental health at baseline (PHQ-9 and GAD-7) in separate regression models to investigate whether the effect of therapy varies by these factors. We will also use forest plots to graphically display treatment effects across subgroups.

Additional exploratory analysis

We plan to potentially carry out additional exploratory analysis to evaluate if parental/carer self-efficacy may influence any effect of MATCH-ADTC on SDQ at 6 months. Further details on such exploratory analyses will be put together in a separate document.

6 ECONOMIC EVALUATION

The economic evaluation will take the NHS/Personal Social Services perspective, as preferred by NICE, and will include health and social care services provided within the education sector.

6.1 Economic measures

Health and social care resource use will be recorded in telephone interview using the Child and Adolescent Service Use Schedule (CA-SUS). Data will be collected from parent/carer at baseline (covering the previous 3 months) and at 6- and 12-months post-randomisation (covering the period since last interview).

Health-related quality of life of young people will be calculated from health states derived from proxy report of the Child Health Utility 9D (CHU9D).[34] Additionally, self-report health related quality of life data will be collected from parent/carer using the EuroQol 5-level questionnaire (EQ-5D-5L).[35, 36] The CHU-9D and EQ-5D-5L measures will be completed by parent/carer at baseline, 6- and 12-months post-randomisation.

6.2 Valuation of resources

For each item of service use reported in the CA-SUS, a nationally applicable unit cost will be applied and the total costs for each participant calculated. Unit costs will be for the most

recent financial year over which the trial data will be collected and will be reported in UK pounds sterling. Discounting of costs and outcomes will not be applied as the period of trial follow-up is not greater than one year.

Resource use items will be reported descriptively and not tested for statistical significance to avoid excessive significance testing and because the focus of the economic analysis is on cost and cost-effectiveness.

The intervention will be directly costed taking a bottom-up (microcosting) approach and using data on participant contacts recorded in trial records. Indirect (non-face-to-face) time will be estimated using a questionnaire completed by therapists on time spent on different activities in a typical week and costs will be estimated using information on therapist salaries and working conditions, including relevant overhead costs (capital, managerial, administrative etc.).

6.3 Analysis of cost and cost-effectiveness

The total costs, as well as costs per sector, in each intervention group will be summarised using the mean and standard deviation/error. Differences in mean costs will be analysed using standard parametric t-tests, despite the skewed nature of cost data to enable inferences to be made about the arithmetic mean.[37]

The primary economic analysis will explore cost-effectiveness in terms of the primary outcome measure (parent/carer reported SDQ) and will be conducted following the ITT principle as described in section 3.2. Secondary economic analysis will consider cost-utility using the CHU-9D to generate QALYs.

Cost-effectiveness will be assessed using the net benefit approach and following standard methods for economic evaluation. Mixed effects linear regression models (described in section 5.2.2) will be used to calculate the mean net monetary benefit between intervention groups. All models will be adjusted for minimisation factors listed in section 5.2.1, plus the baseline variable of interest (cost, SDQ, QALY). A joint distribution of incremental mean costs and effects for intervention groups will be generated using non-parametric bootstrapping to explore the probability that each intervention is the optimal choice, subject to a range of possible maximum values (ceiling ratio) that a decision-maker might be willing to pay for a unit increase in outcomes. Uncertainty around estimates of cost and effectiveness will be presented by plotting these probabilities or a range of possible values of the ceiling ratio on cost-effectiveness acceptability curves.

Sensitivity analyses will explore the impact of combining QALYs for child/young person with QALYs for parent/carer as well as the impact of missing data.

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8 REVISION HISTORY

Version	Date	Edited by	Comments/Justification	Timing in relation to unblinding of Trial Statistician(s)
1.0	28 Oct 2020	KC	First signed draft	Prior
2.0	07 Apr 2022	KC	Clarification on the primary analysis population, defined as all those responding to the SDQ questionnaire within window. Addition of sensitivity analyses - including patients who provided response to SDQ outside the window, in the primary model. Removal of missing data imputation model. 95% of the data are expected to be available from inclusion of the out-of-window patients. PHQ-9 and GAD-7 will be analysed as continuous outcomes, as advised by CI. Further clarification on the exact specifications of the primary model based on the reference paper.	Prior
3.0		KC	Amendment following protocol changes in relation to booster sessions. Added new sensitivity analyses plan.	Prior

9 APPENDICES

Table 1: Baseline Characteristics

Characteristic at screening		**MATCH-ADTC + Usual care** n=	**Usual care** n=	**Total** N=
Age (years)	mean(sd)			
Age (years)	n(%)			
<11				
11 or more				
Gender	n(%)			
Female				
Male				
Primary mental health disorder	n(%)			
Anxiety				
Depression				
Disruptive behaviour				
Trauma				
Autistic spectrum/ autism	n(%)			
No				
Yes				
Intellectual disability	n(%)			
No				
Yes				
SDQ	mean(sd)			
RCADS	mean(sd)			
PedsQL	mean(sd)			
HASS	mean(sd)			
PHQ-9	n(%)			
Minimal or none				
Mild				
Moderate				
Moderately severe				
Severe				
GAD-7	n(%)			
None				
Mild				
Moderate				
Severe				

Table 2: Primary and Secondary outcome

Outcomes		MATCH-ADTC + Usual care	Usual care	Adjusted coefficient (95% CI)	p-value
Primary outcome					
SDQ (parent/carer) at 6 months	mean(sd)				
Secondary outcomes **Mental Health Measures (child/young person)**					
SDQ (parent/carer) at 12 months	mean(sd)				
RCADS (parent/carer) at 6 months	mean(sd)				
RCADS (parent/carer) at 12 months					
HASS at 6 months	mean(sd)				
HASS at 12 months					
PedsQL (parent/carer) at 6 months	mean(sd)				
PedsQL (parent/carer) at 12 months					
Secondary outcomes **Parent's Mental Health Measures**					
PHQ-9 at 6 months	mean(sd)				
PHQ-9 at 12 months					
GAD-7 at 6 months	mean(sd)				
GAD-7 at 12 months					

Table 3: Serious Adverse events

	MATCH-ADTC + Usual care	Usual care	Total
Number of Patients reporting at least 1 SAE, n(%)			
Number of SAEs, n			

Table 4: Moderation analyses

		MATCH-ADTC + Usual care	Usual care	Adjusted coefficient (95% CI)	Interaction p-value
Age (years)	<11				
	11 or more				
Gender	Male				
	Female				
Comorbidity (number of mental health disorder)	1				
	2				
	3				
	4				
Autistic spectrum/ autism	No				
	Yes				
Intellectual disability	No				
	Yes				
HASS					
SDQ Impact	0				
	1				
	2				
	3-10				
PHQ-9					
GAD-7					