The ADEPT Study

The feasibility of Guided Self-Help for depression in adults with Autism

STUDY PROTOCOL

Study Title:

Guided Self-Help for Depression in adults with Autism: A feasibility study

Short Title and Acronym:

ADEPT: Autism Depression Trial

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List of Abbreviations

AE	Adverse Event
ASD	Autism Spectrum Disorder
AWP	Avon & Wiltshire NHS Mental Health Partnership Trust
BRTC	Bristol Randomised Trials Collaboration
ADEPT	Autism Depression Trial
GSH	Guided Self-Help
NTW	Northumberland, Tyne & Wear NHS Trust
PI	Principal Investigator
PIS	Participant Information Sheet
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SSI	Site Specific Information
TMG	Trial Management Group
TSC	Trial Steering Committee

Administrative Information

1. Study Title:

Guided Self-Help for Depression in adults with Autism Disorders: A feasibility study

Short Title and Acronym:
Autism Depression Trial: ADEPT

2. Trial Registration

ISRCTN Number/Clinical trials.gov number

FUNDERS number: NIHR HTA project 14/43/02

Ethics Number: 16/WA/0077 (WALES REC3)

3. Protocol Version

Protocol version 1.1

4. Funding

This study is an NIHR Health Technology Assessment (HTA) funded study.

5. Roles and Responsibilities

Names, affiliations and roles of Protocol Contributors

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Author's Contributions

AR, DK, NW, SB, DR, JP, BI and JH developed the study protocol, AJR and SB developed the intervention, NW provided methodological and statistical expertise in trial design, JH designed the qualitative evaluation, CM provided statistical expertise

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Role of Sponsor and Funder

Avon and Wiltshire Mental Health Partnership NHS Trust (the Trust) is the sponsor for the study. The Trust has agreed to act as sponsor for the Project under the Research Governance Framework for Health and Social Care Second Edition 2005 (as amended from time to time).

Insurance:

Avon and Wiltshire Mental Health Partnership NHS Trust also has extensive insurance cover in place. The Trust shall indemnify against all damages, losses, claims, costs and expenses for which it becomes legally liable as a result of bodily injuries to persons and/or damage to material property to the extent that this shall arise out of any negligent act or omission committed by or on behalf of the Trust during the course of the work.

Employers Liability

This is cover for legal liability to employees for death, injury or disease arising out of the business of the University.

Public and Products Liability

This is cover for legal liability to third parties for accidental loss of or damage to property or for death, injury, illness or disease arising out of our business and including liability arising from goods sold or supplied.

Professional Indemnity

This is cover for legal liability to third parties for breach of professional duty due to negligent act, error or omission in the course of our business.

Monitoring:

The Chief Investigator will be responsible for day to day monitoring and management of the study. Principal Investigators (AR in Bristol and SB in Northumberland) will monitor the management of the study within each site. The Research and Development Department of the study sponsor, Avon and Wiltshire Mental Health Partnership NHS Trust, will monitor and conduct random audits on a selection of studies in its clinical research portfolio. Monitoring and auditing will be carried out in accordance with the DH's research governance framework for health and social care and in accordance with the sponsor's policies and procedures.

Committees

Trial Management Group

Chief Investigator, Trial Co-ordinators, BRTC lead, Statistician, Qualitative Study P.I., Co-applicants
Study Planning
Organisation of Steering Committee
Reporting of Adverse and serious adverse events to TSC, DMEC, sponsors and funders
Development and agreement of study protocol
Recruitment procedures and progress
Data management and oversight

Trial Steering Committee

Agreement of final protocol
Liaison with Chief Investigator and principal investigator for study sites
Reviewing progress of the study and if necessary agreeing any amendments to the protocol

Data Monitoring and Ethics Committee

Ethics role – reviewing and advising on reports of Adverse and Serious Adverse Events
Data Monitoring

Public and Patient Advisory Group

Agreeing aspects of the final protocol that are particularly relevant to recruitment and other procedures directly involving participants. If necessary agreeing any amendments to the protocol
Advising on patient facing materials in terms of content and presentation
Advising on dissemination plans as outlined in the protocol
Assisting with therapist training
Serve on TSC

6. Background & Rationale

Depression is a common mental disorder characterised by low mood, reduced energy, interest or pleasure, feelings of guilt and low self-worth, disturbances in sleep or appetite and poor concentration (ICD-10, WHO 1992). Depression is a debilitating health condition and the leading cause of disability worldwide in terms of total years lost to disability.

The prevalence of depression varies according to gender, age and social economic factors. The estimated life-time point prevalence for a depressive episode for adults aged 16-74 in the UK was 2.3%, with a higher estimate of 9% for mixed depression and anxiety (McManus et al., 2009). There have been few robust epidemiological studies of depression in adults with Autism Spectrum Disorders (ASD) but studies reporting psychiatric co-morbidity have cited high rates of mental disorder in ASD, including depression and anxiety disorders across the life-span (see Mannion and Leader, 2013 for a review). For example, of 122 adults with ASD participating in a study of co-morbidity, Hofvander et al.,

(2009) noted that the most common life-time co-morbid disorder was depression, with 53% of adults with ASD meeting criteria for depression and 34% prescribed anti-depressant medication at some point in their life.

In addition to the relatively high prevalence of depression in Autism Spectrum Disorders (ASD), there is also some evidence that the phenomenology of depression may be atypical. Difficulties with emotional expression by adults with ASD have been reported (Hill et al., 2004) suggesting that verbal descriptions of emotions such as sadness may be atypical or less forthcoming. There are also descriptions of increased social withdrawal and even catatonia (Wing & Shah, 2000), the latter comprising a marked decrease in self-care skills and extreme slowness. Ghazuiddin et al., (2002) review how there may be a change in the intensity or content of a special interest or an increase in obsessive compulsive phenomena when depression is present.

In summary a debilitating mental disorder, depression, occurs commonly in people with Autism Spectrum Disorders. There is some evidence that differences in clinical presentation and problems with emotional expression may make it more difficult for clinicians to identify depression in people with ASD.

The National Institute for Health and Care Excellence (NICE) highlights mild-moderate depression as relevant to Step 2 of the care pathway, with recommended treatment comprising individual guided self-help based on the principles of Cognitive Behaviour Therapy (CBT) and including behavioural activation and problem-solving techniques. Guided self-help should include the provision of written materials (or alternative media) and be supported by a trained practitioner who will facilitate the self-help programme and review progress and outcome over the course of 6-8 sessions (face-to-face and via telephone) usually taking place over 9-12 weeks, including follow-up.

Step 2 interventions are typically delivered in the National Health Service at the level of primary care by Increasing Access to Psychological Therapy (IAPT) services. It is not known whether adults with ASD and mild-moderate depression routinely access IAPT services for treatment. It is known that guided self-help materials for depression have not been specifically developed with adults with ASD in mind.

Cognitive Behavioural Therapy (CBT) adapted for Autism has been shown to be effective in reducing anxiety problems in young people (e.g. Wood et al., 2009) and adults (e.g. Russell et al., 2013). Recent systematic reviews indicate that adapted Cognitive Behavioural Therapy (CBT) is effective in reducing anxiety problems in young people (Lang et al, 2010; Sukhodolsky et al., 2013) and adults with ASD (Spain et al., 2015). Meta-analysis of the paediatric studies report relatively large effect sizes (*d*= 1.19 on clinician rated outcomes and *d*=1.21 on parent rated outcomes) for CBT interventions.

Adaptations to the structure or delivery of CBT are outlined in the NICE clinical guidance for adults with Autism (NICE CG142, 2012). These include a more concrete and structured approach with a greater use of written and visual information, a greater emphasis on changing behaviours rather than cognitions, rules should be made explicit and explained, there should be use of plain English, excessive use of metaphor, ambiguity and hypothetical situations should be avoided, a family member, partner, carer or professional should be involved if the person agrees, and efforts to maintain attention such as offering breaks and incorporating an individual's special interests into therapy should be made. Additional modifications comprising psychoeducation about emotions and multiple choice

worksheets for cognitive strategies are included in the clinical guidance for children and young people with Autism (NICE CG170, 2013).

Despite the high rates of depression reported in Autism and the success in evaluating the effectiveness of adapting CBT for anxiety problems, CBT approaches for treating depression in this group have not as yet been subject to systematic evaluation. There has been just 1 study in this area to our knowledge. McGilliveray and Evert (2014) report the findings from a quasi-experimental evaluation of group CBT for depression and anxiety in 32 young adults (aged 15-25 years) with ASD who were randomly allocated to the CBT or Wait List (WL) group. The 9 session CBT group intervention contained many of the adaptations recommended for ASD. There was a significant effect of time but not treatment group in terms of a reduction in scores on the depression measure. Approximately 60% in the CBT group showed a significant reduction in Depression and Anxiety Stress Scale (DASS) scores compared to 38% in the WL group. However, participants with scores above average on the main outcome measure, the depression sub-scale of the DASS, randomised to the CBT intervention showed significantly greater improvements than the participants allocated to WL.

Summary

There is evidence of elevated rates of depression in ASD across the lifespan. Clinical guidance based on research evidence recommends individual guided self-help based on the principles of CBT as the psychological treatment of choice. Cognitive behavioural interventions for anxiety have been successfully adapted for people with ASD and delivered within the framework of randomised clinical trials with good treatment outcomes. There is some preliminary evidence that an adapted cognitive behavioural intervention can bring about significant reduction in depression symptoms in young people with ASD. However this evidence base comprises a single study, where the intervention within a group format may not be optimal in terms of treatment effects and or practical in respect of service delivery.

There is therefore a need to investigate whether a CBT intervention taking the form of individual guided self-help for depression in line with NICE recommendations can be successfully adapted for people with ASD.

7. Objectives

The key aims and objectives of the research are to conduct a feasibility study:

- To develop self-help materials based on NICE recommended psychological principles for the treatment of depression specifically tailored for adults with ASD and training materials to guide therapists in how best to support adults with ASD in the use of the self-help materials
- To find out how acceptable the materials and the intervention are to adults with ASD and therapists using qualitative methods
- To estimate the rate of recruitment for a large-scale randomised controlled trial (RCT)
- To estimate the retention rates to inform the RCT, particularly the sample size calculation
- To identify the most appropriate outcome measure for the large-scale RCT

Methods: Participants, Interventions, Outcomes

8. Development of the Intervention

The intervention will be developed by 2 clinical psychologists (AR & SB) with training and accreditation in Cognitive Behaviour Therapy (CBT). AR has experience and expertise in adapting CBT interventions for people with Autism. SB has experience and expertise in developing CBT treatments for depression and training IAPT practitioners. The intervention principles have been clearly defined within the background of Behavioural Activation for Depression and the manner in which these will be delivered to adults with Autism via guided self-help (i.e. adapted for Autism) have been clarified. The adaptations are based on principles outlined in the NICE guidance for adults with Autism (CG142, 2012) and previous studies in this area (e.g. Russell et al., 2013).

9. Trial Design

The feasibility study will comprise a Randomised Controlled Trial (RCT) with a nested qualitative evaluation.

Participants will be randomly allocated to Guided Self-help for Depression adapted for Adults with Autism (GSH) or Treatment as Usual (TAU).

Depression will be measured pre-treatment and 10 weeks post randomisation (end of intervention), with additional outcome measurements at 16 and 24 weeks post randomisation.

10. Study Setting

The study will run across 2 NHS sites, Avon & Wiltshire Mental Health Partnership NHS Trust and Northumberland Tyne & Wear NHS Trust.

11. Participants

Inclusion Criteria

- Adults (aged 18 years or over) with a clinic diagnosis of an Autism Spectrum Disorder (ASD) and current depression as measured by a PHQ-9 score ≥ 10 will be eligible to take part.

Exclusion Criteria

- Participants where intellectual disability is known or suspected will be excluded as the self-help materials will not be modified in line with their needs
- 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 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. Risk may increase during the study as evidenced by session by session administration of the PHQ-9 for those in the GSH group. If increased risk is identified following review of the case in clinical supervision, the therapist guide and clinical supervisor will discuss whether referral to statutory health services and discontinuation in the study is indicated.

- Participants with a history of psychosis, current alcohol/substance dependence or untreated epilepsy will be excluded
- 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
- Participants who are non-English speaking as the intervention takes the form of written materials and therapist discussion which requires a sufficient level of English to access.

12. Recruitment

Patient identification

Participants will be identified by (i) clinicians in the Bristol Adult Autism Service (BASS) within AWP, (ii) 'Everybody Included' within AWP, (iii) clinicians in the Adult Autism Clinic in NTW and (iv) the Autism Spectrum Cohort-UK at Newcastle University.

There are different versions of patient identification according to local clinical and recruitment procedures and these are outlined below.

i) Adult Autism Clinic in AWP

The PHQ-9 is administered as part of pre-clinic screening. Clinicians will identify individuals attending the clinic who meet the eligibility criteria i.e. PHQ-9 score ≥ 10 for the study.

The BASS clinician(s) will introduce the study to eligible participants using a brief Expression of Interest form and ask if they give their permission for the research team to contact them about the study. If they agree, the research team will contact the individual and provide them with full information about the study via the Participation Information sheet (PIS). If the individual agrees to meet with a researcher, standard recruitment procedures will be implemented (see below).

ii) 'Everyone Included' in AWP

AWP will also use the 'Everyone Included' approach to identify potentially eligible participants, who will receive a 'Research Opportunity Letter'. 'Everyone Included' is a standard approach to research in AWP, whereby service users are routinely informed about relevant research opportunities by post, unless individuals express a preference not to receive information in this way. As is standard practice, a list of potential participants will be identified via an automated search of the electronic patient record system (RiO), based on the study inclusion /exclusion criteria. The search is authorised and requested by a member of AWP Research & Development (R&D), who are part of the clinical team, and conducted by the Information Analysis team within AWP.

Data is returned directly to the R&D department for processing and excludes people who have declined to receive information via Everyone Included. R&D process and send the 'Research Opportunity Letters' to service users on behalf of the research team. No information is ever accessed by or passed to an external research team without gaining prior permission from the potential participant.

Any research team wishing to use this approach must first submit an Application Form and draft 'Research Opportunity Letter' for approval. These details are reviewed by independent members of the Everyone Included Review Panel (includes service users, carers, clinicians and researchers), who decide whether a study is appropriate.

The 'Research Opportunity Letter' briefly and concisely explains what the study is about and what it involved. The letter does not contain any disclosing information (such as personal references to diagnosis or medications) and invites interested individuals to make contact with the Everyone Included team to express interest if they would like to take part. The letter including details of how to contact the Everyone Included team (by phone, email or post using a free post reply slip) and is signed by the Director of Research & Development and AWP Principal Investigator for the study. If individuals do not respond, nothing further will happen.

Upon initiating contact, potential participants will be provided with a Participant Information Sheet and/or are asked if they expressly give their permission for their interest (i.e name and phone number) to be passed to a research team. At this point standard study recruitment processes proceed.

iii) Adult Autism Clinic in Northumberland, Tyne & Wear NHS Trust (NTW)

Information about the study will be provided to clinicians in the clinic. They will be asked to provide the brief Expression of interest form to individuals who meet criteria for an Autism Spectrum Disorder (ASD) and who they assess as having depression sufficient to warrant signposting/referral to IAPT services as per routine clinical practice. This signposting usually occurs at the end of the diagnostic assessment in NTW at a follow-up appointment (up to 6 weeks post-initial appointment). At the follow-up appointment, feedback is given to the individual about the outcome of the diagnostic assessment and information/recommendations about treatment and support. A summary report is sent to the individual and their GP following this appointment.

At this 2nd appointment, individuals whose summary report confirms a diagnosis of ASD and recommends signposting to local IAPT services for treatment of mild-moderate depression will be provided with the Expression of Interest form for the study. They will be asked if they give their permission for the details to be passed onto the research team who would provide more information about the study. If they agree to contact, the research team will contact the individual via their preferred method of communication and introduce the study. Individuals will be asked to complete the PHQ-9 either by post or on the telephone and to give permission for the results of screening to be communicated to their G.P. Those individuals with a score of ≥ 10 will be provided with comprehensive information about the study via the PIS and standard recruitment procedures will be implemented.

iv) Life-Course database at University of Newcastle

This is a Newcastle University led national cohort study of adults on the autism spectrum funded by Autistica, a U.K based charity. Subject to approval by the research committee, participants registered on the database as part of the cohort can be invited to take part in this study. The study exclusion criteria can be applied to the database and the search can be constrained by post-code i.e. resident in the NTW or Bristol/Bath geographical area. Potentially suitable individuals would be sent the brief information sheet (Expression of Interest form) and asked to contact the research team if they are interested in finding out more about the study.

Individuals contacting the research team would be asked for permission to screen for the study, and this would include completing the PHQ-9 by post or on the telephone. They would also be asked for permission for the outcome of screening to be sent to their GP.

Participants potentially eligible for the study would then be subject to standard recruitment procedures.

Standard Recruitment Procedure

Individuals with a score of ≥ 10 on the PHQ-9 who are potentially eligible to take part in the study in the study will be provided with the Participant Information Sheet by post or email. Follow-up contact will be offered to answer any questions. Those agreeing to take part in the study will be invited to a face-to-face appointment with a researcher to establish eligibility, answer any questions about their participation, and seek written informed consent.

Individuals declining to further participate in the study will be asked for brief details of their reason(s) for non-participation. They will be asked to provide permission for the non-participation information and details about their age and gender to be recorded. This information will inform recruitment strategies for a large-scale trial.

Assessment of Eligibility

Participants screening as suitable for the study will be invited for a full eligibility assessment. They will be asked to complete the PHQ-9 and the Clinical Interview Schedule-Revised (CIS-R). If the PHQ-9 score is ≥10 and the individual gives consent to participate in the study, fully informed consent in writing will be obtained. Participants will be over the age of 16. The researcher will check that participants are providing fully informed consent 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 participants have understood and retained the information provided about the study, and are aware of the voluntary nature of their involvement and their right to withdraw.

Baseline information about sociodemographic details, history of depression, current medication and current/prior psychological treatment for depression will be collected and will inform the eligibility assessment.

If eligible for the study and consenting, the participant will also be asked to complete other quantitative measures at this appointment which will last 60-90 minutes. These will include self-report measures of depression, anxiety, quality of life and social function. An observer measure of depression

will also be completed and consent to audio record the interview will be sought to facilitate additional ratings of the observer measure of depression for reliability purposes. Socio-demographic information will be collected using a tailored questionnaire. Information about current employment, occupation, health/social service use, financial stress and residential status will be sought in a structured format

Participants who do not meet eligibility criteria because of the severity of depression and/or intensity of suicidal ideation (i.e. score of 3 on item 9 of PHQ-9) will be thanked for their time and willingness to participate in the study. It will be explained that the study is not designed to offer effective treatment that might meet their current needs and that the PHQ-9 score and risk indicators will be communicated to their G.P. as per study protocol and to the AWP/NTW Adult Autism clinic if recruited via this pathway.

Participants who do not meet eligibility criteria for depression at the baseline appointment will be thanked for their time and it will be explained that the study is not suitable for them.

Retention strategies

A strategy will be agreed with each individual participant as to the optimal, preferred means and timing of reminders about follow-ups frequency of contact with the research study.
Impairments in Executive function are well documented in adults with Autism with difficulties in organisation and planning frequently noted. Furthermore, Autism is inherently a disorder of social communication with individual preferences for use of the telephone and other forms of communication highly pertinent to effective engagement. Adults develop strategies including reliance on others for communication and organisational activities. All consenting participants will be asked to describe their preference for method and frequency of communication about outcome and follow-up assessments within the parameters of the pre-defined follow-up intervals dictated by the study methods. Ordinarily, 'lost to follow-up' will be recorded if this agreed protocol is completed and contact is not maintained.

Methods: Assignment of Interventions

13. Allocation

Once written informed consent is gained, participants will be randomised to one of two groups: (1) Guided self-help for depression (GSH); or (2) Treatment as usual (TAU). Randomisation will take place by means of a remote automated telephone service administered by the Bristol Randomised Trials Collaboration (BRTC). This will ensure that allocations are concealed from the recruiting researcher. Randomisation will be stratified by centre to predict the workload in terms of delivering GSH across the treatment sites and a minimising factor will be current antidepressant medication.

14. Blinding

It will not be possible to blind participants to their treatment allocation. Observer bias will be avoided through the use of self-completed outcome measures in the main. The observer completed outcome measure of depression (Hamilton Rating Scale for Depression HRSD) will be completed by a research workers on the project who will remain blind to treatment allocation throughout the study. Participants will be reminded that the assessor is blind to group status in letters and in person. We have experience of participants maintaining this blind from other studies. The research worker will be involved in administering assessments for the study, but will not be embedded in the NHS services or involved in the delivery of the intervention.

Intervention and Comparator

Once participants have been randomised, we will aim to start treatment within 2 weeks. Guided self-help (GSH) should begin within this 2 week window and/or information signposting the participant and their GP to Treatment as Usual (TAU) should be completed no more than 2 weeks post-randomisation.

Participants' GPs will be informed about individual involvement in the study and outcome of treatment allocation.

Intervention: GSH

The intervention takes the form of guided self-help for depression adapted for adults with Autism.
Materials for 8 sessions and an accompanying guide for the therapist will be provided.
Sessions will ordinarily last 30-40 minutes in duration, but can be significantly shorter (minimum of 20 minutes) according to individual preference. The initial session will be approximately 60-80 minutes to introduce the treatment and foster engagement.
The intervention will be delivered over a maximum of 10 weeks.
The therapist will encourage the patient to work through the materials, including tasks to complete between sessions to facilitate learning.
The intervention will be informed by the principles underlying Behavioural Activation (BA).
Therapist materials/guidance will accompany the patient facing materials
The therapist will be a 'low intensity' cognitive behaviour therapist or Psychological Wellbeing Practitioner (PWP) i.e. a therapist working at the low intensity step of the care pathway for depression who has knowledge of cognitive behavioural theory of psychological problems and training/experience in delivering manualised interventions. They will not ordinarily have the knowledge and training to develop individualised, formulation driven interventions for psychological problems.
The therapists will be trained in the intervention by AR, SB and an adult with Autism, ideally who is part of the Patient and Public Advisory Group. The training will last 15 hours.

The therapists will receive weekly supervision in the AWP site by AR and NTW site by SB for the duration of the intervention phase of the study. Supervisory cover will be provided via telephone or Skype when required for either site.
The patient can be offered the option of telephone sessions for sessions 6-8.

Comparator

The comparator intervention is Treatment as Usual (TAU). TAU will be carefully recorded in terms of the nature and timing of any intervention received. This will be via the resource use questionnaire.
TAU as usual may include:

1. No treatment
2. Signposting for self-referral to IAPT services
3. Autism clinician recommendation to the GP to make a referral to IAPT services
4. Clinic or GP referral to secondary care mental health services
5. Anti-depressant medication

Concomitant Care

Medication and changes to medication will be recorded.
For participants allocated to GSH, the start of any adjunct psychological intervention (talking therapy) will be delayed for the duration of the intervention. After 10 week assessment, receipt of additional social and psychological interventions will be recorded as part of the follow-up assessments.

15. Outcomes

Measures of depression

- The Patient Health Questionnaire (PHQ-9) (Spitzer et al.,(2006)
- Beck Depression Inventory-II (BDI-II) (Beck et al., 1996)
- Hamilton Rating Scale for Depression (Hamilton, M.(1960) - The Hamilton Depression Rating Scale (HDRS) will be administered according to the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D) (Williams, JBW, 1988). To further consider reliability of this observer rating of depression, consent to record the interview will be sought and/or an additional rater will be present to establish inter-rater reliability

Other Quantitative Outcomes

- Obsessive Compulsive Inventory-Revised (OCI-R) (Foa et al., 2002)
- General Anxiety Disorder Questionnaire (GAD-7) (Spitzer et al., 2006)
- Positive and Negative Affect Schedule (PANAS) (Crawford & Henry, 2004)
- Work and Social Adjustment Scale (WSAS) (Mundt et al., 2002)
- EQ-5D-L (Herdman et al., 2011)
- SF-12 (Ware et al., 1996)
- Economic evaluation - We will pilot data collection on resource use using a questionnaire administered at 10, 16 and 24 weeks to provide information on: use of other primary and community care services (NHS Direct, attendances at walk-in centres, use of community health care services); secondary care related to mental health (number of out-patient visits,

type of clinic, and reason for visit; inpatient stays, length of stay and reason); use of social services and disability payments received; personal costs related to mental health (expenditure on over-the-counter medication, expenditure on prescriptions, travel costs associated with health care visits, loss of earnings, out of pocket expenditure on other services e.g. private counselling or complementary or alternative therapies, child care and domestic help); time off work and unpaid activities. We will also access GP records to provide information on: number of primary care consultations, by type e.g. face-to-face, telephone etc., and who seen; and prescribed medication.

Methods: Data Collection, Management and Analysis

16. Sample Size

This feasibility study will not be powered to detect important clinical differences between intervention and usual care groups. We are proposing to collect data on outcomes that will be used to inform a future large-scale trial. By recruiting a sample of 70 participants with 35 in each randomised group we will be able to decide on the practical issues of conducting the trial and for estimating the standard of the continuous depression outcome with reasonable precision (Teare et al., 2014). Such a number would provide estimates of the completion rates of the intervention and retention rates that would assist in planning the recruitment for a future RCT. For example, if 80% of those randomised to receive the intervention complete guided self-help, the 95% confidence intervals would be 69% and 89%. Similarly, if 85% of those randomised are followed up at 10 weeks, the 95% confidence intervention for the retention rate would be 75% to 93%.

17. Data Collection Methods

Data will be collected through questionnaires administered over the telephone, using a computer and using pen and paper.

Initial screening via the PHQ-9 will be administered by post, on the telephone or in clinic according to participant preference and availability.

At the eligibility assessment, the CIS-R and Hamilton Rating Scale for Depression will be administered with the researcher. The CIS-R is a computerised assessment which can be completed by the participant.

Participants allocated to GSH, the PHQ-9 will be administered at the start of each session as in routine clinical practice. The PANAS and a brief survey of activities during the preceding week will also be administered at the start of each session.

At follow-up, the questionnaires can be administered by pen and paper at a meeting with the researcher. The Hamilton Rating Scale for Depression will be administered via clinical interview with the researcher.

Timing of Data Collection (see Schedule of Events)

Outcome data will be collected at 10, 16 and 24 weeks post-randomisation

Blinding of the HDRS assessor will be evaluated following the 10, 16 and 24 week assessment

18. Data Management

Completed questionnaires will be returned securely to the study team at the University of Bath where they will be stored in compliance with University of bath Data Security policies and the Data Protection Act 1998. Clinical data will be completed on paper. All data will be entered onto a secure database by a member of the study team at the University of Bath. Personal details and administrative data will be entered onto a secure database held on a University of Bristol server (ADEPT study staff entering data will be under honorary contract with University of Bristol and have secure access to the database), and non-identifiable data will be entered onto a secure web-based database (REDCap) via a secure internet link maintained by University of Bristol Information Services. The Clinical Trials Unit (BRTC) database team will develop and set-up the databases.

Data collected on paper case report forms (CRFs) or questionnaires will be identifiable only by Patient Identification Number (PIN). Study sites will be responsible for the secure transfer of completed CRFs by post or NHS email to the ADEPT study office at University of Bath, where it will be stored in a secure locked cabinet in a locked room with limited access.

Information capable of identifying individuals will be held on the database with passwords restricted to authorised study staff only.

19. Statistical Analysis

For this feasibility study, we will calculate: (1) the proportion of adults with ASD consenting to the study; (2) the proportion completing the baseline assessment and entering the randomised phase; (3) for those in the intervention group, the number of guided self-help sessions attended and the proportion completing 5 or more sessions; (4) the proportion completing follow-up assessments at 10 and 16 weeks post-randomisation. We will also compare the continuous scores on the depression outcome measure between groups. The standard deviation of the outcome will inform the sample size calculation for the large-scale RCT.

Methods: Monitoring

20. Data Monitoring

A Data Monitoring and Ethics Committee will be convened with an independent Chair, and will monitor accumulating trial data during the course of the study and make recommendations to the Trial Steering Committee as to whether there are any ethical or safety issues that may necessitate a modification to the trial protocol.

21. Safety assessments and monitoring

Adverse Events (AE)

The recommendations for defining and reporting adverse events and harm from psychological therapies as outlined by Parry, Crawford and Duggan (2016) will be used in the Adept Study.

An Adverse Event (AE) refers to:

(a) A significant episode during or shortly after treatment (e.g. suicide, suicide attempts, mental health related hospital admissions) which if related to or directly caused by treatment amount to harm or severe harm

(b) A sustained and clinically significant deterioration i.e. a worsened mental state after therapy is complete, which can include the emergence of new symptoms. For the purposes of the present study this would be reflected in a categorical negative change in scores on 1 or more of the depression measures used in the study across 2 follow-up points

(c) Report of a negative experience of the psychological intervention and perceived harm on the part of the participant when interviewed for the nested qualitative study.

Serious Adverse Events (SAEs)

A serious adverse event (SAE) is defined as an untoward occurrence that:

(a) results in death;

(b) is life-threatening;

(c) requires hospitalisation or prolongation of existing hospitalisation;

(d) results in persistent or significant disability or incapacity;

(f) is otherwise considered medically significant by the investigator.

The study will monitor the occurrence of any serious adverse event which arises whilst the participant is taking part in the ADEPT trial.

Participants, researchers and clinical staff should notify any adverse event which they believe may have occurred as a result of the trial intervention or the research process. On notification of such an adverse event which may be related to the research process or intervention, a researcher or member of site staff should complete an adverse event report form within 5 working days, paying specific attention to information regarding the nature and timescale of events i.e. when the event started,

were there any specific changes to medication or behaviour preceding the event. Further information should be requested from the participant, clinical team or GP as necessary. A completed form should be securely sent to the Chief Investigator for review and assessment of relatedness and expectedness as follows:

1. Confirmation of seriousness (whether the adverse event is an AE or SAE)
2. Causality – i.e. relatedness of the event to the study intervention, according the following definitions:

    Unrelated – where an event is not considered to be related to the study intervention
    Possibly – although a relationship to the study intervention cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible
    Probably – the temporal relationship and absence of a more likely explanation suggest the event could be related to the study intervention
    Definitely – Known effects of the study intervention, or based on challenge testing, suggest that study intervention is the most likely cause.

3. Expectedness of the event. Is the event an anticipated event even if the research had not been taking place?

Serious Adverse Event reporting

All SAEs will be reported to the Chief Investigator within 24 hours of awareness of the SAE. All SAEs that occur in relation to the intervention must be recorded, together with data including date of onset and resolution, outcome, severity and causality for the intervention.

All SAEs of a related and unexpected nature will require onward reporting to the main REC, and this will be facilitated by the Chief Investigator, in accordance with any procedures of the Sponsor. Related and unexpected SAEs will be immediately reported to the Sponsor. In addition all investigators will be notified, and the TSC will be notified in accordance with Sponsor procedures and timeframe. SAEs which after review are not thought to be treatment related will be brought to the TSC's attention at their next scheduled meeting. The numbers and details of AEs and SAEs will be reported to the Trial Management Group and Trial Steering Committee regularly.

22. Auditing

The Chief Investigator will be responsible for the day to day monitoring and management of the study. The Principal Investigators at each site will monitor the management of the study within that site. The Sponsor will monitor and conduct random audits on a selection of studies in its clinical research portfolio. Monitoring and audit will be conducted in accordance with the DH research Governance Framework for Health and Social Care and in accordance with the Sponsor's policies and procedures.

Nested Qualitative Study

The acceptability of the intervention to adults with Autism and Therapists

In-depth interviews will be conducted with participants (from both arms of the trial) 10 weeks after randomisation (after the primary outcome has been collected). For face-to-face qualitative interviews participants will be asked to complete a written consent form. For telephone qualitative interviews the researcher will verbally explain consent to the participant before the interview starts and, if the participant confirms their agreement to the interview, the verbal consent agreement will be repeated and audio recorded.

These interviews will consider and compare views and experiences of the trial and the acceptability of the guided self-help intervention. All interviews will be conducted by telephone or face-to-face in a location of the participants' choice. At interview, a flexible topic guide will be used to ensure primary issues are covered during all interviews, but without dictating data collection, allowing participants to introduce unanticipated issues. Topic guides will be modified as necessary to reflect emerging findings. Therapists delivering the intervention will also be interviewed towards the end of the trial to illuminate the perceived effectiveness and acceptability of treatments and explore any barriers to its uptake outside of the trial. The researcher will use open-ended questioning techniques to elicit participants' experiences and views of key events. The interviews will be conducted by Doctorate in Clinical Psychology Students and part of the project analysis will serve as an academic assignment for their Doctoral studies i.e. the Service Improvement Research Project. The interviewers will introduce themselves as qualitative researchers.

Interviews with participants are expected to last between 45-60 minutes, will be recorded using a digital voice recorder, transcribed and anonymized. Interviews will be face-to-face where possible but if an individual prefers to conduct the interview on the telephone this will be facilitated. Should participants experience psychological distress during the interview, debrief will be offered and the interviewers will ensure that the participant is aware of how to access appropriate support. If during the interview any concerns are raised, the researcher will contact the principal investigator. The interviewers will be offered support from the principal investigator and qualitative research co-applicant.

Sampling

Purposive sampling will select interviewees in order to attempt to capture maximum variation in views and experiences in order that they adequately reflect those of a range of participants. All participants in the trial will be asked if they are willing to be contacted about taking part in a qualitative interview at the time of trial consent. From participants who indicate that they are willing to be contacted, a purposive sample will be drawn in relation to (i) the trial site, (ii) arm of the trial and (iii) socio-demographic variables such as age, gender, ethnicity and socio-economic status (with participants being selected from areas of high and low social-economic deprivation, based on Index of Multiple Deprivation (IMD2007) score (Noble et al., 2008). Interviews will be analysed in batches, and sampling will continue until no new themes are emerging from the interviews. This is likely to include up to twenty four participants (16 from the CBT group and 8 from the TAU) as well as 2-3 therapist interviews.

Qualitative analysis

Interview transcripts will be checked for accuracy and then imported into NVIVO qualitative data analysis software, to aid management and indexing of data. 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. Thematic analysis (Braun & Clark, 2006), utilising a data-driven inductive approach (Boyzatsis, 1998), 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 (Charmay, 2006). Transcripts from the participants, therapists' and carer interviews will be analysed separately, with coding frames being developed for each separate phase. A subset of transcripts will be independently double-coded by other members of the research team and compared. Discrepancies will be discussed and resolved to achieve a coding consensus.

Ethics

23. Research Ethics Approval

NHS Research Ethics Approval is to be sought and relevant R&D approvals for the 2 NHS sites.

24. Protocol Amendments

Protocol amendments will be presented to the Study Steering Committee for consideration and will be implemented only when approved by the NHS Research Ethics Committee.

25. Confidentiality

All eligible participants will be allocated a unique coded Participant Identification Number. This number will be used to identify patients throughout the study. Where possible, personal identifiable data will be removed from all collected data and replaced with the PIN, thereby providing a level of pseudo-anonymisation. The code will be kept separately from the data/assessments and will be stored securely in a place with limited access.

All personally identifiable study related information will be stored at the University of Bath. Study related information that is not anonymous (i.e. personally identifying information) will be transferred from the NHS site to the University site digitally via nhs.net email or an encrypted USB.

Study records are required, and the digital information will be printed and securely stored at the University site in a locked filing cabinet.

All study materials/record sheets containing identifiable information such as Consent Forms will be stored separately and securely in a place with limited access.

Audio recordings of assessments for the purposes of inter-rater reliability, or of intervention sessions for supervision, will be taken from NHS premises only via secure electronic means and destroyed immediately once inter-rater reliability/use in supervision is completed.

All local databases will be protected via password protection.

26. Declaration of Interests

There are no conflicts of interest or other declarations to report

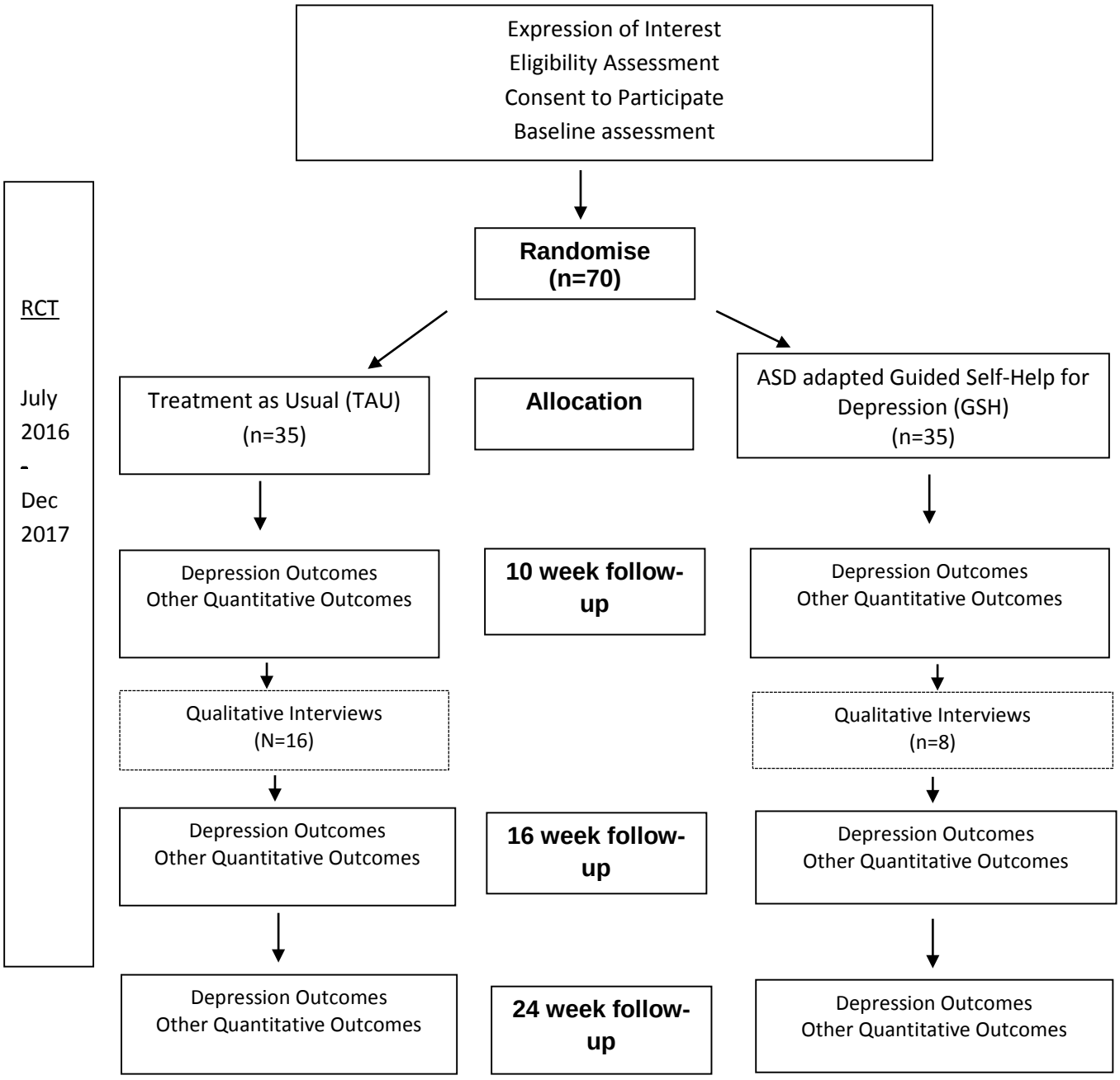
27. Access to data

Access to data will be restricted to the research team. Participant identifiable data will be accessible only to those directly involved in direct patient contact such as the GP and relevant professionals where there are concerns about safety.

28. Ancillary and post-trial care

Adverse Events aside, should participants wish to receive further treatment for depression following their involvement in the study, information will be provided as to how best to access this.

29. Participant Timeline



30. Schedule of Events

Activity/Event	Completed by	Baseline	GSH Group Each Session	10 weeks (End of intervention)	16 weeks	24 weeks
Permission for research contact	Clinic					
Eligibility Assessment	Clinic or RA					
Informed Consent	RA					
Demographics	RA	√				
PHQ-9	P	√	√	√	√	√
CIS-R	P	√				
BDI	P	√		√	√	√
SIGH-D	IA	√		√	√	√
GAD-7	P	√		√	√	√
OCI-R	P	√		√	√	√
PANAS	P	√	√	√	√	√
SF-12	P	√		√	√	√
EQ-5D-5L	P	√		√	√	√
Economic and Service Use Interview	P			√	√	√
Medical Records	RA					√
Current prescribed Medication	RA	√		√	√	√
Qualitative Interview	QI			√		
Adverse events	P, RA		√	√	√	√

RA=Research Assistant, P=Participant, IA=Independent Assessor, QI=qualitative interviewer

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