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)

Health Economics Analysis Plan (HEAP)

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Trial HEAP version:	Version 1.0 (17 March 2025)
Purpose of HEAP:	To prespecify planned analyses and enable reproducibility. Designed to align with the protocol and SAP and should be read in conjunction with them.
Roles and responsibilities:	The HEAP was prepared by Dr Kirsty Garfield (Health Economist) and approved by Dr Joanna Thorn (Lead Health Economist). The trial health economists (Kirsty Garfield and Joanna Thorn) are responsible for conducting and reporting the economic evaluation in accordance with the HEAP.

Approvals: the following people have reviewed the HEAP and are in agreement with the contents:

Role	Name	Signature	Date
Author/health economist	Dr Kirsty Garfield	Kirsty Garfield	17/03/2025
Lead health economist	Dr Joanna Thorn	Joanna Thorn	17/03/2025
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Table of revisions to the HEAP

Date	HEAP version	Summary of revision

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Table of abbreviations

ADEPT-2	Autism Depression Trial
ASD	Autism spectrum disorder
BA	Behavioural action
BDI-II	Beck Depression Inventory II
CBT	Cognitive behaviour therapy
CEAC	Cost-effectiveness acceptability curve
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
GSH	Guided Self-Help
HEAP	Health economics analysis plan
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
INMB	Incremental net-monetary benefit
ModRUM	Modular resource-use measure
NHS	United Kingdom National Health Service
NICE	National Institute for Health and Care Excellence
PHQ-9	Patient Health Questionnaire
PSS	Personal Social Services
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SAP	Statistical analysis plan
TAU	Treatment as usual

Section 1 Trial information

1.1. Background and purpose of the trial

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

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

adequate whilst the two self-report measures were well-aligned. Anecdotal evidence from participants suggested a preference for the BDI-II as a self-report measure with item sets of closed statements less subject to misinterpretation. The findings indicated the GSH intervention was promising.

The clinical effectiveness and cost-effectiveness of this intervention in a large-scale RCT is now warranted.

1.2. Aim of the trial

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

1.3. Objectives of the trial

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.

1.4. Trial 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.

1.5. Intervention and comparators

Guided self help

The GSH intervention 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 (over a maximum treatment window of 16 weeks). Appointments can last up to 45 minutes in duration (except for the first appointment, which can last up to 90 minutes). The session materials are accompanied by a short manual for the therapist guide.

Therapist guides / coaches will receive 15 hours of trial-specific training in the GSH intervention and in working with autistic people. They will receive weekly supervision

facilitated by a clinical psychologist (co-applicant). Supervision will be in a group format but can be offered individually if required. During supervision, progress with clients allocated to GSH will be discussed and issues in supporting an individual to access and apply the GSH intervention principles on an individual basis will be considered.

Participants will be provided a booklet containing the materials for 9 sessions (Guided Self-Help). This booklet can be provided electronically (.pdf) and/or in hard copy format. Participants will be supported in their use of the intervention materials by a therapist (guide) 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.

Treatment as Usual (TAU)

TAU psychological therapists will be provided with 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.

1.6. Trial design

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

1.7. Trial start and end dates

Recruitment started on 15 August 2022 and completed on 29 February 2024.

Section 2 Economic approach

2.1. Aim of the economic evaluation

The aim of the economic evaluation is to estimate the within-trial cost-effectiveness of an adapted low-intensity psychological intervention (Guided Self-Help), compared to treatment as usual, for depression in autistic adults.

2.2. Objectives of the economic evaluation

The primary objective is to conduct a cost-utility analysis to estimate the cost-effectiveness of an adapted low-intensity psychological intervention (Guided Self-Help) for depression in autistic adults from a societal perspective at 12 months follow-up. The secondary objective is to estimate cost-effectiveness from an NHS and personal social services (PSS) perspective.

2.3. Overview of the economic analysis

In the primary analyses, individual patient-level data will be used to assess cost-effectiveness of GSH from a societal perspective over 12 months. If neither arm is dominant (i.e. both cheaper and more effective) then an incremental cost-effectiveness ratio (ICER) will be estimated. The Net Benefit (NB) framework will be used to assess cost-effectiveness at £20,000-£30,000 per QALY. To calculate a robust estimate of the expected NB, between group differences in costs and QALYs will be evaluated using appropriate regression techniques, to account for baseline imbalance, non-normally distributed data and missingness, as appropriate. Uncertainty in the results will be addressed using cost-effectiveness acceptability curves (CEACs) to show how the probability that GSH is the optimal choice over a range of possible values of the ceiling ratio will be constructed. Uncertainty will also be explored in sensitivity analyses. Secondary analyses will explore cost-effectiveness from an NHS and PSS perspective.

2.4. Jurisdiction

The trial will be conducted across six centres in England and Wales where the health system is publicly funded and is free at the point of access.

2.5. Perspectives

As the trial population is likely to be largely working age, and both autism and depression contribute to productivity losses, the primary cost-utility analysis will be conducted from a societal perspective including the NHS, personal social services (PSS), personal expenses, voluntary services, and productivity. A secondary analysis will restrict the perspective to that of the NHS and PSS to conform to the NICE reference case.

2.6. Time horizon

Analyses will assess the cost-effectiveness of GSH compared with TAU at 12 months.

Section 3 Economic data collection and management

3.1. Identification of resources

Resources that were considered important to include: (1) the cost of the intervention; (2) NHS resources: primary, community, emergency and secondary care and prescribed medications; (3) social care resources: social care professional contacts; (4) productivity: time off paid employment; (5) usual activities; (6) personal expenses: private healthcare, over-the-counter medications and travel for healthcare; (7) charity support services.

3.2. Measurement of resources

Intervention costs (including training, delivery, and supervision) will be recorded in study records. All-cause resource use, including primary, community and secondary care, prescribed and over-the-counter medications, social care contacts, time off paid employment, usual activities, travel for healthcare, and charity support services, will be captured via participant-report at 16-, 32- and 52-weeks follow-up. NHS resource use will be captured via ModRUM core module plus depth questions covering NHS counselling or other talking therapies and prescribed medications (10). Workplace productivity and usual activities will be measured via the Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH) (11). Bespoke questions were developed for social care, over-the-counter medications, travel and charity support services.

3.3. Valuation of resources

Measured resources will be valued using standard sources from the most recent cost year available at the time of analysis. Primary and community healthcare will be valued using the latest Unit Costs of Health and Social Care (12). Secondary healthcare will be valued using the National Schedule of NHS costs (13). Prescribed medications will be assigned a unit cost from the Prescription Cost Analysis (14). Time off work will be valued using the Annual Survey of Hours and Earnings (15). If a cost is not available in these sources, alternative sources will be explored and if a cost is available but for a different cost year, the cost will be adjusted using the NHS cost inflation index.

3.4. Identification of outcomes

The primary economic outcome measure is QALYs which will be derived from utility scores, obtained using the EQ-5D-5L quality of life measure collected at baseline, 16-, 32- and 52-weeks follow-up (16).

3.5. Measurement of outcomes

Participants will self-complete the EQ-5D-5L health-related quality of life measure, online at baseline and at 16-, 32- and 52-weeks post-baseline.

3.6. Valuation of outcomes

Patients' EQ-5D-5L profiles will be mapped to the EQ-5D-3L valuation set using the mapping function/value set recommended by National Institute for Health and Care excellence (NICE) at the time of analysis. The current recommend mapping function was developed by the Decision Support Unit (Hernández Alava et al. 2017) and used the 'EEPRU dataset' (17). The mapping function will be implemented using the 'eq5dmap' Stata code (18). The valuation set enables a utility score to be calculated for each patient based on published UK population utility values. QALYs will be estimated from utility scores using the area-under-the-curve approach at 52 weeks.

Section 4 Economic data analysis

4.1. Statistical software for analyses

All analyses will be conducted in Stata statistical software.

4.2. Analysis population

All patients will be analysed in the group they were randomised to (intention to treat), providing they do not withdraw their consent.

4.3. Timing of analyses

Analyses will be conducted at the end of the trial, which will be 12 months following consent of the final participant entering the study and following data lock and data preparation.

4.4. Data preparation

Data will be imported to Stata and cleaned in a consistent manner, irrespective of trial arm. The analyst will be blinded to trial arm until data cleaning of follow-up data is complete. Data related to the intervention will be cleaned after follow-up data to avoid unblinding. Data preparation may involve reformatting data and exploration of missing data.

4.5. Missing data

The proportion of missing data will be assessed and patterns of missingness will be explored. Dependent on the quantity and likely cause of missingness, multiple imputation may be used to impute missing values.

4.6. Discount rate for costs and outcomes

Given the one-year study duration, discounting will not be conducted.

4.7. Adjustment for randomisation variables

In line with the SAP, all analyses will be adjusted for study centre, BDI-II score at baseline, and prescription of antidepressants.

4.8. Analysis of resource use and costs

Resource use and costs will be presented using simple descriptive statistics, including means, standard deviations, 95% confidence intervals and percentages.

4.9. Analysis of outcomes

QALYs will be estimated using the area under the curve approach. Adjusted mean QALYs will be estimated using the appropriate regression technique, taking into account the distribution of the data and adjusting for baseline EQ-5D-5L scores (19).

4.10. Cost-effectiveness thresholds

Cost-effectiveness will be evaluated using the net-benefit framework over a range of values for the QALY, including the UK NICE recommended cost-effectiveness thresholds of £20,000 to £30,000 per QALY.

4.11. Analysis of cost-effectiveness

In the cost-utility analyses, if the intervention is not dominant (lower costs and higher QALYs) nor dominated (higher costs and lower QALYs), incremental cost-effectiveness ratios (ICERs) will be estimated at 12 months follow-up using appropriate regression techniques, such as seemingly unrelated regressions or generalised linear models. ICERs will be interpreted with reference to the standard NICE willingness to pay threshold of £20,000 to £30,000 per QALY. The incremental net monetary benefit (INMB) statistic will also be estimated at threshold willingness to pay values of £20,000 and £30,000.

4.12. Sampling uncertainty

Uncertainty in estimates of the INMB will be presented with 95% confidence intervals surrounding the point estimates. Uncertainty will also be explored using cost-effectiveness acceptability curves which show the probability of the intervention being cost-effective at a range of willingness-to-pay thresholds for the QALY.

4.13. Sensitivity analyses

If imputation is used in the primary analysis, a sensitivity analysis will present the results of a complete case analysis. A further sensitivity analysis will explore uncertainties in the components of intervention cost. Should NICE change their recommendations for valuation of the EQ-5D-5L, a sensitivity analysis will present the results using the current recommended method (17).

4.14. Extrapolation or decision analytic modelling

There are no plans to extrapolate the trial data or develop a model within the funding for this research.

Section 5 Reporting

5.1. Reporting standards

This HEAP follows published guidance (20). The health economic evaluation will be conducted in line with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines (21).

5.2. Reporting deviations from the HEAP

Any deviation from HEAP will be documented and justified in the final published report.

Section 6 References

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