HEALTH ECONOMICS ANALYSIS PLAN (HEAP) for STRATA

VERSION 1.0 (28/10/2024)

Contents

1. Administrative Information

1.1 HEAP Administrative Information

Full Title	A multicentre double-blind placebo-controlled randomised trial of SerTRaline for AnxieTy in adults with a diagnosis of Autism (STRATA)
Trial registration number; registry	ISRCTN registry: 15984604
Source of funding	NIHR HTA 127337
Purpose of HEAP	The purpose of this HEAP is to describe the analysis and reporting procedure intended for the economic analyses to be undertaken. The analysis plan is designed to ensure that there is no conflict with the protocol and associated statistical analysis plan (SAP) and it should be read in conjunction with them.
Trial protocol version; date	This document is based on the unpublished STRATA Protocol Version 7.0 (31/8/2023)
Trial Statistical Analysis Plan (SAP) version, date	This document is based on the unpublished STRATA SAP Version 0.8 (9/10/2024)
Trial HEAP version, date	HEAP Version 1.0, (28/10/24)
HEAP revisions	
Roles and responsibilities	This HEAP was prepared by Dr Maddy Cochrane (health economist) and Dr Jo Thorn (lead health economist). The trial health economists are responsible for conducting and reporting the economic evaluation in accordance with the HEAP. The HEAP was reviewed by an independent Health Economics expert in the Trial Steering Committee (Ms Gemma Shields).

APPROVALS

The following people have reviewed the Health Economics Analysis Plan and are in agreement with the contents.

Role	Name	**Signature**	Date
Author	Dr Maddy Cochrane	Madeleine Cochrane	28th October 2024
Lead Health Economist	Dr Jo Thorn	Joanna Thorn	28 October 2024

Chief Investigator	Professor Dheeraj Rai	Dheeraj Rai	28 October 2024

2. Trial Introduction & Background

2.1 Rationale

Anxiety is common in autistic adults (1-3), and the distress and avoidance behaviours related to it are often more disabling than difficulties related to autism. Most anxiety in the population is managed in primary care, although General Practitioners (GPs) often make prescribing decisions based on anxiety symptoms rather than make diagnoses of specific anxiety disorders (4, 5). Selective serotonin reuptake inhibitors (SSRIs) are commonly used antidepressants but are also first line medications for all anxiety disorders (6).

There is clinical equipoise in relation to SSRI use for anxiety symptoms in autistic adults. SSRIs are widely prescribed amongst autistic adults but without adequate evidence for effectiveness or understanding of adverse effects. The British Association for Psychopharmacology consensus guidelines for autism conclude that there is insufficient information regarding the effectiveness or side effect profile of SSRIs in the treatment of anxiety in autism and calls for large scale trials with adequate follow-up (7). A review of the economic costs of autism in the UK found high medical costs and productivity loss experienced by autistic adults and their families. The authors of the review conclude there is an urgent need to understand the cost-effectiveness of interventions that address the needs of autistic adults (8).

2.2 Aim of the trial

The STRATA trial aims to determine the clinical and cost-effectiveness of the SSRI sertraline in reducing symptoms of anxiety and improving quality of life in adults with a diagnosis of autism compared with placebo and to quantify its adverse effects.

Nested within the STRATA trial is a sub-study of the carers of adults participating in the main trial which aims to explore how the treatment of anxiety for adults with autism influences the burden to their carer(s).

2.3 Objectives of the trial

The primary objective is to determine the difference in Generalised Anxiety Disorder Assessment (GAD-7) anxiety scores at 16-weeks between adults with a diagnosis of autism treated with sertraline and those treated with placebo.

The secondary objectives are:

- To describe the adverse effects reported by adults with a diagnosis of autism treated with sertraline versus those treated with placebo over 52-weeks;
- To determine the effect of up to 52-weeks of treatment with sertraline versus placebo on:
    - GAD-7 anxiety scores and proportionate change in GAD-7 scores including response (defined as 50% reduction in GAD-7 scores);
    - Patient reported effect of medication on symptoms;
    - Social anxiety;

- Obsessive compulsive symptoms;
- Panic attacks;
- Repetitive behaviours;
- Meltdowns;
- Depressive symptoms;
- Composite measure of anxiety and depressive symptoms;
- Functioning and disability;
- Quality of life;
- Carer burden and quality of life;

- To measure adherence to the study medication;
- To determine the cost-effectiveness of sertraline treatment for anxiety in adults with a diagnosis of autism;
- To explore participants' acceptability, experiences of, and adherence to, study processes and treatment (analysis addressing this objective will be conducted by the qualitative research team and will not be outlined here).

2.4 Trial population

The study population encompasses adults with a diagnosis of autism and symptoms of anxiety who would consider medication to help with their anxiety.

Participants are eligible if they:

- Are aged≥ 18 years;
- Have a diagnosis of autism made by a specialist including those with a co-occurring mild intellectual disability (ID). Autism diagnostic terms may include autism/autistic spectrum disorder or other variations, Asperger syndrome/disorder or pervasive developmental disorder;
- Anxiety as measured by GAD-7 score ≥10 at screening.

Participants are excluded if they:

- Are prescribed and regularly using a serotonergic antidepressant/anxiolytic at antidepressant doses in the preceding 8 weeks; these include SSRI and non-SSRI antidepressants including tricyclic antidepressants. Potential participants who are prescribed low (i.e. non-antidepressant) doses of these medications for other indications (e.g. neuropathic pain) or those who had no such medication for the majority of the preceding 8 weeks (e.g. tried for a few days before stopping) may be considered eligible where the site Principal Investigator (PI) confirms this is consistent with usual clinical practice. Individuals regularly using these medications wishing to participate could do so after a washout period of 8 weeks.
- Have been prescribed an irreversible monoamine oxidase inhibitor (Phenelzine, Isocarboxazid or Tranylcypromine) or Pimozide in the preceding 8-weeks;
- Have been diagnosed with moderate-severe ID although people who have up to mild ID will be eligible; For the purpose of this study, a person with known ID will be considered as having a mild

ID if they are able to provide written informed consent, and are able to understand and answer the study questionnaires with the help of reasonable adjustments, if necessary;

- Are unable to provide informed consent and complete study assessments/questionnaires;
- Have been diagnosed with bipolar disorder, manic or hypomanic episodes, or psychosis. Individuals with historical diagnoses where there is clinical consensus or strong suspicion that these diagnoses are no longer valid (e.g. presentations historically labelled as mania/psychosis now considered to be explained by autism) may be considered eligible based on PI discretion;
- Currently have uncontrolled epilepsy;
- Are known to have a current alcohol or drug use problem (i.e. if recorded in patient/medical notes);
- Are known to have allergies to sertraline or placebo/excipients;
- Are currently enrolled in another randomised controlled trial;
- Are women who are pregnant, are planning pregnancy during the trial period, or breastfeeding;
- Have a history of severe liver impairment;
- Have bleeding disorders such as such as haemophilia, Christmas disease and von Willebrand's disease, as well as those with past medical history of bleeding gastric or duodenal ulcers or other significant bleeding disorders;
- Have a history of Long QT syndrome or Torsade de Pointe;
- Have swallowing difficulties or inability to take medication in capsule form;
- Are currently using St. John's Wort.

2.5 Intervention and comparators

All participants will receive usual care without restriction, including referrals to psychological therapies, such as NHS talking therapy services (formerly referred to as Improving Access to Psychological Therapies (IAPT) services). GPs/clinicians can also prescribe other medication as necessary but will be asked to exercise caution in case they plan to prescribe drugs that may interact with sertraline. Participants are randomised (in a 1:1 ratio) to either the Intervention or Placebo groups.

Participants will receive a daily dose of 25mg sertraline (Intervention arm) or matched placebo (Placebo arm) for 2 weeks usually followed by 2x25mg for 4 weeks. Following this initiation period, the medication is dispensed in 50mg capsules and depending upon tolerability, the dose can be flexibly increased by 50mg every 4-weeks to reach the optimal dose. The dose can only be increased if the participant is tolerating it and agrees to try an increased dose, and the prescribing clinician is satisfied that it is appropriate to do so based on the participant's responses to the safety check questionnaire and discussion with the study research team. The dose may go up to a maximum of 200mg by week 14 although some participants will find a lower dose to be optimal (e.g. 25mg, 50mg, 100mg or 150mg). Participants will take this optimal dose for up to 52-weeks post-randomisation. The same regimen is specified for both arms.

2.6 Trial design

STRATA is a two parallel group multi-centre pragmatic double-blinded randomised controlled trial of sertraline versus placebo for reducing anxiety in adults with a diagnosis of autism. Participants are randomised in a 1:1 ratio to sertraline (Intervention) or placebo (Control).

By randomising 306 patients the study will have at least 80% power to detect the following differences in GAD-7 scores between treatment arms:

	Difference in GAD-7 scores between treatment arms at 16-weeks						
	2.5	**2.4**	**2.3**	**2.2**	**2.1**	**2.0**	**1.9**
Power	95.8%	94.3%	92.4%	90.1%	87.2%	83.9%	80%

STRATA is delivered through autism services in four centres in the United Kingdom (UK) and one in Western Australia. These centres will cover the following areas:

1. East Midlands (UK)
2. East of England (UK)
3. South West England (UK)
4. Surrey, Hampshire and Portsmouth (UK)
5. Western Australia

Within each centre there may be several recruiting sites including mental health and/or learning disability service providers, social enterprises, primary care, University primary care/disability services, community organisations and charities. Further recruitment from cohorts/registries can also take place if required.

3. Economic approach

3.1 Aims of economic evaluation

The aim of the economic evaluation is to assess the cost-effectiveness of sertraline plus usual care compared with placebo plus usual care for the treatment of anxiety in autistic adults in the UK.

3.2 Objectives of economic evaluation

The primary objective of the economic evaluation is to estimate the cost-effectiveness of sertraline plus usual care versus placebo plus usual care at 52 weeks post-randomisation from the NHS and personal social services (PSS) perspective.

A secondary objective is to estimate the cost-effectiveness of sertraline plus usual care versus placebo plus usual care at 52 weeks post-randomisation from a societal perspective.

3.3 Overview of economic analysis

The within-trial economic analysis will be performed using individual-level participant data from the STRATA trial. Resource use and outcome data will be collected from UK participants only. The primary economic analysis will be a cost-utility analysis (CUA) comparing the difference in costs to NHS and PSS services, and the difference in quality-adjusted life years (QALYs). Based on trial evidence, both incremental cost-effectiveness ratio and incremental net monetary benefit statistics will be calculated.

The secondary economic analysis will be a cost–consequences analysis (CCA). The CCA will present the differences in costs (including health and social care costs, and productivity loss) and a range of relevant outcomes (including QALYs, GAD-7, carer quality of life) for each arm.

3.4 Jurisdiction

The trial is conducted in the UK and Australia. However, on the advice of the funder, the economic evaluation is restricted to the UK which has a national health service (NHS), providing publicly funded healthcare, primarily free of charge at the point of use.

3.5 Perspectives

The CUA will be assessed from the perspective of the NHS and PSS in the UK. The CCA will additionally include assessment from a societal perspective, including productivity losses.

3.6 Time horizon

All analyses will compare costs and outcomes over the first 52 weeks post-randomisation. The research team have not been funded to conduct longer-term follow up including any extrapolation and evidence synthesis.

4. Economic Data Collection and Management

4.1 Statistical software use for health economic analysis

Stata version 18.0 or higher will be used for all health economic analyses.

4.2 Identification of resources

Resource use data will be taken from the UK only. Resource use will include the cost of the sertraline prescribed or placebo (depending upon randomisation). Resource use for primary care, secondary care and social care contacts, and medications will be measured. Loss in productivity will also be captured.

4.3 Measurement of resource-use data

Resources used by participants (other than sertraline) will be tracked by means of a concise bespoke patient-reported questionnaire (electronic or paper as per participant preference) administered to each group at 24- and 52-weeks post-randomisation. The resource-use questionnaire will cover primary care appointments, home visits, medications prescribed, social care contacts, hospital

admissions (including length of stay), outpatient appointments, emergency department visits. As it may be difficult for participants to accurately identify whether a contact was associated with their anxiety, information on healthcare resources used for any reason will be requested. In addition, participants will be asked to report time off work, if applicable.

The resource use questionnaire (RUQ) has been developed with input from our patient advisory group and was tested for face validity. The RUQ is designed to be short and simple. A key challenge for autistic adults is that they can take longer to process information which can lead to some feeling overwhelmed when presented with too much information to process (9).

4.4 Valuation of resource-use data

Valuations will be assigned to recorded resources using the most recently available standard UK sources at the time of analysis, such as the latest Unit Costs of Health and Social Care series by the Personal Social Services Research Unit (PSSRU) (10) and the latest NHS costs from the National Cost Collection (11). Prescribed medications will be assigned a unit cost from the British National Formulary (BNF) (12). When a unit cost is not available for the year of analysis, it will be inflated to current prices using the NHS cost inflation index (NHSCII) (10). Productivity costs will be derived from the Annual Survey of Hours and Earnings (13) using median pay per hour.

4.5 Identification of outcomes

Economic outcome data will be taken from the UK only. The primary outcome for the economic evaluation will be quality-adjusted life years (QALYs). Secondary outcomes will be the GAD-7 anxiety score and carer quality of life (measured using the Carers Experience Scale (CES) and EQ-5D-5L).

4.6 Measurement of outcomes

QALYs will be derived from measurements recorded using the EQ-5D-5L health-related quality of life instrument (14) after 52-weeks of follow-up. Quality of life (via EQ-5D-5L) will be measured at baseline, 12-, 16-, 24- and 52-weeks post-randomisation. Generalised Anxiety disorder will be measured on a seven-item generalised anxiety disorder scale (GAD-7) (15) 52-weeks post-randomisation. Carer quality of life (captured using the Carers Experience Scale (CES) and EQ-5D-5L) will be measured at baseline, 16- and 52-weeks post-randomisation.

4.7 Valuations of outcomes

Reported EQ-5D-5L health states will be valued using the valuation set recommended by the National Institute for Health and Care Excellence (NICE) at the time of analysis. The valuation set enables a utility score to be calculated for each patient based on published UK population utility values. The area-under-the-curve approach will be used to transform the utility scores into QALYs for the 52-week time horizon.

5. Economic Data Analysis

5.1 Analysis population

All patients who did not withdraw their consent to have their data used in the study will be analysed according to arm they were randomised to. This is in accordance with the “intention to treat” (ITT) principle.

5.2 Timing of analyses

The final analysis will be conducted at the end of the trial, which will be 52 weeks post-randomisation.

5.3 Discount rates for costs and benefits

As costs and benefits will not be assessed beyond 52 weeks post-randomisation discounting will not be required.

5.4 Cost-effectiveness threshold(s)

Adjusted mean costs and QALYs associated with each group will be combined through the Net Benefit (NB) framework. Cost-effectiveness will be evaluated using the NB framework over a range of thresholds, including NICE’s recommended cost-effectiveness thresholds of £20,000-30,000 per QALY. We will use a threshold willingness-to-pay of £20,000 per QALY in the primary analysis.

5.5 Statistical decision rule(s)

Mean differences in costs, QALYs and net benefits between the treatment groups will be estimated with associated 95% confidence intervals.

5.6 Analysis of resource use

Differences in mean resource use between randomised groups will be reported but not compared statistically. Standard deviations (SD) and the number of patients included in each category by arm will also be reported.

5.7 Analysis of costs

Appropriate regression techniques will be used to estimate adjusted mean costs and the difference in adjusted mean costs (and their associated 95% confidence intervals) between randomised groups.

5.8 Analysis of outcomes

The primary economic outcome in the economic evaluation is the QALY. QALYs accrued over the 52-week follow up period will be calculated for each patient from the utility values using the area under the curve approach. Appropriate regression techniques will be used to estimate mean QALYs (adjusted for baseline utility scores) and the difference in adjusted mean QALYs (and their associated 95% confidence intervals) between randomised groups.

5.9 Data cleaning for analysis

Data cleaning will be undertaken prior to unblinding by the economic researcher. Data variables not required for the economic analysis and duplicate data entries will be dropped from the dataset. In addition, face validity checks will be conducted on the data (e.g. to identify misspelt text and to check ranges of variables are appropriate) and queries will be checked against the original source documents. String and numerical values will be standardised and grouped for similar resource items to enable unit costing. All data cleaning will be documented in the Stata do files and log files.

5.10 Missing data

Missing data will be handled depending upon the prevalence. Simple imputation for minor details (e.g. missing drug doses) will be based on reasonable assumptions (e.g. the most frequently prescribed dose for the population of interest). Uncertainty in the methodological decisions applied to handle the missing data will be discussed between two health economists, and, if appropriate, a clinician will be asked to adjudicate. Questionnaire data will not be classed as missing unless the questionnaire is not returned or the majority of responses are uninterpretable.

The likely cause of missingness will be explored. If the mechanism of missingness is believed to be missing at random (MAR), then multiple imputation methods may be used. Imputation models will include: cost measurements, arm, variables used in the randomisation as well as other variables such as baseline EQ-5D score and auxiliary covariates informative of missingness.

5.11 Analysis of cost-effectiveness

Cost and QALY data will be combined to calculate an incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB) statistic from the NHS and PSS perspective. More specifically, net benefit (NB) regression framework will be used to calculate each patient's incremental cost and effect together (17). Regression model choice will be decided by inspecting the distribution of the data. If appropriate, Seemingly Unrelated Regression (SUR) will be used to account for the correlation between the costs and the QALYS.

5.12 Sampling uncertainty

Uncertainty in the point estimates of NMB will be quantified using 95% confidence intervals estimated from the regression equations. NB regression equations estimated for various willingness-to-pay (WTP) thresholds will also be used to indicate how sensitive the cost-effectiveness findings are at different WTP assumptions. Uncertainty will be characterised using cost-effectiveness acceptability curves (CEACs). The CEAC will illustrate the probability of Sertraline being cost-effective compared to Placebo across a range of WTP thresholds.

5.13 Subgroup analyses/Analysis of heterogeneity

We will conduct a subgroup analysis for severity of anxiety at baseline (GAD-7 scores analysed as numeric measures).

5.14 Sensitivity Analyses

Uncertainty in the methodological choices made for the present economic evaluation will be assessed through sensitivity analyses. This will involve making plausible changes to key methodological assumptions in order to understand how changes in the assumptions made impact on the cost-effectiveness result. Examples include:

- If applicable, different approaches to the handling of missing data
- Different estimates where unit costs have not been available.

6. Reporting/Publishing

6.1 Reporting standards

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines will be followed when reporting the health economic evaluation, in a format appropriate to stakeholders and policy makers.

6.2 Reporting deviations from the HEAP

Prior to database lock and any comparative analysis of the final dataset, this HEAP will be finalised and published on the University of Bristol's research repository (PURE). Any deviation in the final analysis from the published HEAP will be documented and justified in the final published report.

7. References

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