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NHS Avon and Wiltshire Mental Health Partnership NHS Trust

NHS Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust

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)

Protocol

Version 3.0, 12-Aug-2024

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This protocol has regard for the HRA guidance

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LIST OF ABBREVIATIONS

AE	Adverse Event
BTC	Bristol Trials Centre
C&C	Confirmation of Capacity and Capability
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus
CRF	Case Report Form
CRN	Clinical Research Network
CSO	Clinical Study Officer
CUA	Cost–Utility Analysis
DIBD	Developmental International Birth Date
DMC	Data Monitoring Committee
EOI	Expression of Interest
EU	European Union
GAD-7	Generalised Anxiety Disorder Assessment
GDPR	General Data Protection Regulation
GP	General Practitioner
GSH	Guided Self-Help
HRA	Health Research Authority
IAPT	Improving Access to Psychological Therapies
GCP	Good Clinical Practice
ID	Intellectual Disability
I.D	Identification
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
ITT	Intention-to-treat
NHS	National Health Service
NHS R&D/R&I	National Health Service Research & Development/Research & Innovation
NHSTT	NHS Talking Therapies for anxiety and depression
NICE	National Institute for Health and Care Excellence
NIHR CRN	National Institute for Health Research Clinical Research Network
NIHR HTA	National Institute for Health Research Health Technology Assessment
PHQ-9	Patient Health Questionnaire
PI	Principal Investigator
PICs	Patient Identification Centres
PIL	Participant Information Leaflet

PPE	Personal Protective Equipment
PPI	Patient and Public Involvement
PQ	Participant Questionnaires
PROM	Patient reported outcome measure
QALY	Quality Adjusted Life Years
RA	Research Assistant
RCT	Randomised Controlled Trial
R&D	Research and Development
REC	Research Ethics Committee
RUQ	Resource-Use Questionnaire
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SLA	Service Level Agreement
SOP	Standard Operating Procedure
SQL	Structured Query Language
SSL	Secure Sockets Layer
TAU	Treatment As Usual
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
UKCRC	UK Clinical Research Collaboration
UniBath	University of Bath
UniBristol	University of Bristol

TRIAL SUMMARY

Trial title	A multicentre randomised controlled trial of guided self-help versus treatment as usual for depression for autistic adults	
Short title	The Autism Depression Trial – 2	
Acronym	ADEPT-2	
Chief Investigator	Professor Ailsa Russell, Professor of Clinical Psychology, University of Bath	
Sponsor	University of Bath (UniBath)	
Funder	National Institute for Health Research Health Technology Assessment Programme (NIHR HTA; reference 132343)	
Trial design	A two parallel group multi-centre pragmatic RCT of Guided Self-Help (GSH) versus treatment as usual (TAU) for reducing depression in adults with a diagnosis of autism.	
Planned sample size	248 - 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	
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	
Exclusion criteria	• Risk of suicide • Have attended > 6 sessions of individual psychological treatment within a cognitive behavioural therapy (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	
Number of study centres	ADEPT-2 will be delivered through at least six regional centres in the UK. Within each centre there can be several recruiting sites for that region. Additional centres/sites will be identified if required	
Treatment duration	Up to 9 GSH sessions (primary outcome at 16-weeks post-randomisation) with follow-up to 52 weeks post-randomisation.	
	Objectives	**Outcome Measures**
Primary	To determine the difference in depression scores at 16-weeks between adults with a diagnosis of autism treated with guided self-help or who received treatment as usual.	Beck Depression Inventory-II (BDI-II)
Secondary	**i)** To determine the long-term effect of up to 9 sessions of treatment with GSH versus TAU at 16 and 52-weeks on:	**-**
	a) depressive symptoms	BDI-II depression score and Patient Health Questionnaire-9 (PHQ-9) and Global Rating of Change
	b) quality of life	EQ-5D-5L and study-specific questionnaire
	c) anxiety	GAD-7
	d) positive and negative affect	Positive And Negative Affect Schedule (PANAS)

	e) work and social function	Work and Social Adjustment Scale (WSAS)
	f) impact on carer	Depression Anxiety Stress Scales (DASS) and Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)
	g) resource use/cost effectiveness	EQ-5D-5L (to calculate QALYs) and study-specific patient resource use questionnaire and Work Productivity and Activity Impairment (WPAI) Questionnaire
	ii) To maximise the quality of outcomes by making interim measurements at 32 weeks on:	-
	a) depressive symptoms	BDI-II depression score and Patient Health Questionnaire-9 (PHQ-9) and Global Rating of Change
	b) quality of life	EQ-5D-5L and study-specific questionnaire
	c) resource use	EQ-5D-5L (to calculate QALYs) and study-specific patient resource use questionnaire
	iii) To explore participants' and therapists' acceptability, experiences of, and adherence to, study processes and treatment to understand contextual factors for implementing the intervention, particularly in respect to participant retention of treatment principles.	Qualitative interviews with participants and therapists
	iv) To determine the effectiveness and use of the intervention materials and training resources.	Qualitative interviews with therapists and WAI-SR and goal attainment scaling (GAS)
Study duration	• Funding start date: 01 September 2021 • Anticipated duration: 46 months • Anticipated end date: 30 June 2025	

TRIAL FLOW CHART

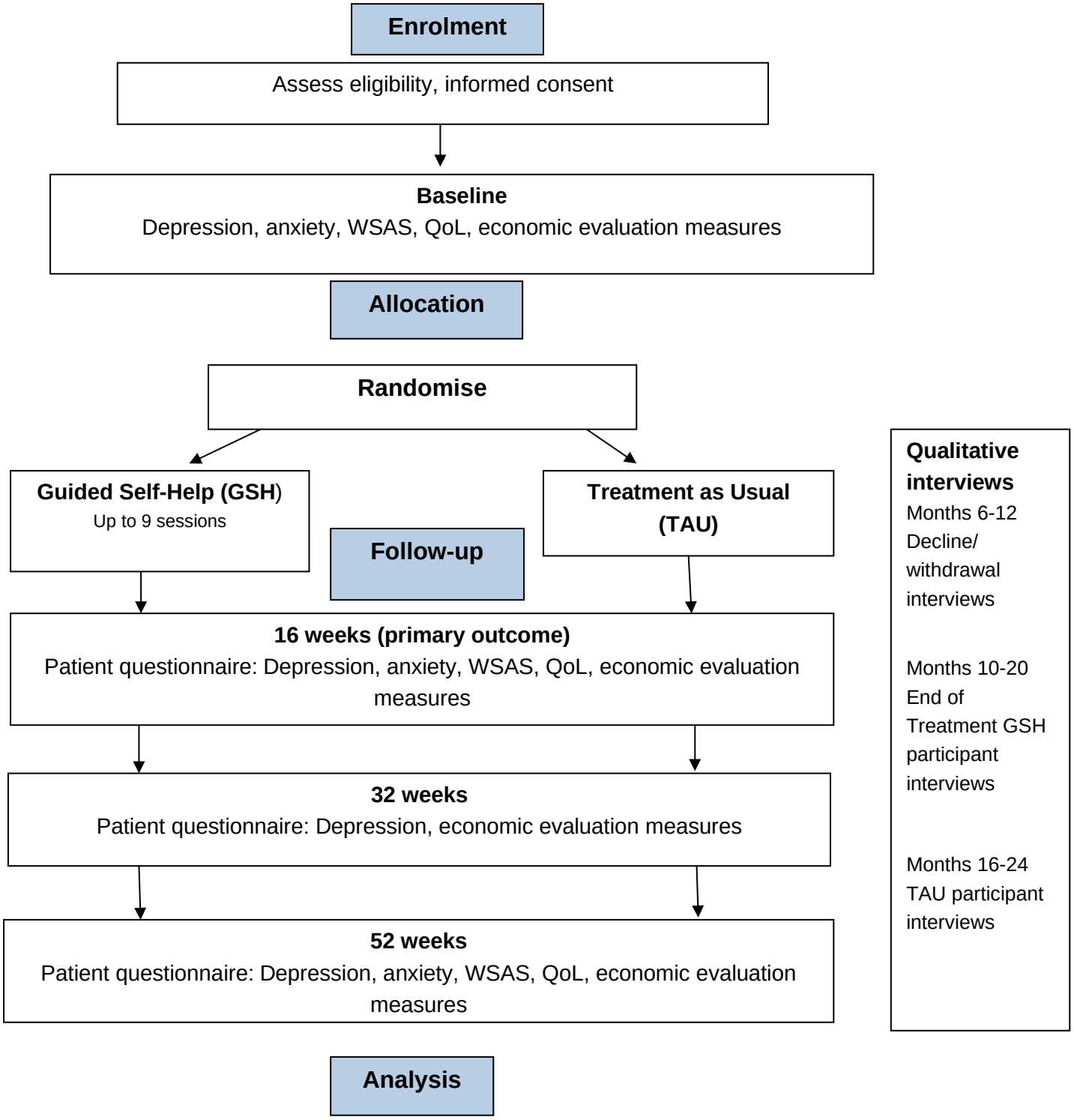


Figure 1 Trial flowchart

TRIAL PROTOCOL TITLE

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).

1 BACKGROUND AND RATIONALE

Autism Spectrum Disorder, characterised by impairments 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, a debilitating mental health condition characterised by low mood, is the leading cause amongst mental health conditions of years lost due to disability (3). Autistic people are disproportionately affected by depression. Depression is 3-4 times more prevalent in autistic people (4) and is related to reduced quality of life (5). A total population study of 223,842 individuals in Stockholm County reported that of the 4,073 who had an Autism diagnosis, 19.8% also had a depression diagnosis by age 27, compared to 6% of the general population (adjusted risk ratio 3.6) (6). A meta-analysis of adult autism studies (n=26,070 participants in 29 studies, 17 U.K. based) reported pooled estimates of current and lifetime prevalence of depression to be 23% and 37% respectively (7) . These figures are in stark contrast to the 3-4% current point prevalence of depression in the U.K. general population (8).

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 (5). Furthermore, elevated rates of suicidal ideation and suicide attempts are reported (9) and it is likely that elevated rates of depression contribute.

The provision of effective empirically supported treatments for depression is a priority for the autistic community and healthcare services. “Which interventions improve mental health or reduce mental health problems in people with autism? How should mental health interventions be adapted for the needs of people with autism?” was the number one research question from a priority setting exercise [https://www.autistica.org.uk/our-research/our-research/your-research-priorities]. The Department of Health and Social Care’s Think Autism Strategy (2018) (10) specifies ‘Timely and appropriate mental health support” to be a key priority. The NHS England long-term plan (2019) [www.longermplan.nhs.uk] cites improving healthcare services for autistic people as an NHS priority, including community mental health support and suicide prevention.

Effective treatments for depression exist. UK National Institute for Health and Clinical Excellence (NICE) guidelines (11) recommend low-intensity psychosocial interventions based on the principles of cognitive behaviour therapy (CBT) as evidence-based treatment for mild-moderate depression.

Autistic people are often not identified or are excluded from clinical trials (12). Clinical guidelines about the treatment of depression are then based on research evidence which may not include autistic people. Furthermore, depression can present atypically in autistic people (13) highlighting the relevance of autism specific research.

There is evidence that CBT can be effective in treating anxiety if adapted to meet the needs of autistic people (14). However, there have been no definitive treatment evaluations of adapted CBT approaches for depression co-occurring with autism in adults to date. A meta-analysis of cognitive behavioural interventions in autism (14) identified two studies of depression treatment meeting inclusion criteria: an investigation of mindfulness-based stress reduction in adults (N=41) (15) and combined anxiety and depression group CBT in adolescents (N=32) (16). There has since been a

study of combined anxiety and depression CBT in adults (N=59) (17), and group CBT for depression in adolescents (N=23) (18). These studies, plus our recent feasibility study, report positive changes in depression scores offering preliminary evidence that adapted CBT may be a helpful intervention for depression, but the findings of these small studies need confirmation in a definitive trial.

Differences in social communication, neurocognition and emotional awareness in autism (19) underpin the need to adapt psychosocial treatments. A recent study provides evidence of an advantage for adapted CBT over standard CBT for anxiety in autistic young people (20). Adaptations for working with children and adults are broadly outlined in NICE guidance (21, 22) and include an increased use of written and visual information, emphasising behaviour change over cognitive approaches, having well explained guidance and rules in therapy, involving a friend, family member or carer, having breaks, incorporating special interests and avoiding ambiguous use of language.

Autistic people report significant barriers to accessing mental healthcare. A systematic review of perceived barriers and facilitators to accessing psychological treatment for emotional or behavioural problems (23) identified 9 studies with 6 of these, 4 qualitative and 2 quantitative, describing adults' self-reported experience. The most frequently reported barriers were a lack of therapist knowledge about autism and therapists being either unwilling or unable to tailor their approach to autism. Qualitative findings from our earlier feasibility study highlighted that negative prior experience of accessing psychological therapy contributed to a lack of clinical equipoise in respect of a preference to be randomised to the GSH treatment of the feasibility RCT (24).

Studies consistently report low levels of autism knowledge amongst healthcare clinicians (25) . Additionally, a lack of experience and low confidence in working with autistic adults with co-occurring mental health problems was reported by community mental health professionals (26). A survey of U.K. cognitive-behavioural therapists attending a training workshop (27) found that while therapists reported moderate levels of confidence in their ability to use their core engagement and assessment skills when working with autistic adults, they were far less confident as to how to use their knowledge when adapting CBT interventions with this group. They identified adapting communication, written information, how best to pace sessions and scaffold emotional literacy difficulties as common challenges they faced.

In summary, depression is a frequently co-occurring condition with autism. Autistic people have social communication and neurocognitive differences which can mean mainstream psychosocial therapies are not readily accessible to them. Furthermore, therapists do not ordinarily receive training in how to work with autistic people. Intervention research has focused on anxiety and younger populations with less attention paid to systematic evaluation of interventions for depression.

In response to a themed call by the HTA (4/043), we demonstrated the feasibility of developing and delivering a low-intensity intervention (Guided Self-Help; GSH) for depression based on behavioural activation (BA) adapted for the needs of autistic adults (28). 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) (29, 30) and one interview measure (Hamilton Rating Scale for Depression) (31) 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.

In summary, there is a need for an empirically supported psychological intervention specifically for depression adapted to meet the needs of autistic adults. The intervention needs to rely on well-developed written and visual materials to include emotion literacy components and therapist training resources to scaffold therapist knowledge and confidence.

The proposed research will better inform healthcare services about best clinical practice for the treatment of depression for autistic adults. This research will ensure autistic adults can access empirically supported depression treatment. Subject to findings, this research will result in an evidence based psychological intervention with training materials which can be rapidly disseminated to providers of mental healthcare.

2 AIMS AND OBJECTIVES

2.1 Aim

To establish the clinical and cost effectiveness of an adapted low-intensity psychological intervention (Guided Self-Help) for depression in autistic adults.

2.2 Primary objective

To determine the difference in Beck Depression Inventory-II (BDI-II) depression scores at 16-weeks post-randomisation between adults with a diagnosis of autism spectrum disorder (ASD) (hereon Autism) treated with guided self-help or who received treatment as usual.

2.3 Secondary objectives

i) To determine the long-term effect of up to 9 sessions of treatment with GSH versus TAU at 16 and 52-weeks on:

   a) depressive symptoms

   b) quality of life

   c) anxiety

   d) positive and negative affect

   e) work and social function

   f) impact on carer (data will be collected in the Carer Sub-Study as detailed in Section 8)

   g) resource use/cost effectiveness

ii) To maximise the quality of outcomes by making interim measurements at 32 weeks on:

   a) depressive symptoms

   b) quality of life

   c) resource use

iii) To explore participants' and therapists' acceptability, experiences of, and adherence to, study processes and treatment, understand contextual factors for implementing the intervention, particularly in respect to retention of treatment principles.

iv) To determine the effectiveness and use of the intervention materials and training resources.

2.4 Primary endpoint/outcome

The primary outcome is the patient reported outcome measure (PROM) BDI-II depression score at 16-weeks post-randomisation. Table 1 (page 19) summarises the primary outcome and measure (tool) for this study.

2.5 Secondary endpoints/outcomes

Secondary outcomes are summarised in Table 1, below. Outcomes will be measured at 16-, 32- and 52-weeks post-randomisation. Consistent with low intensity treatment recommendations, depression and anxiety symptoms will be monitored on a session-by-session basis using the PHQ-9 (29) and

GAD-7 (32) for participants in the GSH intervention. See Table 3 for full details of trial assessments and time-points.

Table 1 Summary of primary and secondary outcomes and measures (tools)

Outcome	Tool / method
Primary Outcome	
To determine the difference in Beck Depression Inventory-II (BDI-II) depressions scores at 16-weeks between autistic adults treated with guided self-help (GSH) or received treatment as usual (TAU).	Beck Depression Inventory-II (BDI-II)
Secondary Outcome	
i) To determine the long-term effect of up to 9 sessions of treatment with GSH versus TAU at 52-weeks on:	-
a) depressive symptoms	BDI-II depression score and Patient Health Questionnaire-9 (PHQ-9) and Global Rating of Change
b) quality of life	EQ-5D-5L and study-specific questionnaire
c) anxiety	GAD-7
d) positive and negative affect	Positive And Negative Affect Schedule (PANAS)
e) work and social function	Work and Social Adjustment Scale (WSAS)
f) carer impact	Depression Anxiety Stress Scales (DASS) and Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)
g) resource use/cost-effectiveness	EQ-5D-5L (to calculate QALYs) and study-specific patient resource use questionnaire and Work Productivity and Activity Impairment (WPAI) Questionnaire
ii) To explore participants' and therapists' acceptability, experiences of, and adherence to, study processes and treatment to understand contextual factors for implementing the intervention, particularly in respect to participant retention of treatment principles	Qualitative interviews with participants and therapists
iii) To determine the effectiveness and use of the intervention materials and training resources.	Qualitative interviews with therapists and WAI-SR and goal attainment records

2.6 Primary outcome data

The primary outcome for this trial is BDI-II (30) score at 16-weeks post-randomisation as a continuous outcome. Use of a self-report measure eliminates the issues around inter-rater reliability of observer measures as encountered in the feasibility study. The BDI-II has been evaluated in terms of psychometric properties for use with autistic adults (33). The BDI-II is also advantaged by being constrained to the research protocol for the study i.e., not used routinely by low-intensity therapists throughout treatment. BDI-II will be measured at baseline, 16-, 32- and 52-weeks post-randomisation.

See Table 3 for full details of trial assessments and timepoints.

2.7 Secondary outcome data

Secondary outcome measures will include depressive symptoms on the PHQ-9 (29), a self-report global rating of change (34), anxiety (GAD-7) (32), positive and negative affect (PANAS) (35), work and social function (WSAS) (36), quality of life (EQ-5D) (37), impact on carer (DASS and WEMWBS) (38, 39) and economic evaluation measures in the form of questionnaire items about health care use and other resources. We will develop methods to measure treatment adherence in the intervention group (see section 9.5). There will be baseline measures of the instruments completed and repeated again at 16-, 32- and 52 weeks post-randomisation. To reduce burden of measurement for participants and improve quality of data at 52 weeks for economic evaluation, measurement at 32 weeks will be limited to the primary outcome measure, the self-report global rating of change, and health-care resource use.

3 TRIAL DESIGN

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

3.1 Project timetable

The funding start date for this trial is 01 September 2021, and the study duration is expected to be 46 months, to 30 June 2025.

3.2 Internal pilot

Following set-up, we will carry out an internal pilot study for six months. We aim to recruit 50 patients across the seven sites by the end of the 6-month pilot study (see Table 2). We will employ a traffic-light system to judge the success of our internal pilot. If we achieve at least 70% of our target for recruitment, then we will continue the study (Go - Green). If we are not reaching our 100% recruitment target, we will explore reasons for under recruitment and whether any modifications to recruitment processes are required dependent on the emerging recruitment rate trajectory. If we achieve between 50% and 69% (Amend - Amber) of our recruitment and/or have not commenced recruitment at any site, then we will discuss with our Trial Steering Committee (TSC) whether we should make any major changes to the recruitment strategy (e.g., additional centres) and discuss whether the study should continue. If we recruit less than 50% (Stop - Red) of our recruitment targets, then we will stop the trial, unless there is a strong case that unanticipated remediable factors have been identified and can be addressed after further discussion with the funder. In respect of criteria (3) engagement with GSH, (4) rates of retention to the study and (5) evidence of differential loss, we will present this information to the TSC at the end of the pilot phase and if there are any areas for concern for other criteria to be met, we will seek guidance from the TSC.

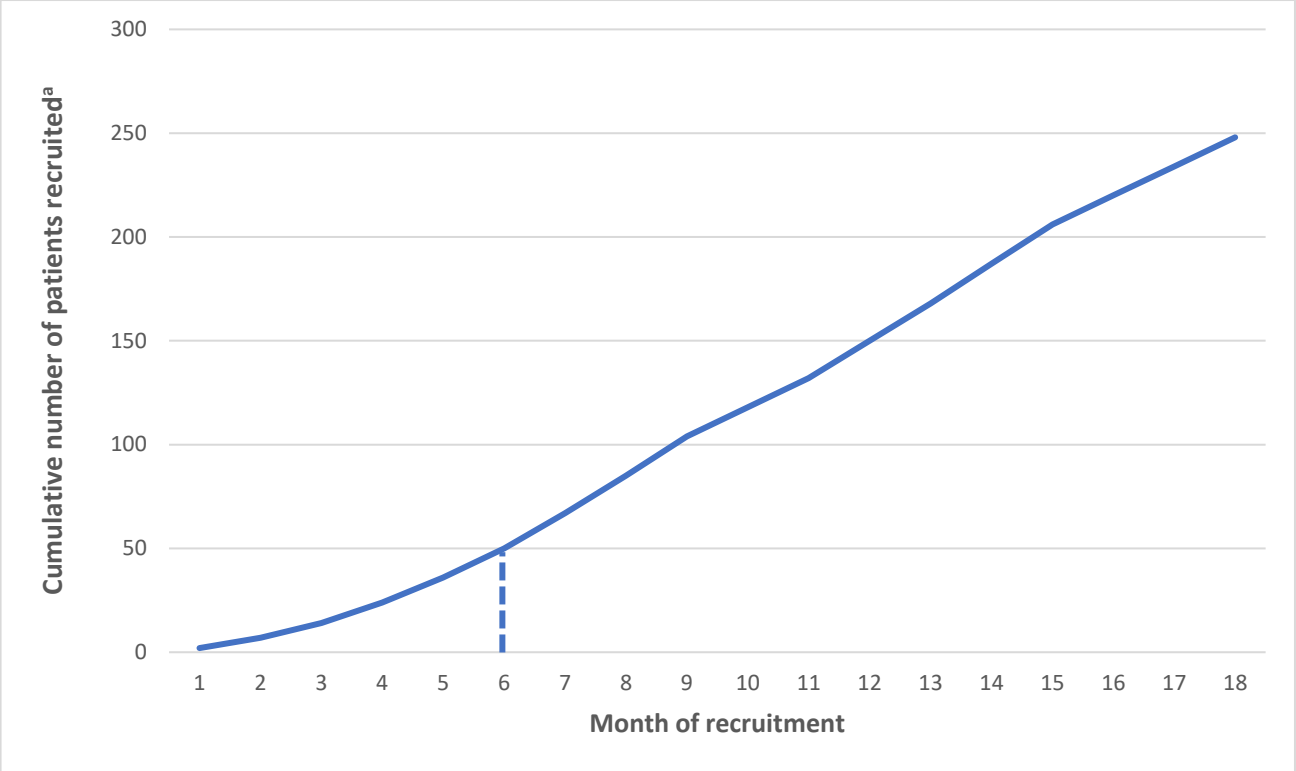
Table 2 Internal Pilot: Stop/Amend/Go criteria

	Criteria	Red	Amber	Green
1	Number of sites recruited over a 6-month period	<3	3-5	≥ 6
2	Number of participants recruited over a 6-month period (% of target = 50 participants)	<25 (<50%)	25-34 (50-69%)	≥35 (≥70%)
3	Number of participants allocated to GSH and engaging with intervention (% of target = 25 participants)	<13 (<50%)	13-17 (50-69%)	≥18 (≥70%) +
4	Rates of retention i.e., Number of participants remaining in the study at 4 months post-randomisation (% of those recruited and who have reached 4 months when assessing pilot data)	(<50%)	(50-79%)	(≥ 80%)
5	Qualitative evidence of differential loss to follow-up (based on the above criteria presented by study group to the trial steering committee).	No individual completing 4 - month outcome in one treatment group	Evidence of potential differential attrition by treatment groups (e.g., <30% retention at 4 months in one group)	No emerging evidence of differential attrition by treatment group

To assess criterion (3), engagement with the intervention will be defined as attendance at ≥50% of appointments scheduled since randomisation (for GSH participants only).

3.3 Planned recruitment rate

The planned recruitment for ADEPT-2 is 248 participants from (at least) seven sites; details about the trial setting are provided in Section 4. An 18-month recruitment period was originally considered sufficient to identify, contact and consent 248 eligible participants. The recruitment period was formally extended in February 2024 to complete the same month. In our recruitment progression estimates (Figure 2), we assumed that the seven centres noted in Section 3.2 would be recruiting by the end of the 6-month internal pilot phase.



[a]*Total expected recruitment is 248 over 18-months across the seven centres. Internal pilot study expected recruitment is 50 at end of month six of recruitment across the seven centres (as indicated by dotted line).*

Figure 2 Participant recruitment projections over 18-month period

4 TRIAL SETTING

This trial will be delivered through at least six regional centres in the UK.

The areas which initial sites cover are:

1) South West England - Avon & Wiltshire

2) North of England - Cumbria, Northumberland, Tyne and Wear

3) North East of England - Tees, Esk and Wear Valleys

4) East Midlands – Leicestershire

5) West Midlands - Coventry and Warwick

6) Wales – Cardiff & Vale

Within each region a variety of recruitment resources and strategies can be utilised. These include but are not limited to: cohorts/registries, mental health and/or learning disability service providers, social enterprises, primary care, University primary care/disability services, community organisations and charities. In addition, individuals can self-refer into the study. More information on participant identification can be found in section 6.4.

Additional centres/sites (including Patient Identification Centres (PICs)) will be identified if required.

5 ELIGIBILITY CRITERIA

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.

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

5.3 Exclusion criteria

- Risk of suicide - participants who endorse a score of 3 on Item 9 of the PHQ-9 will be followed-up by the lead clinical researcher on each site to assess suicidal risk. Where clinic assessment, baseline assessment or research follow-up is indicative that there is a current risk of suicidality such that a low-intensity intervention would not be clinically appropriate, this will be communicated to the relevant health care professional (e.g., referring ASD clinic and/or GP) and the participant will be excluded from the study
- Participants who report that they have attended > 6 sessions of individual psychological treatment within a CBT framework over the past 6 months will be excluded from the study
- 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. This will be established by reviewing the case notes for record of cognitive/educational assessment indicating significant literacy difficulties, on information provided by the referring clinician and/or during the eligibility assessment when it is difficult to gain consent to participate in the research because of difficulties reading and thus comprehending the study information sheet. We will strive to include all adults in the study if supporters are available to help an individual access the treatment where written/spoken English, non-English & Welsh presents a barrier

5.4 Co-enrolment in other research studies

Competing study: Co-enrolment in the ADEPT-2 study and another competing study (e.g., relevant RCT, interventional study such as STRATA NIHR127337) should be avoided due to potential impact on the study objectives and patient burden and safety. If a centre/site team become aware that a participant has enrolled in a 'potentially competing' study whilst taking part in ADEPT-2, they should inform the central research team University of Bristol (UniBristol) and University of Bath (UniBath). The research team will evaluate whether it is appropriate for the patient to continue participating in ADEPT-2. An interventional study for mental health will be considered a competing study.

Sites enrolling participants in ADEPT-2 and a competing study may be provided with guidance on how to offer studies to potential participants who meet the criteria for more than one study. This may include a joint invitation letter, which summarises the details of the studies they are eligible for and presenting eligible participants with the relevant patient information leaflets (PIL). This model of approach will empower potential participants to make an informed choice about which studies they may want to take part in. For potential participants who only meet the eligibility criteria for one study, only that study specific invitation letter and PIL will be provided

Non-competing study: If participants enrolled in the ADEPT-2 study express interest in enrolling in other non-competing studies (e.g., one-off interview(s) or questionnaire(s)) and informs their centre/site, the participant's centre/site team should advise that they consider factors, such as potential burden to them, social support and distances necessary to travel, before taking part. The decision to participate (co-enrol) in another non-competing study will ultimately lie with the individual (participant). If the participant's centre/site team become aware, they should inform the central research team (UniBristol and UniBath).

6 TRIAL PROCEDURES

Two hundred and forty-eight (248) patients will be recruited and randomised (enrolled) over an 19-month period. This section outlines the key trial procedures from identification of potential participants through to end of trial.

6.1 Schedule of trial assessments and outcomes (overview)

Table 3 (next page) depicts the key assessments/outcome measures and participant-related procedures scheduled at various trial timepoints. To summarise, participants in the trial will undergo:

- Identification and screening contact; detailed in Sections 6.4 - 6.6.
- Consent and randomisation (enrolment); detailed in Section 6.7.
- Assessments at baseline (0-weeks) and follow up at 16-(primary outcome), 32- and 52-weeks post-randomisation; detailed in Section 6.8.

Table 3 Trial assessments and key participant-related procedures

Data collection timepoint (→)	**Pre-randomisation**	**Point of randomisation**	**Post-randomisation**						
	Identification / Screening	**Baseline**	**1 – 15 weeks[A]**				**16-weeks**	**32-weeks**	**52-weeks**
Key data capture (measures) / trial procedures (↓)									
Screening	●								
Eligibility assessment	●	●							
Consent to join trial & randomisation		●							
Demographics		●							
Revised clinical interview schedule (CIS-R)		●							
Beck Depression Inventory-II (BDI-II) *(Primary Outcome at 16-weeks)*		●					●	●	●
Generalised Anxiety Disorder Assessment (GAD-7)		●					●		●
Patient Health Questionnaire (PHQ-9) (Depression symptoms)	●	●					●		●
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							●	●	●
Guided Self-Help sessions [A]			←	—	—	→			
Case report form(s) - Therapist records			←	—	—	→			
Working Alliance Inventory (Short Revised) (WAI-SR) [A] (therapist & participant rated)				●	●				
Goal attainment record [A]				●	●				
Qualitative interviews with patients [B]						←	—	→	
Carer Sub-Study: 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 caregiver. [A] Intervention arm only; [B] Months 6-12 Decline/ withdrawal Qualitative Interviews, Months 10-20 End of Treatment GSH participant Qualitative Interviews, 16-24 month TAU participant Qualitative Interviews (see Section 7).*

6.2 Identification and screening of potential participants (overview)

We endeavour to specify a broad range of recruitment pathways for each regional centre to ensure that the adult autism population is fully represented in the study. This section details the likely pathway for the following stages, which are then described in full throughout the remainder of this section of the protocol:

- **STEP 1**: Participant identification and invitation to participate;
- **STEP 2:** Expression of Interest (EOI) and preliminary (eligibility) screening
- **STEP 3:** Invitation to and preparation for the Baseline appointment;
- **STEP 4:** The Baseline appointment*.

To summarise, when potentially eligible participants are identified from any of the possible pathways (Step 1; e.g., clinical appointments and/or lists, research registers, self-referral etc.), they will be directed to an expression of interest form (EOI; online or paper copy where preferred; Step 2). The EOI form will ask the patient to indicate their preferred method of contact to discuss the study further; (a) online via email or video call, (b) by post or (c) via telephone call or text message. The EOI form can be completed by the individual and/or the health care professional referring them to the study. The form will ask a series of questions based on broad inclusion/exclusion criteria, including the items from the PHQ-9. Completed EOI forms are reviewed by the central research team, who may contact the patient for additional information using their preferred method (as above). Individuals for whom the study is considered suitable for them to take part, and they are interested in doing so, will be invited to attend* a Baseline appointment with a suitable participating site (Step 3). At the Baseline appointment (Step 4) the researcher will confirm eligibility, obtain informed consent, and complete any outstanding baseline data collection. Randomisation will be conducted after the site PI is satisfied that eligibility criteria has been met and sessions (if randomised to GSH) can commence. The researcher will arrange subsequent participant follow ups and, where applicable, the therapist will arrange the GSH sessions as per protocol.

> **As detailed in Section 6.7 (and Appendix 1), we anticipate that the majority of Baseline appointments (and other study points of contact) will be conducted via Sponsor/NHS-approved video-conferencing (i.e., to reduce risk of potential exposure to COVID-19 and/or due to a requirement for remote contact by the potential participant). Alternative methods of communication (e.g., face-to-face visits, and/or other remote methods) will be considered and facilitated, where feasible.*

6.3 Screening logs

Local research staff (e.g., RAs) should complete a screening log to record all potential participants screened for ADEPT-2. The ADEPT-2 screening log has been developed in line with the SEAR (Screened, Eligible, Approached, Randomised) framework (40); this framework will enable us to record the flow of potential participants through the recruitment process, in line with recommended Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines (41). Where possible, screening logs will record the reason(s) for non-participation. This will ensure that patients are not approached more than once, as well as highlighting those who are willing to be contacted again in the future (e.g., they were not able to participate when first approached but may be in the future, such as individuals who have attended psychological treatment for depression in preceding 6-months but could do so after 7-months).

It is acknowledged that full completion of screening logs will not be possible for all potentially eligible participants who receive information about the study. However, where a large number of individuals receive study information at the same time (e.g. a mailout via a local charity), this will be recorded as group activity within the screening log alongside an estimated reach size.

6.4 STEP 1: Participant identification and invitation to participate

Likely pathways to identify potential participants include: (a) clinical appointments and/or clinical lists; (b) research registers/cohorts; and (c) other methods, including self-referrals. For each of these, arrangements should be suitably established according to local practice, in discussion with the central research team (UniBristol and UniBath). Centres/sites may also identify other opportunities and methods for identifying individuals and inviting them to take part, which should be utilised. Where applicable, sites should follow their local Trust policies to adhere to the National Data Opt-out.

Individuals identified as potential participants will be sent, by email or post, an ADEPT-2 Study Invitation Pack; this pack will contain at least the study approved invitation letter and Participant Information Leaflet (PIL) including contact details of the local centre research team. The information will contain instructions of what to do if they would like to find out more information or are interested in taking part (i.e. complete an online ADEPT-2 Expression of Interest Form, or, if applicable, paper equivalent using a pre-paid envelope). Alternatively, they may be directed to the study website containing an equivalent Study Invitation Pack for online review if preferred. Other documents will be made available via the website or as requested: a link to the Privacy Notice (containing Health Research Authority (HRA) approved information on data protection and legislation); a list of Autism Support and Mental Health Helplines

Central research staff will monitor completion of the Expression of Interest Form. Where feasible, local (recruitment) research staff will contact individuals who were provided with materials but have not yet responded, to see if they would like to take part. If so, they will be directed to the online (or paper equivalent) ADEPT-2 Expression of Interest Form.

> ***NB:*** *Where the study information pack is sent via email, key documents (e.g. PIL) will be attached to the email. Individuals will be directed to the study website where the remaining supporting documents can be viewed (e.g. privacy notice).*

6.4.1 Clinical appointments and/or lists

Potential participants will be identified within the trial centres/sites by clinical services staff, Clinical Research Network (CRN) or Research and Development (R&D) department staff. This can be done within the context of a clinical appointment or by review of clinical lists.

Within clinical appointment: Clinical staff may discuss the study with individuals during a consultation and complete a paper Expression of Interest form with the individual, and an ADEPT-2 Clinical Referral Form. These documents will initially be given to the local research team (to update their local screening log) and then to the central research team for entry into the study database. Clinical staff may also provide individuals with an ADEPT-2 Study Invitation Pack (paper/online link, as described above) for them to complete themselves.

Clinical teams can also pass on information about potential participants to the local or central research team verbally or via secure email. All discussions about the study with potential participants will be recorded in the participant's medical records by their direct care team.

By review of clinical lists: Individuals identified from clinical lists as potential participants will be sent, by email or post, an ADEPT-2 Study Invitation Pack (paper/online link, as described above).

> ***NB:*** *In light of COVID-19, we are mindful that face-to-face in person appointments bring about higher risk and may not be feasible. To mitigate such risks, ADEPT-2 offers flexibility around assessment and communication methods as noted throughout including face-to face videocall (and see Appendix 1). If face-to-face in person appointments are requested, research staff should assess feasibility and follow the organisation guidance at the time regarding face-to-face contact, including, for example, use of personal protective equipment (PPE) and cleaning procedures.*

6.4.2 Research registers / mailing lists

Where relevant, we will seek approval from the steering committee (or equivalent) of relevant research registers/mailing lists to inform individuals about ADEPT-2. For example, these may include the Adult Autism Spectrum Cohort - UK (AASC-UK) (42) and the Discover Network (Autistica Charity, UK) (43). Other relevant registers/mailing lists that are not listed here may also be approached.

Potential participants who are registered on such a register/mailing list will be sent information about the trial. This may be via an email/postal newsletter which directs interested individuals to the study website for further information, or by providing an ADEPT-2 Study Invitation Pack (as described above). Where feasible, one follow-up reminder can be sent if no reply is received after 2 weeks.

6.4.3 Self-referrals and other methods

Approved ADEPT-2 recruitment materials (e.g., posters, leaflets, electronic animation/video and/or equivalent materials) may be displayed in relevant locations, providing information about how an individual can obtain further information, contact the study team and express and interest to take part by completing the EOI form (see section 6.5) . Equivalent information may also be promoted via relevant social media and traditional media resources (e.g., twitter, websites, press-releases).

Using similar approaches as noted above, we will engage with the NIHR CRNs which cover the UK recruiting centres to disseminate the opportunity to participate in ADEPT-2 to members in their regions. We will also engage with various community organisations including charities, third sector providers of support services and university disability services. Information (e.g., approved posters and leaflets or emails with study weblink) about the study may be provided to local organisations, University disability services and GP surgeries to supplement recruitment from these sources.

6.5 STEP 2: Expression of Interest (EOI) and preliminary (eligibility) screening

The aim of the EOI form is to ask individuals, with/without the support of clinicians, a series of questions based on broad study inclusion/exclusion criteria as a means of preliminary screening (eligibility assessment). For example, questions will include (at least): PHQ-9; whether the individual has an autism diagnosis (for potentially eligible self-referring participants, confirmation of Autism diagnosis should be provided via sharing a letter/document from Autism services or GP confirming the clinical diagnosis with the research team at baseline). Name, date of birth and contact details are also collected to enable the study team to contact (via phone or email, as per their preference) the potential participant to further clarify their eligibility, inform them about their eligibility status and, should they be deemed potentially eligible, assign them to an appropriate site (this will usually be based on their geographical location). Personal details will only be held for the minimum required time for those found to be ineligible.

Entry of the EOI form within the study database (from the weblink or entry from the paper equivalent) will allocate a screening ID to the individual. The central research team will monitor receipt of completed forms, conduct the initial eligibility screen* and contact potential participants to further understand their eligibility if anything within the EOI form is unclear e.g. to gain a better understanding of the type of therapy they have received.

** The central research team may handover some or all of the eligibility assessment to local research teams dependent on capacity. This will be discussed and agreed with the local research teams if necessary.*

If responses to EOI form questions do not meet the necessary trial criteria: the individual is deemed ineligible for this trial and will be notified of this outcome, e.g. via telephone or using the Eligibility Assessment Outcome Letter (or email equivalent)*. They will be thanked for their time and interest in the trial. No further data about the individual will be collected unless they give consent to be contacted by a qualitative researcher for an interview. The central research team responsible for processing the EOI forms (online and paper), will update local research teams so they can update their local screening logs where feasible.

If responses to EOI form questions meet the necessary trial criteria: the individual is potentially eligible to take part and will be notified of this outcome. The potential participant will be asked to confirm that they still wish to participate; this notification may be via an approved letter or alternative methods (e.g., email/video-conferencing/phone) depending on the individual's contact preferences and/or availability. Potentially eligible participants are assigned to one of the participating sites and will be allocated a unique study identification (I.D) number.

** Some individuals may be willing to be contacted again in the future (e.g., they were not able to participate when first approached but may be in the future, such as individuals who have attended psychological treatment for depression in preceding 6-months but could do so after 7-months). In these circumstances, local logs containing their details will be retained but their identifiers will be removed from the study database. A new EOI will need to be completed when re-approached.*

6.6 STEP 3: Invitation to and preparation for the Baseline appointment

The flow for potential participants from this point is summarised in Figure 1. Local research teams should review the EOI form and supporting information for newly assigned potential participants (e.g. to check eligibility status, for example whether confirmation of their autism diagnosis has been received). Local research staff will invite potential participants to attend a Baseline appointment at a convenient time and location, making note of any accessibility needs or reasonable adjustments to be made to facilitate this appointment. The researcher will inform individuals that prior to the appointment (no more than 3-days in advance), they will receive the ADEPT-2 Baseline Questionnaire via secure online link(s). Hard copies* can be posted upon request, which will include clear instructions about when to complete and return the questionnaire booklet. If the baseline questionnaire has not been completed (and/or hard copies returned) by the time of the appointment, they can be completed during the Baseline appointment. The baseline questionnaire should also be reviewed for any potential suicide risk. The purpose and details of the Baseline appointment are outlined in Section 6.7, below.

**The Revised Clinical Interview Schedule (CIS-R)(44) is only available as a computer-based (online) assessment. All other questionnaire outcome measures will be incorporated into one ADEPT-2 Baseline Questionnaire, which will be available online or in hard (paper) copy if required.*

If for any reason the individual has changed their mind and no longer wishes to participate, for research monitoring purposes, the researcher will: (1) ask 'why', however the patient does not have to provide a reason if they prefer not to; (2) update the local screening log and study database

accordingly (their identifiers will be removed from the database); (3) ask whether the individual is happy to be contacted by a qualitative researcher for an interview. Where applicable, all data obtained with reference to the integrated qualitative research (see Section 7) will be retained according to the relevant patient information and separate consent.

6.7 STEP 4: The Baseline appointment

Potential participants will attend a Baseline appointment*. On arrival, the aim of the appointment will be explained (in summary; the baseline questionnaire will be fully completed (if necessary). Eligibility criteria will be reviewed for any changes since last contact, the trial explained; individuals will be able to ask any questions and asked whether they need any further information). Individuals will be offered breaks during this appointment to minimise fatigue and burden. If they require assistance to complete the questionnaires, the researcher can facilitate this. Similarly, a carer/family member or friend can also join the appointment to provide support. The research team will aim to try and make all reasonable adjustments requested by the participant to facilitate this appointment.

6.7.1 The Baseline questionnaire

If the Baseline questionnaire has not yet been fully completed (and/or hard copies of the questionnaire not returned), they should be completed during this appointment. The Baseline questionnaire is fully completed at this stage to fully be able to ascertain eligibility (e.g. risk of suicide). If the Baseline questionnaire was completed more than a month prior to the appointment date (e.g. due to appointment rescheduling) then the questionnaire should be repeated in full.

6.7.2 Confirmation of eligibility

Eligibility criteria will be fully reviewed for any changes since the EOI form was completed. Of note, if a period of more than one month has passed between completion of the EOI form and attendance at the Baseline appointment, the PHQ-9 will be repeated verbally during the appointment. Eligibility will then be provisionally confirmed, and the trial explained; individuals and their carer/supporter will be able to ask any questions.

During this baseline discussion, the researcher will check that individuals are fully informed about the study by asking them to: (a) summarise their understanding of what participating in the study will involve; (b) enquire about the voluntary nature of their involvement; and (c) ask what will happen if they no longer wish to take part. This will enable the researcher to check that they have understood and retained key aspects of the information provided about the study and are aware of the voluntary nature of their involvement and their right to withdraw.

> **As previously noted, (and outlined in Appendix 1), we anticipate that the majority of Baseline appointments (and other study points of contact) will be conducted via Sponsor/NHS-approved video-conferencing (i.e., to reduce risk of potential exposure to COVID-19 and/or due to a requirement for remote contact by the potential participant). Alternative methods of communication (e.g., face-to-face visits, telephone, email and/or other remote methods) will be considered and facilitated, where feasible.*
>
> *If face-to-face appointments are requested, research staff should assess feasibility and follow the organisation guidance at the time regarding face-to-face contact, including, for example, use of personal protective equipment (PPE) and cleaning procedures.*

Once the researcher is satisfied that full eligibility criteria have been met: they can proceed as outlined, below. At this point in the recruitment process, potential participants will have been given a

chance to ask questions and have had more than 24-hours (after receiving the trial PIL) to think about taking part, before providing informed consent and being randomised.

Those who do not meet the full eligibility criteria, or those who are eligible but decline to take part: in such cases the researcher will not proceed with receiving informed consent, nor enrolling in the study. If the individual completed a baseline questionnaire on paper prior to this visit, the researcher will securely destroy these data (in accordance with Sponsor requirements). Personal identifiers will be removed from the study database. The researcher would offer the individual a £10.00 gift voucher to thank them for their time (see Section 6.10), but no further appointments will be made regarding this study, unless the individual consented to be contacted by a study researcher for an interview to explore their views on the study. Where possible, reasons for declining to take part will be recorded.

6.7.3 Consent (main trial)

Delegated staff at sites who are trained on the ADEPT-2 protocol and procedures, and have relevant experience, will be able to receive informed consent. This will include local research associates/assistants, clinicians and CRN staff or other suitably trained staff within each centre/site.

Within the consent process, consent will also be sought for future re-contact and sharing of their anonymised data for other ethically approved studies. Consent will also be sought for details of the participant to be shared with the qualitative researcher so that they can be approached about taking part in an interview. Full details of the integrated qualitative research is discussed separately; see Section 7.

To enable remote and/or face-to-face methods of contact, where feasible, informed consent will be captured via compliant eConsent (online) form and process. An approved paper (wet ink) equivalent will be available where eConsent is not feasible. Further guidance will be provided in study-specific training materials. Four copies of the completed consent form are required:

1) a copy must be filed in the Investigator Site File (ISF) together with a copy of the PIL in recruitment order*;
2) a copy should be provided to the patient*;
3) a copy should be placed in the patient's medical notes with a supporting record of the discussion and a copy of the PIL**; and
4) a copy should be provided to the ADEPT-2 central research team (via the study database).

**If a paper (wet ink) form is completed, the 'original' form should be filed in the ISF. If an eConsent form is completed, a completed copy is automatically emailed to the patient once processed, and additional copies can be obtained via the eConsent (database) system.*

***Besides completing the consent form, centres/sites should record key details of the informed consent process in the patient's medical notes (where feasible); study title and date of consent are on the consent form. Patients are not required to provide reasons for not taking part in the study, but if they are given, then they should also be documented in their notes. For non-NHS recruitment sites without direct access to patient medical notes, a copy of the consent form and supporting information should be sent to the patient's GP alongside the GP Notification letter.*

6.7.4 Further baseline assessments

Following consent, if the necessary baseline assessments identified in Table 3 have not yet been completed, they should be completed at this stage. For example, the Clinical Interview Schedule (CIS-R)(44), which is only available as a computer-based (online) assessment.

6.7.5 Carer involvement

Participants will be asked if they have a carer and if so, whether they would be happy to share with them a Carer Invitation Pack (containing, as a minimum, the Carer Invitation Letter and Carer Participant Information Leaflet). Carers will be recruited in parallel to explore carer impact in a nested sub-study; full details are provided in Section 8 and Table 3 depicts timings of data collection. It is up to the ADEPT-2 participant to define who their carer is; where feasible, it would be one carer who knows them well and is likely to continue caring for them over the 52-week trial period. The carer will be approached only with the agreement of the participant and consented separately. The participant is still able to participate in the trial if their carer does not wish to participate, or if there is no carer. Similarly, the carer can continue involvement if the participant withdraws from the main trial.

6.7.6 Principal Investigator (PI) confirmation of eligibility

At this point, the researcher has completed the eligibility assessment/review, received informed consent and undertaken baseline data collection, thus deeming that it is suitable for the individual to take part in this trial and they are willing to do so. It is essential that the researcher now seeks approval from the site PI, or delegate, to proceed to randomisation (enrolment)*.

If the PI or delegate is satisfied that eligibility criteria have been met and sessions can commence: they (the PI and/or delegate) will proceed with randomisation (as detailed in Section 6.7.3, below).

If the PI or delegate is not satisfied that eligibility criteria have been met and sessions cannot commence: the researcher will notify the individual that it is not suitable for them to take part in the study and update study records, as required. This includes: updating the study database so that the central research team can securely destroy any identifiable data (in accordance with sponsor requirements). A copy of their consent form, however, should be retained in the ISF and patients' medical notes alongside a Change of Participation Status form.

**In some circumstances it may be feasible to arrange for randomisation to take place 'there and then' (i.e., in a clinic setting). It may, however, need to take place separately (i.e., if appointments are conducted remotely, or the local PI is not available); in such cases, the researcher should explain this to the individual (patient), making clear that they will notify them of the outcome as soon as available. This notification may be via telephone/video-call or an approved letter (or email equivalent), depending on participant contact preferences and/or researcher availability.*

***If the patient (individual) has confirmed that they have a carer, the researcher should offer to provide them with an ADEPT-2 Carer Study Information Pack. The individual will be asked if they are willing to forward this to their carer at the earliest opportunity, on behalf of the ADEPT-2 research team.*

6.7.7 Randomisation

Individuals will only be randomised after: (a) informed consent (wet ink or eConsent) has been obtained; (b) baseline assessments have been completed; and (c) eligibility is approved by the local recruiting site PI, or authorised delegate (e.g., "Researcher").

The randomisation sequence will be generated by Sealed Envelope™ (45) and randomisation will be conducted via the study Redcap database. Randomisation will be stratified by centre, depression severity as captured by baseline BDI-II score and prescription of anti-depressant medication. Patients will be randomised to one of two treatment groups on a 1:1 ratio, that is either GSH (intervention arm) or TAU (control arm).

The local PI (or authorised delegate) will sign into the secure online randomisation system, find the individual's (patient's) unique record and enter the necessary minimisation variables; they will then receive the code that allocates the participant to one of the two study groups (GSH or TAU). The allocated therapist will be informed of participants allocated to GSH by the local research team. The unblinded randomisation code will be held by selected members of the Bristol Trials Centre (BTC; see Sections 6.14 and 12.2). Details of the study intervention (GSH) sessions are detailed in Section 9.

6.7.8 End of Baseline appointment / post-randomisation requirements

Following completion of the Baseline appointment (once final recruitment outcome of the individual is known, i.e., randomised or not), the local recruiting centre/site staff should:

1) update the local screening log with the relevant screening outcome;

2) enter any paperwork to the secure online study database (where applicable) and file all paperwork securely (see Section 12, Data Management);

3) ***For all randomised participants:***

a. notify the participant's GP that their patient is taking part in the ADEPT-2 trial, using a study-approved ADEPT-2 GP Notification letter.

b. Let the participant know when their follow up questionnaires are due (and arrange dates if they have requested in-person follow up). As advised by our patient advisory group, arrangements should include: confirming the date and times of the follow up; confirming participant contact details, including methods of contact and any other preferences; and providing the researcher's contact details, including any relevant telephone numbers/caller I.Ds/email address', where applicable. This process allows the participant to plan, knowing who to expect contact from, when and by which method.

c. provide the participant with additional information and materials in the form of an ADEPT-2 Welcome Information Pack, which will either be posted, or provided in person (depending on how the appointment is conducted). Some of the information may also be available via email, or downloadable via the study website. The ADEPT-2 Welcome Information Pack will include (as a minimum):

i. Information about what to expect from GSH sessions or TAU;

ii. An ADEPT-2 Carer Study Information Pack**; as detailed in Section 8.

4) ***If randomised to the intervention group***: the PI or researcher will complete and submit the study-specific referral form to the therapist to initiate the GSH process (see Section 9).

5) ***If randomised to the treatment as usual group***: the PI or researcher should arrange a follow up call for approximately 2 weeks post randomisation, to check that the information about the outcome of randomisation has been received and to answer any questions that the participant may have. For example, if the participant is unsure about how to access TAU services, the PI/researcher can provide further clarification about the information that has been provided. This phone call is also an opportunity to provide further information about the research study and next steps if the participant has questions.

6.8 Follow-up assessments

6.8.1 Follow up assessments: 16-, 32- and 52-weeks post-randomisation

Follow up questionnaires (participants): Participants will be asked to complete an ADEPT-2 Follow Up Questionnaire at each timepoint; each questionnaire will contain PROMs and additional data collection as presented in Table 3. Participants will be asked to complete the questionnaires online and will receive a secure online link at the appropriate timepoints. Alternative methods preferred by the participant will be considered and facilitated where feasible (e.g., by video call (using Sponsor/ NHS-approved video-conferencing tools), postal hard copy, face-to-face, or telephone). If the participant requires assistance to complete the questionnaires, the research team will aim to try and make all reasonable adjustments requested by the participant to facilitate this. Similarly, a carer/family member or friend can provide support, but they will be advised not to answer any questions on behalf of the participant.

Local research staff/teams are responsible for the conduct and monitoring of these follow ups. If they do not receive a response from a participant within a reasonable time of sending each ADEPT-2 Follow Up Questionnaire (e.g., ~3 weeks), then they will contact them according to the participant's stated preferences. At the minimum this will include resending another link/copy with a reminder letter/equivalent contact. For each follow up timepoint, where the participant's preference is paper, the research team will make three contact attempts in total (initial sending, plus two reminders). If the participant's preference is to complete the follow up online, we will allow an additional two contacts from the research team to allow for emails being missed or going to junk mail. If no response is received after the third attempt, the relevant questionnaire will be marked as missing. We will, however, continue to send the next follow up questionnaire as planned, unless the participant requests/confirms that they no longer want to complete them; a similar model has been successfully used in multiple studies conducted by the BTC.

The 16-week post-randomisation follow-up (questionnaire) is the primary outcome end point.

The 32-week post-randomisation follow-up (questionnaire) will be limited to the BDI-II measure, the self-report global rating of change, and health-care resource use.

The 52-week post-randomisation follow up (questionnaire) is the final timepoint and marks the end of participant involvement. The same reminder system noted above will also apply here, where applicable.

Site teams should monitor the completion of study questionnaires to check for increased risk or adverse events (see safety reporting section for further information). Site teams may be required to further investigate any safety risks with the participant.

6.9 Qualitative assessments

The integrated qualitative research is detailed in Section 7, below. Table 3 also depicts timings of data collection.

6.10 Thanking participants for their involvement (payments)

Upon receipt of completed questionnaire booklets at Baseline, 16-, 32- and 52-weeks post-randomisation (or at least provision of key data, e.g., BDI-II, GAD-7, PHQ-9 and EQ-5D-5L), the central research team will offer participants a £10.00 gift voucher (i.e., £10 per time-point, up to £40 in total per patient/participant over the 52-weeks duration of the study). Participants will also be sent

newsletters telling them about the study, including progress and results once available. Section 16 provides further details about dissemination.

In addition, participants and therapists will receive a voucher for £15 for taking part in a qualitative interview. Participants who decline or withdraw from the study will receive a £10 voucher for taking part in a qualitative interview.

6.11 Methods/ procedures to protect against other sources of bias

6.11.1 Loss to follow up (attrition bias)

We have had extensive consultation with our advisory group and incorporated various suggestions to ensure the study is acceptable to potential participants. We will take active measures to minimise loss of participants from the trial in line with ethical and regulatory approval. This may include, for example:

- reminders to participants developed according to individual preference (e.g., post/ email/ video call (using Sponsor/NHS-approved video-conferencing tools)/ text/ telephone);
- ability to complete questionnaires via their preferred method (e.g., online/ post/ telephone/ video call (using Sponsor/NHS-approved video-conferencing tools)/ face-to-face);
- obtaining back-up 'best contact' addresses (including carer/ other family member, where applicable);
- contacting their GP (practice) to check their contact details on record are still valid; (46) and
- using vouchers as retention incentives (47).

In addition, we may access centrally held health data, for example via the NHS Strategic Tracing Service in England and Wales, to find new addresses.

We have extensive experience of using the above strategies and measures and have received Ethics approval to do so in previous studies.

6.11.2 Measurement bias

Validated questionnaires for PROMs will be used to minimise the possibility of measurement bias.

6.11.3 Other sources of bias (detection bias)

All analyses will be clearly pre-defined in the Statistical Analysis Plan (SAP), which will be reviewed and approved by the study TSC and made publicly available prior to the end of follow-up to avoid bias.

6.12 Usual Care – Treatment as usual

This is a pragmatic trial and Treatment as usual will continue without restriction, including referrals to psychological therapies, such as NHS Talking Therapies for anxiety and depression (NHSTT) (formerly Improving Access to Psychological Therapies (IAPT) services) (48). GPs/clinicians can also prescribe medication as necessary.

6.12.1 Measuring treatment as usual

TAU will be measured via health and service resource use questionnaires at 16, 32 and 52 weeks post-randomisation.

6.13 Managing potential risks to participants

The PHQ-9 measure will be completed at each timepoint, including at each GSH session for intervention participants. Participants receiving GSH will also be followed-up by the therapist at each session to check their depressive symptoms are not worsening. A risk protocol outlines the procedure to follow if a therapist is concerned about the risk of depression symptoms such as increased suicidality.

Details of what a participant should do if they experience any problems whilst taking part in the trial are detailed in the ADEPT-2 PIL and Welcome Pack. Participants will be provided with contact details of their local research centre/site team and for the central research team.

If a symptom is troublesome (as explained in the PIL) participants are advised to seek medical help in the normal way (e.g., dialling 111 or contacting their GP). In an emergency they should phone the emergency services or attend an Emergency Department. There will also be information about helplines participants can choose to access for mental health support 24/7.

6.14 Blinding

The Trial Management Group (TMG) will be blinded to the allocation of treatment group, except for one of the two trial statisticians and trial/data managers from the University of Bristol (UniBristol), trial therapists and supervisors of trial therapists. Two statisticians based at the UniBristol will support this trial. The senior (lead) statistician will be blinded throughout the trial. The second trial statistician will perform all disaggregated analyses according to a pre-specified SAP and will attend closed Data Monitoring Committee (DMC) meetings as required. In addition, the health economist(s) (UniBristol) will be blinded when cleaning data and preparing the analysis plan, but unblinded when conducting the analysis. Clinicians (PIs), other researchers and site staff will not be blinded.

6.15 Unblinding

Central research team(s): The lead statistician and health economist(s)will be unblinded once written confirmation has been received that the trial database has been locked. Any incidents of unblinding before the trial database has been locked will be recorded by the central research team.

6.16 Withdrawal from the trial (or change of permissions)

Participants can choose to withdraw for any reason at any time during their involvement in the trial. Participants can withdraw from: (a) attending study GSH sessions; and/or (b) providing questionnaire data to the trial, at any time for any reason without affecting their Treatment as usual.

Risk of suicide may increase during the study as evidenced by session-by-session administration of the PHQ-9 for those in the GSH group. The PI or suitably trained staff member can decide to withdraw participants based on clinical opinion at any time during the trial; a likely scenario might be withdrawing them from attending GSH sessions. This may be due to safety concerns or worsening symptoms. If increased risk is identified following review of the case in clinical supervision, the therapist and clinical supervisor will discuss whether referral to statutory health services is required. The participant will more than likely be discontinued from treatment but can remain in the study to receive follow-up questionnaires if appropriate. Trial specific instructions will be provided to PIs for withdrawal criteria and procedure.

In all cases, efforts will made to report the reason(s) for withdrawal/change of permissions in an ADEPT-2 Change of permissions/Withdrawal form. If a participant who has attended at least one

study GSH session wishes to withdraw from attending any further sessions, efforts will be made to continue to obtain follow up data, with the permission of the patient or family as appropriate (including access to medical notes / databases). The study would also retain, confidentially, any data collected up to the point of withdrawal for analysis, as advised in the PIL.

6.17 End of trial

Participant: The participant ends their involvement with the trial when their last follow up questionnaire is completed and returned (or they have withdrawn from the study).

If they are in the intervention arm their GP will be notified that they have completed their treatment phase (and the primary outcome has been completed).

Trial: The end of trial for ADEPT-2 will be when the last patient has completed their 52-week (12-month) post-randomisation follow-up (which includes completion of the 52-week questionnaire), all data queries have been resolved and the database has been locked, with subsequent data analysis completed.

All participants will remain under care of GP throughout the trial, regardless of their study arm assignment.

6.17.1 Trial stopping rules

The trial may be prematurely discontinued by the Sponsor, Chief Investigator (CI), ethics committee or Funder based on new safety information or for other reasons given by the DMC / TSC or ethics committee concerned.

The trial may also be prematurely discontinued due to lack of recruitment or upon advice from the TSC, who will advise on whether to continue or discontinue the trial and make a recommendation to the Funder. If the trial is prematurely discontinued, no new participants will be recruited, and a decision on data collection on active participants will be made in discussion with the TSC/DMC and Sponsor.

7 INTEGRATED QUALITATIVE RESEARCH

7.1 Integrated qualitative research – experiences and acceptability of study and treatment

We will examine the views and experiences of both the intervention and the trial by conducting in-depth qualitative interviews with a sample of participants and local research staff. Qualitative findings will identify factors that may impact upon the intervention acceptability and effectiveness. The qualitative process evaluation will aim to understand 'what works for whom in what circumstances, when and why?' and 'what are the contextual factors that impact upon this?' This examination of factors involved in intervention delivery is critical to identify any facilitators and barriers that may impact on the success of the trial, or if successful, impact on the intervention uptake outside of the trial to improve implementation.

All participants in the trial will be asked if they are willing to be contacted about taking part in an interview at the time of trial consent. Interviews will be conducted with a sample of trial participants (from both arms of the trial), by telephone or online (using University of Bristol approved secure platforms MS Teams or Zoom). Interviews with GSH participants and therapists at 16 weeks will examine acceptability and experiences of the trial and intervention and identify contextual factors that impacted on implementation and effectiveness. GSH Participant interviews will also investigate recall of treatment principles and enable an in-depth examination of the role of the intervention in any perceived change, informing how successful the intervention is beyond symptom measurement. TAU participants who have psychological therapy will be interviewed to examine their experiences and compare with those of intervention arm participants. Finally, telephone/online interviews will be conducted with a sample who decline trial participation or withdraw to investigate reasons and rapidly provide feedback to advise retention efforts. Purposive theoretical sampling will ensure diversity in demographic characteristics. Sample size will be determined by data saturation (49), with interviews analysed in batches, and sampling continuing until no new themes are emerging from the interviews. We anticipate that up to 40 participant, 10 therapist and 15 decliner/withdrawal interviews will achieve this aim.

Qualitative methods have been chosen as the most appropriate means to achieving a deep understanding of beliefs and perceptions of key medical events (50, 51). Interviews allow for the exploration of complex and sensitive issues, allowing participants to engage in a dialogue in their own language and drawing on their life experiences to explore the issues which are of importance to them. Integrating qualitative methods within controlled trials has long been advocated (52). Such use of qualitative methods in randomised controlled trials, specifically as a means to investigate the experiences of participants receiving, and staff delivering complex interventions is well established (53) and recommended.

7.1.1 Patient consent

Information about patient interviews is provided in the main study PIL. On the main trial Consent Form, participants will be asked if their contact details can be passed on to a study qualitative researcher to contact them about an interview to explore their views on the study. They may agree to this even if they decline trial participation. Participants who consent to this may then be approached by the qualitative researcher who will explain more about the interview, answer any questions, and, if they agree, arrange a convenient time and preferred method (e.g., phone/video) to conduct the interview. Participants will be provided with a consent form to read ahead of the interview. As most interviews will

be conducted remotely, verbal consent for participation in the interview will be obtained from participants before the interview starts. Verbal consent will be obtained from a GCP trained researcher and audio recorded. This will involve the researcher reading out standard consent form statements and if appropriate, the participant verbally agreeing to them. To reduce burden on the participants, verbal consent for the qualitative interviews will not be followed up with written consent. Verbal consent at the time of the interview also ensures the participant understands what is involved and is happy with taking part in the interview at that time. The audio recorded excerpts will be retained for auditing purposes in line with trial archiving policies.

7.1.2 Therapist consent

Therapists will be informed about the interviews through the therapist interview information sheet. Consent for the interviews will be obtained by the qualitative researcher verbally using the same process outlined for Participants (as above)

Members of the Integrated Qualitative Research team where relevant, will be responsible for obtaining appropriate consent for the interviews and maintaining suitable records.

7.2 Analysis of integrated qualitative research data

A flexible topic guide, developed in consultation with our Patient and Public Involvement (PPI) contributors, will be used to assist questioning during interviews. With informed consent, interviews will be recorded (using an encrypted audio recorder for telephone interviews or the secure university approved online platform MS Teams or Zoom), fully transcribed, anonymised, checked for accuracy and imported into NVivo qualitative data analysis software to aid data management. Thematic analysis (54), utilising a data-driven inductive approach, will be used to scrutinise the data in order to identify and analyse patterns and themes of particular salience for participants and across the dataset using constant comparison techniques (55, 56). Analysis will begin shortly after data collection starts, will be ongoing and iterative. Analysis will inform further data collection: for instance, analytic insights from data gathered in earlier interviews will help identify any changes that need to be made to the topic guide during later interviews. The qualitative team will independently analyse a proportion of transcripts to assess the dependability of coding and meet regularly to review coding and descriptive findings, agree further sampling, and discuss theoretical development – all in close collaboration with the CI and the wider study team.

Results from the integrated qualitative research will help to understand how adults with autism accept and experience an RCT and treatment (GSH or TAU) for depression.

7.3 Data management, protection and patient confidentiality in relation to the qualitative research data

Recordings of interviews will be held on an encrypted digital recorder (or alternative secure device/mechanism, including Sponsor/NHS-approved video-conferencing tools) and regularly transferred to the University of Bristol through approved secure data transfer facilities and/or encrypted memory card/flash drives that adhere to NHS Trust policies. If a video-conference platform is used to record discussions, only the audio file will be downloaded and retained for analysis. Interview data captured on audio-recorder will be transferred to a secure server hosted by the University of Bristol as soon as possible after each interview.

Recordings will be transcribed by University of Bristol employees or University approved transcription services. The transfer of recordings and transcripts will adhere to the secure transfer of

recordings/transcripts procedure specified by the University. Transcripts will be labelled with a study I.D number, edited to ensure anonymity of respondents and stored securely adhering to the University's data storage policies. With consent, anonymised quotations and parts of voice modified recordings may be used for training, teaching, research and publication purposes for this and future studies. With consent, anonymised transcripts may be made available by controlled access to other researchers who secure the necessary approvals for purposes not related to this study.

7.4 Safeguarding patients during qualitative research

We will ensure that participants are not subjected to undue distress during the qualitative component of the trial. To mitigate this, and the possibility that participants may disclose information to provoke concern about risk, the interviewer will be an experienced qualitative researcher who will adhere to the following:

Participants will be informed that the interview is strictly confidential, but should they disclose information to suggest that they or others are at significant risk of harm, the interviewer will discuss this with a clinical advisor and may need to disclose these details to the designated safeguarding authority. Should participants become upset or distressed during the interview the researchers will follow a distress protocol (see Appendix 2). The interview will only continue if participants are happy to proceed and engage with the interview topic. If the researcher feels a participant is becoming distressed, they will ask the participant if they wish to have a break or discontinue the interview and will offer support. Participants will also be offered a leaflet with the contact details of support networks.

8 EXPLORATION OF CARER IMPACT

8.1 Objective and outcome measures

To determine the impact on carers of treatment with guided self-help versus treatment as usual for depression for autistic adults at 16 and 52 weeks.

Carers will be asked to complete an ADEPT-2 Carer Impact Questionnaire at Baseline, 16- and 52-weeks post-randomisation of the ADEPT-2 (main trial) participant. The baseline timepoint may be different from the baseline of the randomised patient due to the process of being invited into this part of the trial. We would expect this to be within a 4-week window of the main trial participant's randomisation. Impact on carers will be measured using the Depression Anxiety Stress Scales (DASS) (38) and Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS) (39).

Information about the carer will also be collected at their Baseline, for example (as a minimum): name; contact details and preferences; basic demographic information (e.g. year of birth; gender; ethnicity; employment status; highest level of qualification; marital status); relationship to the ADEPT-2 participant, how they would describe their caring role (if any); whether they are a paid/unpaid carer; full-time/part-time carer and if they are supporting the ADEPT-2 participant directly/indirectly with the study intervention or TAU. Some of this information will also be collected at 16- and 52-weeks post-randomisation, to identify any relevant changes.

8.2 Recruitment and consent

It is up to the ADEPT-2 (main trial) participant to define who their carer is; where feasible, it would be one carer who knows them well and is likely to continue caring for them over the 52-week trial period. A carer will be an individual who provides emotional/practical/informational support to the ADEPT-2 participant either informally or formally.

As noted in Section 6.7, if a participant confirms that they have a carer, the researcher will provide the participant with an ADEPT-2 Carer Study Information Pack. The participant will be asked to forward this pack to their carer at the earliest opportunity, on behalf of the ADEPT-2 research team*.

The ADEPT-2 Carer Study Information Pack will consist of an approved Study Invitation Letter and PIL as a minimum. Contact details of the local research team will be provided in the event of any queries. Where feasible, an online equivalent of the Carer Study Information Pack (or at least the provision of information and 'what to do next' if you are interested in taking part) will be available on the study website.

Alongside explicit consent to participate in the study, consent will be sought for future contact about other research and sharing of their anonymised data for other ethically approved studies (as a minimum).

We envisage the completion and return of consent and Baseline questionnaire (at least) to be via posted paper copies given the initial method of information provision, however alternative remote methods of contact will be available, where feasible. For example, an eConsent (online) form, and data collection via secure online links (surveys) and/or video-conferencing/ telephone calls with the researcher. Further guidance for the researchers will be provided in study-specific training materials.

Three copies of the completed consent form are required;

1) a copy must be filed in the ISF together with a copy of the PIL in recruitment order*;

2) a copy should be given to the carer* (electronically, or via post with the next questionnaire); and

3) a copy should be given to the ADEPT-2 central research team.

**If a paper (wet ink) form is completed, the 'original' form should be filed in the ISF. If an eConsent form is completed, a completed copy is emailed to the participant once processed, and additional copies can be obtained via the eConsent (database) system.*

All carers who agree to take part will be logged with the relevant local research team and allocated a study specific (Carer) I.D number. The relevant research team will send a subsequent Carer Impact Questionnaire at 16- and 52-weeks post-randomisation (of the ADEPT-2 participant); see Table 3. Questionnaires will be available for carers to complete via various alternative methods (e.g., online, telephone/video conferencing, or post) to minimise loss to follow up. If the local research team does not receive a response from a carer within a reasonable time of sending the Carer Impact Questionnaire at 16- and 52-weeks (e.g., ~3 weeks), then they will try calling them, and/or resend another online link/pack with a reminder letter (or email equivalent). For each questionnaire, the research team will make up to three contact attempts (initial sending, plus two reminders). If no response is received after the third attempt, the relevant questionnaire will be marked as missing. We will, however, continue to send the next questionnaire as planned, unless the participant requests/ confirms that they no longer want to complete them; a similar model has been successfully used in multiple studies conducted by the BTC.

Return of a completed 52-week questionnaire marks the end of the carer's direct involvement.

8.3 Information about the study

To thank them for their time and keep them informed, carers will be offered incentive in the form of a £10 shopping voucher on completion of the 52-week questionnaire. They will also be sent relevant newsletters telling them about the study, including progress and results once available. Further details about dissemination are outlined in Section 16.

8.4 Withdrawal criteria

Carers will remain in the study unless they choose to withdraw, or if they are unable to continue for a clinical reason, as notified by the participant. The carer does *not* need to withdraw from the study if the trial participant (i.e., the person for whom they are a carer) withdraws from the main trial. If a carer withdraws consent, data collected up to the point of withdrawal will be retained (confidentially) for analysis, as stated in the PIL. A study Carer Change of Permissions/ Withdrawal Form will be completed in all cases, and databases updated accordingly. Study specific procedures for a carer's change of permissions, or withdrawal, will be outlined in the relevant trial working guidelines, which appropriate members of the research team will be made aware of. The Carer Impact PIL will include information for carers. Carer post-study care does not apply for this element of the ADEPT-2 trial.

8.5 Adverse Events

Adverse events (AEs) are typically defined as *"any unfavourable and unintended signs, including abnormal laboratory results, symptoms or a disease associated with treatment/ procedures required by the protocol".* For the purpose of this (low risk) carer involvement, we do not expect, nor will actively seek, recording of any AEs related to research procedures, such as completing a questionnaire. If, however, we become aware of relevant information about a carer regarding an AE related to taking part in the carer impact element of the trial, we will ensure that it is recorded. In those situations, we

would liaise with the Sponsor within a timely manner, noting their relevant safety reporting standard operating procedures (SOPs) and supporting documents.

8.6 Analysis of carer impact data

See Section 11 (Statistics and Health Economics Analysis) for details.

8.7 Data Management

See Section 12 (Data Management).

9 INTERVENTION / GUIDED SELF-HELP (GSH)

9.1 General information

The intervention is Guided Self-Help (GSH), based on the principles of Behavioural Activation (BA) and adapted for the needs of autistic adults.

9.2 Background to Guided Self-Help (GSH)

BA is the recommended treatment model for low-intensity Cognitive Behavioural Therapy (CBT) for depression and there is good evidence for the effectiveness of BA as a treatment for depression in adults (57). BA is ordinarily achieved through activity scheduling. People are encouraged to become aware of their individual triggers for low mood and the consequences of a range of behaviours. They are encouraged to use this information to promote positive mood and to make changes in line with their individual goals.

BA can be delivered as a low-intensity intervention unlike other effective psychological interventions for depression such as cognitive therapy. Low-intensity interventions are characterised by the provision of evidence-based written information, the use of which can be supported by a therapist.

9.2.1 Rationale for GSH

BA may be highly suited as an intervention for depression for autistic adults if adapted to meet their needs. Firstly, a restricted, repetitive and stereotyped pattern of behaviours, interests and activities is a core characteristic of autism. It is therefore likely that when depressed, autistic people do not readily shift their routines, behaviours and thought patterns to activities and behaviours reducing behavioural changes likely to bring about positive changes in mood. This inherent tendency may form part of the behavioural maintenance cycle of depression symptoms in autism. Secondly, executive function differences which have been well-documented in autism (58) mean that planning and implementing novel behaviour can be compromised in autistic people. BA may be helpful in broadening behavioural repertoires and increasing access to positive experiences, promoting positive mood and ultimately preventing depressed mood.

Low-intensity interventions were developed with the aim of disseminating evidence-based practice to mental health professionals from a range of backgrounds. This may be highly pertinent to autistic adults who can receive support and healthcare from a range of professionals including CBT practitioners who do not have specialist training in autism. Providing the treatment principles in written form means the written materials can also carry many of the adaptations needed for autistic people such as clear and concrete representation of treatment principles with visual aides and exercises to prompt emotional awareness. This reduces the reliance on the therapist who may not have extensive knowledge of or experience in working with autistic adults to know how to best tailor their practice. Many of the key adaptations are delivered through the written materials, with the therapist manual supporting the therapist to guide the individual in their use of the materials.

The low-intensity intervention developed for the present study is designed to be akin to the routinely available, evidence-based treatment for depression that is available to the UK adult population as far as possible. This is to ensure feasibility of delivery and ease of uptake by mainstream practitioners and increase their confidence in working with autistic adults, thus reducing the barriers to accessing effective mental healthcare for this group.

Low-intensity interventions can be delivered as a group intervention. Group interventions may be less suited to autistic adults as joining a group of unfamiliar people, particularly when low in mood, may

present social challenges and act as an additional source of stress and anxiety. Social anxiety is a frequently co-occurring condition in autistic people [47]. Therefore, we have developed GSH for individual delivery.

9.3 ADEPT-2 Guided Self-Help (GSH) Intervention

The Guided Self-Help (GSH) intervention (59) comprises materials for 9 sessions. Participants will be provided with the materials and invited to attend 9 appointments with the therapist guide, ordinarily held at weekly intervals. Appointments can last up to 45 minutes in duration (except for the first appointment, which can last up to 90 minutes). The session materials are accompanied by a short manual for the therapist guide.

Therapist guides are ordinarily graduate level psychological practitioners or other mental health professionals with foundation knowledge in applying cognitive behavioural principles for common mental health problems.

Therapist guides 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 (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 particular issues in supporting an individual to access and apply the GSH intervention principles on an individual basis will be considered.

Therapist guides are referred to as a ‘coach’ in the intervention materials and for consistency this term will be used hereon in.

The GSH session materials based on Behavioural Activation and adapted for autistic people were well received in the feasibility study and have been further refined in line with participant feedback.

The intervention is described in the feasibility study outcome paper (59) where the following adaptations to usual treatment are noted:

- An orientation session, introducing the treatment approach and individual needs in respect of autism
- Consistent and clearly structured format of treatment materials
- Visual images to supplement written accounts of psychological principles
- Scaffolding of emotional literacy and executive function differences
- Use of reminders and flexibility in respect of appointments
- Therapist training in supporting autistic people in their use of GSH
- Longer duration of treatment sessions (up to 45 minutes) and a longer treatment window (16 weeks).

Participants will be provided a booklet containing the materials for 9 sessions (Guided Self-Help). This booklet can be provided electronically (pdf) and/or hard copy format. Participants will be supported in their use of 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. In the feasibility study, the intervention was delivered in-person, 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 (29) and anxiety symptoms with the GAD-7 (32).

9.4 Scheduling of sessions

When the participant is randomised to the GSH intervention arm of the trial, the researcher will complete a referral form that will be passed on to the local PI or delegated individual. The PI/delegate will then allocate the participant to a therapist coach and will pass on the referral form to the therapist coach, to enable them to contact the participant to arrange the first session and decide by what method the participant prefers to have these appointments (in-person or remote). The therapist coach is expected to make this initial contact within 1 week of randomisation with the first session to be held within 2 weeks (+/-1 week) of randomisation. They will then aim to have subsequent appointments every week until they have completed 9 appointments. However, we allow a 2+/- week window for the follow-up appointments to allow for real-life practicalities, for example, if a participant is going to be on holiday for a week or two.

9.5 Assessment of adherence to treatment

ADEPT-2 is a pragmatic trial. While information about the study sessions, including possible ways to aid adherence, will be included in the ADEPT-2 Welcome pack, we do not propose any additional measures to improve poor treatment attendance amongst participants as that may not reflect real life practice and act as an additional intervention. Although the participant will be invited to attend 9 appointments, it is noted that it may not always be possible to cover material from all 9 sessions. At each appointment, the coach will record information on what materials were covered.

9.5.1 Definition of treatment adherence

Attendance at ≥ 6 sessions of GSH will be considered a treatment ‘dose’.

The main treatment principles are presented in sessions 2-6, with session 1 an orientation and introductory session.

9.5.2 Measuring fidelity

The study’s approach to fidelity will follow the structure for manualised treatments identified by Gearing et al (2011) (60); they suggest a four-element fidelity framework of design, training, monitoring of intervention delivery, and intervention receipt. In this study:

Training fidelity will be monitored through delivery of a common training curriculum to the therapists, monitoring of supervision structure and content. Content of supervision will be recorded through written notes by the supervisor. **Monitoring of intervention delivery -** Adherence to Guided Self-Help therapy content will be measured through a scale specific to the manual identifying key elements of therapy for each session. Therapist coaches will complete a self-rating of adherence to content for each session using this scale.

When each participant is allocated to a therapist coach, two random numbers will be generated representing the two appointments (one from the first five sessions and one from the remaining four) that therapist coaches will be expected to audio-record for fidelity purposes. Of these recorded sessions, 20% will be randomly sampled for rating of adherence to treatment. These independent ratings will be used to validate the therapist self-rating of adherence. Where significant discrepancy exists between self and independent ratings of adherence, a further sample of recorded sessions will

be independently rated to establish if this discrepancy is consistent and pervasive across all therapist ratings.

To develop the adherence to treatment rating, six recorded GSH appointments will be separately rated by two co-applicants expert in the intervention. Ratings will be discussed to identify disagreements and clarify wording of the items, their descriptors and develop operationalisation information. A consensus rating of these recordings will be agreed and used as a criterion for training additional raters if required.

'Monitoring of intervention delivery' will include participants and therapist coaches recorded therapeutic alliance, using client and therapist versions of the WAI-SR (61) which has been identified as the most frequently used measure of therapeutic alliance in CBT for people with depression (62). This measure will be completed separately by therapist coach and participant, once within the first five appointments and once within the remaining four appointments.

Further delivery adherence data will be available from therapist coaches recorded session duration, sessions attended and therapist reported planned treatment elements covered in each session.

'Intervention receipt' will be monitored through therapist records of participants' completed exercises and homework activity, ease of delivery and client engagement with the materials. Further data will be available through qualitative interviews which will include exploration of the elements of therapy that the participants found most helpful and their views on ease of implementation of the therapy content.

9.5.3 Non-compliance with GSH treatment

In the case of persistent non-attendance to treatment, a pragmatic clinical decision will be made. For example, if a participant does not attend more than two consecutive scheduled GSH sessions, it will be discussed with them whether they would like to continue with the treatment or would prefer to withdraw i.e., treatment discontinuation. They will still be sent future study questionnaires and remain in the trial, unless they withdraw from the study completely. Such decisions will be made by the therapist with their clinical supervisor on a case-by-case basis.

9.6 Discontinuation of trial intervention

If the participant discontinues the GSH sessions by choice, they will be encouraged to remain enrolled in the trial (unless they explicitly withdraw; see section 6.16) and complete the further assessments as per protocol.

Once study intervention is discontinued, participants may not resume trial treatment but as this is a pragmatic trial, they may be referred to other services in line with the stepped care model.

9.7 Post-trial

Once a participant has completed their GSH sessions, their GP will be informed as the professional with clinical responsibility. If secondary care or other specialist services are also involved with the individual's care, they will be advised that the participant has completed the intervention.

9.8 Intervention and COVID-19 considerations

Please see Appendix 1 for a summary of considerations and actions made by the central research team in relation to the trial and COVID-19. This includes examples regarding trial conduct and intervention considerations.

10 SAFETY REPORTING

10.1 Event definitions

Term	Definition
Adverse Event (AE)	Any unfavourable and unintended sign or symptom that develops or worsens during trial participation, whether or not it is considered to be related to the trial intervention. AEs are not continuous and persistent disease or symptoms, present before the trial, which fail to progress; signs or symptoms of the disease being studied (in this case autism and depression); or treatment failure.
Serious Adverse Event (SAE)	A serious adverse event is any untoward occurrence that: • results in death • is life-threatening[A] • requires inpatient hospitalisation or prolongation of existing hospitalisation[B] • results in persistent or significant disability/incapacity Other 'important events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. *[A]The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.* *[B]The definition of hospitalisation is an unplanned overnight stay. Note, however, that the patient must be formally admitted – waiting in outpatients or an Accident & Emergency Department (A&E) would not count as hospitalisation (even though this can sometimes be overnight). Prolongation of an existing hospitalisation qualifies as a SAE. Planned hospital stays would not be counted as SAEs, nor would stays in hospital for "social reasons" (e.g., respite care, the fact that there is no-one at home to care for the patient). Also, if patients had a day-case operation, this would not qualify as hospitalisation. However, if a planned operation was brought forward because of worsening symptoms, this would be considered as an SAE. Hospitalisations for the purpose of the intervention are an exception to SAE reporting unless complications occur.*

10.2 Classification of severity

Mild event:	An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
Moderate event	An event that is sufficiently discomforting to interfere with normal everyday activities.
Severe event:	An event that prevents normal everyday activities.

10.3 Classification of relatedness

Not related	Temporal relationship of the onset of the event, relative to administration of the intervention, is not reasonable or another cause can by itself explain the occurrence of the event.
Unlikely to be related	Temporal relationship of the onset of the event, relative to administration of the intervention, is unlikely and it is likely there is another cause which can by itself explain the occurrence of the event.
Possibly related	Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable but the event could have been due to another, equally likely cause.

Probably related	Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable and the event is more likely explained by the intervention than any other cause.
Definitely related	Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive.

10.4 Safety reporting period

Data on adverse events will be collected for the duration from randomisation to 52-weeks post randomisation. Related AEs will be recorded by local research teams on the study Non-Serious Adverse Events Log, provided to the central research team via secure email on approximately a monthly basis. All SAEs will be recorded on the SAE summary log. All fatal SAEs and unexpected related SAEs will require expedited reporting by local research teams to the study Sponsor, Chief Investigator and central research team at the same time, via email. No patient identifiers will be included with the SAE reports. The central research team will manage any onward reporting to the REC and/or DMC as required.

10.5 Identification of AEs

AEs are expected to occur throughout the course of the trial. Local research teams are responsible for recording appropriate AEs for their participants during the trial.

We anticipate that some AEs may be identified during GSH appointments for participants allocated to GSH up until the 16 week follow up, where AEs will be detected via study questionnaires (across both TAU and GSH groups). We are aware that AEs may occur within the TAU group during this time, but up until the 16 week follow up there will be no mechanism for identifying them and we will not actively monitor for events outside of study questionnaires. However, central and/or local research team will report any AEs that occur should they become aware, as below.

We anticipate that most AEs will be identified via study questionnaires. For example, a high BDI score within a study questionnaire may indicate high risk of suicide and lead to further investigation for safety events by the site teams, the central and/or local research team will communicate with the local PI (or appropriate delegate) and sites if additional information is required, e.g., to ascertain the nature and severity of an AE. If the study team become aware of an AE, they will assess and log this according to trial recording and reporting procedures; see below.

10.6 Classification of (S)AEs

The PI of each participating site (or appropriate delegate, e.g., clinician) is responsible for assessing all AEs and categorising whether they are serious, expected, and related. A list of events that can be expected during this trial or within this patient population can be found below. In this study population, expected events may be due to the participants autism diagnosis, depressive symptoms or other co-occurring mental health conditions.

The following events are classified as expected during this trial:

- 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.

10.7 Recording and reporting non-serious AEs

A non-serious AE is an adverse event which does not satisfy the above definition of an SAE.

Only non-serious AEs that are assessed as being **possibly, probably or definitely related to the intervention (i.e., GSH) and/or study procedures**, should be recorded using the ADEPT-2 Non Serious Adverse Events Log. A copy of the log will be requested approximately monthly by the ADEPT-2 central research team. The event should also be recorded in the participant's clinical notes and/or research case notes by a suitable member of the local research team. The participant should be followed up by the local research team until the event subsides or the Sponsor confirms no further reports are required. The recording framework for non-serious AEs is shown in Figure 3.

If the event is defined as 'serious' the local research team should proceed to follow reporting procedures for SAEs, outlined below (see section 10.8).

Non-serious AEs (with the exception of new mental health diagnoses/symptoms) that are unrelated to the intervention do not need to be recorded.

The central research team will prepare regular summary reports of all recorded non-serious AEs for discussion at relevant oversight meetings, including with the Sponsor.

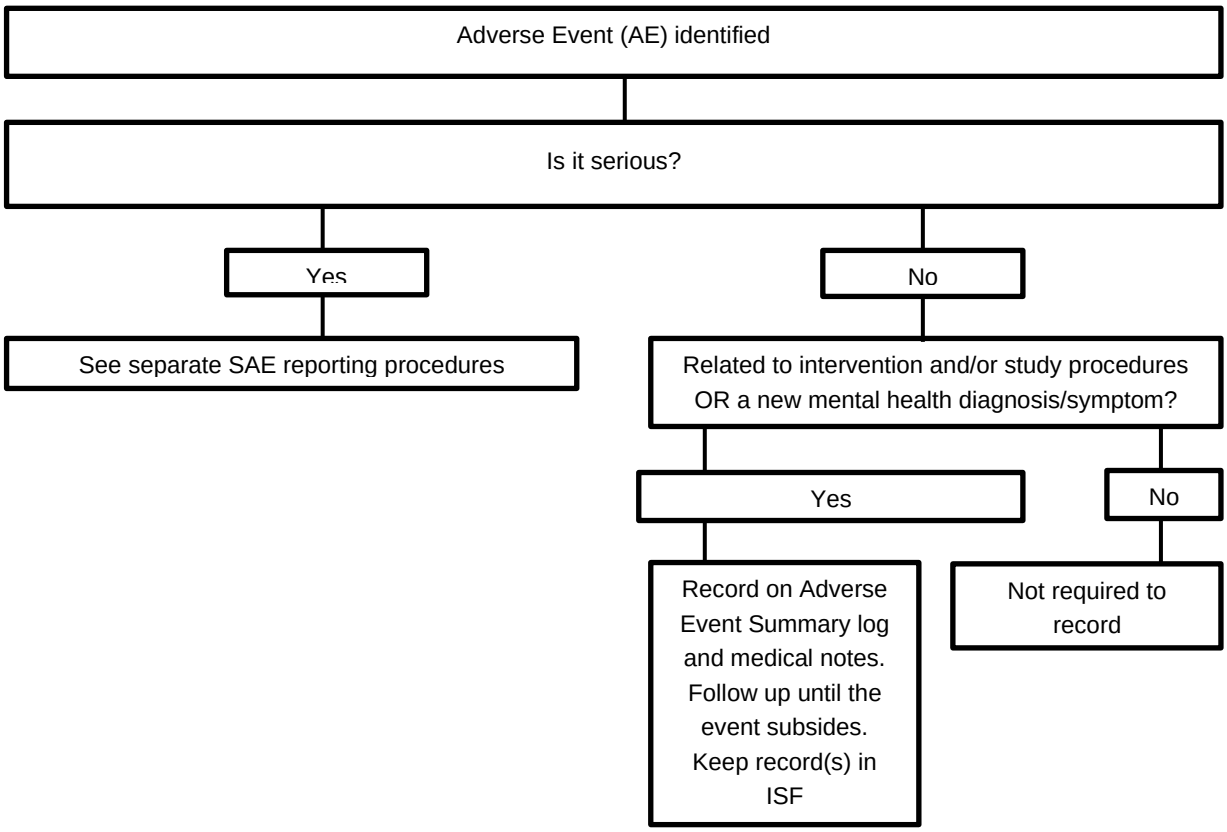


Figure 3 Recording framework for AEs assessed as non-serious.

10.8 Recording and reporting Serious AEs (SAEs)

10.8.1 SAEs that require expedited reporting

SAEs will require expedited reporting to the Sponsor if they are (i) fatal AND assessed as expected, or (ii) assessed as unexpected AND assessed as being possibly, probably or definitely related to the intervention and/or study procedures. The PI, or appropriate delegate, should complete these assessments.

For SAEs that require expedited reporting, a full SAE Initial Report Form should be completed. The initial report may be provided orally but a written SAE Initial Report Form must be completed within 24 hours of staff becoming aware of the event. Sites should scan and email the form, with high importance, to the (i) Sponsor, (ii) ADEPT-2 central trial team (Trial Management) secure mailbox, and (iii) cc'd Dr Ailsa Russell, Chief Investigator; see 'Key Trial Contacts' for contact details (pages 2-3). Information not available at the time (such as test results) must be forwarded once available.

The central research team will confirm email receipt with the local research team, as well as ensuring receipt by UniBath for review and, if required, forward the completed form to the REC within the reporting periods (see Figure 4 below).

> ***NB:*** *typical working hours of the central research team (UK): Monday to Friday, 09:00-17:00 (subject to change). In the event of University closure dates and/or being unavailable, an out of office automatic response will notify recipients of alternative contact details/reporting arrangements.*

Any change of condition, or other follow up information relating to a previously reported SAE, will be reported on a separate trial SAE Follow Up Report Form. All SAEs will be followed up until the event has resolved, or a final outcome has been reached in the opinion of the PI. The reporting framework for SAEs is shown in Figure 4, below.

Each SAE will be reported separately and not combined on one SAE form.

10.8.2 SAEs that do not require expedited reporting

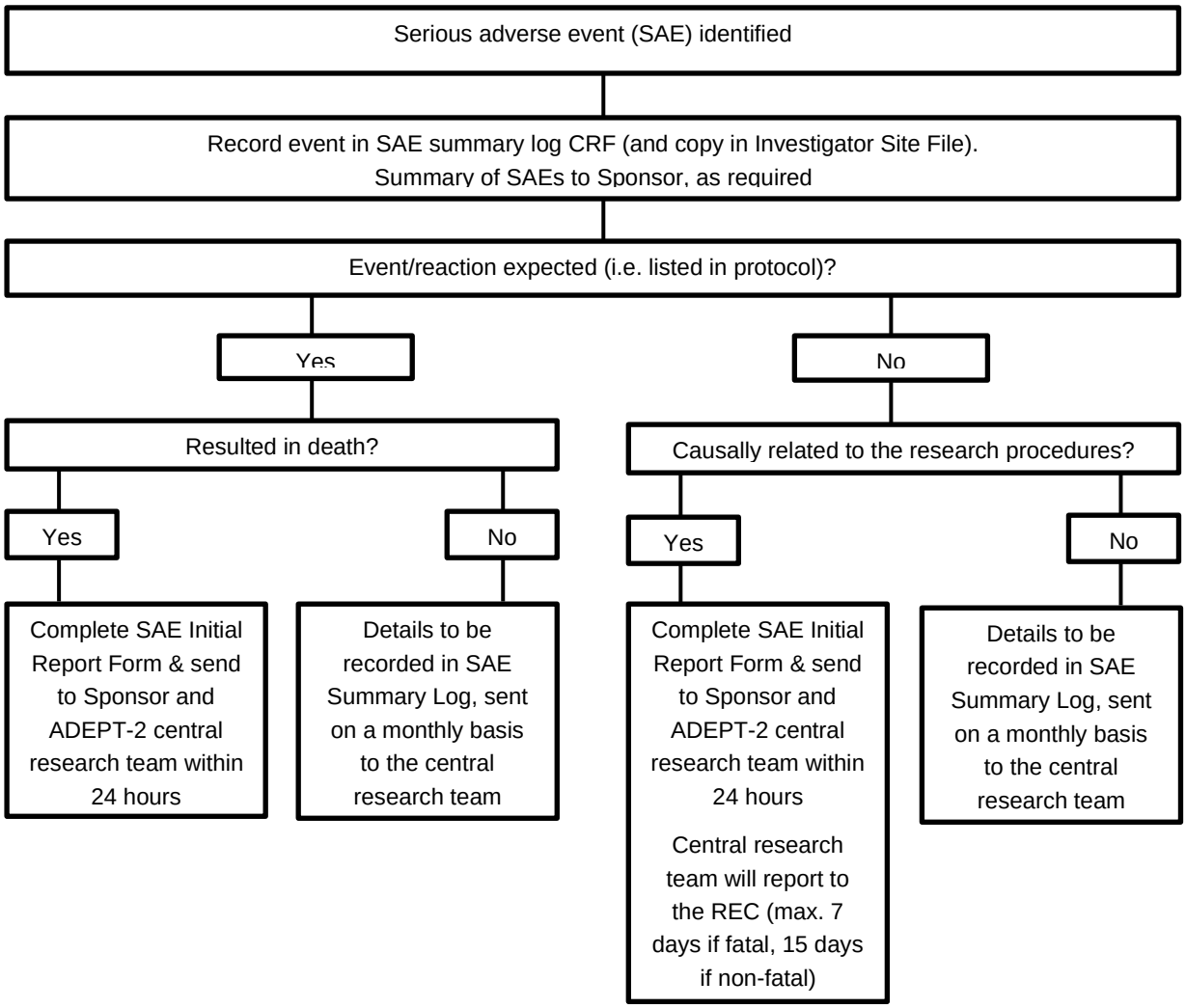
Local research teams should record all SAEs in the ADEPT-2 SAE Summary Log, which should be retained in the ISF. The central research team will request a copy and review the SAE Log approximately monthly for monitoring and reporting purposes, and will prepare regular summary reports of all SAEs for discussion at relevant oversight meetings, including with the Sponsor.

Events should also be recorded in the participants' clinical notes and/or research case notes by a suitable member of the research team.

Non-fatal SAEs assessed as expected do not require expedited reporting. SAEs assessed as unexpected and unrelated to the intervention and/or study procedures do not require expedited reporting. These SAEs should however be recorded in the ADEPT-2 SAE Summary Log.

The central research team will be responsible for all other reports to relevant regulatory authorities and/or trial oversight committees.

Figure 4 Overview of safety reporting requirements for AEs assessed as being serious (SAEs).



11 STATISTICS AND HEALTH ECONOMICS ANALYSIS

11.1 Sample size calculation

11.1.1 Main trial

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) (63) with a 90% power at the 5% significance level.

11.2 Statistical analysis

All analyses and reporting will be in line with CONSORT guidelines (41). Primary analyses will be based on the intention-to-treat (ITT) basis, analysing participants in the groups to which they were randomised. A full SAP will be developed by the Statisticians and central research team and agreed by the TSC prior to undertaking analyses for the main trial.

11.2.1 Primary outcome analysis

The primary analysis will follow the ITT principle, comparing the groups to which participants were randomly allocated. The treatment effect on the primary outcome, depression measured by the BDI-II at 16 weeks will be estimated by a linear regression model with covariates including the baseline BDI-II measure, study centre and treatment group allocation. The treatment effect will be estimated as the coefficient of the treatment group allocation covariate, with 95% confidence interval and p-value. This approach will be adapted to the secondary measures. Sensitivity analyses will explore the impact of any missing primary outcome data.

11.2.2 Subgroup analysis

A number of pre-defined subgroup analyses will be carried out to assess the difference in treatment effect on the primary outcome according to characteristics assessed at baseline. Effect modification will be assessed by including an interaction term in the regression model and formal tests of interaction will be performed to test whether the treatment effect differs between these groups. As the study was not powered to detect such effects, results will be interpreted with caution.

11.2.3 Carer impact sub-study

The carer sub-study will have its own section within the SAP. A key issue will be making an unbiased comparison between the study groups, given that a carer won't be recruited for all participants.

Scores based on standardised questionnaires will be calculated based on the developers' scoring manuals and missing erroneous items will be handled according to these manuals.

11.3 Missing data

The sensitivity of the primary analysis to the impact of missing data will be investigated. The data will first be explored before a decision is made on what approach to utilise. These include exploring the amount of missingness, differences between arms, variables associated with/predictive of missingness and if reported, reasons for missingness. The approach taken to handling missing data will then depend on the assumptions about the nature of the missingness deemed to be appropriate. For example, if an assumption of Missing At Random is deemed appropriate then multiple imputation will be carried out and the primary analysis repeated using the imputed data.

11.4 Economic evaluation

11.4.1 Aim

The aim of the economic evaluation is to assess the cost-effectiveness of the low-intensity guided self-help ADEPT-2 intervention compared with treatment as usual for treating depression in an autistic adult population. The primary perspective will be societal (including productivity losses); a secondary analysis will be conducted from the perspective of the NHS and personal social services (PSS).

11.4.2 Outcomes

The primary outcome for the economic evaluation will be quality-adjusted life years (QALYs) derived from measurements recorded using the EQ-5D-5L(37) health-related quality of life instrument after 52 weeks of follow-up. Quality of life will be measured at baseline, and after 16, 32 and 52 weeks of follow-up. EQ-5D-5L health states will be valued using the method recommended by the National Institute for Health and Care Excellence (NICE) at the time of analysis; the current position statement recommends the use of the Van Hout crosswalk to map to EQ-5D-3L values (64).

11.4.3 Cost measurement

Intervention costs (including the booklet, therapist time for training, delivery and supervision, and mode of delivery) will be recorded in study records. Other health and social care resource use will be measured by bespoke patient-reported questionnaires at 16, 32 and 52-weeks of follow-up. As it may be difficult for participants to identify care that is directly related to their depression, care for all causes will be included. NHS and PSS resources will include primary care contacts, hospital stays and day cases, emergency care contacts, outpatient appointments, medications and social care contacts. Costs borne by patients themselves (such as travel expenses and over the counter medications) will also be included. Wider societal productivity losses will be estimated using the Work Productivity and Activity Impairment Questionnaire (WPAI)(65) administered at baseline, 16, 32 and 52 weeks months post randomisation. Measured resources will be valued using standard sources from the most recent cost year available at the time of analysis, such as the Unit Costs of Health and Social Care (66) for primary and community care, NHS National Cost Collection data (67) for secondary care contacts and the British National Formulary (68) for prescribed medication costs.

11.4.4 Analysis

A pre-defined health economics analysis plan will be prepared to guide the analysis. The primary cost–utility analysis (CUA) will be conducted from the societal perspective. A secondary analysis will restrict the perspective to that of the NHS and PSS to conform to the NICE reference case. The CUA will compare the difference in costs with the difference in QALYs between the GSH and TAU groups after 52 weeks of follow-up. Incremental cost-effectiveness ratio (ICER) and incremental net monetary benefit (NMB) statistics will be calculated to assess cost-effectiveness. Uncertainty will be explored through cost-effectiveness acceptability curves, one-way sensitivity analyses and by deriving confidence intervals for the NMB statistic. As the period of follow-up is 52 weeks (one year) only, discounting of either costs or benefits is not required.

12 DATA MANAGEMENT

12.1 Source data and documents

Source data for this trial will by default consist of electronic versions of preliminary screening and expression of interest forms, consent form(s), participant and carer completed questionnaires and other CRFs designed specifically for the study. However, where electronic data collection is not possible, equivalent paper documents will become the source data. Data obtained by paper will be entered onto the database as soon as practical by the centre/site research teams, and where applicable or required, by the central research team. Any paper documents containing identifiable information will be stored in a locked filing cabinet at the centre/site, which only members of the local research team have access to.

Local centre/site teams must keep a paper record of their participants (and carers involved in the carer element of the study) PIL and consent form(s) in their ISF for monitoring purposes, regardless of the method of data collection. Paper-completed CRFs should also be retained in their ISF. To enable remote-working, electronic records will suffice until a time when they can be printed and suitably filed.

12.2 Data handling

Data from all participants will be collected and retained in accordance with the UK Data Protection Act 2018 and UK General Data Protection Regulation 2018 (GDPR). All trial patients (including carers involved) will be allocated a unique study I.D number during the screening process, which will remain assigned to them.

Participants will be asked to consent to their personal information and research data being stored by the University of Bristol during the trial and their research data being transferred to and stored by the University of Bath at the end of the trial. Furthermore, for randomisation purposes only, participant information (including personal details, e.g., initials, gender and date of birth) will be entered into the secure online randomisation system provided by Sealed Envelope™ (45). For the purpose of conducting the trial only, all data that are entered on to the Sealed Envelope™ system is done so via secure sockets layer (SSL) connections and stored on secure servers located in the UK and Ireland that comply with UK regulations on data privacy. User-access to the system will be managed by the central research team, who will in turn generate password-protected user-accounts for authorised centre/site staff.

Standardised outcome instruments will be used throughout the trial; the components and timing of follow-up measures are detailed in Section 2 (Aims and Objectives) and shown in Table 3. All participant data will be entered into and stored on password-protected Structured Query Language (SQL) databases maintained by the University of Bristol. Secure access to the internet is required for all appointments conducted remotely. For face-to-face appointments, if internet access is not available, paper documents will be available, where feasible and entered on to the database at a later stage when internet access is available. Any data stored on laptops will be encrypted.

Section 7.3 provides supporting details regarding the ‘Data management, protection and patient confidentiality’ in relation to the qualitative research data.

12.3 Database platform(s)

Full details will be outlined in the ADEPT-2 Data Management Plan. To summarise:

All administrative and clinical study data will be stored in separate REDCap instances. REDCap is a secure, web-based electronic data capture (EDC) system designed for the collection of research data. The system has been developed and supported by Vanderbilt University. BTC at the University of Bristol (UniBristol) has set up its own infrastructure so that all systems are hosted at and supported by UniBristol.

A Relational Database Management System will be used to provide integration services between administrative and clinical databases. These data will be stored here, to support the workflow of the study team. These data will not be made available for analysis. These data are stored in a SQL Server system maintained by the UniBristol.

The central research team will manage user-access rights to the database. This includes managing access to participant data according to the centre/site they are recruited from, and restricting access to any information that may identify the treatment received by the participant to staff who are blinded to the allocation.

12.3.1 Administrative data

The administrative data (i.e. data containing patient identifiers) will be kept in a secure database that is only accessible from within the UniBristol firewall. All users will require (at least honorary) contracts with UniBristol to access it.

12.3.2 Clinical data

The clinical data (i.e. pseudonymised data) will be stored on a separate server to the administrative data. Anonymised clinical data is linked by a study participant I.D. Email addresses are collected as they are essential for the correct functioning of the online survey (questionnaire) feature. The 'Email Address' field is flagged as an identifier and not included in the export for the statistician, so the data set can be considered pseudonymised at export and does not need further processing.

12.4 Storage and access to data

The University of Bristol and University of Bath are joint data controllers for the ADEPT-2 trial. Data will be held at the University of Bristol and will conform to the University of Bristol Data Security Policy and in compliance with the UK GDPR, alongside the Data Protection Act 2018.

For monitoring purposes, the CI will allow monitors from the Sponsor (or delegate), persons responsible for the audit, representatives of the REC and other Regulatory Authorities to have direct access to source data/documents.

The Trial and Data Managers (in collaboration with the CI) will manage access rights to the data set. Prospective new users must demonstrate compliance with legal, data protection and ethical guidelines before any data are released.

12.5 Archiving and destruction of trial materials

An archiving plan will be developed for trial materials in accordance with the BTC SOPs. Data will be held in compliance with the Sponsor's standard procedures. All research data will be retained securely during the conduct of the trial. Data will be retained for *at least* 5-years after the end of the trial, and at the end of the archiving period, will be destroyed by confidential means with the exception of a final dataset which will be made available for data-sharing purposes (see Section 12.6, below). Where electronic records are in use, the University of Bath (Sponsor) policy will be followed. The approval of University of Bath, as well as the trial CI, will be sought prior to destruction of the data.

Participating centres/sites will be responsible for ensuring that all study records held at their centre/site are archived appropriately when notified by the Sponsor/BTC (central research team/ UniBath).

12.6 Access to the final trial data set

Anonymous research data, which may include qualitative audio-recordings and/or associated data such as anonymised transcripts, will be stored securely and kept for future analysis with participant consent. We anticipate that anonymised trial data will be shared with other researchers to enable prospective meta-analyses. Members of the TMG will develop a data sharing policy consistent with UniBristol policy. Data will be kept anonymous on research data storage facility (RDSF). Requests for access to data must be via a written confidentiality and data sharing agreement (DSA) available from the RDSF website which will be confirmed by the CI (or appointed nominee).

The DSA should cover limitations of use, transfer to third parties, data storage and acknowledgements. The person applying for use of the data will be scrutinised for appropriate eligibility by members of the research team.

13 TRIAL MANAGEMENT

The CI will take overall responsibility for managing the various components of the trial, with the support of the Trial Manager(s) and will meet regularly (as required) with the leads for each component. The Bristol Trials Centre (BTC), a UK Clinical Research Collaboration (UKCRC) registered trials unit, will support the delivery and conduct of the trial.

13.1 Trial management group (TMG)

The TMG will have responsibility for the day-to-day management of the trial and will report to the TSC. The TMG will meet on a regular basis with a core working group of staff having frequent progress meetings. They will link to the network of site research teams to facilitate continuous feedback and early troubleshooting of local site issues that arise. Meetings will be in person and/or by teleconference to maximise attendance.

13.2 Trial Steering committee (TSC)

The TSC will be established in conjunction with a TMG. Membership, responsibilities and reporting mechanisms of the TSC will be formalised in a TSC charter. The TSC will make recommendations/key decisions during the trial to the TMG and minutes will be sent to the funder.

The TSC will comprise of an independent chair, plus at least three others; see Table 4 below for nominations (correct at time of original submission)*. The independent members will cover expertise in (at least) statistics, trials and autism. Ailsa Russell (CI) will also be a formal (not-voting) non-independent member of the TSC. Observers may also attend (including other members of the TMG or members of other professional bodies) at the invitation of the Chair. The TSC will meet for the first time prior to recruitment of the first participant and then at agreed intervals thereafter.

13.3 Data monitoring committee (DMC)

The DMC will meet once prior to recruitment of the first participant and, going forward, will convene prior to the TSC meeting to review the AE data and any other ethical aspects that arise and report to the TSC. Responsibilities and reporting mechanisms of the DMC will be formalised in a DMC charter.

The DMC will comprise of an independent chair, plus at least two others; see Table 4 below for nominations (correct at time of original submission)*. In addition, Ailsa Russell (CI) and the Trial Manager will attend the open session only. The Senior Statistician will attend the open session only and the unblinded Trial Statistician will attend both the open and closed sessions.

13.4 Patient and public involvement (PPI)

An advisory group comprising adults with a diagnosis of autism and CBT therapists with lived experience has been set up to support the trial. Members of the advisory group will be involved throughout the study. This will involve autistic advisory group meetings, specific roles on the TMG and TSC, review of the protocol, logo design, participant information, consent and data collection forms and informing dissemination of the research findings to participants.

13.5 Sponsor and funding

This trial will be sponsored by University of Bath (UniBath). The sponsor will be responsible for overall oversight of the trial.

This study is funded by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (Reference 132343). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Table 4 TSC and DMC member composition (correct at time of amendment)*

Role	Name	Job Title	Institution	Expertise
Trial Steering Committee (TSC)				
Independent chair	Tim Nicholls	Head of Policy, Public Affairs and Research Partnerships	National Autistic Society	Research involvement and policy development - Autism
Independent member	Barney Dunn	Professor in Clinical Psychology	University of Exeter	Clinical expert - psychological treatment of depression
Independent member	Christopher Sutton	Deputy Director (methods) and Lead Statistician	Clinical Trials Unit, University of Manchester	Statistical and trials methods expertise
Independent member	Holly Judge	Autism Coordinator	Brent Council	Expert by experience
Independent member	Anna Taylor	Social Researcher	National Autistic Society	Expert by experience
Non-Independent member	Ailsa Russell	Professor of Clinical Psychology	University of Bath	Chief Investigator
Data Monitoring Committee (DMC)				
Independent chair	Sally-Ann Cooper	Professor and Consultant Psychiatrist in Intellectual Disability & Mental Health	University of Glasgow	Clinical expert
Independent member	Sarah Cassidy	Assistant Professor of Psychology	University of Nottingham	Clinical expert and Trialist
Independent member	Dr Batiste Leurent	Lecturer in Medical Statistics	University College London	Statistician
Independent member	Dr Jonathan Weiss	Associate Professor	Work University, Toronto	Clinical Psychologist and Academic

**if for any reason named members of the TSC and/or DMC are unable to continue as a member of the committee, then a suitable replacement will be sourced*

14 MONITORING, AUDIT AND INSPECTION

14.1 Monitoring

The trial will be monitored and audited in accordance with the Sponsor's policy, which is consistent with the UK Policy Framework for Health and Social Care Research. All trial related documents will be made available on request for monitoring and audit by the Sponsor, the relevant Research Ethics Committee (REC) and other licensing bodies.

A Trial Monitoring Plan will be developed by the Sponsors and agreed by the TMG and CI based on the trial risk assessment which may include on-site monitoring. This will be dependent on a documented risk assessment of the trial.

The sponsor usually delegates some of the monitoring to the central research team. The following checks would be typical:

- that informed consent has been properly documented
- that data collected are consistent with adherence to the trial protocol
- that CRFs are only being completed by authorised persons
- that S/AE recording and reporting procedures are being followed correctly
- that no key data are missing
- that data are valid
- review of recruitment rates, withdrawals and losses to follow up.

On a regular basis we will monitor the percentage of patients that meet the eligibility criteria and report the percentage of participants who consent. To assess the generalisability of the participants, the available characteristics of consenting participants and non-consenting will be compared. We will also report to the DMC if requested, preliminary data on event rates observed in the trial population: SAE rates and dropout rates.

14.2 Protocol compliance

There will be no prospective, planned deviations or waivers to the protocol. Any protocol breaches will be documented and reported to the Trial Manager, CI and Sponsor immediately (see Key Trial Contact for contact details). Information about protocol breaches will also be included in routine reports to the DMC and TSC. Protocol breaches identified by the central research team will be reported to the relevant local PI, site team, local NHS R&I and Sponsor as soon as possible. The Sponsor will determine the seriousness of the breach.

In the event of systematic protocol breaches, investigation and remedial action will be taken in liaison with the CI, DMC and the TMG.

14.3 Notification of Serious Breaches to GCP and/or the protocol

A "serious breach" is a breach which is likely to effect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial; or
- the scientific value of the trial

The Sponsor will be notified immediately by the central research team of any breaches; they will determine the seriousness of the breach. The Sponsor (or authorised delegate) will report Serious Breaches to the RECs within 7-days of the Sponsor becoming aware of them.

15 ETHICAL AND REGULATORY CONSIDERATIONS

15.1 Governance and legislation

This trial will be conducted in accordance with:

- Conditions and principles of Good Clinical Practice (GCP)
- UK Policy Framework for Health and Social Care Research
- Data Protection Act 2018
- General Data Protection Regulation (GDPR)

Any amendments to the trial must be assessed and approved by the Sponsor prior to submission to the REC and HRA.

Before any site can enrol participants into the trial, the CI or designee will obtain confirmation of capacity and capability (C&C) (or equivalent organisation approval) for each centre/site in-line with Health Research Authority (HRA) processes along with other documentation required for the Sponsor to grant sites a greenlight letter.

Where applicable, CI or designee will ask for confirmation from the sites' R&D departments that C&C is ongoing for relevant amendments.

This research trial will be conducted in accordance with conditions and principles of GCP. GCP is the international ethical, scientific, and practical standard to which all clinical research is conducted. Compliance with GCP provides public assurance that the rights, safety, and well-being of people taking part (trial participants) are protected and that research data are reliable.

15.2 Research Ethics Committee (REC) review and reports

Ethics review of the protocol for the trial and other trial related participant facing documents (e.g., PIL and consent forms) will be carried out by a UK REC. Any amendments to these documents, after a favourable opinion from the REC/HRA has been given, will be submitted to the REC/HRA for approval prior to implementation.

All correspondence with the REC will be retained in the Trial Master File (TMF)/ISF. An annual progress report will be submitted to the REC within 30-days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The CI will notify the REC of the end of the trial and if the trial is ended prematurely (including the reasons for the premature termination). Within one year after the end of the trial, the CI will submit a final report with the results, including any publications/abstracts, to the REC.

GCP training will be carried out by certain staff members depending on their delegated responsibilities within the trial, the level of training required will be determined according to the NIHR Delegation and Training Decision Aid. Informed consent to participate in the trial will be sought and obtained according to GCP guidelines.

15.3 Peer review

The proposal for this trial has been peer-reviewed through the NIHR HTA (UK) peer-review process, which includes independent expert and lay reviewers.

15.4 Poor quality data

The quality of the trial data will be monitored throughout the trial and data completeness will be reported to the TSC, and any cause for concern over data quality will be highlighted and an action plan put in place.

15.5 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

The research team and all PIs must disclose any ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial. Competing interests will be reported in all publications and in the final report.

15.6 Indemnity

The necessary trial insurance is provided by the Sponsors.

16 DISSEMINATION POLICY

An engagement plan will be produced with the TMG, collaborators and members of the Patient Advisory Group. A dissemination group will be set-up to have oversight of the plans and process. This will include clear processes around membership of the dissemination group, timeframes for review of proposed outputs strategy for dissemination of individual outputs. We will seek input from the Trial Steering Committee about the suitability of engagement plans and the dissemination policy.

In terms of the overall study findings, we will develop short and medium-longer term dissemination plans.

Short-term plans:

Study findings: We will compile a final bulletin telling the story of the study for participants and disseminate to relevant stakeholders. Stakeholders will include autism charities, advocacy groups, psychological practitioner forums, mental health service providers and commissioner forums. We will involve the Patient Advisory Group (PAG) in supporting accessible and appropriate dissemination. The study social media accounts and website will also be used to keep interested participants, managers and policy makers up to date with trial progress and findings.

On completion of the trial, a final report will be prepared for the Funder (NIHR HTA) and once approved made publicly available on their website and via publication in the NIHR HTA journal. The findings of the research will also be submitted for publication in journals interested in evidence- based treatments for autistic people and developments in CBT practice. The findings of the research will be submitted for presentation at national and international conferences of relevance to the topic of autism and mental health.

The final study report with the permission of the funders will be made available to the national autism team at NHS England and the NHS Autism Strategy group in Scotland. Strategy leads for dissemination in Wales and Northern Ireland will be sought.

Individual study outputs will be agreed with the involvement of the dissemination group.

Medium-longer term dissemination plans.

Guidance from the NHS dissemination unit about dissemination to policy makers and service managers will be sought, including how best to disseminate the treatment materials, practitioner manual and therapist training resources, dependent on the study findings. It may be possible to use the electronic learning for health platform as a way to disseminate the intervention materials consistent with co-applicant previous experience in disseminating the BEAT-IT intervention e.g. https://www.e-lfh.org.uk/programmes/intellectual-disability-and-depression-talking-therapies/ or the Future NHS platform.

HTA terms and conditions and acknowledgements

HTA terms and conditions for publications and dissemination will be adhered to.

Copies of all project outputs (publications and presentations) will be submitted to the HTA programmes using an “output notification form”.

17 Amendments to protocol

Amendment number (i.e. REC and/or MHRA amendment number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
Amendment 4	1.1	19MAY2022	2.0	28.03.2023	• PI update for AWP • Updated contact details for sponsor • Updates DMC members • Typographical errors updated throughout • Definitions added for progression criteria • Updated section 6 to better clarify and reflect the patient pathway and processes. • Addition of call 2 weeks post randomisation for TAU participants • Safety reporting section to reflect safety reporting procedures as agreed with sponsor	02.05.2023
Amendment 11	2.0	28MAR2023	3.0	04.07.2024	• Update to clarify & correct errors in Table 3 • Removal of reference to “exit call” at 52 weeks • Update of recruitment and study end dates/timelines • Clarification of GP having clinical responsibility throughout for both TAU and GSH arms • Update to clarify blinding information	

18 SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in UK Policy Framework for Health and Social Care Research, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the **Study Sponsor:**

Signature:

Date:

Name (please print): Julie Barnett

Chief Investigator:

Signature:

Date:

Name (please print):

Professor Ailsa Russell

Senior Statistician:

Signature:

Date:

Name (please print): Professor Chris Metcalfe

18 REFERENCES

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APPENDIX 1 COVID-19 Considerations

Research, including randomised controlled trials (RCTs), provides essential high-quality evidence that guides medical advancements around the world, influencing the quality of health and lives of all. Due to the coronavirus pandemic (COVID-19), research in the UK and globally has had to respond to the various COVID-19 mitigation efforts (e.g., societal lockdowns, social distancing and shielding measures) and unprecedented demands on healthcare professionals and resources. This has resulted in many research projects that are not related to the pandemic, being paused or in some cases, halted altogether. It is imperative that we consider how research can continue during, and beyond, COVID-19, or equivalent scenarios. Here, we summarise key considerations and actions taken to enable the continuation of ADEPT-2 in the UK, which are based on (rapidly evolving) guidance from relevant research bodies (e.g., NIHR, HRA), supporting literature (e.g. (69)) and preliminary interview data.

Trial conduct considerations

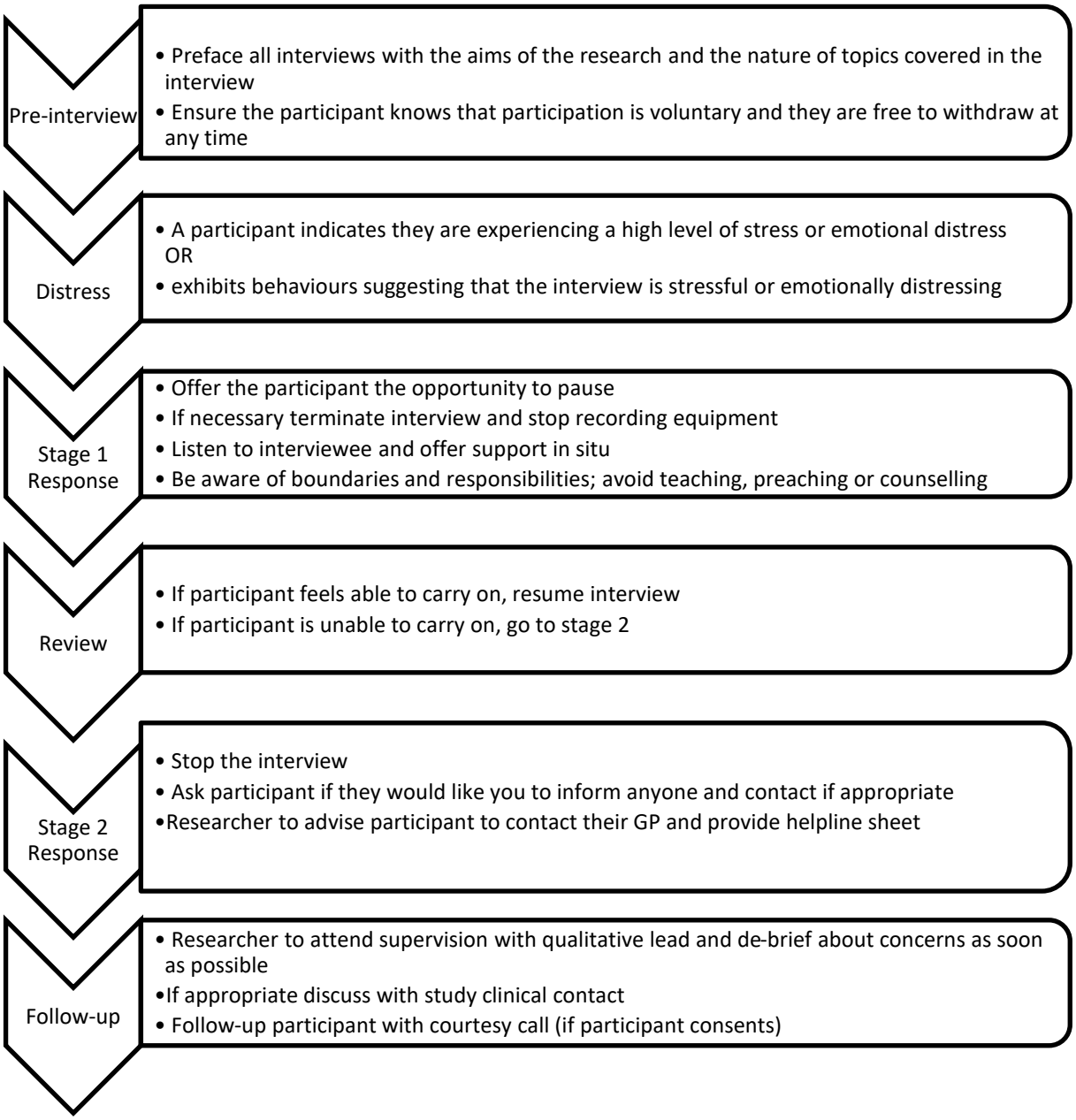
Adapting consent and data collection: We anticipate that the majority of Baseline appointments (and other study points of contact and assessments) will be conducted via Sponsor-approved video-conferencing (i.e., to reduce risk of potential exposure to COVID-19 and/or due to a requirement for remote contact and data collection by the potential participant). Alternative methods of communication (e.g., other remote methods and/or face-to-face visits) will be considered and facilitated, where feasible. Online eConsent and questionnaires will be available, in addition to more traditional methods such as paper copies or completed over the telephone. In addition, given the increased pragmatic nature of ADEPT-2, we anticipate the need for flexibility surrounding the timings of some points of contact and assessment, so have provided acceptable timings for these. From the researcher perspective, direct data entry into the secure online database minimises data protection concerns. The study also proposes collecting back up ‘best contact’ alternatives (e.g., the contact details of others including carer/ other family member, where applicable) in case contact with the participant is lost.

Furthermore, when face-to-face in person appointments are “permitted”, we recognise they bring about higher risk and may not (always) be feasible. To mitigate such risks, ADEPT-2 offers flexibility around assessment and communication methods as noted above (and throughout the protocol). If face-to-face in person appointments are requested, research staff should assess feasibility and follow the organisation guidance at the time regarding face-to-face in person contact, including, for example, use of personal protective equipment (PPE) and cleaning procedures. Research staff would be encouraged to help participants avoid situations where risk of exposure may be greater (e.g., public transport) and remind participants that they have a choice of contact and data collection methods to suit their needs and preferences.

Intervention delivery considerations

Similar to the above, those receiving the intervention GSH sessions can receive the session remotely or in person.

APPENDIX 2 Distress Protocol for Participants during Research Interviews



APPENDIX 3 Study Within A Trial (SWAT)

Objective

To inform the design of interventional randomised controlled trials for autistic adults with a Treatment as usual condition

Research questions

Does providing information about enhancement to treatment as usual impact autistic adults' perception of equipoise when consenting to randomisation and reduce the likelihood of attrition from Treatment as usual in a randomised controlled trial (RCT) of a psychological intervention for depression?

Does providing autism awareness training to psychological therapists delivering Treatment as usual affect therapists' perception of equipoise about psychological interventions for autistic adults and impact on their practice?

Background

Equipoise in RCTs relates to the uncertainty principle i.e., that participants and researchers are unsure about which intervention will confer most benefit to participants in the study. Participants can have a treatment preference prior to randomisation, and this can be based on perceived risks of the novel intervention, a general tolerance for novel interventions, concerns about side-effects and expectations of benefit for either intervention. A recent systematic review established however that there is no evidence that treatment preferences influence attrition in RCTs (70).

In an earlier feasibility RCT on the topic of guided self-help for depression in autism, a greater proportion of participants withdrew or were lost to follow-up from the TAU arm than the new intervention arm (Guided Self Help;GSH;)(59). In some instances, withdrawal was contingent on the outcome of randomisation to TAU. Some participants expressed the view that they had joined the study to access therapy specifically tailored for autistic people as they had prior negative experience of TAU (24). In brief, several participants who took part in the interviews did not hold a view of clinical equipoise.

An RCT design using Treatment as usual (TAU) or existing practice as the comparator arm for a new intervention is subject to potential participants' views about and expectations of TAU. Where TAU is perceived as inadequate, this can raise ethical and clinical issues as well as impact on participant perceptions of equipoise and affect recruitment and retention to the study. TAU for mild-moderate depression includes low-intensity cognitive behavioural interventions, ordinarily delivered by NHS Talking Therapies for anxiety and depression (NHSTT) (formerly, Increasing Access to Psychological Therapies (IAPT) services). Working with autistic people is not included in the core training curriculum for NHSTT practitioners. Cognitive behavioural therapists report a lack of confidence in adapting their practice to meet the needs of autistic people (27). Autistic adults report barriers to accessing psychological therapy services, specifically a lack of therapist knowledge about autism and therapist unwillingness/inability to adapt their practice (23) . It is plausible that TAU for mild-moderate depression is perceived as less than optimal by autistic adults and TAU therapists.

Based on published studies about autistic adults' experiences of accessing psychological therapy and the findings of the ADEPT feasibility study, it is considered appropriate to enhance TAU for the proposed full-scale RCT (ADEPT-2) which aims to investigate the effectiveness and cost-effectiveness of GSH and to evaluate the impact of this enhancement on perceptions of equipoise.

The aim of this study within a trial (SWAT) is to increase participants' perception of equipoise in the ADEPT-2 RCT. This aim will be met by providing participants with information about enhancements to TAU prior to randomisation. The enhancements will comprise the provision of training resources for TAU psychological therapists. These training resources will provide information about how to adapt standard CBT practice 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.

Design and Methods

Information about the enhancements to TAU will be included in the Patient Information Leaflet (PIL) for the ADEPT-2 study. This will be carefully worded, as it is not certain that all therapists in TAU services will access the training resources.

Autism training resources will be made available to TAU psychological therapy services in the participating NHS sites for the ADEPT-2 study.

This SWAT will use primarily qualitative methods to answer the research questions.

(a) To investigate the impact of providing information about enhancement to TAU on participant randomisation preference and retention to the TAU arm of ADEPT-2, we will draw on the data as part of the overall study protocol for ADEPT-2. Qualitative interviews carried out with participants consenting and not-consenting to take part in ADEPT-2 as part of the overall study protocol, will include questions about their views about the enhancements to TAU as part of these interviews.

(b) We will seek TAU therapists' views about the training resources which constitute the enhancement to TAU. We will ask therapists to complete a short online survey prior to accessing the training resources asking them about their experience of working with autistic people, confidence in adapting practice and perceived usefulness of CBT. We will ask them to complete a short online survey immediately following their access to the training resources. This survey will ask them about the perceived usefulness of the resources. We will ask participating therapists to complete a further survey 5 months following their access to the training resources to understand further any impact the training had on their practice, changes in confidence in working with autistic people, and any new areas that would be helpful to receive training in. We will invite participating therapists to join a focus group with other therapists to further understand their experiences.

Participants

Participants will be adults ≥ 18 years of age eligible and consenting to participate in the ADEPT-2 study. Consent for these data to be used will be part of the general consent processes for the ADEPT-2 study participants.

Psychological therapists working in the primary care/NHSTT services in the sites/centres for the ADEPT-2 study consenting to take part in the study.

Psychological therapists will be invited to take part in the study when accessing the therapist training resources on the ADEPT-2 project website.

Consent to take part in the online survey pre and post accessing the training resources by TAU psychological therapists will be sought. Therapists consenting to take part in the online survey will be invited to take part in follow-up focus group or survey if they so wish.

We will seek a convenience sample of TAU psychological therapists, with no a-priori same size calculation as this is a primarily qualitative study.

Measures

Baseline:

Quantitative information:

- Randomisation preference expressed prior to randomisation by participants eligible and consenting to the ADEPT-2 study.
- Rates of retention to the GSH and TAU arms in the ADEPT-2 study.
- Therapist uptake of the training resources measured by number of times the resources are accessed by participating region. (Website traffic)
- Therapist satisfaction with the training resources (survey following access)
- Therapist confidence in working with autistic people as measured by the Adapted Therapist Confidence Scale

Qualitative Information:

ADEPT-2 study participants – participants consenting and non-consenting to take part in the ADEPT-2 study will be invited to take part in qualitative interviews (see main study protocol). We will include a question in these interviews about the provision of information about enhancement to TAU and their views about this information.

Follow-up:

TAU therapists accessing the training resources will be invited to complete a survey 5 months after the training to understand any impact the resources have had on their practice and any new areas which could have been included in the training pack.

TAU therapists will be invited to attend a focus group online with other therapist participants (4-6 participants per group) in the study to discuss their use of the training resources and any associated changes in practice. There will be 4 focus groups held, to gain a sample size of between 15 and 25 therapists. Focus groups will have a flexible topic guide, with questions covering similar areas to the quantitative questionnaire. Areas covered by the topic guide will include therapist views on equipoise in the ADEPT trial; changes to knowledge regarding adapting to work with autistic people; how useful therapists found the training materials; whether therapists have changed their practice following the training; future avenues for training. A qualitative researcher will guide the discussion to ensure that key areas are discussed. The focus group will be recorded on MS Teams or encrypted audio recorder and later transcribed using a professional transcription service. Recordings will be deleted once analysis is complete. Anonymised transcripts will be analysed using thematic analysis.

Study Setting

NHS (or NHS Commissioned) Talking Therapies for anxiety and depression (formerly, Increasing Access to Psychological Therapy (IAPT) services) in the participating regions/centres of the ADEPT-2 study will be contacted. These services will be provided with information about the ADEPT-2 study and will be invited to access the therapist training resources using a link to the study website.

Analysis

Information gathered from the therapist survey will be analysed using descriptive statistics in respect of frequency of survey access and therapist demographics in using the survey. Pre-post- change in therapist confidence will be investigated using repeated measures ANOVA.

Responses to open-text survey items enquiring about helpful aspects of the therapist training resources and further areas suggested for training will be analysed using content analysis.

Thematic analysis will be used to understand the therapist experiences of using the training in practice as captured by the focus groups. This analysis will be conducted using a data driven inductive approach, and following the steps outlined by Braun and Clarke (2006) (54). Data analysis will be conducted in tandem with data collection, and the topic guide may be amended based on early findings to ensure that a rich dataset is developed from the focus groups.

Protocol Contributors

This protocol was developed by investigators on the ADEPT-2 study (AR, PL, DD, KC, NW, JH) and a PPI member (VW), a CBT therapist with lived experience.

Patient and Public Involvement

VW was involved in designing the research protocol and therapist survey.

DISCLAIMER

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