Protocol Synopsis

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

Protocol Version	Version 1.0 dated 11th December 2020
Chief Investigator	Dr Dheeraj Rai. Consultant Senior Lecturer in Psychiatry, University of Bristol, UK (Email: strata-rct@bristol.ac.uk)
Background	Anxiety is common in autistic adults and can be more disabling than the core features of autism. Medications for anxiety are often prescribed for autistic adults but their effectiveness or side effects in this population are not well known. Research findings in non-autistic populations may not apply to autistic adults. This study aims to find out whether the drug sertraline is an effective treatment for anxiety in adults with a diagnosis of autism. We will compare the use of sertraline in autistic adults with placebo, a non-active identical capsule. We are interested to see whether the treatment improves symptoms of anxiety, enhances quality of life, and is effective in the longer term. We are also interested in understanding side effects of the treatment. We will run this trial in five geographical regions in England and Western Australia. We aim to include 306 people who will be allocated at random to receive either encapsulated sertraline or identical inactive placebo, which they will be asked to take for up to 12 months. They will be asked to complete questionnaires about themselves, their anxiety and mental health, use of services, and any adverse effects they may experience at several time points. We will interview some participants about their experiences of being in the study and taking the study medications, and their reasons for continuing or withdrawing from the study. The results will help understand whether sertraline is an acceptable treatment and whether it is better or not than placebo in the treatment of anxiety in autistic adults.
Trial design	A two parallel group multi-centre pragmatic randomised controlled trial (RCT) of sertraline versus placebo for reducing anxiety in adults with a diagnosis of autism
Primary Objective	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
Number of study centres	STRATA will be delivered through Autism services in (at least) four regional centres in the UK (South West England; East Midlands; East of England; Surrey, Hampshire and Portsmouth) and (at least) one in Western Australia (Perth). Within each centre there can be several recruiting sites for that region which may include sites within 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 and Patient Identification Centres (PICs) can take place, if required. Additional centres/sites will be identified if required.
Sponsors	University of Bristol (UK) & University of Western Australia (Australia)
Funders	This study is funded by the National Institute for Health Research (NIHR) HTA Programme (Ref: 127337).The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. The authors and University of Western Australia acknowledge funding from the National Health and Medical Research Council (Project Grant 1171206). The contents of the published material/website are solely the responsibility of the authors and do not reflect the views of NHMRC.
Planned sample size	306
Inclusion criteria	Adults (≥18-years); A diagnosis of autism made by a specialist including those with a co-occurring mild intellectual disability [autism diagnostic terms may include autism/autistic spectrum disorder or other variations, Asperger syndrome/disorder or pervasive developmental disorder]; and anxiety as measured by GAD-7 score ≥10 at screening

Exclusion criteria	Prescribed a serotonergic antidepressant/anxiolytic in preceding 8-weeks; Prescribed an irreversible monoamine oxidase inhibitor or Pimozide in the preceding 8-weeks; Diagnosis of moderate-severe intellectual disability (ID); Inability to provide informed consent and complete study assessments / questionnaires; History of bipolar disorder, manic or hypomanic episodes, or psychosis; Currently uncontrolled epilepsy; Known current alcohol or drug use problem; Known allergies to sertraline or placebo/excipients; Currently enrolled in another RCT; Women who are pregnant, are planning pregnancy (during the trial period), or breastfeeding; History of severe liver impairment; Bleeding disorders such as such as haemophilia, Christmas disease and von Willebrands disease, as well as those with past medical history of bleeding gastric or duodenal ulcers or other significant bleeding disorders; History of Long QT syndrome or Torsade de Pointes; and Swallowing difficulties or inability to take medication in capsule form; Currently using St. John's Wort.
Treatment	The active investigational medicinal products are over-encapsulated 25mg or 50mg Sertraline tablets with a back fill of microcrystalline cellulose powder. The placebo product is a matched capsule filled with microcrystalline cellulose powder.
Treatment duration	52-weeks in total (primary outcome at 16-weeks post-randomisation)
Dosing schedule	All participants will receive a daily dose of 25mg sertraline or placebo for 2 weeks followed by 2x25mg for 4 weeks. Following this initiation period, the medication will be dispensed in 50mg capsules and depending upon tolerability, the dose will be **flexibly** increased by 50mg every 4-weeks to reach the optimal dose. The dose will 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 RA, as described above. The dose may go up to a maximum of 200mg by week 14, although it is anticipated that for many patients the optimal dose may be lower than this amount (e.g. 50mg, 100mg or 150mg) and reached before this time. Participants will take this optimal dose for up to 52-weeks post-randomisation. The placebo regimen will be identical.
Trial schedule	• Identification and screening • Consent and Randomisation (enrolment) • Brief contact (safety checks) at 1 to 2-, 4-, 8-, 12- and 36- weeks post randomisation to assess safety (adverse effects), medication dose titration, and anxiety and mood symptoms • Assessments at baseline (0-weeks) and follow up at 16- (primary outcome), 24- and 52-weeks post-randomisation. For all outcome assessments, delegated research staff at the research centres will be blinded to the participant's treatment allocation.
Study duration	Expected duration: 48 months (total) Grant start date: 01 October 2019 Proposed grant end date: 30 September 2023
Internal pilot	Following set-up, we will carry out an internal pilot study for nine months, first opening the South West England centre, followed by staggered openings of other centres (Western Australia, the Surrey, East of England, and East Midlands centres). We aim to recruit 78 patients across the five centres by the end of the 9-month pilot study.
Duration of Recruitment	2 years (24 months)
Target recruitment	3-4 patients per ***centre*** per month (recruitment rate across sites will vary depending on number of sites within the centre)
Site staff required	• Principal Investigator • Co-PI and/or Investigators with delegated responsibility for prescribing. *N.B. the prescribers can be the Principal Investigator and Co-PI* • Staff to identify patients via clinical lists

Recruiting Site Activities	*N.B. There are multiple recruiting sites within each centre. Each centre has a university-employed Research Associate that the recruiting site should maintain close contact with regarding study matters. The bulk of study activity lies with the research associates, minimising the amount of resources needed at research sites, which is focused towards patient identification, checking eligibility and prescribing of trial medication.* Recruiting sites will be asked to: <u>Set-Up</u> • Attend a site initiation meeting • Set-up the study locally and take part in ongoing staff training in conjunction with study sponsor (e.g. Good Clinical Practice), completing local delegation and training logs as required. • Promote study with poster and flyers <u>Patient identification and screening</u> • Identify potential participants (via clinical lists, routine clinic appointments, or advertisements), signposting them to an expression of interest form; this can also be completed by the clinician, with the patient, during a clinic appointment. Where possible, GAD-7 screening should be embedded in the identification process so that individuals with a diagnosis of autism who score ≥10 on the GAD-7 are invited to the study. • Maintain a log of patients invited to the study <u>Consent and randomisation (enrolment)</u> • Confirm final eligibility for a patient to take part in the study. • Randomise patients using the study online randomisation system called 'Sealed Envelope' • Prescribe study medication to patients recruited to the study using the study prescription form (study medication will be dispensed by a central study pharmacy, not the site pharmacy). • Provide a consultation room for a centre-employed Research Associate to conduct a face-to-face baseline appointment (if required by participants as remote appointments are preferred). <u>Brief contact (safety checks) at 1 to 2-, 4-, 8-, 12- and 36- weeks post randomisation</u> • Oversee dose titration as per study protocol. The participant safety reviews will be conducted by the centre Research Associate who will collect data on safety and adverse effects. The Research Associate will discuss this information with the PI who will make a final decision regarding further prescribing as per trial protocol or identify the need for further review (by themselves, or the participant's GP in case of safety concerns). • Prescribe study medication to patients recruited to the study using the study prescription form (study medication will be dispensed by a central study pharmacy, not a local pharmacy). <u>Assessments at baseline (0-weeks) and follow up at 16- (primary outcome), 24- and 52-weeks post-randomisation.</u> • The centre Research Associate is responsible for the conduct and monitoring of study assessments. <u>General</u> • Provide clinical oversight of patients recruited to the trial at the site, such as offering to review/speak to the patient where required and signposting to GP or other services if/where relevant. • Assess and categorise adverse events and serious adverse events (the centre Research Associate is responsible for recording appropriate adverse events for their participants during the trial). • Sign-off case report forms where required (e.g. participant withdrawal and adverse event forms). • Maintain an Investigator Site File when held at site • Archive study documents held at site when notified by sponsor • Participate in an interview with a researcher about patient recruitment procedures in the trial (optional).
Primary Care Activities	*N.B. Primary care is not recruiting patients to this trial; therefore, will not receive accruals for patients recruited (accruals go to the recruiting site only). However, reimbursement for certain activities will be available through service support costs from the local clinical research network.* Pre-randomisation: • Advertise the study using approved STRATA recruitment materials (e.g. posters, leaflets, electronic animation/video or equivalent materials).

	• Identify potential participants in clinic and signpost them to the study • Complete a patient safety check during screening to confirm that it is safe for a patient to take the study medication (responsibility for confirming eligibility status remains with the site team). Post-randomisation: • Receipt notification of patient randomisation (enrolment) in the trial from the site team • Where safety of the participant taking the study medication becomes a concern to the site team, provide input via a GP appointment with the participant and/or discussion with the site team to help with clinical management. • Confirm participant contact details are still valid in event participant is lost to follow-up and no contact can be made by the site team. End of study: • In cases where the participant wants to continue treatment after their involvement with the study has ended, continue/initiate sertraline treatment (GPs and participants will be notified of the study treatment allocation).

TRIAL FLOW CHART

Total recruitment phase (24-months): (a) Internal pilot phase: ≥5 centres, 9-months recruitment; and **(b) Main phase:** same pilot centres, additional 15-months recruitment. **Follow-up phase**: 36-months total.

QuinteT Recruitment Intervention (QRI)

[UK sites only]

QRI to understand and optimise recruitment to the trial.

Phase I: Developing an understanding of recruitment processes/ challenges.

Phase II: Feedback to CI/TMG, sites and trial recruiters; and implementation of plan to optimise recruitment.

Conducted during first 18- months of recruitment, including Pilot phase.

Pre-screening and Eligibility

Pre-screening: individuals with a diagnosis of autism who score ≥10 on the GAD-7, and/or individuals who have a diagnosis of autism and who may be seeking support for their anxiety will be invited to take part.

Eligibility: Confirmed following: (i) completion of Preliminary Screening and Expression of Interest Form; (ii) safety check by GP (doctor) for those who meet minimal eligibility requirements and consent to contact GP; and (iii) conversation with member of local

Enrolment

Baseline (first study) appointment:
Review and confirm eligibility; obtain informed consent; additional data collection (case report forms); baseline questionnaires; and conduct randomisation.

Randomised Allocation (n=306)

Control: Placebo (n=153)

Intervention: Sertraline (n=153)

Integrated Qualitative Research

[UK sites only]

Clinical qualitative study to explore participants' decisions, acceptability and experiences of trial participation and study medication.

Conducted alongside the QuinteT Recruitment Intervention (QRI).

Follow Up

1 to 2-, 4-, 8- and 12-weeks post-randomisation[A]: Brief case report form / questionnaire data collection on safety and adherence to medication; including (at least) GAD-7, PHQ-9, modified Toronto side effects scale, suicidality item, and other medications. Plus, EQ-5D-5L at 12-weeks.

16-weeks post-randomisation[A]: Case report form / questionnaire data collection, including (at least) GAD-7*, adverse effects, quality of life, adherence to medication and other anxiety and quantitative outcomes. *(*Primary Outcome)*

36-weeks post-randomisation[A]: Brief case report form / questionnaire data collection on safety and adherence to medication; including (at least) GAD-7, PHQ-9, modified Toronto side effects scale, suicidality item, and other medications.

24- and 52-weeks post-randomisation[A]: Case report form / questionnaire data collection, including (at least) GAD-7, adverse effects, quality of life, adherence to medication, health and social care resource use and other anxiety and quantitative outcomes.

End of Participant Involvement