A multicentre randomised controlled trial of guided self-help versus treatment as usual for depression for autistic adults

The Autism Depression Trial – 2 (ADEPT-2)

Statistical Analysis Plan

Version 1.0, 11 March 2025

Based on Protocol v3.0, August 12th, 2024

ISRCTN 17547011

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List of Abbreviations:

ADEPT-2: Autism Depression Trial – 2
ADHD: Attention Deficit / Hyperactivity Disorder
ASD: Autism Spectrum Disorder
BA: Behavioural Activation
BDI-II: Beck Depression Inventory – II
CACE: Causal Average Complier Effect
CBT: Cognitional Behavioural Therapy
CI: Chief Investigator
CIS-R: Clinical Interview Schedule - Revised
GSH: Guided Self Help
HTA: Health Technology Assessment
ICH: International Conference on Harmonisation
TAU: Treatment as Usual
RCT: Randomised Controlled Trial
SAE: Serious Adverse Event
SAP: Statistical Analysis Plan

1. Introduction

1.1 Scope

The statistical analysis plan (SAP) for the ADEPT-2 trial has been written following BTC standard operating procedures, the CONSORT statement, and International Conference on Harmonisation (ICH) Statistical Principles for Clinical Trials E9, and covers the statistical analysis to be reported in the primary final reports and paper(s).

This document details the rules proposed and the presentation that will be followed, as closely as possible, when analysing and reporting the main results from the ADEPT-2 Trial.

The SAP aims to:

- Ensure that the analysis is appropriate for the aims of the trial, reflects good statistical practice, and that the interpretation of a priori and post hoc analyses is appropriate.
- Explain in detail how the data will be handled and analysed to enable others to perform the analysis in the event of sickness or other absence.

Additional exploratory or auxiliary analyses of data not specified in the protocol are permitted but fall outside the scope of this analysis plan (although such analyses would be expected to follow Good Statistical Practice).

The analysis strategy will be made available if required by journal editors or referees when the main papers are submitted for publication. If considered appropriate, additional analyses suggested by reviewers or editors will be performed following the principles of the Analysis Plan and declaring the motivation of such post hoc analyses.

Amendments to the statistical analysis plan will be described and justified in the trial's final report.

1.2 Data monitoring and safety committee

The ADEPT-2 study is overseen by a Data Monitoring and Safety Committee (DMSC) and a Trial Steering Committee, the relationship with each being laid out in the committee charters. The DMSC will receive at least annual reports of safety data; no interim analyses of primary and secondary outcomes are planned.

2. Synopsis of study design and procedures

This summary of the ADEPT-2 study is presented solely to inform the Statistical Analysis Plan; the current version of the protocol should be referred to for all other purposes.

2.1 Background and study rationale

Autism Spectrum Disorder, characterised by differences in social communication and a restricted, repetitive and stereotyped pattern of behaviours, interests and activities, is a neurodevelopmental condition which affects 1.1% of the U.K. population (1). High rates of mental health problems are reported to co-occur with autism, particularly common mental health problems such as anxiety and depression. The economic costs associated with autism are high (2) with loss of productivity and healthcare use significant factors contributing to associated costs for adults without intellectual disability.

Depression symptoms have been found to be significantly related to reduced quality of life on physical and psychological well-being domains for autistic adults and adolescents above and beyond accounting for autism symptom severity (3). Furthermore, elevated rates of suicidal ideation and suicide attempts are reported (4) and it is likely that elevated rates of depression contribute. There is evidence that a psychological therapy, Cognitive Behaviour Therapy (CBT) can be effective in treating anxiety if adapted to meet the needs of autistic people (5). However, there have been no definitive treatment evaluations of adapted CBT approaches for depression co-occurring with autism in adults to date.

In response to a themed call by the HTA (4/043), we demonstrated the feasibility of developing and delivering a low-intensity CBT intervention (Guided Self-Help; GSH) for depression based on behavioural activation (BA) adapted for the needs of autistic adults (6). The intervention (GSH) comprised materials for 9 individual sessions facilitated by a low intensity psychological therapist who received 15 hours of training and a manual. It was possible to recruit the target number of participants (n=70) on time to the study. Rates of withdrawal from the GSH arm of the study were low (9%), retention at 16 weeks was high (86%) suggesting the research design with randomisation was acceptable. Rate of withdrawal from the TAU arm was 17% and retention at 16 weeks was 54%. The GSH was well-received by participants and therapists; 86% of participants attended the pre-defined 'dose' of 6 treatment sessions and 71% attended all 9 sessions. We used two self-report (PHQ-9 and BDI-II) (7, 8), and one interview measure (Hamilton Rating Scale for Depression) (9) of depression in the feasibility study. Inter-rater reliability for the interview measure was less than adequate whilst the two self-report measures were well-aligned. Anecdotal evidence from participants suggested a preference for the BDI-II as a self-report measure with item sets of closed statements less subject to misinterpretation. The findings indicated the GSH intervention was promising.

The clinical effectiveness and cost-effectiveness of this intervention in a large-scale RCT is now warranted. The aim of the ADEPT-2 study is to establish the clinical and cost-effectiveness of an adapted low-intensity psychological intervention (Guided Self-Help) for depression in autistic adults.

2.2 Trial design

A two parallel group multi-centre pragmatic RCT of GSH versus treatment as usual (TAU) for reducing depression in adults with a diagnosis of autism.

2.3 Randomisation procedures

Sealed Envelope™ will generate the randomisation sequence (11), and the randomisation will be conducted via the study's RedCap database. Patients will be randomised into one of two treatment groups in a 1:1 ratio: either GSH (intervention arm) or TAU. Randomisation will be stratified by:

1) Site (Avon and Wiltshire; Cumbria Northumberland, Tyne and Wear; Teeside, Esk and Wear Valleys; Leicestershire; Coventry and Warwick; Cardiff and Vale)

It will also be minimised by:

1) Severity of depression, as captured by the baseline BDI-II score (0 to 25; 26 to 35; 36 to 63).
2) Prescription of anti-depressant medication (Yes or No).

2.4 Sample size calculation

A correlation of 0.5 will be assumed between the baseline and post-intervention measures of the primary outcome BDI-II. Allowing for 80% of participants having sufficient data to be included in the primary analysis, we will require a total sample size of 248 participants (124 in each group) to demonstrate a true effect size of 0.4 of a standard deviation (approximately 4 points on the BDI-II scale) (13) with a 90% power at the 5% significance level.

2.5 Eligibility criteria

2.5.1 Subject Population

Adults with a clinical diagnosis of an autism spectrum disorder (ASD) and symptoms of depression who would consider a low-intensity psychological intervention (Guided Self-Help) to help with depression.

2.5.2 Inclusion Criteria

- Adults aged ≥18-years
- A clinical diagnosis of Autism Spectrum Disorder (ASD)
- Current depression measured by the PHQ-9 with a score of ≥ 10 at screening
- Can be on medication but dose should be stable for 6 weeks prior to randomisation

2.5.3 Exclusion Criteria

- Risk of suicide such that a low-intensity intervention would not be clinically appropriate
- Participants who report that they have attended > 6 sessions of individual psychological treatment within a CBT framework over the past 6 months
- A history of psychosis
- Current alcohol/substance dependence
- Untreated epilepsy
- English, non-English & Welsh literacy levels such that the treatment materials are inaccessible without reasonable adjustments and a supporting person is not available.

2.6 Description of interventions

2.6.1 Guided Self Help

The GSH intervention (12) comprises materials for 9 sessions. Participants will be provided with the materials and invited to attend 9 appointments with the therapist guide, ordinarily held weekly (over a maximum treatment window of 16 weeks). Appointments can last up to 45 minutes in duration (except for the first appointment, which can last up to 90 minutes). A short manual for the therapist guide accompanies the session materials.

Therapist guides / coaches will receive 15 hours of trial-specific training in the GSH intervention and in working with autistic people. They will receive weekly supervision facilitated by a clinical psychologist (CI and co-applicant). Supervision will be in a group format but can be offered individually if required. During supervision, progress with clients allocated to GSH will be discussed, and issues in supporting an individual in accessing and applying the GSH intervention principles on an individual basis will be considered.

Participants will be provided a booklet containing the materials for 9 sessions (Guided Self-Help). This booklet can be provided electronically (.pdf) and/or in hard copy format. Participants will be supported in using the intervention materials by a therapist (coach) by attending weekly in-person or remote individual appointments. They can choose to vary the mode of attendance. The intervention was delivered in person in the feasibility study, but some participants attended remotely using video conferencing. Offering remote attendance to all participants provides greater flexibility for participants and reduces the risk of disruption to the study in the event of future constraints on social interaction.

Consistent with low-intensity treatment recommendations, depression symptoms will be monitored during each appointment using the PHQ-9 (7) and anxiety symptoms with the GAD-7 (10).

2.6.2 Treatment as Usual

TAU psychological therapists will be provided with information about adapting standard CBT practices to meet the needs of autistic adults. The training resources will not include training in the GSH intervention or in working with depression specifically. They will comprise training materials about generic adaptations to CBT practice and closely match the foundation training resources available to the GSH therapists.

2.7 Outcome measures

2.7.1 Primary outcome

The primary outcome is the patient-reported outcome measure (PROM) BDI-II depression score at 16 weeks post-randomisation. Table 1 ummarises the primary outcome and measure (tool) for this study.

2.7.2 Secondary outcomes

The following secondary outcomes are considered over the 52-week study period:

- Positive and negative affect: The International Positive and Negative Affect Schedule-Short Form (I-PANAS-SF).

- Depressive symptoms: Patient Health Questionnaire (PHQ-9).
- Anxiety symptoms: Generalized Anxiety Disorder Assessment (GAD-7).
- Impairment in functioning: Work and Social Adjustment Scale (WSAS).
- Perception of change: Global Rating of Change.
- Recovery: GAD-7; PHQ-9.
- Carer Burden and Quality of Life: Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS) Depression Anxiety Stress Scales (DASS)

Consistent with low-intensity treatment recommendations, depression and anxiety symptoms will be monitored on a session-by-session basis using the PHQ-9 (7) and GAD-7 (10) for participants in the GSH intervention. These measures will only be used for exploratory analysis.

The algorithms for the calculation of derived variables in this study are described in Table 1.

2.8 Procedures for missing data

The occurrence of missing data will be indicated in the results tables. For the primary outcome of BDI-II at 16 weeks, we will use descriptive statistics to describe the baseline characteristics of patients who do and do not have missing primary outcome data. The impact of missing data on the primary outcome treatment effect estimate will also be explored as part of the sensitivity analysis described in section 5.3.

2.9 Assessment time-points

All questionnaires will be analysed with regard to the intended assessment time points. We will analyse the timing of questionnaire returns by generating descriptive statistics and comparing them across treatment groups. If notable differences are identified between the groups, we will conduct a sensitivity analysis, adjusting for return timing, to evaluate the potential impact of late questionnaire submissions.

2.10 Changes to participation

For any reason, participants can choose to change their participation in the study: (a) they can stop attending study GSH sessions and/or (b) they can stop providing questionnaire data to the trial at any time without affecting their care. All participants changing their participation continue to be followed up until study completion unless they completely discontinue from the study. All data previously collected by the participant will be used in the analysis.

Table 1. Summary of outcome measures

Outcome	Tool/method
Beck Depression Inventory-II (BDI-II)	Each item of the BDI-II is rated on a 4-point scale ranging from 0-3, and the BDI-II is scored by summing the ratings for each of the 21 items. Higher scores indicate higher levels of depression. To the best of our knowledge, there are no published guidelines for dealing with missing items in this questionnaire. We will use participant-wise mean imputation in missing items if the questionnaire has less than two items missing.

Table 1 continued. Summary of outcome measures

Outcome	Tool/method
PHQ-9	Each of the nine items in the questionnaire scores symptoms of depression in the last two weeks on a scale of 0-3: 0 (Not at all), 1 (Several Days), 2 (More than half the days), and 3 (Nearly every day). The total score ranges from 0 to 27, with higher scores indicating higher depressive symptoms. Questionnaires with one missing item will be substituted with the average score of the non-missing items.
GAD-7	For each of the seven items, scores of 0, 1, 2, and 3 will be allocated the response categories of “not at all,” “several days,” “more than half the days,” and “nearly every day,” respectively. The total score will be derived by summing the scores for the seven items. Questionnaires with two or fewer missing items will be substituted with the average score of the non-missing items.
NHS-TT Recovery	NHS Talking Therapies (NHS-TT) classifies a participant as a clinical case if their baseline scores on the PHQ-9 exceeds 10 points. After treatment, participants are considered to have recovered if their scores fall below this threshold.
NHS-TT Reliable improvement	NHS-TT designates a participant as having achieved reliable improvement if, after therapy, there is a reduction of 6 points or more in the PHQ-9 score from baseline to follow-up.
NHS-TT Reliable recovery	NHS-TT considers a case as a reliable recovery if a participant meets both recovery and reliable improvement criteria.
I-PANAS-SF	Two scales: (i) positive affect (PA) and (ii) negative affect (NA). PA encompasses items: active, attentive, alert, determined and inspired. NA contains items: hostile, ashamed, upset, afraid and nervous. For each of the ten items, scores of 0, 1, 2, 3, 4, and 5 will be allocated the response categories “Very slightly or not at all”, “a little”, “moderately”, “quite a bit” and “extremely”, respectively. Each scale score ranges from 5 to 25, with higher scores suggesting more positive and negative PA and NA affects, respectively. No imputation will be performed.
WSAS	WSAS is a validated, self-report questionnaire to assess depression with five items, and scores range from 0, “not at all” to 8, “Very severely”. The total score ranges from 0 to 40, and it is derived by summing the scores of the five items. Higher scores suggest worse psychopathology. No imputation will be performed.
DASS	DASS is a self-report four-point Linkert scale questionnaire made up of 42 items reflecting a negative emotional symptom over the past week. Scores of 0, 1, 2, and 3 will be allocated the response categories “Did not apply to me at all”, “applied to me to some degree”, “applied to me a to a considerable degree”, and “applied to me very much”, respectively. The DASS is used in the carer sub-study. No imputation will be performed.

Table 1 continued. Summary of outcome measures

Outcome	Tool/method
WEMWBS	WEMWBS has fourteen affirmation items to assess mental health over the past week. Scores of 1, 2, 3, 4, and 5 will be allocated to response categories “None of the time”, “Rarely”, “Some of the time”, “Often”, “All of the time”, respectively. The WEMWBS is used in the carer sub-study. No imputation will be performed.
Global Rating of Change	The Global Rating of Change (GRC) is a single-item measure used to assess a patient's overall perception of change in their health status over a specified period. It asks participants to rate the amount of change they have experienced on a scale from Much Worse to Much Better.
EQ-5D-5L	The analysis of this measure will be reported in the Health Economics Analysis Plan (HEAP).

Table 2. Data capture timepoints

Data collection timepoint (→)	**Point of randomisation**	**Post-randomisation**						
	Baseline	**1 – 15 weeks[A]**				**16-weeks**	**32-weeks**	**52-weeks**
Key data capture (measures) (↓)								
Beck Depression Inventory-II (BDI-II) *(Primary Outcome at 16-weeks)*	●					●	●	●
Generalised Anxiety Disorder Assessment (GAD-7)	●	←	—	—	→	●		●
Depressive symptoms - Patient Health Questionnaire (PHQ-9)	●	←	—	—	→	●		●
Work and Social Adjustment Scale (WSAS)	●					●		●
Self-rating of global change						●	●	●
Positive and Negative affect (PANAS-SF)	●					●		●
Quality of life/utility (EQ-5D-5L)	●					●	●	●
Work Productivity and Impairment Questionnaire: General Health (WPIA:GH)	●					●	●	●
Health and social care resource use questions						●	●	●
<u>Carer Sub-Study:</u> Depression Anxiety Stress Scales (DASS) and Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)	◊					◊		◊

***Key**: ● data capture/outcome measures; completion methods may vary depending on participant preferences. ◊ completed by the caregiver. [A] Intervention arm only - Therapists will complete CRFs after each session.*

3. Description of participant characteristics

3.1 Disposition

The flow of participants through the trial will be summarised in a CONSORT diagram that includes eligibility, reasons for exclusion, participants' consent, the number of participants randomised to the two treatment groups, losses to follow-up, and the numbers analysed for the primary outcome. The proposed CONSORT diagram is shown in section 7.

3.2 Baseline characteristics

Summary statistics for patient characteristics at baseline will be presented by allocation to treatment and the completion of the 16-week questionnaire. The table will include all information retrieved from each participant at baseline and will be presented as in section 7.2.

4. General analysis considerations

4.1 Analysis of populations

The treatment effect on primary and secondary outcome measures and safety measures will be estimated by comparing the groups as allocated without imputing missing data (sometimes referred to as modified intention-to-treat, ITT, analysis).

4.2 Statistical software

All analyses will be carried out using the most recent version of Stata available at the time of analysis (currently Stata v18).

4.3 Model assumptions

Model assumptions will be checked using graphs and summary statistics. If the data deviates strongly from model assumptions, alternative analysis methods will be considered.

4.4 Protocol violations

Protocol violations will be reported in supplementary material.

5. Analysis of effectiveness

5.1 Primary analysis

The primary outcome is the BDI-II score assessed at 16 weeks. A linear regression model will estimate the treatment effect as the coefficient for a covariate distinguishing the two groups as allocated. The model will adjust for the study site, which was used as a stratification variable in the randomisation; as well as the continuous baseline BDI-II score, and prescription of antidepressants, divided into three categories (No, yes, and unsure), which were minimisation variables.

We will present the mean and standard deviation of the outcome at 16 weeks for each treatment group and the resulting difference in adjusted means with a 95% confidence interval and P-value. Furthermore, the effect size will be presented using Cohen's d.

The following equation can represent the model for estimating the treatment effect:

$$BDI_{16w} = \beta_0 + \beta_1(Group) + \beta_2(BDI_{bl}) + \beta_3(StudySite) + \beta_4(Antidepressants) + \varepsilon$$

5.2 Secondary analyses

The intervention's effect on secondary outcomes at 16, 32 (if available), and 52 weeks will be analysed using linear regression, adjusting for baseline scores and randomisation variables. These analyses will be conducted only at specified timepoints. We will check the normality assumptions of linear regression models. Alternative methods of analysis will be considered if the assumptions of the model are not met.

For the Global Rating of Change, ordered logistic regression will be used to capture any difference between the allocated groups as an odds ratio, with randomisation variables included as covariates.

A repeated measures analysis using BDI-II scores at all follow up timepoints will be carried out to examine the effect of the intervention over 52-weeks. A linear mixed model (repeated outcome observations (level 1) nested within participants (level 2)) will also be conducted to incorporate all time points.

Following the guidance of NHS-TT, we will report the recovery rates, reliable recovery rates and reliable improvement rates in both arms using the PHQ-9 questionnaire at each follow-up time.

We will present how many participants were included in this analysis and include a graph presenting individual participant changes in PHQ-9 from baseline to follow-up at 16- and 52-weeks.

5.3 Sensitivity analysis

5.3.1 Baseline imbalance

Should there be an imbalance between treatment groups on baseline characteristics (larger than a difference of 0.5 SD for continuous measures or 0.1 for binary measures), as described in Section 7.2, the primary analysis will be repeated, adjusting for variables showing and imbalance at baseline. This sensitivity analysis will only be performed for the primary outcome.

5.3.2 Intervention adherence and Complier Average Causal Effect (CACE) analysis.

Summary statistics for the primary outcome measure will be presented for those allocated to the GSH intervention, according to the number of sessions attended (0, 1-5, 6 or more). Six or more sessions is considered as an effective "dose".

The treatment effect in those participants who attend a full dose will be estimated in a complier average causal effect (CACE) analysis if >20% of intervention group participants do not attend any sessions. The CACE estimates will be obtained using instrumental variable regression. The model will include the same variables used in the primary analysis with the randomised group as the instrumental variable and the indicator variable for compliance. Under the assumptions of the CACE model, this approach will provide an unbiased estimate of the intervention effect among participants who receive a full dose.

Furthermore, we will conduct a sensitivity analysis to assess how slight changes to the definition of a full dose, reducing the minimum required sessions to one or more, affect the results. However, this should be interpreted cautiously given the possibility of "resentful demoralisation" in this study.

5.3.3 Missing primary outcome data

We will plot the means of the primary outcome for each group, with separate curves for those responding to only the baseline, baseline and 16 weeks only, baseline, 16 weeks and 32 weeks only, and all four assessment points.

If more than 10% of primary outcome measures are missing, baseline variables (Section 7.2) will be compared between participants who completed and those who did not complete that measure. If variables that predict missing responses are identified, the primary analysis will be repeated with those variables included as additional covariates, the resulting estimate being less subject to bias due to data being "missing at random."

A tipping point analysis using Stata's "rctmiss" command (14) will look at how strongly missing data needs to be associated with the participants' (unobserved) outcomes to be responsible for an observed treatment effect.

5.4 Subgroup analysis

Four pre-defined subgroup analyses will be conducted to assess the difference in treatment effect on the primary outcome at 16 weeks according to characteristics assessed at baseline. Effect modification will be evaluated in each case by including an interaction term in the regression model. Formal interaction tests will be performed to test whether the treatment effect differs between these groups. The study was not powered to detect such effects, so that results will be interpreted cautiously. As well as presenting the p-value for the test for interaction, we will also demonstrate any effect modification using graphs.

The baseline characteristics investigated for subgroup analyses are:

- CIS-R Anxiety disorder as primary diagnosis (defined as diagnosed vs not diagnosed)
- Baseline depression severity (BDI-II scores analysed as numeric measure)
- Structured occupation (defined as any employment or student vs. unemployed)

- Therapists with more than two participants (defined as experienced therapist vs unexperienced)

5.5 Safety measures

All serious adverse events will be tabulated by allocated group. The number of individuals experiencing one or more serious adverse events will be tabulated (see structure in section 7.5). Data will be collected from baseline until the 12-month follow-up period or withdrawal. The nature of the SAEs will also be described.

5.6 Intervention Fidelity

Adherence to the Guided Self-Help delivery manual will be evaluated using observation of recorded session and will be a single score made up of responses to six items indicating expected elements of the session are present, one item identifying that the session remained within the intended focus of the session and did not consider broader factors in the participant's life and one item that identified that the therapist did not introduce any therapeutic elements not associated with behavioural activation. Ratings will be carried out on a randomly selected 45 sessions and reliability ratings carried out on 23 of these sessions. There are two raters external to the team , one rating 45 sessions for the core data and one rating 23 sessions for reliability purposes. We will report the inter-rater reliability of the reliability coding scheme using Cohen’s Kappa.

6. Carer Sub-Study

6.1 Objective

The objective of the carer sub-study is to determine the effect of up to 52 weeks of treatment with GSH versus TAU on the carer burden.

6.2 Outcomes

Carers are asked to complete an ADEPT-2 Carer Burden Questionnaire at Baseline, 16, and 52 weeks post-randomisation of ADEPT-2 (main trial) participants. Carer burden will be measured using the Depression and Anxiety Stress Scale (DASS) and the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS). Derived scores are described in Table 1.

6.3 Sample size

No sample size calculation was conducted for the sub-study. This study will include all consenting carers of randomised ADEPT-2 participants.

6.4 Statistical analysis

Outcome measures will be presented as summary statistics for the two groups as allocated.

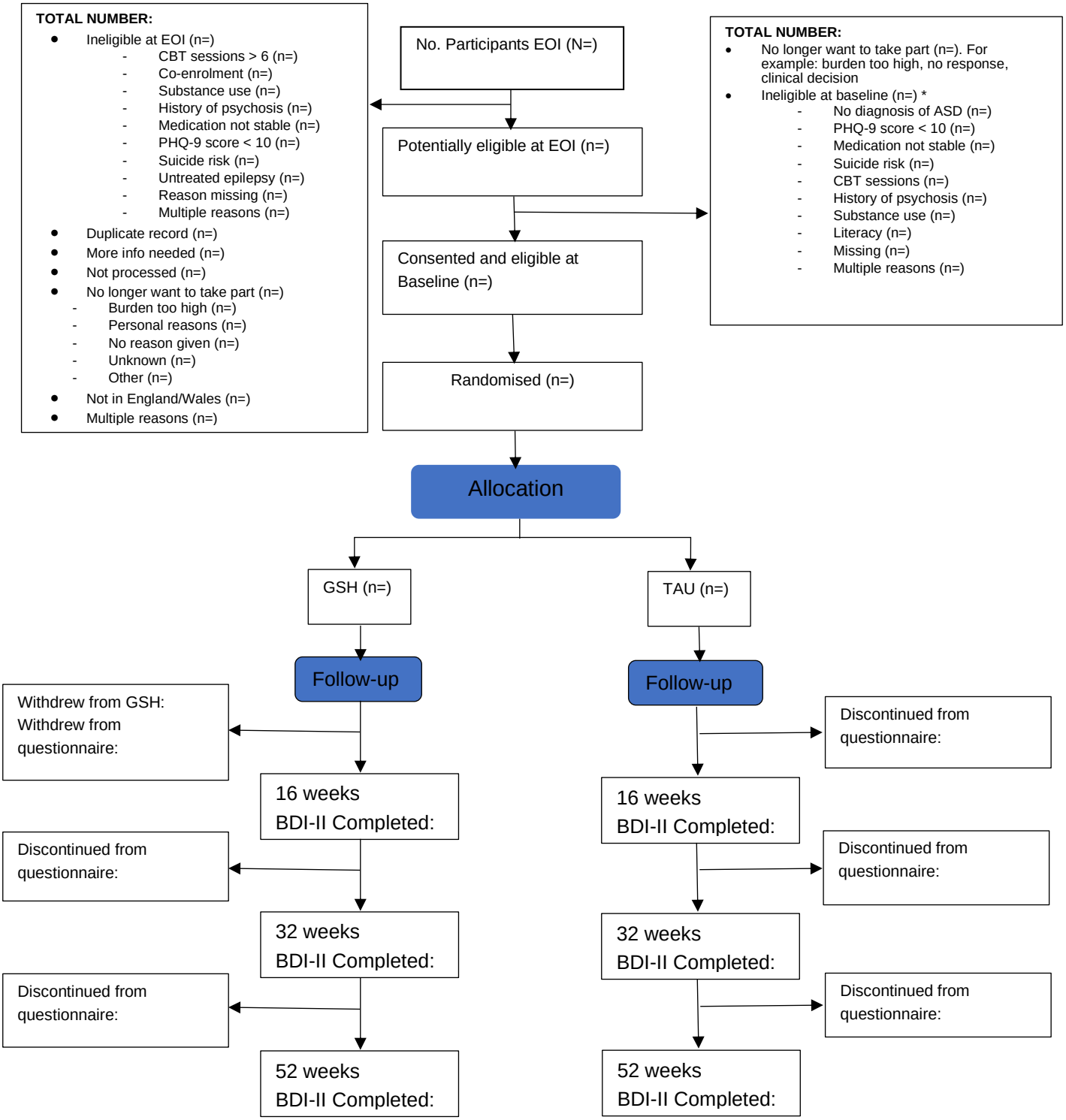
7. Changes to the SAP

All changes made to the planned statistical analyses are described below:

Previous version	Previous date	New version	New date	Brief summary of changes

8. Final report tables and figures

Figure 1. CONSORT Flowchart



* there can be more than one reason given for being ineligible
** randomised participants who withdrew all procedures/questionnaires and have not completed the follow-up questionnaire at the time point.

Table 1. Baseline Characteristics

	Treatment As Usual (N=)	Guided Self Help (N=)
Recruitment centre: n (%)		
Avon and Wiltshire		
Cumbria, Northumberland, Tyne and Wear		
Teeside, Esk and Wear Valleys		
Leicestershire		
Coventry and Warwick		
Cardiff and Vale		
Baseline BDI-II score: n(%)		
0 - 25		
26 - 35		
36 - 63		
Mean (SD)		
Taking antidepressant medication (Yes): n(%)		
Taking other medication for mental health problems or epilepsy (Yes): n(%)		
Mean age in years (SD)		
Mean age at autism diagnosis (SD)		
Sex(Male): n(%)		
Gender: n(%)		
Male		
Female		
Non-binary		
Prefer not to say		
Other		
Missing		

Table 1 continued. Baseline Characteristics

	Treatment As Usual (N=)	Guided Self Help (N=)
Ethnicity: n(%)		
White		
Asian/ Asian British/ Asian other		
Mixed/ Multiple ethnic groups		
Black/ Caribbean/ Black British/ Black Other		
Do not wish to disclose		
Other		
Missing		
Index of Multiple Deprivation		
1/2		
3/4		
5/6		
7/8		
9/10		
Missing		
Highest qualification: n(%)		
A-level or above		
GCSE / O-level / CSE / none (i.e. below A-level)		
Employment status: n(%)		
Employed - full time		
Employed - part time		
Student		
Unable to work		
Other		
Missing		

Table 1 continued. Baseline Characteristics

	Treatment As Usual (N=)	Guided Self Help (N=)
Residential status: n(%)		
Supported residence / residential home		
Living with family (i.e. mother, father, or siblings)		
Independent living		
Missing		
Financial stress: n(%)		
Moderate/severe stress		
Less stress		
Missing		
Martial status: n(%)		
Single		
Married/civil partnered		
Co-habiting with partner		
Separated/Divorced		
Widowed		
Do not wish to disclose		
Type of Accommodation: n(%)		
Owner occupied		
Tenant/rented		
Housing association		
Local authority		
Other		

Table 1 continued. Baseline Characteristics

	Treatment As Usual (N=)	Guided Self Help (N=)
Previous experience of Psychological/Talking therapy: n(%)		
No		
Yes		
Unsure		
If Yes – Number of sessions:		
0-3		
4-6		
7-9		
10 or more		
ADHD Diagnosis: n(%) *		
No		
Yes – as a child (before age 18)		
Yes – as an adult (18 years and older)		
Difficulties learning to read/write: n(%) *		
No		
Yes		
Received extra help with learning at school n(%) *		
No		
Yes – for some subjects only		
Yes – attended a special school with other children who had learning problems		
Diagnosis of learning or intellectual disability: n(%) *		
No		
Yes		

Table 1 continued. Baseline Characteristics

	Treatment As Usual (N=)	Guided Self Help (N=)
Patient Health Questionnaire – 9: Mean(SD)		
Generalized Anxiety Disorder – 7: Mean(SD)		
WSAS		
PANAS-SF PA		
PANAS-SF NA		
Express preference for Guided Self Help: n(%)		

*Variable introduced as part of an amendment; therefore 120 participants were not approached for this information.

Table 2. CIS-R at baseline

	Treatment As Usual (N=)	Guided Self Help (N=)
Primary hierarchical diagnosis: *No diagnosis identified* *Mixed anxiety & depressive disorder (mild)* *Generalised anxiety disorder (mild)* *Obsessive-compulsive disorder* *Mixed anxiety and depressive disorder* *Specific (isolated) phobia* *Social phobia* *Agoraphobia* *Generalised anxiety disorder* *Panic disorder* *Mild depressive episode* *Moderate depressive episode* *Severe depressive episode*		
Secondary hierarchical diagnosis : n(%) *No diagnosis identified* *Mixed anxiety & depressive disorder (mild)* *Generalised anxiety disorder (mild)* *Obsessive-compulsive disorder* *Mixed anxiety and depressive disorder* *Specific (isolated) phobia* *Social phobia* *Agoraphobia* *Generalised anxiety disorder* *Panic disorder*		
Suicidal intent *No hopelessness or suicidal thoughts* *Feels hopeless but no suicidal thoughts* *Feels like life isn't worth living* *Patient has had suicidal thoughts* *Patient has had suicidal plans*		
Anxiety profile *Generalised anxiety disorder* *Obsessive-compulsive disorder* *Specific phobia* *Agoraphobia* *Panic disorder* *Social phobia*		
Depression profile *Mild depressive episode* *Moderate depressive episode* *Severe depressive episode* *Mixed anxiety and depressive disorder*		

Table 3. Analysis of Beck Depression Inventory-II (BDI-II)

Analyses	**Treatment as Usual**		**Guided Self Help**		**Comparison**			
	N	**Mean (SD)**	**N**	**Mean (SD)**	**Adjusted* difference in means**	**95%CI**	**p-value**	**Effect size (Cohen's d)**
Baseline score								
Primary analysis:								
16 weeks								
32 weeks								
52 weeks								
Over-time**								
Sensitivity analyses:								
Baseline imbalance								
CACE analysis								
Model adjusted for baseline predictors of missingness								

*Adjusted for study centre, prescription to antidepressants and BDI-II score at baseline.
**Including scores at all follow-up times.

Table 4. Analysis of secondary outcomes

Outcome		Treatment as Usual	Guided Self Help	Adjusted* difference in means (95% CI)	p-value
		Mean (SD), n	Mean (SD), n		
PHQ – 9	Baseline*				
	16 weeks				
	52 weeks				
GAD – 7	Baseline*				
	16 weeks				
	52 weeks				
WSAS	Baseline*				
	16 weeks				
	52 weeks				
PANAS-SF PA	Baseline*				
	16 weeks				
	52 weeks				
PANAS-SF NA	Baseline*				
	16 weeks				
	52 weeks				

* Baseline summary statistics based on those participants who completed the 16-week assessment

Table 5. Global rating of change

	Treatment as Usual	Guided Self Help	Odd ratio (95% confidence interval)	
	n (%)	n (%)		p-value
16 weeks				
Much better				
A bit better				
No different				
A bit worse				
Much worse				
Missing				
52 weeks				
Much better				
A bit better				
No different				
A bit worse				
Much worse				
Missing				

Table 6. Safety measures

	Treatment as Usual	**Guided Self Help**
Adverse Events		
A significant mental health episode (e.g., suicide, suicide attempts, mental health related hospital admissions).		
A sustained and clinically significant deterioration i.e., a worsened mental state, which can include the emergence of new symptoms.		
An event with a significant negative impact for an individual in terms of , mental and physical wellbeing, and/or social/everyday function e.g., safeguarding concerns.		
Serious Adverse Events		
Hospitalisation		

Table 7. List of Serious adverse events

Study ID	**Allocation**	**Description of the event**	**Related to intervention**	**Seriousness(a)**	**Outcome(b)**

[a] Seriousness: 1= Resulted in death, 2=Was life threatening; 3=Required hospitalisation or prolongation of existing hospitalisation; 4=results in persistent or significant disability or incapacity; 5=resulted in congenital anomaly/birth defect

[b] Outcome: 1=resolved; 2=resolved with sequelae; 3=unresolved; 4=worsening; 5=fatal; 6=not assessable

Table 8. Fidelity to the manual

Session	**N. of sessions coded: N(%)***	**N. of times something compulsory was not done: N(%)**	**N. of times therapy did not remain within the focus of the session: N.(%)**	**N of times other therapeutic activities were introduced: N(%)**
Randomised		**-**	**-**	
1				
2				
3				
4				
5				
6				
7				
8				
9				

* The denominator is the randomly selected coded sessions.

Table 9. Subgroup Analysis

Subgroup	**N. providing data at 16 weeks**	**Difference in BDI-II means at 16 weeks between treatment arms (95% CI)**	**p-value for interaction**
CISR Anxiety disorder as primary diagnosis			
Other diagnosis			
Anxiety diagnosis			
Baseline Depression Severity*			
Below median			
Median or above			
Structured Occupation			
Employed or student			
Unemployed			
Therapist			
Experience therapist (3 or more patients			
Unexperienced			

*Interaction p-value based on the depression severity score

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10. Supplementary

Table A. Return from questionnaire

Weeks	**Treatment as usual**		**Guided Self Help**	
	N	**Mean(SD)***	**N**	**Mean(SD)***
16				
24				
52				
Days since baseline. As a reference, 16-, 24-, and 52 weeks have 112-, 168-, and 364 days, respectively.				

Table B. Baseline Characteristics for participants returning their questionnaire at 16 weeks

	Participants returning their 16- weeks questionnaire: N (%)	Participants not returning their 16-weeks questionnaire: N (%)
Allocated to GSH (N(%))		
All Baseline characteristics presented in Table 1.		

Table C. Descriptive statistics of NHS-TT Recovery, reliable improvement and reliable recovery rates by treatment group at 16 and 52 weeks using the PHQ-9.

	TAU	GSH
Questionnaires returned at 16 weeks		
Recovery (N(%))		
Reliable Improvement (N(%))		
Reliable Recovery(N(%))		
Questionnaires returned at 52 weeks		
Recovery (N(%))		
Reliable Improvement (N(%))		
Reliable Recovery (N(%))		
The denominator in the proportion is the number of questionnaires returned at each follow-up time.		

Table D. Summary statistics for carer sub-study

		TAU Mean (SD)	GSH Mean (SD)
DASS (range)	Baseline		
	16 weeks		
	52 weeks		
WEMWBS	Baseline		
	16 weeks		
	52 weeks		

Figure A. Individual participant changes from baseline in PHQ-9 score. (Graph was taken as an example from another study) (15).

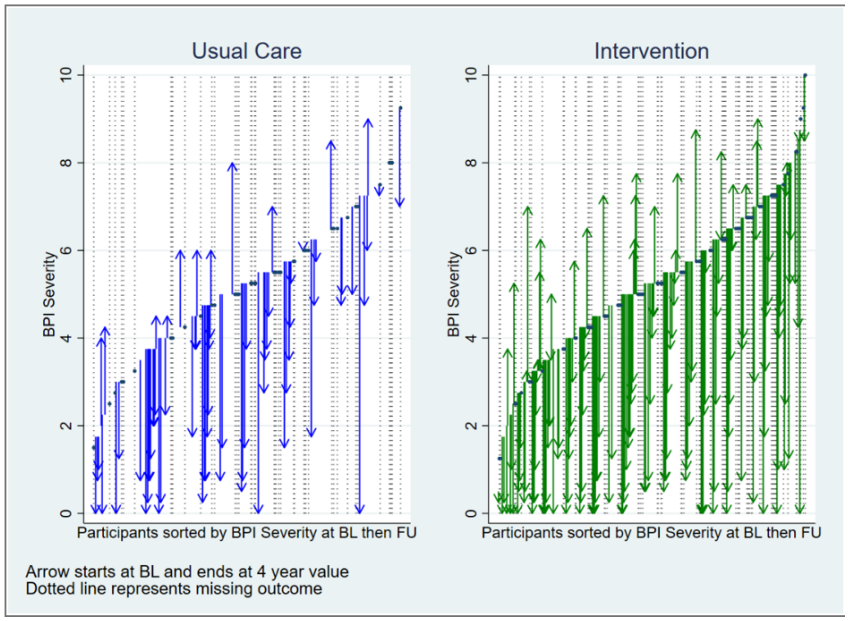

Table E. List of Coaches and Number of Participants Treated

Therapist ID	Frequency	Percent
AW01	11	8.33%
AW02	6	4.55%
AW03	16	12.12%
AW04	1	0.76%
AW05	7	5.30%
CN06	3	2.27%
CN07	6	4.55%
CN08	2	1.52%
CN09	1	0.76%
CN10	4	3.03%
CN11	1	0.76%
CN12	3	2.27%
CN13	3	2.27%
CN14	1	0.76%
CN15	2	1.52%
CN16	1	0.76%
CV17	3	2.27%
CV18	8	6.06%
CV19	7	5.30%
CV20	2	1.52%
CV21	2	1.52%
CW22	2	1.52%
CW23	3	2.27%
CW24	2	1.52%
CW25	2	1.52%
CW26	2	1.52%
CW27	1	0.76%
CW28	2	1.52%
CW29	4	3.03%
CW30	2	1.52%
CW31	1	0.76%
LE32	2	1.52%
LE33	1	0.76%
LE34	4	3.03%
TE35	1	0.76%
TE36	2	1.52%
TE37	3	2.27%
TE38	2	1.52%
TE39	1	0.76%
TE40	1	0.76%
TE41	2	1.52%
TE42	2	1.52%
Total	132	100.00%