REACH-ASD Trial

A randomised controlled trial of psycho-education and acceptance & commitment therapy of parents of children recently diagnosed with ASD

Statistical Analysis Plan

Version 1.0

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Trial statistician: Petrina Chu
Signed: Date: 18 Jul 2023

Senior trial statistician: Prof Richard Emsley
Signed: Date: 18th July 2023

Principal investigator: Prof Jonathan Green
Signed: Date: 25/7/2023

TSC chair: Prof Bryony Beresford
Signed: Date: 21 July 2023

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This document contains up to date statistical analysis plans (with version numbers and dates of any amendments).

REACH-ASD Team

Chief investigator
Prof Jonathan Green

Principal Investigators
Dr Kathy Leadbitter
Prof Linda Davies
Prof Penny Bee
Louisa Harrison
Dr Latha Hackett
Dr Alison Dunkerley
Prof Richard Emsley
Dr Leo Kroll

Trial manager
Richard Smallman

Trial statisticians
Petrina Chu
Kirsty James
Prof Richard Emsley

Health economist
Prof Linda Davies

A) Quantitative analysis plan

1. Description of the trial

See protocol publication (1).

1.1 Principal research objectives to be addressed

Overall aim
To evaluate the effectiveness and cost-effectiveness of the Empower-Autism intervention compared to treatment-as-usual.

Objective 1
To test the effectiveness of the Empower-Autism intervention over usual care on: (i) caregiver mental health (primary outcome); (ii) caregiver knowledge, wellbeing, health status, and adjustment; and (iii) parenting stress and self-efficacy, at 12-, 26- and 52-week follow-up.

Objective 2
To test the effect of the intervention on: (i) family wellbeing and (ii) child wellbeing, behaviour, and adaptive functioning at 52-week endpoint.

Additionally, health economic outcomes relating to cost-effectiveness will be addressed in a separate health economics (HE) analysis plan.

1.2 Trial design including blinding

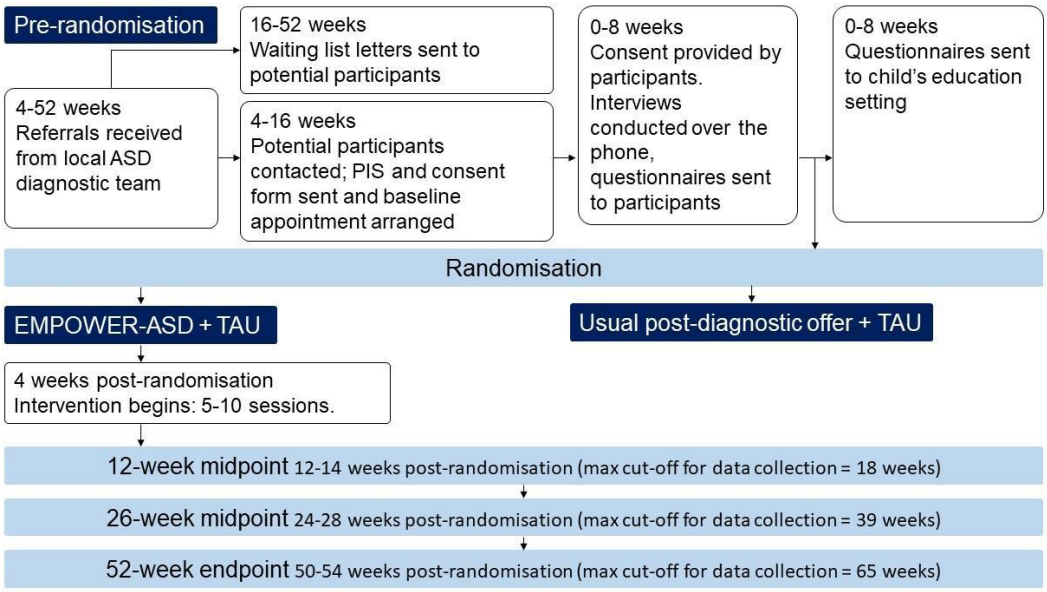
A multi-centre two parallel group single (researcher)-blinded randomised controlled trial of the EMPOWER-ASD programme plus TAU versus the usual local post-diagnostic offer plus TAU. Parents in the trial intervention arm will access the EMPOWER-ASD programme in place of

their usual local post-diagnostic offer. Parents in the TAU arm will receive the usual post-diagnostic offer of their local area. Parents in both trial arms can access all other services and interventions on offer in their locality, as per usual care.

All data collection staff and their supervisors will be kept blind to group allocation; intervention practitioners and supervisors and families cannot be blinded. Parent-rated primary and secondary outcomes are not blind-rated; researcher-scored/coded secondary outcomes will be blinded (and subject to reliability checking), as will teacher-rated secondary child outcomes. Data collection staff will be uninformed on the details of the intervention.

The trial statistician (PC) will be kept blind until the SAP has been approved and signed off, the senior trial statistician (RE) will remain blind until the main analysis has been completed. All analysis will be pre-specified. The trial dataset may be generated with a dummy variable for group allocation to enable blinded review of primary analysis coding/reporting and the primary analysis will be conducted prior to unblinding RE to group identities.

Figure 1. Trial design flow diagram



1.3 Method of allocation of groups

Randomisation will be conducted through the online randomisation service of the King's College London Clinical Trials Unit web-based randomisation service. Randomisation will be on an individual child basis, with one "index" parent per child, using a 2:1 ratio (10 to intervention, 5 to TAU), and stratification by recruitment centre. Supervising clinicians will contact families to feedback allocation and invite to intervention groups where applicable.

Justification for 2:1 randomisation ratio:

i. Recruitment: Individual parents and children will be recruited and consented at each centre as they meet eligibility criteria. Since the intervention groups are closed groups of minimum 10 (plus up to 10 accompanying adults), this means there is a potential delay in these groups forming until 15 families have consented, and the first families in each cycle will have a longer wait than those who consent and complete the set of 15 families. To mitigate against this, baseline assessments and randomisation will not be conducted until all 15 families are consented. Using 2:1 randomisation means that this process can be carried out after 15 families are consented. The use of 1:1 randomisation would require 20 families to consent before randomisation could be performed, which would lead to a longer delay for some families. This increased efficiency and reduced wait time aims to mitigate any risk of drop out between consent and treatment.
ii. Clinical reasons: Effective post-diagnostic support ideally takes place soon after diagnosis. Our proposed recruitment rate (please see section 5.7), a group size of 10 parents and a 2:1 ratio results in 3 intervention groups per centre/year, meaning parents will wait a maximum of 4 months between consent (which in most cases will occur soon after diagnosis) and commencement of the intervention group, which is a clinically appropriate timescale.
iii. Design: This is a partially nested design as there is group-level clustering in the intervention arm and no clustering in the control arm. The optimal procedure for such a design is for a greater number of participants allocated to the group intervention arm in order to account for the intra-cluster correlations in the groups - additional power is not gained here by making the two groups of equal size.

1.4 Duration of the treatment period

4 weeks post randomisation the intervention begins and will consist of 5-10 sessions.

1.5 Frequency and duration of follow-up

Participants will complete follow up measures at 12-, 26- and 52- weeks after randomisation.

1.6 Visit windows

12-week will be 12-14 weeks post-randomisation, max cut off for data collection is 18 weeks
26-week will be 24-28 weeks post-randomisation, max cut off for data collection is 39 weeks
52-week will be 50-54 weeks post-randomisation, max cut off for data collection is 65 weeks

1.7 Data collection

Baseline data collection will take place once 15 families have been recruited within a recruitment centre and as close to randomisation as possible. Baseline and follow-up data will be collected either via visits to participants' homes, or remotely via the use of email, postage of consent forms/questionnaires, online surveys, phones and/or videoconferencing. Researchers will sit and/or discuss over the phone/videoconference with parents during questionnaire completion to assist with understanding where necessary and to minimise missing data. Interviews will also be completed either at the parental home and/or remotely. Teacher measures will be collected by baseline and endpoint either via school/nursery visits and/or remotely, to maximise engagement and data completeness.

Eligibility screening

Inclusion criteria

- At consent, child aged between 2 years 0 months and 15 years 11 months. This is the age-range typically seen by ASD diagnostic teams.
- At referral, child with a diagnosis of ASD from an NHS professional within the last 12 months.
- One “index” adult (child’s parent/primary caregiver; must be aged 18 years or over) per child, nominated by family on “intention to participate” basis
- Child with ASD is a patient of one of the trial collaborating centres

Exclusion criteria

- Adult with insufficient English to preclude participation
- Adult with significant learning disability or significant hearing/visual impairment to preclude participation
- Adult with current severe psychiatric condition to preclude participation
- Significant current safeguarding concerns within family, identified by referring clinician

Measures

Baseline

Demographics (including parent age and ethnicity, child age, family socio-economic status, number of people in the household, number and age of children cared for by the index parent, languages spoken), clinical information (date of child’s ASD diagnosis, other child medical diagnoses, parental mental health or neurodevelopmental diagnoses; medical diagnoses of siblings), child autism severity (Social Communication Questionnaire, SCQ); and adaptive behaviour (VABS) as a proxy for IQ.

Primary outcome measure

Parental mental health (General Health Questionnaire-30) at 52-week follow-up. GHQ-30 is measured at baseline and 12-, 26- and 52-week follow-up.

Secondary outcome measures

Parent measures, measured at baseline and 12-, 26- and 52-week follow-up (unless otherwise stated):

- Parental ASD knowledge (Knowledge of Autism Questionnaire – UK (KAQ-UK) developed for current UK context) (administered at baseline and 12- and 52-week only).
- Parental wellbeing and quality of life, using the Warwick and Edinburgh Mental Wellbeing Scale WEMWBS a core outcome measure
- Parental Health Status EuroQol Five Dimensions Health Questionnaire, 5L version (EQ 5D-5L) - Self reported version
- Parental adjustment to diagnosis (The Reaction to Diagnosis Questionnaire, RDQ) (administered at baseline and 52-week only).
- Parenting stress (Autism Parenting Stress Index, PSI)
- Parenting self-efficacy (Tool to measure Parenting Self Efficacy, TOPSE)
- Parental flexibility (Acceptance and Action Questionnaire – II, AAQ-II)

Family Measures, measured at baseline and 52-week endpoint

- Family wellbeing, by a parent-nominated self-report measure of family experience and wellbeing developed through parent consultation within our previous trials (Autism Family Experience Questionnaire, AFEQ)
- Expressed Emotion as a blind-rated measure of family emotional climate (Autism Five Minute Speech Sample)

Child Measures at baseline and 52-week endpoint (unless otherwise stated)

- Child adaptive functioning (parent- and teacher (blind)-rated Vineland Adaptive Behaviour Scales, VABS)
- Child wellbeing and health status: parent-rated Child Health Utility-9D Index (CHU-9D), valued to allow calculation of QALYs collected at 12, 26 and 52 weeks
- Child emotional and behaviour difficulties (parent- and teacher (blind)-rated Strengths and Difficulties Questionnaire, SDQ)

Adverse events

For all participants we will collect information about adverse events at each follow-up visit. We will capture adverse events that pertain to the trial index adult and the index child.
It is possible that during the intervention sessions, parents may report "adverse events" to the Trial Practitioners. These events will be referred to as 'therapy reported negative events' as they will only be applicable to one arm of the Trial.

COVID-19 Impact

After protocol version 6 (29 Jan 2021), a non-validated COVID-19 impact questionnaire was added to the list of measures and collected at baseline and weeks 12/26/52.

1.8 Sample size estimation (including clinical significance)

Using the Stata – clsampsi- command, we powered on the basis of minimum clinical superiority compared to TAU. Inputs into the sample size calculations were derived as conservative estimates. We account for: differential clustering because of the partial nested design, with groups of size 10, variation in group size of 10 and ICC=0.02 in treatment arm, and considering participants in TAU-only arm as clusters of size 1; baseline-endpoint correlation of 0.3 (a likely underestimate because of the repeated measures analysis); a two-sided significance level of 0.05; 2:1 allocation; an effect size of 0.4 based on effects in similar trial. 90% power requires 285 participants in the analysis set: 190 participants in the treatment arm and 95 in TAU. An estimate of attrition of 15% across both arms gives a recruitment total of 330 participants: 22 groups of 10 in the treatment arm. In a general adult population survey, the GHQ-30 had a standard deviation of 10.8; hence a 0.4 effect size corresponds to a 4.3 point change.

At the request of the funder in November 2021, the sample size recalculation was performed again using the following assumptions: average group size 8, variation in group size of 8 with ICC = 0.02 in treatment arm, increased attrition rate of 25%. 90% power required 285 participants in the analysis set (192 in EMPOWER-ASD arm, 92 in TAU). 25% attrition across both arms gives a recruitment total of 380 participants; 32 groups of average size 8 in the treatment arm (about 256 participants) and about 124 participants randomised to the TAU-only arm.

1.9 Brief description of proposed analyses and any pre-analysis statistical checks required

Analyses will be carried out by the trial statistician PC and overseen by KJ and RE. PC will remain blind to treatment allocation until the SAP has been finalised and approved, RE will remain blind until all analyses have been completed. KJ will be unblinded to enable production of closed reports for data monitoring committee meetings.

Prior to database lock the trial statistician will perform data checks and generate queries for review by those responsible for entering data on the following:

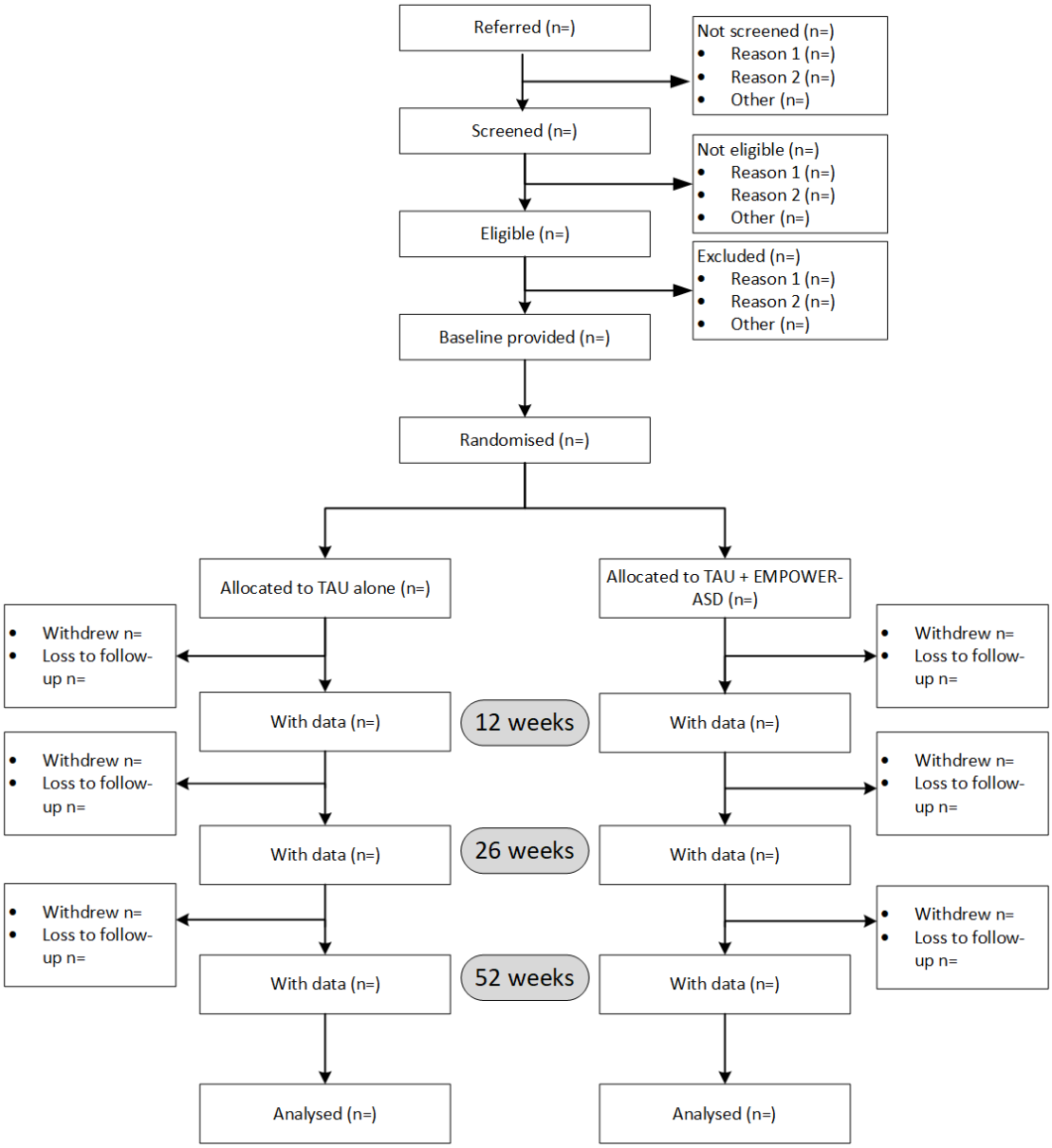
- Ensuring that the CONSORT diagram can be completed with agreement between status forms/withdrawal forms and available data.
- Ensuring that all available primary and secondary outcome data has been entered by providing lists of pins of participants who do not have each measure entered
- Checking inconsistencies between data entered in the trial database and data extracted from the randomisation system
- Missing baseline data

2. Data analysis plan – Data description

2.1 Recruitment and representativeness of recruited patients

CONSORT flow chart will be constructed (2) – see Figure 2. This will include the number of eligible patients, number of patients agreeing to enter the trial, number of patients refusing, then by treatment arm: the number continuing through the trial, the number withdrawing, the number lost to follow-up and the numbers excluded/analysed.

Figure 2. Template CONSORT diagram for REACH-ASD



2.2 Baseline comparability of randomised groups

Summary statistics will be calculated, specifically the mean and standard deviation for all normally distributed continuous measures and median and quartiles for continuous measures with skewed distributions. Discrete outcomes will be described using both the number and proportion (percentage) of the total number in the group being described. Summaries will be provided by group and overall. No significance testing will be carried out.

2.3 Analysis populations and estimands

All analysis will be conducted using the intention-to-treat population, including all participants who are randomised in the group to which they are randomised. The target estimand for the primary analysis will be the treatment policy estimand.

2.4 Adherence to allocated treatment and treatment fidelity

To ensure ongoing adherence to the treatment protocol 10% of randomly selected workshop sessions for each therapist will be formally coded for fidelity over the course of the study.

The following definition of compliance to EMPOWER-ASD will be used: participants randomised to the EMPOWER-ASD arm are compliant if they attended at least 3 out of 5 sessions, one of which needs to be the ACT session (session #4). The number of participants randomised to EMPOWER-ASD who are compliant / not compliant will be summarised. Baseline characteristics by compliance status may also be summarised.

2.5 Loss to follow-up and other missing data

The reasons for withdrawal from the trial will be summarised.

The proportions of participants missing each measure will be summarised in each arm and at each time point.

The analysis approach will allow for missing outcome data under the Missing At Random assumption; we may also use multiple imputation to adjust for non-adherence to allocated treatment and other post-randomisation variables as predictors of future loss to follow-up. A potential Missing Not At Random (MNAR) assumption may be explored in sensitivity analyses.

2.6 Adverse event reporting

Adverse events (AE), adverse reactions (AR), serious adverse events (SAE) and serious adverse reactions (SAR) will be summarised by randomised group.

Adverse Events will be monitored by the DMEC and TSC. Serious adverse events (SAEs) will be reported to the project management group and sponsor. If any of the SAEs are a suspected unexpected reaction to the intervention (it is acknowledged that this is highly unlikely in this trial), these will be reported immediately to the sponsor, research ethics committee and DMEC.

2.7 Assessment of outcome measures (unblinding)

Any unblinding of treatment to interviewers will be reported.

2.8 Descriptive statistics for outcome measures

The primary and secondary measures in section 1.7 (along with responses from the non-validated COVID-19 impact questionnaire) will be summarised using appropriate summary statistics, for the entire trial population and by randomised group at each time point. The distributions of the continuous outcome measures will be inspected, and a judgement made

on whether the variables are normally distributed or not. The mean and standard deviation will be presented for all normally distributed measures, median and quartiles for skewed distributions and proportions and frequencies for categorical measures.

2.9 Description of the intervention

Parents randomised to the experimental treatment arm will access the EMPOWER-ASD programme instead of their usual local post-diagnostic group-based programme offer (where one is offered). Like the TAU group, they will continue to access any general TAU services and interventions on offer in their locality, as per usual care. The EMPOWER-ASD programme is a closed-group manualised intervention composed of 5 x 3-hour sessions (session structure may alter if online delivery occurs due to the COVID-19 pandemic). Ten index parents will attend each group (with one additional non-trial adult per family, if desired), although group size will vary. Details on therapy experiences are collected in a separate therapy database and will be summarised using descriptive statistics.

3. Data analysis plan – Inferential analysis

3.1 Main analysis of treatment differences

3.1.1 Analysis of primary outcomes

Treatment effects on the primary outcome (GHQ-30) will be estimated using linear mixed models fitted to outcome variables at all time points. Fixed effects will be centre, baseline assessment for the outcome under investigation, treatment, time and time*treatment interactions. Participant and intervention group will be included as random intercepts, treating the control participants as ‘groups’ of size 1.

The primary endpoint is GHQ-30 at 52 weeks follow-up. Marginal treatment effects will be estimated at each time point and reported separately as adjusted mean differences between the randomised groups with 95% confidence intervals and two-sided p-value, significance has been pre-specified at 5%.

3.1.2 Analysis of secondary outcomes

Secondary outcomes that are also measured at 12 and/or 26 weeks will follow the same approach as the primary analysis (linear mixed models).

For secondary outcomes only measured at baseline and 52 weeks (VABS, SDQ) the same approach will be used without the time*treatment interaction and time as fixed effects, since there is only one measurement occasion. This approach will allow for missing outcome data under the Missing At Random assumption.

3.1.3 Statistical considerations

Time points
Outcomes are collected at baseline, 12-, 26- and 52-weeks post randomisation. Secondary outcome data collection timings are described in section 1.7.

Stratification and clustering
Randomisation will be stratified by site and so site will be included in all models as a covariate.

The random effect structure will account for repeated measures and clustering due to the partial nested design and allow estimates of the ICC in the intervention arm. For all analyses, each intervention group will contain only the outcome measures on an index parent, and so beyond the group-level clustering, no further adjustment for multiple parents is required.

Missing items in scales and subscales

The number (%) with complete data will be reported. The ideal approach would be to use missing value guidance provided for scales.

For the GHQ-30, guidelines suggest that any omitted item should be scored as a low score of 0. A more conservative approach of standard prorating if 20% or less missing values will be used. For scales where no guidance is available this same approach will be used. For example, in a scale with 10 items, prorating will be applied to individuals with 1 or 2 items missing. The average value for the 8 or 9 complete items will be calculated for that individual and used to replace the missing values. The scale score will be calculated based on the complete values and these replacements. Full details on scoring algorithms is provided in the appendix of this document.

Missing baseline data
Missing baseline data should not be an issue for the primary analysis. Some extensions to this analysis may use other baseline variables; if these contain missing data, the number with complete data will be reported and they will be imputed using a method suitable to the variable as per the recommendations of White and Thompson (3).

Missing outcome data
Where there are two or more outcome time points, missing post-randomisation assessments will be dealt with by fitting linear mixed models to all the available data using maximum likelihood methods. Such an approach provides valid inferences under the assumption that the missing data mechanism is ignorable (or MAR). If post-randomisation variables such as EMPOWER-ASD compliance are found to be predictive of missingness of the primary outcome at the final timepoint, multiple imputation will be considered to impute missing outcome variables at all timepoints.

Method for handling multiple comparisons
There is only one primary comparison, therefore no formal adjustment for multiple comparisons will be used. P-values for secondary analyses will be provided if requested.

Method for handling non-compliance (CACE analyses)
In addition to the primary analysis, the effect of receiving treatment in the subgroup of compliers will also be estimated (see Section 2.3 for potential definition of compliance).

A complier average causal effect (CACE) analysis will be used where the treatment effect for the primary GHQ-30 outcome will be estimated within the subgroup of compliers. We will use an instrumental variables approach that requires the exclusion restriction assumption (i.e. that on average, the GHQ-30 of potential non-compliers in the TAU arm is the same as the GHQ-30 of observed non-compliers in the EMPOWER-ASD arm).

Model assumption checks
The models assume normally distributed outcomes; this will have been checked when describing the data and if substantial departures from normality occur, transformations will be considered. Residuals will be plotted to check for normality and inspected for outliers.

3.1.4 Sensitivity analyses

The following sensitivity analyses may be performed if appropriate:

- **MNAR sensitivity analysis**: It may be possible that missing data is missing not at random (MNAR). For the primary GHQ-30 outcome, we will use a range of delta values (i.e. on average, dropouts have a difference of X points on the GHQ-30 compared to those retained) and examine the estimated treatment effects under different values of X. An appropriate method may be utilised (e.x. mean-score method, or utilising delta after multiple imputation).

3.1.5 Planned subgroup analyses

No subgroup analyses were planned in the original protocol, but after discussion (but before review of final data) with the trial management group, the following subgroup analyses may be performed by specifying an interaction term with treatment as a fixed effect:

- Baseline RDQ subgroup (defined by tertiles)
- National Statistics Socio-economic (NS-SEC) subgroup (defined by presence/absence of adult in household in professional or administrative occupation using NSEC levels 1 / 2 vs 3 - 8)
- Baseline mental health as defined by GHQ-30 when using 00-11 scoring and using score of 5+ as a cut-off to define those with low vs high levels of mental health difficulties
- SATQ subgroup (defined by tertiles)

3.2 Exploratory analyses

We will repeat the primary analysis using the same linear mixed model with the additional inclusion of a random coefficient for treatment for each group. This is to assess if there is variation in the treatment effects between each group. We will consider whether the confidence interval of the variance of the random coefficient includes the null effect (i.e.zero) and perform a likelihood ratio test to see if the fit of the model is a significant improvement relative to the model without the random coefficient.

3.3 Exploratory mediator analysis

None planned.

3.4 Interim analysis

None planned.

4. Software

Data management: An online data collection system for clinical trials (MACRO; InferMed Ltd) will be used. This is hosted on a dedicated server at KCL and managed by the KCTU. The KCTU Data Manager will extract data periodically as needed and provide these in Stata format. The revised KAQ-UK scores will be made available to the trial team via an Excel spreadsheet.

Statistical analysis: Stata 17 or higher will be used for data description and the main inferential analysis.

B) Schedule of assessments and measures

Form code	Research data type	Form name	Enrolment / Baseline	Allocation	Follow up (12 Weeks)	Follow up (26 Weeks)	Follow up (52 Weeks)	Ongoing
REG	Baseline characteristics	1. Registration Form	X					
ELI	Baseline characteristics	2. Eligibility	X					
RAN	CONSORT data	3. Randomisation Form		X				
STA	CONSORT data	4. Status Form			X	X	X	
DEM	Baseline characteristics	5. Demographics	X					
PAH	Baseline characteristics	6. Parental Health	X			X	X	
CAA	Health economics evaluation	7. Carer SUI – Section A	X			X	X	
CAB	Health economics evaluation	8. Carer SUI – Section B	X			X	X	
CAC	Health economics evaluation	9. Carer SUI – Section C	X			X	X	
CAD	Health economics evaluation	10. Carer SUI – Section D	X			X	X	
CHA	Health economics evaluation	11. Child SUI – Section A	X			X	X	
CHB	Health economics evaluation	12. Child SUI – Section B	X			X	X	
CHC	Health economics evaluation	13. Child SUI – Section C	X			X	X	
AFM	Secondary outcome	14. Autism Five Minute Speech Sample	X				X	
VAP	Secondary outcome	15. VABS III - Parent Interview	X				X	
GHQ	Primary outcome	16. General Health Questionnaire-30 (GHQ-30)	X		X	X	X	
WEM	Secondary outcome	17. WEMWBS	X		X	X	X	
EQ5	Secondary outcome	18. EQ-5D-5L	X		X	X	X	
AAQ	Secondary outcome	19. Acceptance and Action Questionnaire – II (AAQ-II)	X		X	X	X	
SAT	Secondary outcome	20. Subthreshold Autism Trait Questionnaire (SATQ)			X			
TPS	Secondary outcome	21. Tool to measure Parenting Self Efficacy (TOPSE)	X		X	X	X	
AFE	Secondary outcome	22. Autism Family Experience Questionnaire (AFEQ)	X				X	
APS	Secondary outcome	23. Autism Parent Stress Index (PSI)	X		X	X	X	
RDQ	Secondary outcome	24. Reaction to Diagnosis Questionnaire (RDQ)	X				X	
AKQ	Secondary outcome	25. Knowledge of Autism Questionnaire-UK (KAQ-UK)	X		X		X	
S2P	Secondary outcome	26. SDQ (2-4) - Parent	X				X	
S4P	Secondary outcome	27. SDQ (4-17) - Parent	X				X	
CHU	Secondary outcome	28. Modified Child Health Utility 9D Index (CHU-9D)	X		X	X	X	
SCQ	Baseline characteristics	29. Social Communication Questionnaire (SCQ)	X					
S2T	Secondary outcome	30. SDQ (2-4) - Teacher	X				X	
S4T	Secondary outcome	31. SDQ (4-17) - Teacher	X				X	
VAT	Secondary outcome	32. VABS III - Teacher Interview	X				X	
WD	CONSORT data	33. Withdrawal Form						X

Form code	Research data type *(delete as appropriate)*	Form name	Enrolment / Baseline	Follow up (26 Weeks)	Follow up (52 Weeks)	Ongoing
TRG	Baseline characteristics	1. Therapy Registration Form	X			
PGQ	Health economics evaluation/Treatment Description	2. Parent Groups Questionnaire	X	X	X	
TDL	Treatment Description	3. Therapy Dosage Log				X
WEB	Treatment Description	4. EMPOWER-ASD Website Variables		X		
AE	Safety	5. Adverse Events Log				X

SAP Amendments after TSC sign-off

Old version number	New version number	Date	Amendment

Appendix

A1 Scoring guidelines

A1.1 Primary outcome

GHQ-30 is collected at baseline 12-, 26- and 52-week follow-up using 0-1-2-3 scoring means the highest possible score is 90.

Total is obtained by summing all 30 items with no reverse scoring, the higher the score the more severe the condition.

Guidelines suggest that any omitted item should be scored as a low score of 0. A more conservative approach of standard prorating if 20% or less missing values will be used.

A1.2 Parent secondary outcomes

KAQ-UK is collected at baseline 12- and 52-week follow-up. This measure is scored externally, and total scores are inputted into the database for analysis. The revised scores will be provided separately to the trial statisticians.

WEMWBS is collected at baseline 12-, 26- and 52-week follow-up with the highest possible score being 70.

Total is obtained by summing all 14 items with no reverse scoring, the lower the score the more severe the condition.

No guidelines provided for missing data, a conservative approach of standard prorating if 20% or less missing values will be used.

RDQ is collected at baseline and 52-week follow-up with the highest possible score being 210.

Recode item 45 as follows: 0 = 1; 1 = 2; 2 = 3; 3 = 4; more than 3 = 5.
Reverse code the following items: 3, 5, 6, 8, 11, 12, 13, 14, 15, 16, 18, 21, 22, 23, 24, 25, 26, 27, 28, 29, 31, 33, 34, 35, 37, 38, 39, 40, 44.
Calculate the mean score of the RDQ items excluding items 1, 7, 17, and 45. The higher the score the better the parent adaptation is.

No guidelines provided for missing data, a conservative approach of standard prorating if 20% or less missing values in the items that contribute to the total will be used.

ASD-PSI is collected at baseline 12-, 26- and 52-week follow-up with the highest possible scoring being 65

Total is obtained by summing all 13 items with no reverse scoring, the higher the score the more severe the condition.

No guidelines provided for missing data, a conservative approach of standard prorating if 20% or less missing values will be used.

TOPSE is collected at baseline 12-, 26- and 52-week follow-up with the highest possible score being 480

Reverse code the following items: 6, 23, 31, 32, 33, 39. Total is obtained by summing all the items, the higher the score the less severe the condition.

No guidelines provided for missing data, a conservative approach of standard prorating if 20% or less missing values will be used.

AAQ-2 is collected at baseline 12-, 26- and 52-week follow-up with the highest possible score being 49.

Total is obtained by summing all the items, the higher the score the more severe the condition.

No guidelines provided for missing data, a conservative approach of standard prorating if 20% or less missing values will be used

A1.3 Family secondary outcomes

AFEQ is collected at baseline and 52-week follow-up with the highest possible score being 240.

Reverse score the following items: 1, 6, 8, 9, 11, 12, 14, 15, 22, 27, 30, 32, 36, 38, 41, 42, 46, 47, 48. Total is obtained by summing all of the items, the higher the score the more severe the condition.

Guidance suggests prorating if 8 or less items are missing.

Autism Five Minute Speech Sample is collected at baseline and 52-week follow-up. This measure is scored externally, and total scores are inputted into the database for analysis.

A1.4 Child secondary outcomes

VABS parent and teacher is collected at baseline and 52-week follow-up. This measure is scored externally, and total scores are inputted into the database for analysis. The ABC standard score from the parent interview will be the summary measure.

CHU-9D is collected at baseline 12-, 26- and 52-week follow-up with the highest possible score being 45.

Total is obtained by summing all the items, the higher the score the more severe the condition.

No guidelines provided for missing data, a conservative approach of standard prorating if 20% or less missing values will be used.

SDQ parent and teacher is collected at baseline and 52-week follow-up with the highest possible score being 40.

Reverse score the following items: 7, 11, 14, 21, 25

Emotional problems subscale items: 3, 8, 13, 16, 24.
Conduct problems subscale items: 5, 7, 12, 18, 22
Hyperactivity subscale items: 2, 10, 15, 21, 25
Peer problems subscale items: 6, 11, 14, 18, 23
Prosocial subscale items: 1, 4, 8, 17, 20

Total is obtained by summing all the items from all the subscales except the prosocial scale, items 1, 4, 8, 17 and 20. The higher the score the more severe the condition.
The total score is classed as missing if one of the 4 component scores is missing. Missing subscale items can be prorated if at least 3 items are completed.

A1.5 Baseline measures

SCQ is collected at baseline only with the highest possible score being 39.

Total is obtained by summing all the items (except for the first question, which determines if questions #2 – 7 are asked). Higher scores indicate more impairment to social communication.

No guidelines provided for missing data, a conservative approach of standard prorating if 20% or less missing values will be used.

A1.6 Other measures

SATQ is collected at 12-week follow-up with the highest possible score being 72

Reverse score the following items: 1 / 3 / 4 / 5 / 7 / 9 / 11 / 12 / 13 / 14 / 15 / 17 / 19 / 21 / 23. Total is obtained by summing all the items, the higher the score the more severe the condition.

No guidelines provided for missing data, a conservative approach of standard prorating if 20% or less missing values will be used.

Reference list

(1) Leadbitter K, et al. REACH-ASD: a UK randomised controlled trial of a new post-diagnostic psycho-education and acceptance and commitment therapy programme against treatment-as-usual for improving the mental health and adjustment of caregivers of children recently diagnosed with autism spectrum disorder. Trials 2022 Jul 22;23(1):585.

(2) Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 2001 Apr 14;357(9263):1191-4.

(3) White IR, Thompson SG. Adjusting for partially missing baseline measurements in randomized trials. Stat Med 2005 Apr 15;24(7):993-1007.