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Trials

STUDY PROTOCOL

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A randomised controlled trial to evaluate the clinical and cost-effectiveness of Stimulant compared with Non-stimulant medication for adults with Attention-deficit/hyperactivity disorder and a history of Psychosis or biPolar disordER: SNAPPER

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Abstract

Background Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder involving inattention, hyperactivity and impulsivity, which starts in childhood and frequently persists into adulthood. Stimulant and non-stimulant medication are the mainstay of treatment in adults. ADHD in adults is commonly comorbid in people with severe mental illness (SMI) such as bipolar disorder (bipolar) and psychosis. There is substantial uncertainty over the effectiveness of stimulant and non-stimulant medication in adult ADHD comorbid with SMI. There is also concern that they could trigger or worsen psychotic or manic symptoms. Whilst National Institute of Health and Care Evidence (NICE) ADHD guidelines indicate available evidence does not justify a deviation from their main recommendations of using stimulants first line, this is based on limited studies within this comorbid population. A randomised controlled trial (RCT) is needed to address this evidence gap. We present a protocol for a pragmatic, observer-blind, multi-centre, two-arm, RCT called SNAPPER that aims to investigate the clinical and cost-effectiveness of stimulant compared with non-stimulant medication for adults with ADHD and a history of SMI.

Methods The recruitment target is 244 participants, aged 18 years or above, who have a history of SMI (either bipolar disorder or psychosis) with ADHD. Having provided informed consent for screening, participants will undergo validated diagnostic screening assessments to re-confirm the diagnosis of bipolar or psychosis and confirm an ADHD diagnosis. Those with confirmed diagnoses will provide informed consent for entry to the main trial and will then be randomised to receive either stimulant (lisdexamfetamine) or non-stimulant (atomoxetine) medication. The primary outcome measure is observer-rated ADHD symptom severity at 6 months. Secondary outcomes include ADHD

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symptom severity at 12 months, emergence of symptoms of bipolar or psychosis, health-related quality of life, occupational, daily functioning, substance misuse, cost-effectiveness, adherence, concomitant medication and process outcomes at 6 and 12 months.

Discussion Given that untreated ADHD is associated with poor clinical outcomes, unemployment and criminal justice system involvement, clear evidence in this area is likely to improve recovery for individuals with ADHD and a history of SMI, reducing costs for the individual, the NHS and society.

Trial registration ISRCTN79796233. Registered on 19/05/2022. https://www.isrctn.com/ISRCTN79796233.

Keywords Bipolar disorder, Psychosis, Attention-deficit/hyperactivity disorder, ADHD

Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Title {1}	A randomised controlled trial to evaluate the clinical and cost-effectiveness of Stimulant compared with Non-stimulant medication for adults with Attention-deficit/hyperactivity disorder and a history of Psychosis or biPolar disordER: SNAPPER Study protocol for a pragmatic, observer-blind, multi-centre, two-arm randomised controlled trial.
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Name and contact information for the trial sponsor {5b}	Research Strategy and Services Central – Research Governance Research Park University of Birmingham Birmingham B15 2TT researchgovernance@contacts.bham.ac.uk
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Introduction

Background and rationale {6a}

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder involving inattention, hyperactivity and impulsivity, which starts in childhood and frequently persists into adulthood [1]. It is common, affecting 3–4% of adults worldwide [2, 3]. It negatively affects relationships and employment and is linked to driving accidents and criminality [1]. It is thus very costly for the individual and society. ADHD in adults is commonly comorbid with bipolar disorder (bipolar) or psychosis. Bipolar and psychosis are commonly considered Severe Mental Illnesses (SMI). Of those with a diagnosis of either bipolar or ADHD, 5–20% also have the comorbid condition [4–7], and these patients have an earlier age of onset of bipolar, shorter periods of wellness, and a greater risk of substance misuse and other psychiatric comorbidities [8]. Comorbidity between psychosis and ADHD has a prevalence of 10–47% [9, 10] whichever condition is primary, and is linked to poorer social and occupational functioning and treatment resistance [10–12].

Stimulant and non-stimulant medication are the mainstay of treatment for ADHD in adults. The UK National Institute of Health and Care Evidence (NICE) ADHD guidelines recommend stimulants (Lisdexamfetamine or Methylphenidate) as first-line medications, as they are more effective than the non-stimulant

Atomoxetine [13]. NICE note an absence of data from randomised controlled trials (RCT) on the longer-term effects of ADHD medications. A systematic review and network meta-analysis concluded that in adults with ADHD, amphetamines (e.g. lisdexamfetamine) (standardised mean difference (SMD): −0.79, 95% confidence interval (CI) −0.99 to −0.58), methylphenidate (SMD: −0.49, −0.64 to −0.35), and atomoxetine (SMD: −0.45, −0.58 to −0.32) were more effective in reducing ADHD symptoms [14] compared with placebo.

People with psychosis or bipolar are usually excluded from ADHD treatment trials, so effectiveness in these populations is unclear. A literature review investigating Atomoxetine vs. placebo in people with ADHD and psychiatric comorbidity reports standardised mean differences ranging from 0.47 to 2.21 for improvement in ADHD symptoms [15]. The only study centred on comorbidity with bipolar was open label ($N = 12$, mean age 11.3 years) [16]. No studies in that review included adults with comorbid psychosis. It is unknown whether stimulants or Atomoxetine vary in efficacy to improve ADHD symptoms in people with ADHD and comorbid psychosis or bipolar [14].

The extent to which ADHD medications could be harmful in adults with ADHD with a history of bipolar disorder or psychosis is also unclear and causes clinicians concern. Evidence from the UK Medicines and Healthcare products Regulatory Agency's (MHRA) Yellow Card scheme showed that, out of 1335 drug reaction reports related to Methylphenidate sent to the scheme, 15.8% were related to psychotic symptoms or psychosis [17]. In an RCT, psychotic symptoms emerged in 1 person out of 143 given methylphenidate compared to no incidence of psychotic symptoms in the placebo group [18]. In a Canadian population-based study of 12,856 young people receiving stimulants, there was an increased risk of hospitalisation for psychosis or mania in the subsequent 60 days (odds ratio 1.86; 95% CI 1.39 to 2.56) [19]. However, a large population cohort study concluded that there was no increased risk of psychotic events at 1 year after Methylphenidate initiation, even in people with a history of psychosis [20]. A pharmaco-epidemiological study found increased episodes of mania within 3 months of methylphenidate initiation (hazard ratio (HR) = 6.7, 95% CI 2.0 to 22.4) in people with bipolar. The risk of mania was lower after starting Methylphenidate (HR = 0.6, CI 0.4 to 0.9) for people on mood stabilisers [21]. Case studies suggest Atomoxetine may trigger manic symptoms in people with or without bipolar [22–24] but no evidence from higher quality studies than these is available to guide treatment decisions.

Currently there is a lack of clarity over the effectiveness of both stimulant and the non-stimulant Atomoxetine in people with bipolar disorder and psychosis. Because the quality of current evidence in this area is inadequate, a high-quality RCT is needed to guide clinical decisions and improve the care for this group of patients, whose outcomes are poorer than the population without comorbidity.

Objectives {7}

Primary objective

To evaluate the clinical and cost-effectiveness of stimulant (Lisdexamfetamine) compared with non-stimulant (Atomoxetine) medication for adults with ADHD and a history of psychosis or bipolar disorder.

Secondary objective

To evaluate in adults with ADHD and a history of psychosis or bipolar disorder on the impact of stimulant vs. non-stimulant medication on:

- ADHD symptom severity at 6 months; emergence of symptoms of psychosis or bipolar disorder over 6 and 12 months;
- Health-related quality of life, occupational, functional, substance misuse, cost-effectiveness; and
- And process outcomes (reasons for discontinuation) at 6 and 12 months.

Trial design {8}

SNAPPER is a pragmatic, observer-blind, multi-centre, two-arm, 1:1 individually randomised controlled trial. The framework is superiority.

Methods: participants, interventions and outcomes

Study setting {9}

The trial will take place in NHS secondary and tertiary, community, and inpatient mental health services, and research clinics across the UK. This is primarily where care is provided for the target population and where the clinical uncertainty is faced.

Eligibility criteria {10}

For each potential participant, eligibility for the trial will be confirmed by a medically qualified practitioner.

Inclusion criteria

- Diagnosis of ADHD according to Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) based on the DIVA-5.
- Psychosis (schizophrenia spectrum disorders) OR Bipolar disorder diagnosis according to Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) based on the MINI.
- Clinically stable enough in the opinion of the clinical investigator to be able to engage in trial procedures.
- Males and females aged 18 years and over.
- Not currently (or within the last month) on medication for ADHD.
- Able to give written signed informed consent.

Exclusion criteria

- ADHD medication contra-indicated.
- Currently in an acute episode of psychosis or bipolar disorder according to referring clinician assessment.
- Severe suicide risk or severe risk of violence to others (as assessed by the referring clinician).
- Severe drug seeking behaviour or a current drug/alcohol withdrawal syndrome according to referring clinician.
- History of epilepsy or seizures.
- Congenital or acquired long QT syndrome (LQTS); OR family history of QT prolongation; OR on medication associated with increased risk of QT interval prolongation such as class IA and III anti-arrhythmics, moxifloxacin, erythromycin, methadone, mefloquine, tricyclic antidepressants or cisapride.
- Currently taking CYP2D6 inhibitors other than fluoxetine, doxepin, duloxetine, haloperidol, paroxetine, promethazine, risperidone, trazadone or venlafaxine as these are routinely used in the target population and clinically accounted for in prescribing ADHD medication dosing and scheduling.
- Participating in another conflicting/incompatible clinical trial.
- Females of child-bearing age only:
  - Pregnant. *Note: Spot urine test will be performed at screening and/or randomisation to rule out pregnancy in females of child-bearing age*
  - Not willing to take highly effective contraceptive measures to prevent pregnancy during the study participation period AND for 30 days following administration of the last trial medication dose.

During the trial, it is recommended that people with bipolar disorder or psychosis are on maintenance medication for that condition wherever possible.

Who will take informed consent? {26a}

It is the responsibility of the Principal Investigator (PI) to obtain written informed consent for each participant prior to performing any trial-related procedures, including the screening assessments. The process for taking consent can be delegated to members of the local research team or the direct clinical care team working on the trial at the site. Delegation of this duty will be authorised by the PI and captured on the Site Delegation Log.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Optional consent for access to mental health NHS records and GP contact for health service usage data will additionally be requested (as part of the consent process) to complete the health economics analysis.

Participants will be offered optional consent choices to allow linkage of their data available in NHS routine clinical datasets, including primary care data (e.g. Clinical Practice Research Datalink, The Health Improvement Network, QResearch) and secondary care data (Hospital Episode Statistics) through NHS Digital and other central UK NHS bodies. This will allow us (subject to receipt of additional funding) to assess longer-term impact and health service usage data without needing further contact with the trial participants. In addition, optional consent will include the participant's agreement to record and store the interviews conducted with the researchers for the purposes of inter-rater reliability.

Supporter consent

Participants will be asked to nominate a person close to them (the person who is most important in supporting their health and wellbeing, e.g., carer/close person, family member, partner, friend) who may act as their supporter. The participant will be provided with a 'Supporter Pack' to hand to their nominated supporter, which will consist of an approved supporter specific information sheet together with paper versions of the sample supporter ICF, sample Self-Registration Form and sample questionnaires to measure their quality of life. If the supporter wishes to participate in the trial, they can do so (after the participant related to the supporter has been randomised into the trial) by using the online link or QR (Quick Response) code provided in the Supporter Pack to provide their consent online, complete the electronic Self-Registration Form and complete the subsequent electronic supporter questionnaires.

Interventions

Explanation for the choice of comparators {6b}

Lisdexamfetamine will be the stimulant used in SNAPPER. Lisdexamfetamine is a pro-drug, which is metabolised by red blood cells to its active metabolite d-amphetamine and L-lysine [25]. Studies have shown that because it is a pro-drug, it has a lower potential for abuse or diversion than the alternative immediate-release stimulant methylphenidate [26, 27]. Lisdexamfetamine lasts longer in the day than Methylphenidate, allowing once-daily dosing, which is likely to facilitate better adherence. Lisdexamfetamine was found to be slightly more effective than Methylphenidate in a recent network meta-analysis [14], and is widely used in the UK already. Atomoxetine is the only non-stimulant for adult ADHD recommended by NICE [13].

Intervention description {11a}

Participants will be randomised to receive either:

- Lisdexamfetamine (stimulant) initiated at 30 mg once daily, and increased to a maximum of 70 mg once daily for 6 months; OR
- Atomoxetine (non-stimulant) initiated at 40 mg daily, and increased to a maximum of 100 mg daily for 6 months

The ADHD medication will be prescribed from the day of randomisation by the participant's consultant psychiatrist, medical team or non-medical prescriber, e.g. advanced nurse practitioner. Patients will be expected to start their allocated treatment as soon as they have received their prescription from their community or hospital pharmacy and within 28 days of randomisation.

Criteria for discontinuing or modifying allocated interventions {11b}

For emergence of short-lived relapse symptoms of psychosis or mania, clinical judgement will be applied to decide whether medication is stopped temporarily and then re-started if the symptoms resolve. For emergence of significant or severe psychotic or manic symptoms, or these symptoms getting worse, intervention medication will be modified or discontinued.

Intervention treatment will be permanently discontinued should any of the following events occur:

- Seizure
- Cardiovascular or cerebrovascular event
- Jaundice or laboratory evidence of liver injury
- Participant starts prohibited therapy
- Pregnancy
- At the discretion of the clinical investigator

Details and reasons for temporary and permanent discontinuation of lisdexamfetamine or atomoxetine will be documented.

Withdrawal criteria

- The patient withdraws consent for any or no reason
- The patient withdraws from the trial intervention
- Patient is experiencing worsening of symptoms and chooses to discontinue medication
- For safety reasons as judged by the investigator
- The patient is pregnant and therefore cannot continue medication as part of the trial

Participants who discontinue the intervention will be encouraged to continue with follow-up measures.

Strategies to improve adherence to interventions {11c}

Reasons for temporary or permanent discontinuation of medication will be documented. Adherence to trial medication will be assessed using the Medication Adherence Rating Scale (MARS) [28] at 6 months and participant self-report of adherence during the previous 3 months, collected at 6 months.

Relevant concomitant care permitted or prohibited during the trial {11d}

The intervention medication will be given in addition to antipsychotic medication (in the case of psychosis) or mood stabilisers (in the case of bipolar) where prescribed. Usual practice of dose changes or changes in antipsychotic medication and/or mood stabilisers during the intervention will be documented on the study CRF by the local research team on inspection of the electronic/paper patient records over the time period of the trial.

Any medication which is contraindicated in people taking lisdexamfetamine or atomoxetine according to the British National Formulary (BNF) will be prohibited. Specifically, monoamine oxidase inhibitors (MAOI) and CYP2D6 inhibitors (other than fluoxetine, doxepin, duloxetine, haloperidol, paroxetine, promethazine, risperidone, trazadone or venlafaxine) are prohibited.

Provisions for post-trial care {30}

At the end of the trial, the intervention continues if supported by the clinician and patient, and accessible within the constraints of NHS services and policies (primary and secondary care) as the medications are licensed as indicated for use and available under an NHS prescription.

Outcomes {12}

Primary outcome

ADHD symptoms at 6 months post-randomisation, as measured by the Conners Adult ADHD Rating Scale-Observer (CAARS-O) total score [29]. Researchers blinded to the treatment allocation will complete the CAARS-O with participants.

Secondary outcomes

- ADHD symptoms at 12 months post-randomisation, measured by the CAARS-O total score.
- Emergence of hypomania/mania symptoms over 6 and 12 months post-randomisation, defined as the total number of weeks with mania over the 12 months following randomization measured using the Longitudinal Interval Follow-up Evaluation (LIFE) [30], at 3, 6, 9 and 12 months post-randomisation, assessing weeks with symptoms of mania over the previous 3 months.
- Emergence of psychotic symptoms over 6 and 12 months post-randomisation, measured at 3, 6, 9 and 12 months following randomisation using the Positive and Negative Symptoms Scale (PANSS) positive symptom subscale [31], providing a score ranging from 7–49, where a low score indicates fewer symptoms.
- Depression over 12 months post-randomisation, defined as total weeks with depression over the 6 and 12 months following randomisation, measured using the LIFE scale at 3, 6, 9 and 12 months post-randomisation, assessing weeks with symptoms of depression over the previous 3 months.
- Emotional dysregulation at 6 and 12 months post-randomisation, measured by the Difficulties in Emotion Regulation Scale (DERS-16) [32]. Items are scored on a 5-point scale ranging from 1 (almost never) to 5 (almost always). Scores range from 16 to 80 where a low score indicates no difficulties in emotional regulation. Emotional dysregulation will also be measured using selected sections from the Wender-Reimherr Adult Attention Deficit Disorder Scale-Interview (WRAADS-Interview) [33], specifically temper, affective lability, emotional over-reactivity and impulsivity, where items are scored from 0 (non, not present) to 3 (very clearly present much of the time) providing a score ranging from 0 to 36, where a low score indicates no problems with emotional regulation.
- ADHD specific QOL at 6 and 12 months post-randomisation assessed by the Adult ADHD QOL Measure (AADHD QOL) [34]. Items are scored on a 5-point Likert scale ranging from 1 (not at all/never) to 5 (extremely/very often). Scores range from 29 to 145, where a low score indicates lower quality of life.
- Health-related QoL at 6 and 12 months post-randomisation, for both the participant and supporter, assessed by the EQ-5D-5L [35] where 1 is equal to full health (top level across all 5 items); 0 is health state equal to death; −0.59 is worst health state (bottom level across all five items).
- Capability Wellbeing score at 6 and 12 months post-randomisation, for both the participant and supporter, assessed by the ICECAP-A [36–38]. Score 1 indicates full capability wellbeing (top level across all five items) and 0 indicates absence of capability wellbeing (bottom level across all five items).
- Occupational and daily functioning at 6 and 12 months post-randomisation, measured using the Functioning Assessment Short Test (FAST) [39]. The overall score, which ranges from 0 to 72 will be used where a higher score indicates severe difficulty in functioning.
- Employment status (yes/no), (role, paid, unpaid, voluntary, hours/week) assessed at 6 and 12 months post-randomisation.
- Currently in Education (yes/no), (type, qualification being studied for) assessed at 6 and 12 months post-randomisation.
- Problem drug use at 6 and 12 months post-randomisation measured using the Drug Abuse Screening Test-(DAST)10 [40]. A score of 3 and above will be used to indicate problems related to drug use, as indicated by the instrument authors.
- Problem drinking at 6 and 12 months post-randomisation, measured using the Alcohol Use Disorders Identification Test (AUDIT) [41]. A score of 8 and above will be used to indicate problem drinking as indicated by the instrument authors.
- Adherence during the last week at 6 and 12 months post-randomisation, measured using the Medication Adherence Rating Scale (MARS) [28] which has a range of 0–10 and lower scores indicating greater adherence levels.
- Self-report adherence during the last 3 months at 6 and 12 months post-randomisation, measured by asking participants whether over the last 3 months they have taken their lisdexamfetamine or atomoxetine 0–24%, 25–49%, 50–74%, 75–99 or 100% of the time. Additionally, whether over the last 3 months participants have taken their prescribed medication for psychosis or bipolar medication 0–24%, 25–49%, 50–74%, 75–99 or 100% of the time will be asked.
- Type and dose of concomitant medication, start date and stop date (duration) will be recorded at 6 and

Table 1 Participant timeline

Visit	Screening	Baseline*	Month 3 ±21 days	Month 6 ±21 days	Month 9 ±21 days	Month 12 ±21 days
Eligibility check	x	x				
Spot urine test *(females only, if appl.)*	x	x[a]				
Valid informed consent	x	x				
DIVA-5 and MINI	x					
Supporter Pack provided	x					
Supporter ICF & Self-Registration		x				
Demographic information		x				
Relevant medical history taken		x				
Concomitant medication		x		x		x
Randomisation		x				
Participant completed self-reports/questionnaires						
CTQ		x				
AADHD QOL		x		x		x
AUDIT		x		x		x
DAST-10		x		x		x
DERS-16		x		x		x
EQ-5D-5L (participant and supporter)		x		x		x
ICECAP-A (participant and supporter)		x		x		x
Compliance self-report				x		x
MARS				x		x
Research team completed interviews with the participant						
CAARS-O		x		x[b]		x[b]
WRAADS-Interview		x		x[b]		x[b]
FAST		x		x[b]		x[b]
LIFE		x	x	x[b]	x	x[b]
PANSS		x	x	x[b]	x	x[b]
Adverse Events Scale		x	x	x	x	x
CSRI		x		x		x
SAE monitoring			x	x	x	x
Pregnancy monitoring			x	x	x	x

*Baseline assessments can be completed on the same day as screening or preferably within ~30 days of the screening visit

[a] Only required if the participant is not randomised on the same day as the screening assessments

[b] Blinded assessments to be completed by the study-funded RA, with participants recruited from other centres

12 months post-randomisation, using the electronic patient record, and presented descriptively.
- All cause discontinuation of randomised treatment.
- Measured by the modified Client Service Receipt Inventory (CSRI) at 6 and 12 months. We will use an adapted version of the CSRI [42] to measure service users' health and social care resource use, as well as wider societal costs to informal carers, employment, and criminal justice sectors [43].
- Use of acute care services retrieved from electronic patient records at 6 and 12 months by the local research team.
- Health related QoL and Capability Wellbeing scores for the supporter at 6 and 12 months post-randomisation. As described in participants will be asked to nominate a supporter (carer/close person). If they consent to participate, the EQ-5D-5L and ICECAP-A outcomes will be collected from these individuals. This information will be used as part of the cost-effectiveness analysis.

Participant timeline {13}
The participant timeline is shown in Table 1.

Sample size {14}
The ADHD symptom severity primary outcome is a continuous measure. Assuming 80% power and

2-sided 5% significance, a sample size of approximately 200 patients would be required (100 per arm) to detect an effect size of 0.4 of a standard deviation in the Investigator-rated Conners Adult ADHD Rating Scale-Observer (CAARS-O [total score]). Assuming a correlation between baseline and follow-up CAARS-O of 0.3 consistent with a previous study [44, 45], the sample size required would be 182 $((1-0.3^2)*200)$. Accounting for 25% loss to follow-up [46, 47], this will mean that a total of 244 participants $(182/(1-0.25))$ would be required (122 per arm). This translates to a difference of 4 points in the CAARS-O measure assuming the standard deviation is 10 [45], and is considered to represent a clinically meaningful difference between stimulants and non-stimulants for ADHD symptoms.

Recruitment {15}

Participants who will be identified from secondary care mental health trusts (community mental health teams, early intervention services, mood or psychosis (cluster) services) or specialist ADHD teams in 2 ways:

1. Patients who are seen by the clinical care team and have a pre-existing diagnosis of ADHD with either a history of psychosis or bipolar, who are not taking ADHD medication, will be identified by medical and other mental health professionals who will discuss the study with them at a routine clinic appointment.
2. It is likely that a significant proportion of the eligible population will not already have ADHD diagnosed and will be under the care of a wide range of secondary mental health services (e.g. early intervention services, community mental health teams), without contact with a specialist ADHD service. This group will be identified by clinicians/research team members (e.g. research assistants (RAs)/research nurses (RNs) or Clinical Study Officers (CSOs)) who will meet with clinicians to discuss their caseload lists of patients with psychosis or bipolar for potential eligibility, or by communication with potential patients who directly contact the study team after coming across the study in social media channels or through contacts by charities. Patients in whom a clinical suspicion of Adult ADHD exists will be assessed as per standard care using the Adult ADHD Self-Report Scale (ASRS) to consider whether a full diagnostic assessment for ADHD is warranted. The ASRS is a self-report scale and can be completed in 5 min either at a face-to-face appointment or by the patient at home and returned to the clinician.

At some sites, participants will be recruited via participant identification centres (PICs) and referred to the main randomising centre.

Working with the Clinical Research Network, potential patients will be identified for eligibility from primary care trusts (PCTS) using GP (General Practitioner) registries. The identified GP practices will act as Participant Identification Centres (PICs). Those patients identified via the GP registries will be contacted by the GP practice via text message or other communication about the study and will be asked to contact the study researcher directly at the participating secondary care NHS Trust should they wish to participate in the trial.

Assignment of interventions: allocation

Sequence generation {16a}

Participants will be stratified by whether they have a history of bipolar or psychosis and then randomised at the level of the individual in a 1:1 ratio to either lisdexamfetamine or atomoxetine.

In addition, for each stratum, a minimisation algorithm will be used in the online randomisation system to ensure balance in the treatment allocation over the following variables:

- Recruiting centre (mental health trust)
- Number of previous acute care episodes related to either diagnosis of psychosis or bipolar disorder where there has been crisis/home treatment team intervention or hospital admission (categorised as ≤ 3, 4–6, and > 6)
- Whether participant has had previous pharmacological treatment for ADHD as a child (yes/no/not known)—self reported

To avoid the possibility of the intervention allocation becoming predictable, a 'random element' will be included in the minimisation algorithm, so that each participant has a probability (unspecified here) of being randomised to the opposite treatment that they would have otherwise received.

Concealment mechanism {16b}

Randomisation will be provided by a secure online randomisation system at the Birmingham Clinical Trials Unit (BCTU) (available at https://bctu-redcap.bham.ac.uk.

Implementation {16c}

After a clinician has confirmed participant eligibility, informed consent has been given, (a pregnancy test done again after informed consent, to rule out pregnancy in females of child-bearing age ONLY if randomisation is not taking place on the same day as screening assessments), and all baseline assessments completed, the participant can be randomised into the trial using a secure online system at the Birmingham

Table 2 Case report forms in SNAPPER

Form name	Schedule for completion	Schedule for online submission	Online submission by
Screening Informed Consent Form (ICF)	At the screening visit prior to completing any diagnostic assessments	At screening consent	Site, if applicable
Main trial ICF	At the baseline visit prior to completion of any baseline assessments	At main trial consent, prior to randomisation	Site
(F1A) Baseline Assessments: Clinical Form	At the baseline visit prior to randomisation	As soon as possible after completion	Site
(F1B) Baseline Assessments: Participant Form	At the baseline visit prior to randomisation	As soon as possible after completion	Participant
(F2) Randomisation Form	At the baseline visit to randomise the participant	As soon as possible after the participant has been randomised	Site
(F3) Prescription Start Form	After first prescription for medication start issued	As soon as possible after completion	Site
(F4) 3 and 9 Month Assessments: Clinical Form	At 3 and 9 months assessments	As soon as possible after completion	Site
(F5A) 6 and 12 Month Assessments: Clinical Form	At 6 and 12 months assessments	As soon as possible after completion at each follow-up assessment time point	Site
(F5B) 6 and 12 Month Assessments: Participant Form	At 6 and 12 months assessments	As soon as possible after completion at each follow-up assessment time point	Participant
(F5C) 6 and 12 Month Assessments: Blinded Assessor Form	At 6 and 12 months assessments	As soon as possible after completion at each follow-up assessment time point	Site
Ad hoc forms			
(F6) IMP Medication Stop/Re-Start Form	On the participant stopping or re-starting trial medication	At the end of participant's participation	Site
(F7) Participant Change of Status Form	On change of status	At the point of discontinuation or withdrawal (see Sect. 8.3)	Site
(F8) Serious Adverse Event CRF	On becoming aware of an SAE	If expedited: emailed within 24 h of site research team becoming aware of event If non-expedited emailed within 4 weeks of site research team becoming aware of event	Site
(F9A) Pregnancy Notification Form	On becoming aware of a pregnancy	As soon as possible after a pregnancy is confirmed	Site
(F9B) Pregnancy Release of Information Form	On becoming aware of a pregnancy	As soon as possible after a pregnancy is confirmed	Site
(F9C) Pregnancy Outcome Form	Outcome of pregnancy and/or birth of the child	As soon as possible after becoming aware of the pregnancy outcome	Site
Supporter Forms			
Supporter ICF	As soon as possible after the participant has been randomised	As soon as possible after supporter has consented to the study	Supporter
(S1) Supporter Self–Registration Form	As soon as possible after the supporter has provided their consent	As soon as possible after supporter has registered to the study	Supporter
(S2) Supporter Baseline, 6 and 12 Month Form	After registration at baseline and then at the 6 and 12 months time-points	As soon as possible after completion	Supporter

Clinical Trials Unit (BCTU). Randomisation is carried out by site staff who have been delegated this responsibility, as documented on the SNAPPER Site Delegation Log, using unique usernames and passwords.

Assignment of interventions: blinding

Who will be blinded {17a}

This is an observer-blinded trial. The study-funded researchers are the blinded observers in the trial and will be blinded to the treatment allocation of participants randomised from other sites. The blinded researchers will complete the CAARS-O, WRAADS-Interview, LIFE, PANSS and FAST assessments at 6 and 12 months.

Procedure for unblinding if needed {17b}

Unblinding the treatment allocation to the blinded research is not permissible.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Case report forms will be completed for each individual subject according to Table 2.

All research investigators and staff are required to undergo extensive and documented training on the study protocol. Assessors of outcome measures will undergo specific training and assessment on the reliability of scores to ensure accuracy and standardisation.

Plans to promote participant retention and complete follow-up {18b}

Participants will be provided shopping vouchers as reimbursement for their time attending and completing follow-up assessments. Reminders for follow-up assessments will be sent to all participants via their preferred method of contact.

Data management {19}

Data entry will be completed online by the research team using the electronic CRF required for each individual participant within the protocol listed timeframes.

Processes will be employed to facilitate the accuracy of the data included in the final report. These processes will be detailed in the trial-specific Data Management Plan. Coding and validation will be agreed between the trial manager, statistician and programmer, and the trial database will be signed off once the implementation of these has been assured.

The data capture system will conduct automatic range checks for specific data values to ensure high levels of data quality. Queries will be raised using the data verification function in the data capture system.

Confidentiality {27}

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018.

Participants will always be identified using their unique trial identification number and initials on the Case Report Form and in correspondence between sites and BCTU. Participants and supporters will give their explicit consent for the storage of their completed consent form at BCTU. This will be used to perform in-house monitoring of the consent process.

BCTU will maintain the confidentiality of all participants' data and will not disclose information by which participants may be identified to any third party. Representatives of the Trial Office and Sponsor may be required to have access to participants' notes for quality assurance purposes, but participants should be reassured that their confidentiality will be respected at all times.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

This section is not applicable as laboratory samples are not collected.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

The primary analyses will be based on the intention to treat principle.

For all outcome measures, appropriate summary statistics and differences between groups, e.g. mean differences, risk ratios and risk differences, will be presented, with 95% confidence intervals. Intervention effects will be adjusted for the baseline value (if applicable) and the minimisation and stratification variables.

Primary outcome analysis

The primary outcome is ADHD symptoms at 6 months post-randomisation measured by the CAARS-O. Mixed effects linear regression methods will be used. Adjusted mean differences and 95% confidence intervals will be presented. The p-values from the associated tests of the final models will be presented.

Secondary outcomes analysis

Analysis will be performed as per the primary outcome for all continuous secondary outcomes at each time-point.

For binary outcomes, a logistic regression model using a logit link function will be used, followed by the marginal standardisation approach for covariate adjustment to calculate an adjusted risk ratio and an adjusted risk difference.

Interim analyses {21b}

Interim analyses of safety and efficacy for presentation to the independent DMC will take place during the trial. This is likely to include the analysis of the primary and major secondary outcomes and full assessment of safety (SAEs) at least at annual intervals. Criteria for stopping or modifying the trial based on this information will be ratified by the DMC. Details of the agreed plan will be written into a DMC Charter and the Statistical Analysis Plan.

Methods for additional analyses (e.g. subgroup analyses) {20b}

Further sensitivity analysis for the primary outcome will include three analyses based on the per-protocol population, whereby participants who did not adhere to their randomised allocation will be excluded from the analysis, as determined by the two adherence measures.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Every attempt will be made to collect complete follow-up data on all study participants; it is thus anticipated that missing data will be minimal. Participants with missing primary outcome data will not be included in the primary analysis in the first instance. This presents a risk of bias, and sensitivity analyses will be undertaken to assess the possible impact of the risk. In brief, this will include multiple imputation methods.

Economic evaluation

The economic evaluation will assess the cost-effectiveness of Lisdexamfetamine (stimulant) vs. Atomoxetine (non-stimulant) medication for patients with ADHD and psychosis and/or bipolar. Cost-effectiveness will be estimated in terms of the cost per case reduction in ADHD symptom severity and cost per quality-adjusted life year (QALY) gained from a payer perspective. The analysis will be extended to consider capability wellbeing outcomes and wider societal costs. Initially, a within-trial cost-effectiveness analysis will be conducted based on cost per case of a reduction in the CAARS-O measure of 4 points, cost per QALY estimated using the EQ-5D-5L and cost per year of full capability using the ICECAP capability measure. Decision modelling will be undertaken, based on evidence of long-term impacts, to extrapolate beyond the results of the trial and assess the effect of these interventions on the longer-term costs and outcomes.

Plans to give access to the full protocol, participant-level data and statistical code {31c}

The final dataset will be available to members of the Trial Management Group (TMG) who need access to the data to undertake the final analyses.

Requests for data generated during this study will be considered by BCTU. Only scientifically sound proposals from appropriately qualified research groups will be considered for data sharing. The request will be reviewed by the BCTU Data Sharing Committee in discussion with the CI and, where appropriate (or in the absence of the CI), the Trial Sponsor, the Trial Management Group, and/or independent Trial Steering Committee.

The full protocol is publicly accessible online via the trial website.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

Trial management group

The Trial Management Group (TMG) will take responsibility for the day-to-day management of the trial and will include (but is not limited to) the CI, trial statistician, trial manager, health economist, co-investigators and senior BCTU oversight staff whose role is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The TMG will also be responsible for drafting the final report and submission for publication. TMG meetings will be scheduled frequently to discuss trial progress, management, publications and any issues arising during the course of the trial. Minutes of the meetings and any action points arising at the meetings will be recorded and circulated to the TMG.

Trial steering committee

A Trial Steering Committee (TSC) will be established for the SNAPPER trial. The TSC will include members who are independent of the investigators, their employing organisations, funders and sponsors. The TSC composition will be chaired by an independent member and will include an independent statistician, clinicians, a health economist and a patient representative. The TSC will operate in accordance with a trial-specific TSC Charter. The TSC will meet at least annually, as agreed by the Committee and documented in the Charter.

Composition of the data monitoring committee, its role and reporting structure {21a}

Data analyses will be supplied in confidence to an independent Data Monitoring Committee (DMC), which will meet prior to trial commencement to agree on the manner and timing of such analyses. The DMC will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of participants. The DMC will operate in accordance with a trial-specific DMC Charter. The DMC will meet at least annually as agreed by the Committee and documented in the Charter.

Adverse event reporting and harms {22}

Adverse event (AE) checks will occur at every visit and will be collected and reported in accordance with the UK Policy Framework for Health and Social Care (2017), the Medicines for Human Use (Clinical Trials) Regulations 2004 and all other regulatory requirements. Since the screening visit will be minimally invasive, the reporting period for AEs in SNAPPER will start from the day of randomization until the end of trial follow-up. AEs are common in this patient population. As the safety profiles of Lisdexamfetamine and Atomoxetine are well characterised, a strategy of targeted reporting of AEs will not affect the safety of participants. Only some AEs classed as Serious (SAEs) will be reported as SAEs.

Serious adverse events (SAEs) are classified in one of three ways: as safety reporting exempt SAEs, which require the PI to record in medical notes but not report to BCTU (e.g. pre-planned hospitalisation); those that require recording in notes and reporting to the trial office in a non-expedited manner within 4 weeks of becoming aware of the event on a trial-specific SAE form (e.g. attendance at A&E for a mental health-related reason, referral to mental health crisis team, referral to liaison psychiatry); or SAEs, which require expedited reporting to BCTU within 24 h (e.g. all SAEs not covered by the above categories).

Frequency and plans for auditing trial conduct {23}

The sponsor will conduct monitoring of research sites in accordance with the trial risk assessment and monitoring plan. On-site monitoring visits may be initiated based on various factors, such as low CRF return rates, data quality concerns, unusually high or low SAE reporting rates, or an excessive number of participant withdrawals or protocol deviations. All monitoring activities are reported to the coordinating center, with any identified issues tracked and resolved.

Additionally, BCTU routinely reviews incoming ICFs and CRFs to ensure protocol compliance, data consistency, and completeness. Sites receive monthly data queries requesting missing information or clarification of any inconsistencies or discrepancies.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Any substantial amendments to the trial protocol will be submitted for review to the Research Ethics Committee (REC), Health Research Authority (HRA), Medicines and Healthcare products Regulatory Agency (MHRA) and Research and Development Department at the trial sites. If a substantial amendment affects a participant's decision to continue in the trial, this new information will be communicated to them by the local research team with an updated Patient Information Sheet. If the participant is willing to continue, re-consent will be obtained.

Dissemination plans {31a}

The investigators are responsible for publicly disseminating results, study materials, and procedure manuals.

The trial is registered at (ISRCTN79796233). Results of this trial will be disseminated through publication in a peer-reviewed journal, presentations and through the study website www.birmingham.ac.uk/snapper.

Patients and the public

The PPI representatives will help to develop a detailed dissemination plan for the trial. Public contributors will design a 'plain English' summary of the study findings suitable for dissemination to a non-clinical audience.

Discussion

Given that untreated ADHD is associated with poor clinical outcomes, unemployment and criminal justice system involvement, clear effectiveness evidence in this area is likely to improve recovery for individuals with ADHD and a history of psychosis or bipolar, reduce costs for the individual, the NHS and society. We will provide definitive evidence as to the clinical and cost-effectiveness of Lisdexamfetamine vs. Atomoxetine in the treatment of adults with ADHD and a history of psychosis or bipolar, as well as the risks of adverse events associated with each medication. The results will provide clear guidance to NICE, clinicians, and service users.

Trial status

Protocol version number and date: version 5.0 dated 10 October 2024. The trial recruited its first participant on 27 May 2021. The trial is actively recruiting and recruitment is anticipated to end on 30 April 2027.

Abbreviations

AADHD QOL	Adult ADHD QOL
ADHD	Attention-deficit/hyperactivity disorder
AE	Adverse event
ASRS	Adult ADHD Self-Report Scale
AUDIT	Alcohol Use Disorders Identification Test
BAP	British Association for Psychopharmacology
BNF	British National Formulary
BCTU	Birmingham Clinical Trials Unit
CAARS-O	Conners Adult ADHD Rating Scale-Observer rated
CI	Chief Investigator
CRF	Case report form
CSO	Clinical Study Officer
CSRI	Client Service Receipt Inventory
CTQ	Childhood Trauma Questionnaire
CYP2D6	Cytochrome p450 2d6
DAST-10	Drug Abuse Screening Test-10
DCF	Data Clarification Form
DERS-16	Difficulties in Emotional Regulation Scale-16
DIVA-5	Diagnostic Interview for ADHD in Adults-5
DMC	Data Monitoring Committee
DSA	Data Share Agreement
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5th edition
EQ-5D-5L	EuroQoL- 5 Dimension- 5 Level
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FAST	Functioning Assessment Short Test
GCP	Good Clinical Practice
GP	General Practitioner
HR	Hazard ratio
HRA	Health Research Authority
HTA	Health Technology Assessment
ICECAP-A	ICEpop CAPability measure for Adults
ICERs	Incremental cost-effectiveness ratios
ICF	Informed Consent Form
ISRCTN	International Standard Randomised Controlled Trial Number
LIFE	Longitudinal Interval Follow-up Evaluation
LQTS	Long QT syndrome

MARS	Medication Adherence Rating Scale
MHRA	Medicines and Healthcare products Regulatory Agency
MINI	Mini International Neuropsychiatric Interview
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PANSS	Positive and Negative Symptoms Scale
PCTS	Primary care trusts
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QOL	Quality of life
QALY	Quality-adjusted life year
REC	Research Ethics Committee
RCT	Randomised controlled trial
RGT	University of Birmingham Research Governance team
RA	Research Associate
RN	Research nurse
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SMD	Standardised mean difference
SMI	Severe mental illness
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
UoB	University of Birmingham
WRAADS-Interview	Wender-Reimherr Adult Attention Deficit Disorder Scale-Interview

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Authors' contributions {31b}
SL trial manager, team leader and protocol development. PJ lead (blinded) researcher in Birmingham. RO team leader, protocol development, co-applicant. RW lead statistician, protocol review and co-applicant. EG medical statistician. PA, AY, HAJ, MB, co-applicants and protocol development. AR co-applicant and PP lead. NG lead (blinded) researcher in London. PH lead (blinded) researcher in Newcastle. DS researcher in London. PS, MJ, RN, TM and MZK Principal Investigators and TMG members. SM Chief Investigator. All authors read and approved the final manuscript.

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Data availability {29}
Initially, only the members of the study group will have access to the final trial dataset while the results are analysed and published.

Declarations

Ethics approval and consent to participate {24}
The study was reviewed and approved by the Central Bristol Research Ethics Committee (20/EM/0216) on 26th November 2021. It was granted a Clinical Trial Authorisation by the Medicines and Healthcare Products Regulatory Agency on 25th January 2022. Written, informed consent to participate will be obtained from all participants.

Consent for publication {32}
Not applicable.

Competing interests {28}
PA received honoraria for consultancy and educational talks from Janssen, Takeda, AGB-pharma and Flynn-pharma.
PS received sponsorship from Takeda for education and training purposes.
RN received sponsorship from Takeda Medicine pharmaceuticals to attend educational events.

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