A multicentre double-blind placebo-controlled randomised trial of SerTRaline for AnxieTy in adults with a diagnosis of Autism (STRATA).

Statistical Analysis Plan

Version 1 (21/10/2024)
Based on Protocol version 7.0 (dated 31/8/2023)
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The following people have reviewed the Statistical Analysis Plan and are in agreement with the contents

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List of abbreviations

Acronym	Details
ADEPT	Autism DEPression Trial
AE	Adverse Event
BTC	Bristol Trials Centre
CACE	Complier Average Causal Effect
CES	Carer Experience Scale
CI	Confidence Interval
CoBalT	Cognitive behavioural Therapy as an adjunct to pharmacotherapy for primary care patients with treatment resistant depression: a randomised controlled trial
CONSORT	Consolidated Standards of Reporting Trials
DMC	Data monitoring committee
EQ-5D-5L	EuroQol 5-dimension 5-level
GAD-7	Generalised Anxiety and Depression Assessment
GP	General Practitioner
HEAP	Health Economics Analysis Plan
IAPT	Improving Access to Psychological Therapies
ID	Intellectual Disability
IMD	Index of Multiple Deprivation
IQR	Inter-Quartile Range
ITT	Intention to Treat
NHS	National Health Service
NICE	National Institute of Clinical Excellence
OCD	Obsessive Compulsive Disorder
OCI-R	Obsessive Compulsory Inventory Revised
PHQ	Brief Patient Health Questionnaire
PHQ-9	Patient Health Questionnaire-9
PI	Principal Investigator
PRIME-MD	Primary Care Evaluation of Mental Disorders
RBQ-2A	Adult Repetitive Behaviours Questionnaire-2
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event (subset of AE)
SAP	Statistical Analysis Plan
SD	Standard Deviation
SPIN	Social Phobia Inventory
SSRI	Selective Serotonin Reuptake Inhibitors
STRATA	SerTRaline for AnxieTy in adults with a diagnosis of Autism
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
UoB	University of Bristol
WHODAS 2.0	World Health Organization Disability Assessment Schedule 2.0

1. INTRODUCTION AND PURPOSE

This document details the rules proposed and the presentation that will be followed, as closely as possible, when analysing and reporting the main results from STRATA. The trial management group, the independent trial steering committee and the STRATA autistic advisory group were consulted in the development of this plan.

The purpose of the plan is to:

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

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

The analysis strategy will be made available if required by journal editors or referees when the main papers are submitted for publication. Additional analyses suggested by reviewers or editors will, if considered appropriate, be performed in accordance with this analysis plan, but if reported the source of such a post-hoc analysis will be declared.

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

2. BACKGROUND AND RATIONALE

2.1 Rationale

Autism spectrum disorders (henceforth autism) are developmental conditions characterised by difficulties in social interaction and communication (1), associated with significant long-term personal, familial and societal cost (2). Autistic adults, particularly those without intellectual disabilities (ID) have a greater burden of mental health problems than the general population (3-6), higher rates of premature mortality (7, 8), with suicide as an important contributor (7).

Anxiety is common in autistic adults (1, 9, 10), 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 (11, 12). Selective serotonin reuptake inhibitors (SSRIs) are commonly used antidepressants but are also first line medications for all anxiety disorders (13).

There is clinical equipoise in relation to SSRI use for anxiety symptoms in autistic adults. Based on the paucity of evidence, 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 call for large scale trials with adequate follow-up (13).

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 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).

2.2 Trial objectives

2.2.1 Primary objective

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.

2.2.2 Secondary objectives

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 carer 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 (Analyses addressing this objective to be outlined in a separate Health Economics Analysis Plan);
- 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).

2.3 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.

2.4 Trial centres

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. A full outline of recruiting sites is provided in the STRATA protocol (14).

2.5 Eligibility criteria

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

2.5.1 Inclusion criteria

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.

2.5.2 Exclusion criteria

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 Pointes;
- Have swallowing difficulties or inability to take medication in capsule form;
- Are currently using St. John's Wort.

2.6 Treatments

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.

2.7 Recruitment, screening and consent

Likely pathways to identify potential participants include:

- During clinical appointments;
- When centres/sites perform list reviews;
- Research registers/cohorts;
- Self-referral

Individuals identified in these ways are directed to a preliminary online screening questionnaire and expression of interest form. Centres may also identify other opportunities and methods for identifying individuals and inviting them to take part which should be utilised.

Interested participants who meet the eligibility criteria (see **section 2.5**) are asked for consent to contact their GP for patient safety checks and for their personal and their GP's contact details. Where consent is given, GPs are contacted to ensure that it is safe for the individual to take the study medication should they decide to participate. Using secure methods of contact, the GP practice will be provided with relevant information about the trial and asked to confirm that it is safe for their patient to take the study medication if they decided to take part (i.e. complete a study specific GP Patient Safety Check Form or return a GP Patient Medical Summary, which should be returned directly to the individual's local research centre team). If the local research centre team already has access to medical records held for the individual (e.g. on SystmOne) then a medical summary can be obtained without contacting the GP practice directly. The individual's local research centre team will then confirm provisional eligibility status.

Randomisation occurs when the local (or delegated) principal investigator/prescriber is satisfied that eligibility criteria has been met, the patient has been consented and baseline data collected.

Patients who have given consent to participate, have been randomised and subsequently withdraw from the study prior to taking their first dose of the study treatment (only when the IMP bottle is confirmed to have not been tampered with) are considered screening failures and are thus not considered in the total number of patients randomised (15).

2.8 Randomisation

Participants are randomised in a 1:1 ratio to sertraline (Intervention) or placebo (Control) using a randomisation sequence generated by Sealed Envelope™ (16). Randomisation is stratified by centre (categories outlined as in section 2.4), with minimisation to ensure balance in baseline GAD-7 score (<15 and ≥15), gender (male, female and non-binary), age (18-34 years, 35-49 years and ≥50 years), presence of ID (yes or no) and previous medication use for anxiety or depression (yes or no).

2.9 Sample size justification

The sample size calculations are based on the literature regarding the primary outcome (GAD-7) and experience in the NIHR-funded ADEPT (Autism DEPression Trial) trial in adults with autism (3). There is uncertainty about the minimum clinically important difference for the GAD-7 with a recent finding that a 20% reduction can be a useful guide for patients with moderately severe symptoms (17) and earlier work suggesting an absolute reduction of 2 to 3 points on the total GAD-7 score as being important (18). Consequently, based on the latter evidence, this trial is designed to detect a difference of 2.2 points on the GAD-7 between treatment arms at 16-weeks. The results from the ADEPT study suggest a standard deviation (SD) in GAD-7 scores of 5.7 and a correlation between baseline and follow-up GAD-7 scores of 0.37 (3). Recruiting 306 participants will allow the trial to detect a difference of 2.2 points on the GAD-7 with 90% power (assuming 20% loss to follow-up, SD of 5.7, correlation between baseline and follow-up of 0.37 and alpha of 0.05).

The power the trial will have to detect other differences (by randomising 306 patients) is described below:

	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%

2.10 Blinding

The central research team, clinicians, other researchers, site staff and participants are blinded to the allocation of treatment group, except for one of the two trial statisticians and database manager (University of Bristol, UK) and trial pharmacists (UK and Australian for their respective participants).

Two statisticians based at the University of Bristol 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 this SAP and will attend closed Data Monitoring Committee (DMC) meetings as required.

2.11 Interim analyses

No interim analyses are planned.

2.12 Trial oversight

2.12.1 Trial management group (TMG)

The TMG have responsibility for the day-to-day management of the trial and report to the Trial Steering Committee. The TMG will meet on a regular basis with a core working group of staff having frequent progress meetings.

2.12.2 Trial steering committee (TSC)

The role of the TSC is to provide the overall supervision of the trial, monitor trial progress and conduct and advise on scientific credibility. The membership consists of an independent chair (Prof. Nick Freemantle), together with five other independent members including an autistic member. The trial manager and the Chief Investigator also attend as non-voting members. Observers may also attend, as may other members of the TMG or members of other professional bodies, at the invitation of the Chair. The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee or equivalent and ultimately carries the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy. Once the first participant is recruited the TSC will meet at regular, agreed intervals.

2.12.3 Data monitoring committee (DMC)

The Data Monitoring Committee (DMC) has an independent chair (Prof Louise Marston) and two other independent members and monitors accumulating trial data during the trial and makes recommendations to the TSC as to whether there are any ethical or safety issues that may necessitate a modification to the protocol or closure of the trial. The DMC will convene prior to TSC meetings. In accordance with the Trial Terms of Reference for the DMC, this group is responsible for assessing safety and efficacy of the trial.

2.13 Outcome measures

2.13.1 Primary outcome

The primary outcome is the GAD-7 anxiety score measured at 16-weeks post-randomisation as a continuous variable.

2.13.2 Secondary outcomes

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

- Adverse effects: Modified Toronto side effects scale and open-ended questions (including suicidality item). Side-effects to be considered individually and summarised as the number of symptoms in the past 2 weeks. Additional questions on sexual function will be described separately;
- GAD-7 and proportionate change in GAD-7 since baseline including treatment response (50% reduction in GAD-7);
- Patient reported effect of medication on symptoms: study specific questionnaire;
- Social anxiety: Social Phobia Inventory (SPIN);
- Obsessive compulsive symptoms: Obsessive Compulsory Inventory Revised (OCI-R);
- Panic attacks: Brief Patient Health Questionnaire (PHQ) from Primary Care Evaluation of Mental Disorders (PRIME-MD);
- Repetitive behaviours: Adult Repetitive Behaviours Questionnaire-2 (RBQ-2A);
- Meltdowns based on single item added to GAD-7 scale;
- Depressive symptoms: Patient Health Questionnaire-9 (PHQ-9) ;
- Composite anxiety and depressive symptoms : sum of PHQ-9 and GAD-7 scores;
- Functioning and disability : World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0);
- Carer burden and quality of life: Carer Burden Scale, Carer Experience Scale (CES) and EQ-5D-5L questionnaire;
- Adherence to the study medication: study specific questionnaire adapted from the GENPOD and PANDA trials

Additional to the secondary outcomes listed above are those relating to cost-effectiveness and participants' experience of participating in the trial:

- Cost-effectiveness of sertraline treatment for anxiety in adults with a diagnosis of autism
- Participants' acceptability, experiences of, and adherence to, study processes and treatment.

Cost-effectiveness and quality of life derived from the EQ-5D-5L are analysed as part of the health economics analysis described in the separate Health Economics Analysis Plan (HEAP). The participants' acceptability, experiences of, and adherence to, study processes and treatment are analysed as part of the qualitative analysis. These will be analysed elsewhere.

3. GENERAL ANALYSIS CONSIDERATIONS

3.1 Analysis populations

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

Per protocol analyses will be conducted on all participants in the Full Analysis set who remained on the trial medication.

Safety analyses will be conducted on all randomised participants according to the group they were randomised to.

3.2 Derived variables

The algorithms for the calculation of derived variables in this study are described below:

GAD-7 score	For each of the seven items rating anxiety, scores of 0, 1, 2, and 3 will be allocated the response categories of "not at all" (0), "several days" (1), "more than half the days" (2), and "nearly every day" (3) respectively. The total score will be derived by summing the scores for the seven items.
Modified Toronto side effects scale	The modified Toronto side effects scale is a 18-item instrument enquiring about the frequency of central nervous system (CNS) and gastrointestinal (GI) side effects. In addition, the presence/absence of sexual side effects in the last two weeks are also enquired about. For the purpose of analysis, each side effect is considered separately as either present or absent and related to whether or not the side effect was new since baseline. Participants are also given the space to report the frequency of up to eight additional symptoms in the free text. As well as considering each side effect individually, the number of symptoms present in the past two weeks will be analysed.
SPIN	For each of the 17 items, respondents are asked how much the statement applied to them over the past week. Items are scored 0-4 (0: "Not at all"; 1: "A little bit"; 2: "Somewhat"; 3: "Very much"; 4: "Extremely") and scores are summed for a total SPIN score.
OCI-R	For each of the 18 items, respondents are asked how much the statement distressed or bothered them in the past month. Responses to each item are scored on a scale of 0-4 (0: "Not at all"; 1: "A little"; 2: "Moderately"; 3: "A lot"; 4: "Extremely). The obsessive compulsive disorder (OCD) component of the OCI-R is derived from the sum of the scores for items 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 14, 15, 16, 17 and 18. The hoarding disorder subscale is derived from the sum of the scores of items 1, 7 and 13.
RBQ-2A	The RBQ-2A is formed of 20 items. For the first six, respondents are given four options and items are scored on a scale of 1-4 (1: "Never or rarely"; 2: "One or more times daily"; 3: "15 or more times daily"' 4: "30 or more times daily"). Items 7 to 12 have three options and items are scored on a scale of 1-3 (1: "Never or rarely"; 2: "Mild or occasional"; 3: "Marked or notable"). Items 13-19 have four options and items are scored on a scale of 1-4 (1:"Never or rarely"; 2:"Mild or occasional"; 3:"Marked or notable"; 4:"Serious or severe"). The final item has three options and is scored on a

	scale of 1-3 (1:"A range of different and flexible self-chosen activities"; 2:"Some varied and flexible interests but commonly choose the same activities"; 3:"Almost always choose from a restricted range of repetitive activities"). The total repetitive behaviours score is derived by adding the scores of the individual items with responses "3" and "4" combined as "3". The mean score (total divided by the number of items) will be used for analysis purposes.
PHQ-9	Each of the nine items in the questionnaire score symptoms of depression over the last 2 weeks on a scale of 0-3 (0: "Not at all"; 1: "Several days"; 2: "More than half the days"; 3: "Nearly every day"). Scores are summed across items for a total score.
PHQ-ADS	The PHQ-9 score is summed with the GAD-7 score to derive a combined anxiety and depression symptoms score.
WHODAS 2.0	The 12-item (short) version of the WHODAS is used where items relating to functioning and disability are scored 0-4 (0: "No difficulty"; 1: "Mild difficulty"; 2: "Moderate difficulty"; 3: "Severe difficulty"; 4: "Extreme difficulty or cannot do") then summed and divided by 48.
EQ-5D-5L	The EQ-5D-5L questionnaire comprises 5 items rating health-related quality of life, each having 5-level responses coded 1-5. Derivation of this variable and its analysis will be reported separately in the HEAP. .
Caregiver Burden Scale	In the Caregiver Burden Scale, caregivers are asked about 15 general areas where the person with autism may require assistance. The perceived burden is defined as the sum of the number of items for which the person with autism required assistance *and* for which the caregiver provided assistance *and* the caregiver reported that providing this assistance was stressful.
CES	Based on the responses to the different items different caring states are defined and these will be scored according to Al Jabani (19)
Meltdowns	Participants are asked if they have had a meltdown in the previous 2 weeks. Responses are coded as 0: "Not at all", 1: "Several days", 2: "More than half the days" or 3: "Every day".
CISR	The CISR will be used to identify hierarchical primary and secondary ICD10 diagnoses for depression and anxiety based on a diagnostic algorithm. A total CISR score across all symptoms will be calculated, alongside the anxiety profile of the patient (Generalised anxiety, OCD, Specific phobia, Social phobia, Agoraphobia, Panic disorder).
ASRS	Participants are asked about the frequency of six different symptoms related to attention deficit disorder. If four or more of the six symptoms are reported "sometimes", "often" or "very often" (or just "often" or "very often" for symptoms of delaying the start of tasks, fidgeting, or feeling like

	being driven by a motor) then the participant is considered to have symptoms consistent with traits of attention deficit hyperactivity disorder.
Brief PHQ from PRIME-MD	Participants are asked to complete a multi-item questionnaire asking about the presence of symptoms experienced over the last month (20). This includes two items on panic attacks ("Have you had an anxiety attack (suddenly experiencing fear or panic?" and, if yes, "Do some of the attacks come suddenly out of the blue – that is, in situations where you don't expect to be nervous or uncomfortable?) If the participant responds positively to both they will be considered to have had a panic attack (coded as present/absent).
Suicidality	Determined from the suicidality item from the PHQ-9 and trial-specific open-ended questions.

For the PHQ-9 and GAD-7, individual missing items were addressed using the following rule adopted in the CoBalT study (Cognitive behavioural Therapy as an adjunct to pharmacotherapy for primary care patients with treatment resistant depression: a randomised controlled trial) (21). If > 10% of the items were incomplete then the data collected on that measure for that participant were disregarded. However, if < 10% of items on a particular measure were missing, missing item(s) were imputed using the mean of the remaining items (rounded to an integer). For PHQ-9 and GAD-7 the 10% rule meant that only a single item would be imputed. The number of cases for which values were imputed will be reported. For the WHODAS 2.0, the developers suggest that when only one item is missing a value the mean of the other items is used to assign a score to the missing item. This is only done if only one item is missing.

3.3 Procedures for missing data

In all tables, missing data will be indicated using footnotes. For the primary outcome of the GAD-7 at 16 weeks, we will use descriptive statistics to describe the baseline characteristics of patients who do and do not have missing primary outcome data. Missing primary outcome data may also be imputed as part of a sensitivity analysis described in **section 6.3.4**.

3.4 Study centre effects

Randomisation of participants is stratified by centre and all analyses will adjust for centre and all minimisation variables.

3.5 Outliers

Prior to analysis the trial statistician will use graphs and descriptive statistics to identify potential outliers in the data. These will be queried with the trial manager who will verify available records to confirm whether or not they are data entry mistakes.

3.6 Visit windows

All questionnaires will be analysed regardless of when they are returned. The average time between baseline and receipt of questionnaires will be presented, however. This data will be presented as mean (SD) or median (IQR) as appropriate.

4. DESCRIPTION OF PARTICIPANT CHARACTERISTICS

4.1 Disposition

The flow of participants through the trial will be summarised in a CONSORT diagram that will include the eligibility, reasons for exclusion, participants consenting, numbers of participants randomised to the two treatment groups, losses to follow up and the numbers analysed for the primary outcome.

4.2 Baseline characteristics

Baseline characteristics of participants will be compared between the two arms by reporting relevant summary statistics to determine whether any potentially influential imbalance occurred by chance. Baseline characteristics will be summarised using means (SD), medians (Inter-quartile-range; IQR) or number (%) depending on the nature of the data and its respective distribution.

Due to differences in demographics and the educational systems of the UK and Australia, questions regarding ethnic background and educational attainment were different in both countries. When describing the characteristics of the randomised participants, categories will be collapsed and combined where possible to harmonise the reporting of this data.

5. ASSESSMENT OF STUDY QUALITY

5.1 Eligibility checks

The numbers of participants and reasons for exclusions will be described.

5.2 Selection bias

Where data are available, we will use descriptive statistics to compare the demographic characteristics of those who did and did not attend baseline assessment screening (either by actively declining or failing to attend), those who were and were not deemed eligible at the baseline assessment and those who did and did not consent to randomisation.

5.3 Data validation

Once the data are downloaded by the trial statistician, internal consistency checks will be performed by them in preparing the data for analysis in Stata. They will aim to identify spurious values or inconsistencies in responses. When inconsistencies are identified, these will be reported to the trial manager who will verify against available records.

Where adherence data are missing from questionnaires, the trial manager will refer to participant appointments and other communications to supplement the missing data.

5.4 Study completion

For the purposes of reporting, we define the end of trial data collection as the collection of the last 52-week follow-up for trial participants. Cleaning of the data is an ongoing process and the database will be locked once all data queries are resolved and the last data item is collected. Final analyses will be run once the database is locked. The number of patients followed-up and lost to follow-up will be reported for each treatment arm in the CONSORT Flow Diagram. The end of the grant funding this trial is 31/3/2025

5.5 Protocol deviations

There will be no prospective, planned deviations or waivers to the protocol. Any protocol breaches will be documented and reported to the Trial Manager, Chief Investigator and Sponsor immediately. Information about protocol breaches will also be included in routine reports to the DMC and TSC.

6. ANALYSIS OF EFFECTIVENESS

Stata version 16 (or higher) will be used for all STRATA analyses. Two-tailed tests will be used with effect estimates, 95% confidence intervals (CI) and p-values presented. A significance level of 5% will be used and no adjustment will be used for multiple testing. Analyses using regression models will adjust for stratification and minimisation variables as well as baseline values of the outcome studied. The primary approach for analysis will be on an intention-to-treat (ITT) basis defined as analysing participants according to the arm to which they were randomised.

6.1 Summary of primary and secondary endpoints

The primary and secondary endpoints are summarised below:

Outcome	Measure	Timepoints	Interpretation	Range
Primary				
Anxiety	GAD-7	Baseline and 16 weeks (also collected at 1-2, 4, 8, 12, 24, 36 and 52 weeks)	Higher scores correspond to more severe symptoms of anxiety	0-21
Secondary				
Adverse effects	Modified Toronto side effects scale (and additional sexual function symptoms)	Baseline and 1-2, 4, 8, 12, 16, 24, 36 and 52 weeks	For each side effect we will describe whether it is present (1) or absent (0)	0-1
			Number of symptoms in the past two weeks (excluding sexual function symptoms)	0-18
	Suicidality item from the PHQ-9	Baseline and 1-2, 4, 8, 12, 16, 24, 36 and 52 weeks	Described as whether it is present (1) or absent (0)	*0-1*
Social anxiety	SPIN	Baseline and 16, 24 and 52 weeks	Higher scores indicate worse symptoms of social anxiety	0-68
Obsessive compulsive symptoms	OCI-R (OCD subscale)	Baseline and 16, 24 and 52 weeks	Higher scores indicate worse symptoms of obsessive-compulsive disorder	0-60
Panic attacks	PHQ from PRIME-MD	Baseline and 16, 24 and 52 weeks	Categorised as present (1) or absent (0)	0-1
Repetitive behaviours	RBQ-2A	Baseline and 16, 24 and 52 weeks	Higher scores indicate more frequent repetitive behaviours	20-60
Depressive symptoms	PHQ-9	Baseline and 1-2, 4, 8, 12, 16, 24, 36 and 52 weeks	Higher scores indicate more depressive symptoms	0-27

Functioning and disability	WHODAS 2.0	Baseline and 16, 24 and 52 weeks	Continuous measure with larger values indicating greater levels of disability	0-1
Carer burden and quality of life	Carer burden scale	Baseline, 16 and 52 weeks	Higher scores indicate greater levels of burden on carers	0-15
	CES		Continuous measure with larger values reflecting better quality of life	0-100
	EQ-5D-5L		Continuous measure with larger values reflecting better quality of life	values depend on the valuation being used
Adherence to the study medication	Study questionnaire	1-2, 4, 8, 12, 16, 24, 36 and 52 weeks	Patients are deemed adherent/not adherent.	0-1
Meltdowns	GAD-7	Baseline and 1-2, 4, 8, 12, 16, 24, 36 and 52 weeks	Higher scores indicate greater frequency	0-3

6.2 Primary analysis

The primary outcome is GAD-7 score collected at 16-weeks post-randomisation. It will be described in each treatment group using means and standard deviations. Comparisons between treatment arms will be made using a multivariable linear regression model adjusting for baseline GAD-7 scores and variables used in the randomisation. The results will be presented as the difference between group means, corresponding 95% confidence interval and P-value.

We will check the normality assumptions of the model using graphs and summary statistics. The t-distribution is very robust to departures from Normality, but in the presence of skewed data a supportive analysis using bootstrapping will be done. This will involve repeated sampling (5000 model iterations) with replacement from the observed data. Ordinary least squares are then used to estimate the treatment effect in each of the 5000 bootstrap samples, The distribution bias and corrected (BCa) confidence interval for the treatment effect is then estimated from the distribution of these estimates. This confidence interval can then be presented alongside the primary analysis not using bootstrapping.

A number of analyses are proposed to assess the sensitivity of the primary analysis to various assumptions. These are described below. Sensitivity analyses will be presented alongside those of the primary analysis so they can be compared and contrasted. As these will be exploratory in nature, differences, 95% confidence intervals and p-values will be presented, but will be interpreted with due caution.

6.2.1 Imbalance between treatment groups

Should there be evidence of imbalance between treatment groups on important baseline characteristics as described in **section 4.2**, sensitivity analyses will be conducted where the primary analysis is repeated, adjusting for variables showing an imbalance. This sensitivity analysis will be performed for the primary outcome only.

6.2.2 Per protocol analysis, Complier Average Causal Effect (CACE) analysis and mediation analysis

A per protocol analysis of the primary endpoint will be conducted restricted to those who remained on their trial medication at that time. Data for this interaction will be analysed following the method outlined in section 6.3.

Recognising the inherent bias in estimates derived from per protocol analyses, we will also conduct a CACE analysis for the primary outcome. The CACE estimates will be obtained using instrumental variable regression including the same variables used in the primary analysis with randomised group as the instrumental variable and the indicator variable for compliance.

Participants are said to have complied with (or adhered to) treatment at week 16 are those who reported to be currently taking their medication (i.e. not formally withdrawn from medication) and to be taking it every day or nearly every day. If participants failed to actively answer whether they were currently taking their medication, they were deemed adherent if they went on to say that they were taking it every day or nearly every day.

A mediation analysis (as proposed by Emsley 2010 – SJM to insert ref) will also be performed to estimate the direct and indirect effects of the intervention on GAD-7 at 16-weeks. A two-stage least squares estimator will be used and the instrumental variables will be all two-way interactions of baseline characteristics with the treatment allocation.]

Descriptive analyses will be performed of adherence more broadly and will present the number withdrawn from medication over time, the mean (SD) dose (placebo/Sertraline) over time among those taking their trial medication and descriptions of the other treatments/therapies received.

6.2.3 Missing outcome data

The sensitivity of the primary analysis to the impact of missing data will be investigated. The amount of missing data will be explored along with differences in missingness between arms, variables associated with/predictive of missingness and, if reported, reasons for missingness.

A number of approaches to missing data will be adopted and findings then compared and contrasted with the results of the primary analysis. These include, imputing missing outcome data using "better" and "worse" case assumptions and multiple imputation by chained equations (MICE) where appropriate. Multiple imputation models will include baseline, 2-, 4-, 8- and 12-week GAD-7 (as available), arm, variables used in the randomisation as well as other variables such as baseline and auxiliary covariates informative of missingness. Sensitivity analyses will be performed to assess the impact of changing assumptions on MICE estimates.

During trial conduct, we will make strenuous efforts to maintain contact with trial participants and hence minimise the amount of missing data, and in our sample size calculations have allowed for up to 20% missing data at 16 weeks.

6.2.4 Timing of the return of questionnaires

The primary analysis will incorporate all questionnaires returned regardless of whether they are returned on time (within 4 weeks of return) or not. Descriptive statistics will be used to describe the timing of the return of questionnaires and the data will be explored to determine whether this differed by treatment group or by GAD-7 scores. A sensitivity analysis of the primary outcome will additionally adjust for the timing of the return of these questionnaires in order to assess the impact of any late returns (defined as more than 4 weeks late).

6.3 Secondary outcomes analyses

The approach for the analysis of the secondary outcomes will be on an ITT basis defined as analysing all participants according to the group they were randomised to.

The effect of the intervention on the secondary outcomes collected at 16-, 24-, 36- (where available) and 52-weeks post-randomisation will also be examined using linear regression for continuous outcomes, and logistic

regression for binary outcomes, adjusted for baseline values of the outcome being investigated and variables used in the randomisation. Ordinal variables will be analysed using a proportional odds model adjusted for baseline values of the outcome being investigated and variables used in the randomisation.

Descriptive analyses will be conducted to evaluate how individual adverse reactions (as reported in the Toronto side effect scale) vary over time.

As it is possible that adherence to treatments will decrease over the 52-week follow-up, we will describe this at each timepoint by arm as well as the use of additional or alternative medications or other treatments.

A repeated measures analysis using GAD-7 and PHQ-9 outcome data collected at multiple follow up timepoints will be carried out to examine the effect of the intervention over 52-weeks. A linear mixed model (repeated outcome observations (level 1) nested within participants (level 2)) will also be conducted to incorporate all time points.

We will check the normality assumptions of linear regression models using graphs. Alternative methods of analysis will be considered if the assumptions of the model are not met. This might include, for example, using a bootstrap framework to estimate confidence intervals. The proportional odds assumption for the proportional odds model will be assessed using the Brant test.

6.4 Subgroup analyses

Four pre-defined subgroup analyses will be carried out to assess the difference in treatment effect on the primary outcome at 16 weeks according to characteristics assessed at baseline. In each case, 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. As well as presenting the p-value for the test for interaction, we will also demonstrate any effect modification using graphs.

The baseline characteristics investigated for subgroup analyses are:

- Timing of an autism diagnosis (defined as <18 years vs ≥ 18 years)
- Presence of a mild ID (defined as present or absent)
- Screening positive for ADHD characteristics (defined as present or absent)
- Severity of anxiety at baseline (GAD-7 scores analysed as numeric measures)

7. ANALYSIS OF SAFETY

All serious adverse events (SAEs) will be tabulated by allocated group. The number of events, number of patients having at least one event and the number of patients with more than one event will be tabulated. The nature of the SAEs will also be described.

8. CARER SUB-STUDY

8.1 Objective

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

8.2 Outcomes

Carers are asked to complete a STRATA Carer Burden Questionnaire at Baseline, 16- and 52- weeks post-randomisation of the STRATA (main trial) participant. Carer burden will be measured using the Caregiver Burden Scale. Other outcomes/measures include the EQ-5D-5L and CES and brief questions about the anxiety and autism of the main trial participant (i.e. the person for whom they are a carer).

8.3 Sample size

No *a priori* sample size calculation was conducted for the sub-study. This study will include all eligible and consenting carers of randomised STRATA participants. Should all 318 STRATA participants have a recruited carer participating in the study, the study will have 90% power (alpha=0.05) to detect a 0.4 SD difference in the carer burden scale assuming 30% attrition. Should half of STRATA participants have a recruited carer participating in the study, the study will have 90% power (alpha=0.5) to detect a 0.6 SD difference in the carer burden scale, assuming 30% attrition.

8.4 Statistical analysis

Descriptive statistics will be used to describe the baseline characteristics of carers participating in the carer burden sub-study as well as the randomised participants they are caring for. These results will be used to determine whether there are imbalances at baseline between treatment groups and suggest whether appropriate additional adjustment should be performed. Continuous measures will be presented as means and SDs or medians, inter-quartile ranges, and ranges depending on their distribution. Categorical data will be presented as frequencies and proportions.

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. The carers' EQ-5D-5L health states will be valued using the method recommended by National Institute for Health and Care Excellence (NICE) at the time of analysis. The effect of the intervention on the carer burden scale, carers experience scale and EQ-5D-5L collected at 16- and 52-weeks post-randomisation will be examined using linear regression adjusting for baseline values, variables used in the randomisation and any variables found to be imbalanced at baseline.

9. CHANGES TO THE SAP

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

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

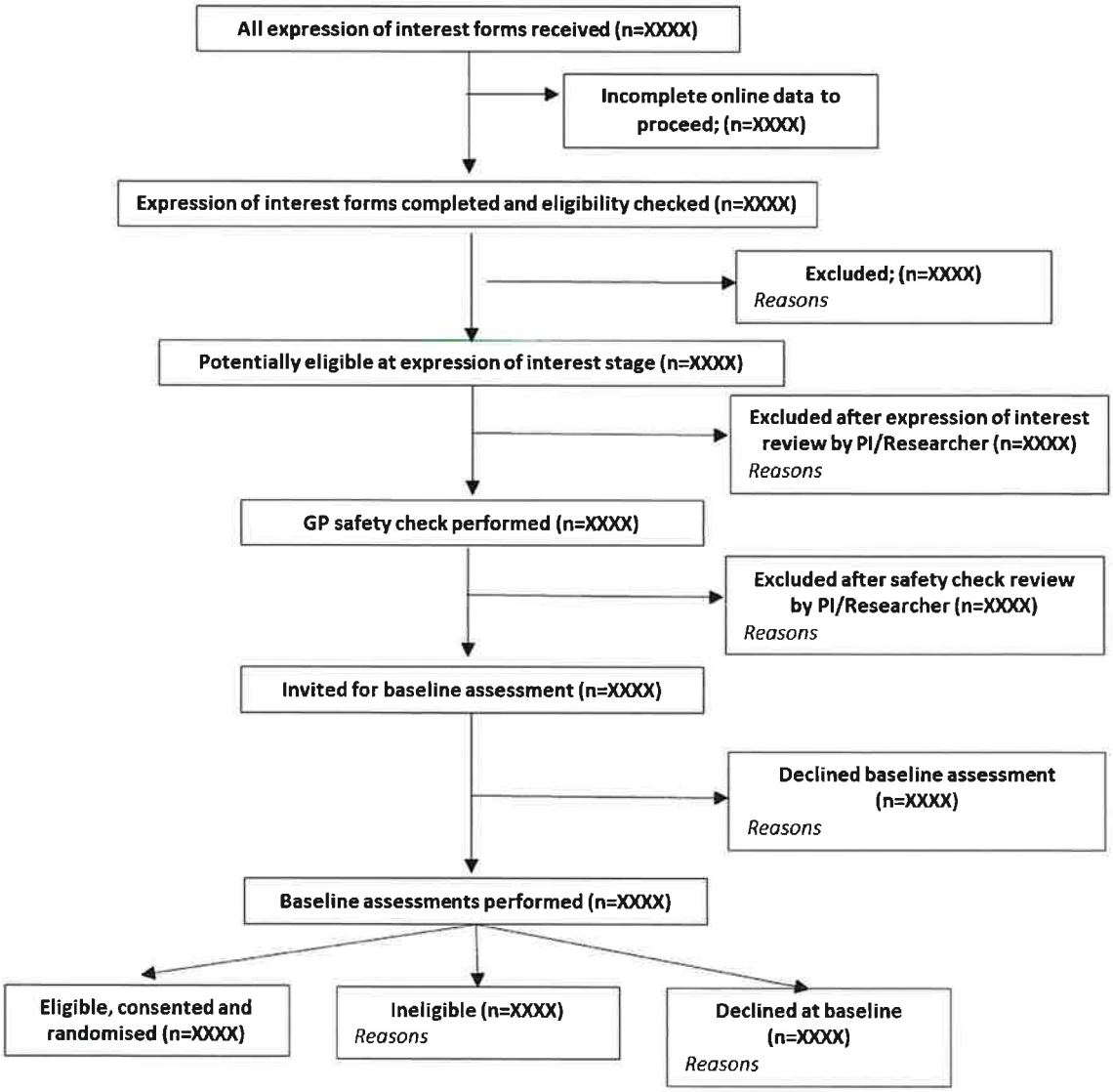
10. FINAL REPORT TABLES AND FIGURES (SUBJECT TO CHANGE)

10.1 Population

Figure F1 Predicted and actual recruitment

X axis: Month; Y axis: Number of patients recruited

Figure F2 **Flow of participants: recruitment pathway**



Notes:
Some patients may be ineligible or excluded for more than one reason

Figure F3 **Flow of participants: randomisation onwards**

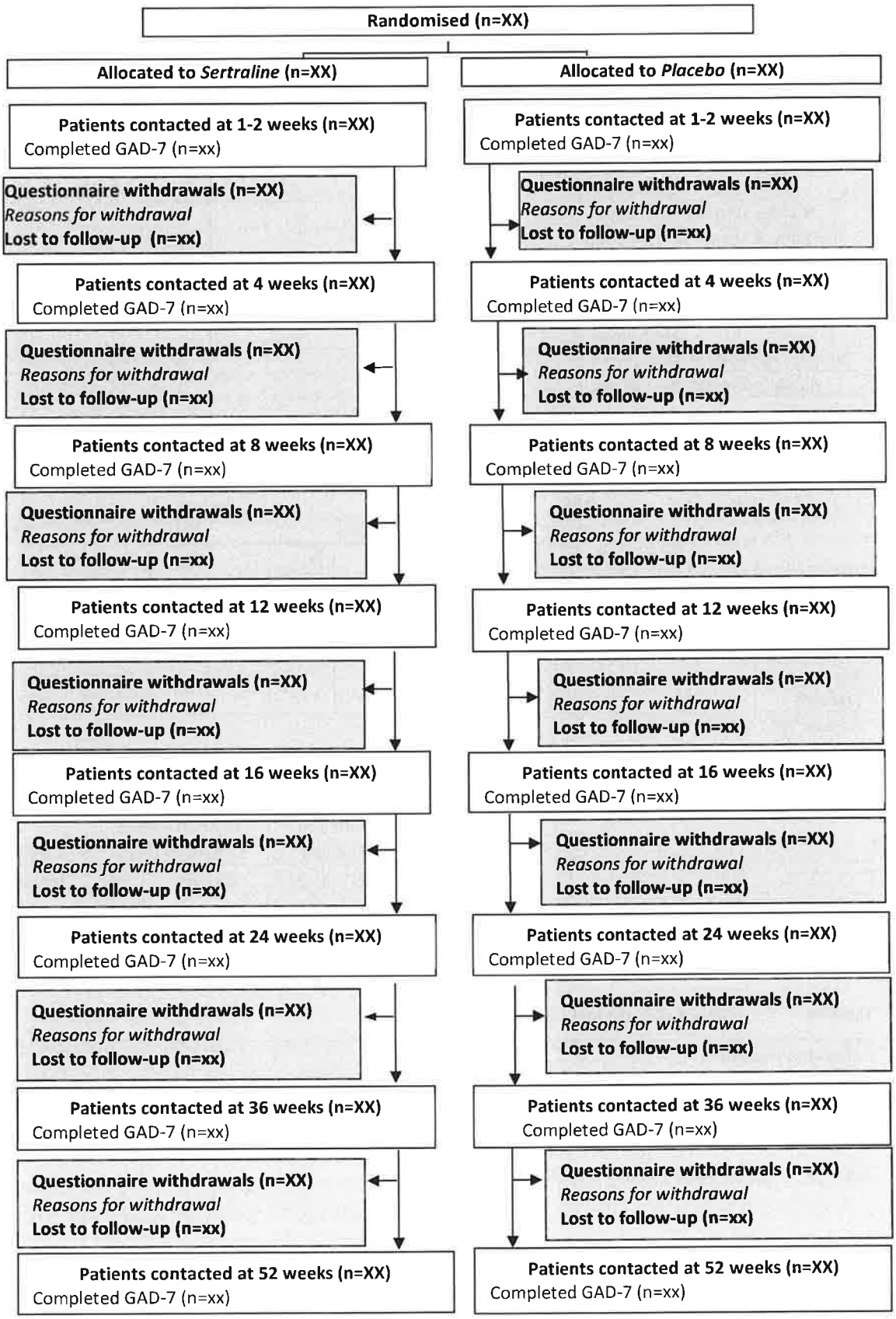


Table T1 **Recruitment statistics by centre**

	South West England	Surrey, Hampshire and Portsmouth	East of England	East Midlands	Western Australia	Total
Number of recruiting sites						
GP safety checks						
Number of safety checks performed						
Number of patients deemed ineligible at the GP safety check stage						
Baseline assessments						
Number of baseline assessments performed						
Number excluded at assessment						
Number of patients declining						

Table T2 **Comparison of age and gender of those completing the baseline assessment and those declining to attend or not responding**

	N	Age			Gender								
					Female			Male			Other		
		n[a]	Mean	SD	n[a]	N	%	n[a]	N	%	n[a]	N	%
No (declined or not responding)													
Yes (agreed)													

[a] *Number with available data*

Table T3 **Protocol breaches**

	Randomised to Sertraline (n=)		Randomised to Placebo (n=)		Overall (n=)	
	Patients	%	Patients	%	Patients	%
Any protocol breach						
.....						

Table T4 **Details of individual protocol breaches**

Allocated treatment group	Centre	Further details (exact nature dependent upon type of deviation)
...		

Table T5 **Discontinuation from the trial medication**

	Randomised to Sertraline (n=XX)		Randomised to Placebo (n=XX)		Overall (N=XX)	
	n	%	n	%	N	%
Any discontinuation from the trial medication *All* *By 16 weeks follow-up* *After 16 weeks follow-up*						
Reason						

10.2 Baseline data

Table T6 Baseline comparability of randomised groups

	Sertraline (n=xx)	Placebo (n=xx)	Total (n=xx)
Stratification variable: centre n(%)			
South-West England *Surrey, Hampshire and Portsmouth* *East of England* *East Midlands* *Western Australia*			
Minimisation variables			
Gender: n (%) *Female* *Male* *Other*			
Age; n(%) *18-34 years* *35-49 years* *≥50 years* **Mean (SD)** **Median (IQR)**			
Baseline GAD-7: n(%) *<15* *≥15* Mean (SD) Median (IQR)			
Previous medication use; n(%) No Yes			
Socio-demographic and mental health variables			
Sex assigned at birth; n(%) *Female* *Male*			
Ethnic group: n(%) *Categories to be harmonised between UK and Australia according to the distribution of available data			
Marital status: n(%) *Categories to be harmonised between UK and Australia according to the distribution of available data			

Employment status: n(%) *Categories to be harmonised between UK and Australia according to the distribution of available data			
Educational attainment: n(%) *Categories to be harmonised between UK and Australia according to the distribution of available data			
Current living arrangements: n(%) *Living alone* *Living with spouse/partner* *Living with other family* *Living with non-family members* *Living in residential care home* *Other* *Not disclosed*			
Primary hierarchical diagnosis according to the CIS-R: *No diagnosis identified* *Mixed anxiety and depressive disorder (mild)* *Generalised anxiety disorder (mild)* *Obsessive-compulsive disorder* *Mixed anxiety and depressive disorder* *Specific (isolated) phobia* *Social phobia* *Agoraphobia* *Generalised anxiety disorder* *Panic disorder* *Mild depressive disorder* *Moderate depressive disorder* *Severe depressive disorder*			
Secondary psychiatric diagnosis according to the CIS-R: n(%) *No diagnosis identified* *Mixed anxiety and depressive disorder (mild)* *Generalised anxiety disorder (mild)* *Obsessive-compulsive disorder* *Mixed anxiety and depressive disorder* *Specific (isolated) phobia* *Social phobia* *Agoraphobia* *Generalised anxiety disorder* *Panic disorder* *Mild depressive disorder* *Moderate depressive disorder* *Severe depressive disorder*			
ASRS score; **mean (SD)** **median (IQR)**			
PHQ-9 score: **mean (SD)** **median (IQR)**			
Brief PHQ PRIME-MD; n(%)			

Panic attack ***No*** ***Yes***			
SPIN score: **mean (SD)** **median (IQR)**			
OCI-R score **mean (SD)** **median (IQR)**			
RBQ-2A score **Mean (SD)** **Median (IQR)**			
WHODAS 2.0 score **Mean (SD)** **Median (IQR)**			
EQ-5D-5L score: mean (SD)			
CIS-R score: mean (SD)			
Suicidal ideation (CIS-R thoughts/plans): n (%)			

Note: Where data are incomplete for some variables, the numbers with information available are listed here

Table T7 Treatments/therapies for mental health problems (at and prior to baseline)

Treatments and therapies	**Sertraline (n=xx)**	**Placebo (n=xx)**	**Total (n=xx)**
Currently receiving medications for mental health problems; n(%) *No* *Yes* **Medications reported among those currently receiving medications (note that participants can report more than one treatment); n (% of medications reported)** *List*			
Ever received medications for mental health problems; n(%) *No* *Yes* **Among those ever receiving medications, when were they received; n(%)** *In the past year* *In the past 2-5 years* *6 years or more ago?* **Medications reported among those ever receiving medications (note that participants can report more than one treatment); n (% of medications reported)** *List*			
Currently having talking therapies for mental health problems; n(%) *No* *Yes*			

Therapies reported among those currently having talking therapies (note that participants can report more than one therapy); n (% of therapies reported) *List*			
Ever had talking therapies for mental health problems; n(%) *No* *Yes* **Among those ever having talking therapies, when were they had; n(%)** *In the past year* *In the past 2-5 years* *6 years or more ago?* **Talking therapies reported among those ever having talking therapies (note that participants can report more than one treatment); n (% of therapies reported)** *List*			
Currently receiving other treatments for mental health problems including complementary/alternative treatments; n(%) *No* *Yes* **Treatments reported among those currently receiving other treatments (note that participants can report more than one treatment); n (% of treatments reported)** *List*			
Ever received other treatments for mental health problems including complementary/alternative treatments; n(%) *No* *Yes* **Among those ever receiving other treatments, when were they received; n(%)** *In the past year* *In the past 2-5 years* *6 years or more ago?* **Treatments reported among those ever receiving other treatments (note that participants can report more than one treatment); n (% of treatments reported)**			

List			

Note: Where data are incomplete for some variables, the numbers with information available are listed here

Table T8 Modified Toronto Side Effects scale comparability at baseline of randomised groups

Symptoms experienced in the last 2 weeks	Sertraline (n=xx)	Placebo (n=xx)	Total (n=xx)
Headaches; n(%)			
Not at all			
Some days			
More than half the days			
Every day			
A rapid heartbeat; n(%)			
Not at all			
Some days			
More than half the days			
Every day			
Feeling agitated; n(%)			
Not at all			
Some days			
More than half the days			
Every day			
Dry mouth; n(%)			
Not at all			
Some days			
More than half the days			
Every day			
Blurred vision; n(%)			
Not at all			
Some days			
More than half the days			
Every day			
Shaking or trembling of hands or body; n(%)			
Not at all			
Some days			
More than half the days			
Every day			
Excessive sweating; n(%)			
Not at all			
Some days			
More than half the days			
Every day			
Indigestion or stomach pains; n(%)			
Not at all			
Some days			
More than half the days			
Every day			
Constipation; n(%)			
Not at all			
Some days			
More than half the days			
Every day			
Diarrhoea; n(%)			
Not at all			
Some days			
More than half the days			

Every day			
Feeling sick or nauseous; n(%) *Not at all* *Some days* *More than half the days* *Every day*			
Difficulty sleeping; n(%) *Not at all* *Some days* *More than half the days* *Every day*			
Feeling sleepy during the day; n(%) *Not at all* *Some days* *More than half the days* *Every day*			
Light headed or dizziness; n(%) *Not at all* *Some days* *More than half the days* *Every day*			
Increased appetite; n(%) *Not at all* *Some days* *More than half the days* *Every day*			
Decreased appetite; n(%) *Not at all* *Some days* *More than half the days* *Every day*			
Weakness or fatigue; n(%) *Not at all* *Some days* *More than half the days* *Every day*			
Difficulty or pain passing urine; n(%) *Not at all* *Some days* *More than half the days* *Every day*			
Other self-reported symptoms will be outlined here if reported in the free text			

Note: Where data are incomplete for some variables, the numbers with information available are listed here

Table T9 Sexual symptoms reported at baseline

Symptoms experienced in the last 2 weeks	**Sertraline (n=xx)**	**Placebo (n=xx)**	**Total (n=xx)**
A low sex drive; n(%) *No* *Yes*			
Difficulty achieving an orgasm during sex or masturbation; n(%) *No*			

Yes			
Difficulty getting or maintaining an erection (men only); n(%) *No* *Yes*			
Difficulty ejaculating (men only); n(%) *No* *Yes*			

Note: Where data are incomplete for some variables, the numbers with information available are listed here

Figure F4 Modified Toronto side-effects at baseline
(stacked bar chart by treatment group)

Table T10 Summary of baseline variables related to missing GAD-7 data at 16 weeks

	Sertraline (n=xx)	**Placebo (n=xx)**	**Total (n=xx)**
Stratification variable: centre n(%)			
South-West England *Surrey, Hampshire and Portsmouth* *East of England* *East Midlands* *Western Australia*			
Minimisation variables			
Gender: n (%) *Female* *Male* *Other*			
Age; n(%) *18-34 years* *35-49 years* *≥50 years* **Mean (SD)** **Median (IQR)**			
Baseline GAD-7: n(%) *<15* *≥15* Mean (SD) Median (IQR)			
Previous medication use; n(%) No Yes			
Socio-demographic and mental health variables			
Sex assigned at birth; n(%) *Female* *Male*			
Ethnic group: n(%) *Categories to be harmonised between UK and Australia according to the distribution of available data			
Marital status: n(%) *Categories to be harmonised between UK and Australia according to the distribution of available data			

Employment status: n(%) *Categories to be harmonised between UK and Australia according to the distribution of available data			
Educational attainment: n(%) *Categories to be harmonised between UK and Australia according to the distribution of available data			
Current living arrangements: n(%) *Living alone* *Living with spouse/partner* *Living with other family* *Living with non-family members* *Living in residential care home* *Other* *Not disclosed*			
Primary hierarchical diagnosis according to the CIS-R: *No diagnosis identified* *Mixed anxiety and depressive disorder (mild)* *Generalised anxiety disorder (mild)* *Obsessive-compulsive disorder* *Mixed anxiety and depressive disorder* *Specific (isolated) phobia* *Social phobia* *Agoraphobia* *Generalised anxiety disorder* *Panic disorder* *Mild depressive disorder* *Moderate depressive disorder* *Severe depressive disorder*			
Secondary psychiatric diagnosis according to the CIS-R: n(%) *No diagnosis identified* *Mixed anxiety and depressive disorder (mild)* *Generalised anxiety disorder (mild)* *Obsessive-compulsive disorder* *Mixed anxiety and depressive disorder* *Specific (isolated) phobia* *Social phobia* *Agoraphobia* *Generalised anxiety disorder* *Panic disorder* *Mild depressive disorder* *Moderate depressive disorder* *Severe depressive disorder*			
ASRS score; **mean (SD)** **median (IQR)**			
PHQ-9 score: **mean (SD)** **median (IQR)**			
Brief PHQ PRIME-MD; n(%)			

Panic attack ***No*** ***Yes***			
SPIN score: **mean (SD)** **median (IQR)**			
OCI-R score **mean (SD)** **median (IQR)**			
RBQ-2A score **Mean (SD)** **Median (IQR)**			
WHODAS 2.0 score **Mean (SD)** **Median (IQR)**			
EQ-5D-5L score: mean (SD)			
CIS-R score: mean (SD)			
Suicidal ideation (CIS-R thoughts/plans): n (%)			

Note: Where data are incomplete for some variables, the numbers with information available are listed here

10.3 Primary outcome and sensitivity analyses

Table T11 GAD-7 at 16 weeks

Analysis	**Sertraline**			**Placebo**			**Difference in means**	**95% CI**	**p-value**
	N	**Mean**	**SD**	**N**	**Mean**	**SD**			
Primary ITT analysis							[a]		
Sensitivity analysis additionally adjusting for baseline imbalances							[b]		
Sensitivity analysis adjusting for the timing of the questionnaire return							[c]		

[a] *Adjusted for baseline GAD-7 score and the stratification and other minimisation variables*
[b] *Adjusted for baseline GAD-7 score and the stratification and other minimisation variables as well as variables found to be imbalanced at baseline*
c *Adjusted for baseline GAD-7 score and the stratification and other minimisation variables as well as the timing of the return of the questionnaire*

Table T12 Timing of questionnaire returns

Follow-up time	**Sertraline**			**Placebo**		
	Number of questionnaires returned	**Mean number of days from baseline to questionnaire return**	**SD**	**Number of questionnaires returned**	**Mean number of days from baseline to questionnaire return**	**SD**
16 weeks (112 days)						
24 weeks (168 days)						
52 weeks (364 days)						

Table T13 GAD-7 at 16 weeks: ITT vs Per protocol vs CACE analyses

Analysis	Number of patients in model	Difference in means[a]	95% CI	p-value
ITT				
Per protocol				
CACE				

[a] *Adjusted for baseline GAD-7 score and the stratification and other minimisation variables*

Table T14 Comparison of the results of the ITT analysis of complete cases and different approaches to dealing with missing GAD-7 at 16 weeks

Analysis	Number of patients in model	Difference in means[a]	95% CI	p-value
Complete case				
"Better"=case scenario				
"Worse"-case scenario				
MICE				

[a] *Adjusted for baseline GAD-7 score and the stratification and other minimisation variables*

10.4 Secondary outcomes

Table T15 Repeated measures analyses of continuous GAD-7 at 16, 24, 36 and 52 weeks

Follow-up assessment (weeks)	Sertraline			Placebo			Difference in means[a]	95% CI	p-value
	N	Mean	SD	N	Mean	SD			
1-2									
4									
8									
12									
16 (primary)									
24									
36									
52									
Over time (also including pre-16 week data collected at safety checks)									
Group by time interaction									

[a] *Adjusted for baseline GAD-7 score and the stratification and other minimisation variables*

Table T16 Repeated measures analyses of percentage change in GAD-7 at 16, 24, 36 and 52 weeks compared with baseline

Follow-up assessment (weeks)	Sertraline			Placebo			Difference in means[a]	95% CI	p-value
	N	Mean	SD	N	Mean	SD			
16									
24									
36									
52									
Over time (also including pre-16 week data collected at safety checks)									

Group by time interaction	

[a] *Adjusted for baseline GAD-7 score and the stratification and other minimisation variables*

Table T17 Repeated measures analyses of treatment response (defined as a 50% or greater reduction in GAD-7 symptoms compared to baseline) at 16, 24, 36 and 52 weeks

Follow-up assessment (weeks)	Sertraline			Placebo			OR[a]	95% CI	p-value
	N	n	%	N	n	%			
16									
24									
36									
52									
Over time (also including pre-16 week data collected at safety checks)									
Group by time interaction									

[a] *Adjusted for baseline GAD-7 score and the stratification and other minimisation variables*

Table T18 Repeated measures analyses of continuous secondary outcomes of social anxiety symptoms (SPIN), obsessive compulsive symptoms (OCI-R), repetitive behaviours (RBQ-2A), depressive symptoms (PHQ-9) and depression and anxiety symptoms (combined composite PHQ-9 and GAD-7) at 16, 24 and 52 weeks

Follow-up assessment (weeks)	Sertraline			Placebo			Difference in means[a]	95% CI	p-value
	N	Mean	SD	N	Mean	SD			
Social anxiety symptoms (SPIN)									
16									
24									
52									
Over time									
Group by time interaction									
Obsessive compulsive symptoms (OCI-R)									
16									
24									
52									
Over time									
Group by time interaction									
Repetitive behaviours (RBQ-2A)									
16									
24									
52									
Over time									
Group by time interaction									
Depression symptoms (PHQ-9)									
16									
24									
52									
Over time									
Group by time interaction									
Combined anxiety and depression symptoms (composite of PHQ-9 and GAD-7 scores)									
16									

24									
52									
Over time									
Group by time interaction									
Functioning and disability (WHODAS 2.0)									
16									
24									
52									
Over time									
Group by time interaction									

[a] *Adjusted for baseline outcome score and the stratification and other minimisation variables*

Table T19 Repeated measures analyses of binary secondary outcomes of panic attacks (PRIME-MD)_and patient reported effect on symptoms at 16, 24 and 52 weeks

Follow-up assessment (weeks)	Sertraline			Placebo			OR[a]	95% CI	p-value
	N	n	%	N	n	%			
Panic attacks (PRIME-MD)									
16									
24									
52									
Over time									
Group by time interaction									
Patient-report of improvement of symptoms									
16									
24									
52									
Over time									
Group by time interaction									

[a] *Adjusted for baseline outcome score (where available) and the stratification and other minimisation variables*

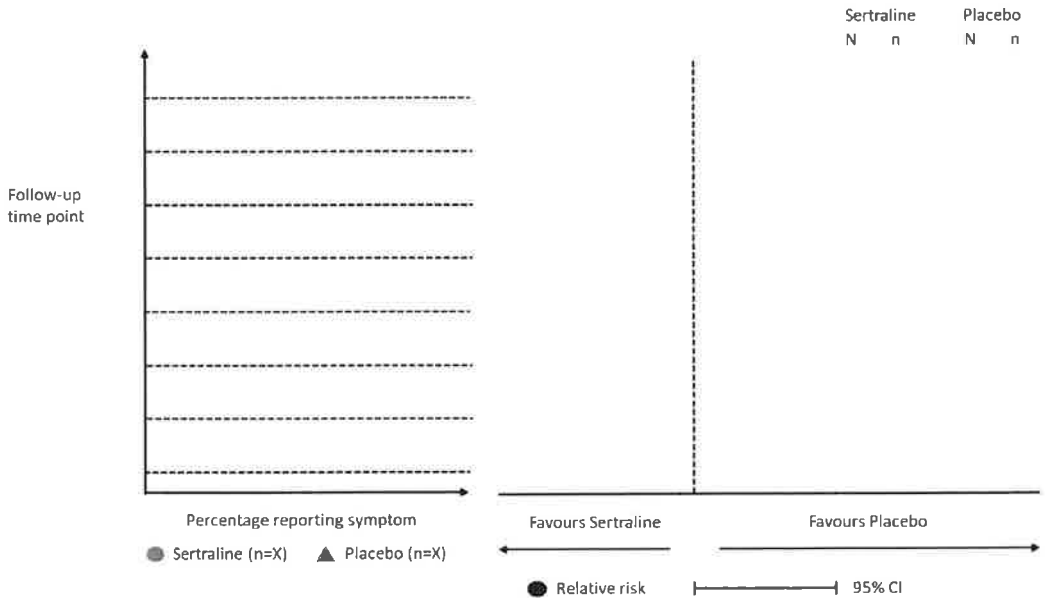
Table T20 Repeated measures analysis of meltdowns at 16, 24 and 52 weeks

Follow-up assessment (weeks)	Sertraline				Placebo				Common OR[a]	95% CI	p-value
	N	n		%	N	n		%			
Meltdowns											
16		Not at all				Not at all					
		Several days				Several days					
		More than half the days				More than half the days					
		Nearly every day				Nearly every day					
24		Not at all				Not at all					

		Several days				Several days					
		More than half the days				More than half the days					
		Nearly every day				Nearly every day					
52		Not at all				Not at all					
		Several days				Several days					
		More than half the days				More than half the days					
		Nearly every day				Nearly every day					
Over time											
Group by time interaction											

[a] *Adjusted for baseline outcome score and the stratification and other minimisation variables*

Figure F5: Dot plot of the emergence of new side effects over time not present at baseline (one graph per adverse effect)



10.5 Descriptive analyses of adherence

T21 Study medication use over time

Follow-up	Sertraline				Placebo			
	N allocated	Cumulative number withdrawn from treatment	Number adherent to treatment (% of allocated with adherence data)	Median dose among those adherent [IQR]	N allocated	Cumulative number withdrawn from treatment	Number adherent to treatment (% of allocated with adherence data)	Median dose among those adherent [IQR]
1-2 weeks								
4 weeks								
8 weeks								
12 weeks								
16 weeks								
24 weeks								
36 weeks								
52 weeks								

Figure F6 Other treatments taken/received

Bar chart of proportion of patients receiving new medication, new talking therapies, and other treatments for mental health problems by arm and follow-up point

Table T22 Description of other treatments received at any point over follow-up

	Sertraline	Placebo
	N	N
Other medications List		
Other talking terapies List		
Other treatments List		

10.6 Serious adverse events

Table T23 Listing of serious adverse events

Allocation	Brief description of the event	SAE or not	Seriousness [a]	Related to IMP	Outcome [b]

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

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

10.7 Carer sub-study

Table T24 Baseline comparability of carers and the trial participants they are caring for

	Sertraline (n=xx)	Placebo (n=xx)	Total (n=xx)
CARER CHARACTERISTICS			
Age			
Gender ;n(%) Male Female Other			
Ethnic group: n(%) *Categories to be harmonised between UK and Australia according to the distribution of available data			
Educational attainment: n(%) *Categories to be harmonised between UK and Australia according to the distribution of available data			
Employment status: n(%) *Categories to be harmonised between UK and Australia according to the distribution of available data			
Marital status: n(%) *Categories to be harmonised between UK and Australia according to the distribution of available data			
Roles as a carer			
Do you get paid for your role as a carer?; n(%)			
Are you a full-time or part-time carer? n(%) *Full time* *Part time*			
How often do you see the person you care for?; n(%) *I live with them* *Every day* *More than once per week* *Less than once per week*			
Outcome measures			
EQ-5D-5L; mean (SD)			
CES; mean (SD)			
TRIAL PARTICIPANT CHARACTERISTICS			
Stratification variable: centre n(%)			
South-West England *Surrey, Hampshire and Portsmouth* *East of England* *East Midlands* *Western Australia*			
Minimisation variables			
Gender: n (%) *Female* *Male* *Other*			

Age; n(%) *18-34 years* *35-49 years* *≥50 years* **Mean (SD)** **Median (IQR)**			
Baseline GAD-7: n(%) *<15* *≥15* Mean (SD) Median (IQR)			
Previous medication use; n(%) No Yes			
Socio-demographic and mental health variables			
Sex assigned at birth; n(%) *Female* *Male*			
Ethnic group: n(%) *Categories to be harmonised between UK and Australia according to the distribution of available data			
Marital status: n(%) *Categories to be harmonised between UK and Australia according to the distribution of available data			
Employment status: n(%) *Categories to be harmonised between UK and Australia according to the distribution of available data			
Educational attainment: n(%) *Categories to be harmonised between UK and Australia according to the distribution of available data			
Current living arrangements: n(%) *Living alone* *Living with spouse/partner* *Living with other family* *Living with non-family members* *Living in residential care home* *Other* *Not disclosed*			
Primary hierarchical diagnosis according to the CIS-R: *No diagnosis identified* *Mixed anxiety and depressive disorder (mild)* *Generalised anxiety disorder (mild)* *Obsessive-compulsive disorder* *Mixed anxiety and depressive disorder* *Specific (isolated) phobia* *Social phobia* *Agoraphobia* *Generalised anxiety disorder*			

Panic disorder *Mild depressive disorder* *Moderate depressive disorder* *Severe depressive disorder*			
Secondary psychiatric diagnosis according to the CIS-R: n(%) *No diagnosis identified* *Mixed anxiety and depressive disorder (mild)* *Generalised anxiety disorder (mild)* *Obsessive-compulsive disorder* *Mixed anxiety and depressive disorder* *Specific (isolated) phobia* *Social phobia* *Agoraphobia* *Generalised anxiety disorder* *Panic disorder* *Mild depressive disorder* *Moderate depressive disorder* *Severe depressive disorder*			
ASRS score; **mean (SD)** **median (IQR)**			
PHQ-9 score: **mean (SD)** **median (IQR)**			
Brief PHQ PRIME-MD; n(%) Panic attack ***No*** ***Yes***			
SPIN score: **mean (SD)** **median (IQR)**			
OCI-R score **mean (SD)** **median (IQR)**			
RBQ-2A score **Mean (SD)** **Median (IQR)**			
WHODAS 2.0 score **Mean (SD)** **Median (IQR)**			
EQ-5D-5L score: mean (SD)			
CIS-R score: mean (SD)			
Suicidal ideation (CIS-R thoughts/plans): n (%)			

Table T25: Carer outcomes over time

Follow-up assessment (weeks)	Sertraline			Placebo			Difference in means[a]	95% CI	p-value
	N	Mean	SD	N	Mean	SD			
EQ-5D-5L									
16									

52									
CES									
16									
52									

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