UNIVERSITY OF BIRMINGHAM | BCTU Birmingham Clinical Trials Unit

TRIAL PROTOCOL

A randomised controlled trial to evaluate the clinical and cost-effectiveness of **S**timulant compared with **N**on-stimulant medication for adults with **A**ttention-deficit/hyperactivity disorder and a history of **P**sychosis or bi**P**olar disord**ER**:

SNAPPER

This protocol has regard for the HRA guidance and is compliant with the SPIRIT guidelines (2013)

Version Number: **5.0**

Version Date: **10.10.2024**

Protocol Amendments

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version:

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
#01	10-Oct-2024	5.0	Substantial	• Change of title to remove 'stratified' • Primary outcome and objective time-point changed from 12 to 6 months • Secondary outcome data collected on those pts that reach 12 months before the end of trial • Secondary outcome pill counting adherence measure removed • Combination of previous separate bipolar disorder and psychosis strata into a single SMI group • Reduction in overall study sample size • Inclusion criteria relating to mood stabilisers and antipsychotic amended • Exclusion criteria relating to CYP2D6 inhibitors amended • Treatment duration changed from 12 to 6 months • Justification of trial design amended • Internal pilot objectives removed • Telephone contact added as a method for initial patient approach • Process for who can obtain participant consent amended • Timeline to remove Screening ICF from database updated • Window between screening and baseline extended • Inclusion of GP PIC sites added • Inclusion of patient targeted advertising added • Confirmatory randomisation e-mail to Site staff amended • Timeline between randomisation and treatment start added • Collection of additional demographic data included • Prohibited medications updated • Revisions to justification of reduced sample size calculations • Updates to health economic analysis time-points • References updated

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National Institute for Health Research: Health Technology Assessment	Medication for ADHD in adults with a history of psychosis or bipolar disorder
Funder's reference number:	
NIHR 129817	

This protocol was written in response to a commissioned call from the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (19/34 *Medication for ADHD in adults with a history of psychosis or bipolar disorder*, see appendix 1). The Funder of the trial will have no role in the data collection, data analysis or data interpretation.

This project is funded by the NIHR HTA Programme project reference 129817. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Chief Investigator (CI) Signature Page

As Chief Investigator, I confirm that I have read and agree with the following protocol, and that I will conduct the trial in compliance with the version of this protocol approved by the REC and any other responsible organisations.

I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest, accurate and transparent account of the study will be given; and that any discrepancies from the study as stated in this and any subsequent approved protocol will be explained.

Trial Name:	**SNAPPER**
Protocol Version Number: Protocol Version Date:	Version: 5.0 10/Oct/2024
CI Name:	Professor Steven Marwaha
Trial Role:	Chief Investigator
Signature and date:	

Sponsor statement

Where the University of Birmingham takes on the sponsor role for protocol development oversight, the signing of the IRAS form by the sponsor will serve as confirmation of approval of this protocol.

Compliance statement

This protocol describes the SNAPPER trial only. The protocol should not be used as a guide for the treatment of participants not taking part in the SNAPPER trial.

The trial will be conducted in compliance with the approved protocol, UK Policy Framework for Health and Social Care Research, Medicines for Human Use (Clinical Trials) Regulations 2004, Data Protection Act (2018) and the Principles of Good Clinical Practice (GCP) as set out in the UK Statutory Instrument (2004/1031) and subsequent amendments thereof.

Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

Principal Investigator (PI) Signature Page

As Principal Investigator, I confirm that the following protocol has been agreed and accepted, and that I will conduct the trial in compliance with the approved protocol where this does not compromise participant safety.

I agree to ensure that the information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

Trial Name:	**SNAPPER**
Protocol Version Number: Protocol Version Date:	Version: 5.0 10/Oct/2024
PI Name:	
Name of Site:	
Signature and date:	_____ __ __ / __ __ __ / __ __ __ __

ADMINISTRATIVE INFORMATION

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Sponsor number	RG_19-246
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Trial website	www.birmingham.ac.uk/SNAPPER

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Professor Chris Hollis	Chair of Child & Adolescent Psychiatry
Professor Belinda Lennox	Professor of Psychiatry

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ABBREVIATIONS

Abbreviation	Term
AADHD QOL	Adult ADHD QOL
ABPI	Association of the British Pharmaceutical Industry
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
CHI	Community Health Index Number
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
DSUR	Development Safety Update Report
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
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
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
PI	Principal Investigator
PICs	Participant Identification Centres
PIS	Participant Information Sheet
QOL	Quality of Life
QR	Quick Response
QALY	Quality-adjusted life year
REC	Research Ethics Committee
RCT	Randomised Controlled Trial
RGT	University of Birmingham Research Governance team
RSI	Reference Safety Information
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
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UoB	University of Birmingham
USM	Urgent Safety Measure
WRAADS-Interview	Wender-Reimherr Adult Attention Deficit Disorder Scale-Interview

TRIAL SUMMARY

Title

A randomised controlled trial to evaluate the clinical and cost-effectiveness of **S**timulant compared with **N**on-stimulant medication for adults with **A**ttention-deficit/hyperactivity disorder and a history of **P**sychosis or bi**P**olar disord**ER**: **SNAPPER**

Aim

The aim of the study is to evaluate the clinical and cost-effectiveness of stimulant (Lisdexamfetamine) compared with non-stimulant (Atomoxetine) medication for adults with Attention-Deficit/Hyperactivity Disorder (ADHD) and a history of either psychosis or bipolar disorder.

Primary Objective

To evaluate in adults with ADHD and a history of psychosis or bipolar whether stimulant vs. non-stimulant medication reduces ADHD symptom severity at 6 months.

Secondary Objectives

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

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

Trial Design

A pragmatic, observer-blind, national, multi-centre, 2-arm, parallel group randomised controlled trial.

Participant Population and Sample Size

244 participants, male and female, aged 18 years or above with ADHD and a history of psychosis or bipolar disorder, will be recruited from NHS mental health services, and through other means from across the UK (See Section 6.0 further details).

Setting

NHS secondary and tertiary community and inpatient mental health services across the UK.

Eligibility Criteria

Inclusion Criteria

- Diagnosis of ADHD according to the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) based on the Diagnostic Interview for ADHD in Adults-5 (DIVA-5)
- Psychosis (schizophrenia spectrum disorders) OR Bipolar disorder diagnosis according to the DSM-5 based on the Mini International Neuropsychiatric Interview (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 informed consent

Exclusion Criteria

- ADHD medication contra-indicated
- Currently in an acute episode of psychosis or bipolar disorder
- Severe suicide risk or severe risk of violence to others
- Severe drug seeking behaviour or a current drug/alcohol withdrawal syndrome
- 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 routine 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.

We recommend that people with bipolar disorder are on mood stabilising medication and people with psychosis are on maintenance medication wherever possible.

Interventions

- ADHD stimulant medication (Lisdexamfetamine) initiated at 30mg once daily, increasing to 70mg (maximum) once daily for 6 months

Vs

- ADHD non-stimulant medication (Atomoxetine) initiated at 40mg daily increasing to 100mg (maximum) daily for 6 months

Starting doses will be amended (typically reduced), and dose escalation will be slower as clinically indicated consistent with good quality routine care.

Outcome Measures

Primary outcome:

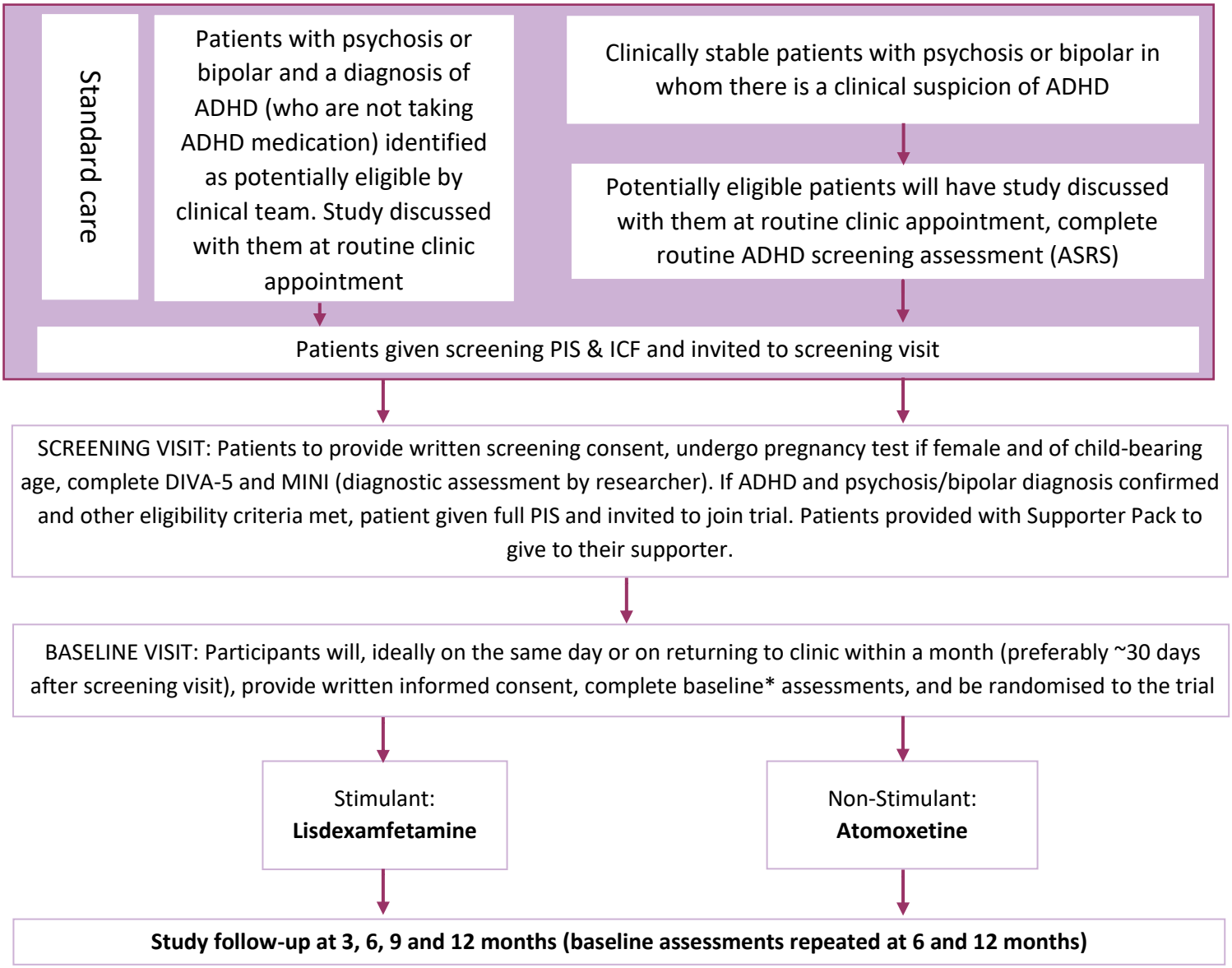
- ADHD symptoms at 6 months, as measured by the Conners Adult ADHD Rating Scale (CAARS-O) total score

Secondary outcomes:

The secondary outcomes will be collected at 6 months and 12 months unless otherwise stated.

- Clinical (ADHD symptoms using CAARS-O total score, emergence of hypomania/mania symptoms, emergence of psychotic symptoms and depression; emotional dysregulation).
- Quality of life (QOL) (ADHD specific QOL for participants only using the Adult ADHD QOL (AADHD QOL); health-related QOL and capability wellbeing for both the participant and supporter (close person)) using the EQ-5D-5L and ICECAP-A.
- Occupational and functional outcomes (occupational and daily functioning, employment, education) using the Functioning Assessment Short Test (FAST).
- Substance misuse (problem drug use, problem drinking).
- Adherence (Medication Adherence Rating Scale (MARS) and self-reported adherence
- Process outcomes (all causes for discontinuation of treatment).
- Resource use (modified Client Service Receipt Inventory (CSRI) and use of acute services).
- Concomitant medication use (type, dose and duration).

TRIAL SCHEMA



***Baseline assessments and 6/12 month outcome measures (including assessments at 3/9 months):**

- Conners Adult ADHD Rating Scale (CAARS-O) total score
- Emergence of hypomania/mania and depression symptoms: weeks with mania and depression measured by the Longitudinal Interval Follow-up Evaluation (LIFE); also assessed at 3 and 9 month clinic visits
- Emergence of positive psychotic symptoms: positive symptom severity measured by the Positive and Negative Symptoms Scale (PANSS); also assessed at 3 and 9 month clinic visits
- Emotional dysregulation: Difficulties in Emotional Regulation Scale-16 (DERS-16) and Wender-Reimherr Adult Attention Deficit Disorder Scale-Interview (WRAADS-Interview)
- Health-related quality of life (QOL): assessed using the EQ-5D-5L and ICEpop CAPability measure for Adults (ICECAP-A) for participants and supporters (where supporters consent); Adult ADHD QOL measure
- Functional/occupational outcomes: Functioning Assessment Short Test (FAST), employment (type, yes/no, length), education (type)
- Substance misuse: Drug Abuse Screening Test-10 (DAST-10), Alcohol Use Disorders Identification Test (AUDIT)
- Cost-effectiveness: modified Client Service Receipt Inventory (CSRI); acute care services retrieved from patient records
- Adherence: Medication Adherence Rating Scale (MARS) and self-report at 6 and 12 months
- Concomitant medication use (type, dose and duration) at 6 and 12 months

TABLE OF CONTENTS

1. BACKGROUND AND RATIONALE

1.1. Background

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 disorder 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 their bipolar, shorter periods of wellness, greater risk of substance misuse and of 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 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 recent systematic review and network meta-analysis concluded that in adults with ADHD, compared with placebo, 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].

People with psychosis or bipolar are usually excluded from ADHD 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), and indicated Atomoxetine significantly reduced ADHD symptoms at 8 weeks [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]. As such there are no high-quality studies supporting the use of either stimulants or non-stimulants in this patient group.

The extent to which ADHD medications could be harmful in adults with ADHD with a history of bipolar 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 1,335 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 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], [23], [24] but no evidence from higher quality studies than these is available to guide treatment decisions.

1.2. Trial Rationale

Whilst the most recent NICE ADHD guidelines [13] indicate available evidence does not justify a deviation from their main recommendations of using stimulants in adults, this is based on limited studies of individuals with ADHD and severe mental illness (SMI). Currently there is a lack of clarity over the effectiveness of both stimulant and the non-stimulant Atomoxetine in people with SMI.. Because the quality of current evidence in this area is inadequate, NICE recommends 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. This trial is answering a commissioned call from the NIHR HTA Programme and therefore is recognised as an important question that needs answering.

Adult ADHD is under-recognised and under-treated, despite the multiple harms associated with the condition [25], including limiting the symptomatic and functional recovery of people with psychosis or bipolar [26]. In part, the under-treatment may be linked to the fact that clinicians are also concerned that these medications may provoke or exacerbate psychosis or mania [27], and are therefore likely to be cautious in this area of therapeutics. This is because stimulant medications used in adult ADHD have a dopaminergic action, and given that both psychosis [28] and bipolar disorder [29] have been linked to increased levels of central cortical dopamine, medications used for ADHD could theoretically trigger psychotic or bipolar symptoms. As such, we do not fully understand the potential harms in patients with adult ADHD and comorbid psychosis or bipolar, but resolving this is critical for clinicians and this patient group, so that informed decisions can be made, under-treatment tackled, and recovery optimised.

1.2.1. Justification for participant population

Adults with ADHD and comorbid psychosis or bipolar are undertreated and have a poorer outcome than people without comorbidity. In part this is because of clinical uncertainty about the effectiveness of stimulant vs non-stimulants in reducing ADHD symptoms in this population. There is also clinical and patient concern that ADHD medication may exacerbate symptoms of psychosis and bipolar.

Patients will be recruited from NHS secondary and tertiary community and inpatient mental health services across the UK. This is primarily where care is provided for the target population and where the clinical uncertainty is faced.

1.2.2. Justification for design

We will combine psychosis comorbidity and bipolar disorder comorbidity into SMI comorbidity. This is meaningful to clinicians as the evidence for the effectiveness of stimulants or non-stimulants in each comorbid population (history of bipolar disorder or psychosis) is equally absent. Secondly clinician concern about the safety of using stimulants in people with bipolar disorder or psychosis is based on stimulants increasing cortical dopamine (by blocking a dopamine transporter) thereby putting the patient at increased risk of relapse as hyperdopaminergia is known to occur in both psychosis [30] and bipolar disorder [31] as part of those conditions. Combining the two types of comorbidity means we can address the primary purpose of the trial and provide evidence that will improve clinical care.

1.2.3. Justification for choice of intervention

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 [32]. 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 [33], [34]. 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].

2. AIMS AND OBJECTIVES

The aim of the study is 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.

2.1. Main Trial Objectives

2.1.1. Primary objective:

To evaluate in adults with ADHD and a history of psychosis or bipolar whether stimulant vs. non-stimulant medication reduces ADHD symptom severity at 6 months.

2.1.2. Secondary objectives:

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

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

3. TRIAL DESIGN AND SETTING

3.1. Trial Design

A pragmatic, observer-blind, national, multi-centre, 2-arm, 1:1 individually randomised parallel group RCT.

3.2. Trial Setting

NHS secondary and tertiary community and inpatient mental health services, and research clinics across the UK.

3.3. Assessment of Risk

All clinical trials can be considered to involve an element of risk and, in accordance with Birmingham Clinical Trials Unit (BCTU) standard operating procedures, this trial has been risk assessed to clarify any risks relating uniquely to this trial beyond that associated with usual care. A Risk Assessment has been conducted and concluded that this trial corresponds to the following categorisation:

Type A, in accordance with a risk-adapted approach to Clinical Trials of Investigational Medicinal Products (CTIMPs).

- Type A = No higher than the risk of standard medical care

4. ELIGIBILITY

4.1. 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

4.2. 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.

NB: Highly effective contraceptive measures include:

- *Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:*
    - oral, intravaginal or transdermal
- *Progestogen-only hormonal contraception associated with inhibition of ovulation:*

- oral, injectable or implantable
  - *Intrauterine device (IUD)*
  - *Intrauterine hormone-releasing system (IUS)*
  - *Bilateral tubal occlusion*
  - *Vasectomised partner*
  - *Sexual abstinence (True abstinence: When this is in line with the preferred and usual lifestyle of the subject)*

We recommend that people with SMI are on maintenance medication for that condition wherever possible.

4.3. Co-enrolment

Participants in SNAPPER can participate in any observational study. Co-enrolment in other trials if compatible with SNAPPER can be considered after discussion with the CI.

5. CONSENT

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, all of whom should have undergone Good Clinical Practice (GCP) training. Delegation of this duty will be authorised by the PI and captured on the **Site Delegation Log.**

Potentially eligible patients will be approached either during a routine clinical appointment or via telephone call by their usual clinical care team who will inform them of the study and introduce them to the local research team. We will advertise the study on social media channels and the NIHR Involve Me website. Study researchers will discuss SNAPPER with these potentially eligible participants who respond to these advertisements. The care or research team will briefly discuss the trial to ascertain interest and the patient will be informed that their participation is voluntary and choosing not to participate will not affect their usual care.

During this contact, if the participant expresses an interest in participating in the trial, a member of either the care team or the research team will provide the participant with a copy of the Participant Information Sheet (PIS) and Informed Consent Form (ICF) (paper or electronic if e-mailed) to facilitate the full screening consent process followed by a separate PIS and ICF for randomisation into the trial. Consent to the trial will be completed by either a member of the care team or researcher (care team member or researcher who has been delegated to undertake this duty by the PI) using the electronic online consent forms. Paper copies of the PIS and ICF will also be available from the Trial Office and will be printed or photocopied onto the headed paper of the local NHS Trust.

5.1. Screening consent

As described above, members of the care team or research team will present potential participants with further details of the trial and provide a short Screening PIS explaining the screening process.

Prior to obtaining consent, potential eligibility will first be assessed according to the study inclusion and exclusion criteria and confirmation of initial eligibility (i.e. all criteria met except those relating to the DSM-5) will be documented by a medically qualified clinician.

At the screening visit, if potential participants meet the initial eligibility criteria and are interested in taking part in the study, they will be asked to electronically sign and date the latest electronic version of the screening ICF which will be available to all sites online.

A printed copy of the ICF will be given to the participant. Should participants wish to do so, they can receive a copy of the signed ICF by consenting to provide an e-mail address for the ICF to be e-mailed instead. A record will be made in the medical notes for when the consent was taken and a copy placed in the medical notes. A copy will also be stored electronically in the site-specific section of the database. A copy will be printed for the Investigator Site File (ISF).

If the participant is later randomised into the trial, their trial number will be entered on the original screening ICF maintained in the ISF and the TNO linked against the ICF stored in the database. At the time of screening consent, the participant will be asked to give explicit consent for the signed screening ICF to be stored in the database for internal review and audit purposes. If the participant does not enter the main trial, then the signed screening ICF will be removed from the viewable data set 35 days after the date of the screening consent. The screening consent record therefore will not be available to view by BCTU and staff at participating Sites, unless required for regulatory purposes.

Following consent for screening, the DIVA-5 (Diagnostic Interview for ADHD in Adults; previously DIVA 2.0 [35]) and MINI (Mini-International Neuropsychiatric Interview version 7.0.2) will be completed to confirm diagnosis of ADHD and psychosis/bipolar and full eligibility to the study.

If ADHD and psychosis/bipolar are confirmed and all other eligibility criteria continue to be met, the participant will be given the full trial PIS (if not already provided at screening). At this stage, the PI or delegate will provide further details of the study, i.e., adequately explain the aim of the trial, the trial interventions, and the anticipated benefits and potential hazards of taking part in the trial and will ensure that the potential participant has the opportunity to ask questions. The PI or delegate will again explain that participation is voluntary and that the participant is free to decide whether to take part in the trial and may withdraw from the trial at any time. They will be given sufficient time to consider the trial and, should the participant feel the need to do so, discuss participation with friends and family.

Details of confirmation of full eligibility and the informed consent discussions (for both screening and randomisation) will be recorded in the participant's medical notes in accordance with GCP. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIS given to the participant, version number of ICF signed and date consent was obtained. As consent for screening will be obtained on the same day that trial related assessments start (specifically the DIVA-5 & MINI assessments) a note should be made in the medical notes clearly stating what time consent was obtained and what time assessments started.

Should the participant wish to do so, they can consent for the full trial and complete the baseline assessments on the same day as the screening visit or, if they prefer, they can return to clinic for a separate baseline visit within a month (~30 days) of the screening visit.

5.2. Main trial consent

The participant will be given the opportunity to ask any further questions regardless of whether they consent to the full trial at the screening visit or at a separate baseline visit. If they wish to take part in the full trial, the participant will be asked to sign and date the latest online version of the main ICF before any baseline assessments are carried out. Management of the ICF will follow the same

process as set out above in Section 5.1 and optional consent for an electronic copy of the signed ICF to be sent via e-mail to the participant will again be made available.

The participant must give explicit consent for the regulatory authorities, members of the research team and/or representatives of the Sponsor to be given direct access to the participant's medical records.

At each visit the participant's willingness to continue in the trial will be ascertained and documented in the medical notes. Throughout the trial the participant will have the opportunity to ask questions about the trial.

Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participants' decision to continue, participants will be given time to consider and if happy to continue will be re-consented by means of a new PIS and ICF that includes the new information. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

5.3. Additional consent

Consent for the participant's preferred method of contact, i.e., e-mail address and/or mobile number, will be obtained to send participants online links to complete the electronic questionnaires.

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 (see Section 14).

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. If participants agree, they will consent to the Trial Office sending their name, date of birth and NHS/CHI number to the relevant national registry and then for the national registry to link this to their data and send the information back to the Trial Office. The consent will also allow access to other new central UK NHS databases that will appear in the future. This will allow us (subject to receipt of additional funding via another grant application) 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 training and inter-rater reliability. These will be recorded either using supplied trial-specific tablets or as per local practice and will be stored appropriately and securely.

All additional and optional consent choices will be made available during the main consent process.

5.4. Supporter consent

At the screening visit, 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. At this visit, 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. 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. During the online consent, the supporter's full name and their preferred method of contact (email address or mobile phone number) for sending the online link to complete the questionnaires will be collected. A copy of the completed ICF will be sent directly to the supporter's email address and a copy will also be printed for the ISF.

The local researchers will follow-up with participants to prompt and facilitate supporter participation. They will also be given as the contact should the supporter have any questions, in addition to the SNAPPER Trial Office e-mail address.

The interventions may affect the quality of life of supporters in addition to participants. Any such quality of life effects need to be quantified for a robust health economic analysis. The questions asked of supporters will be limited to quality of life data to include the EQ-5D-5L (health-related QoL) and ICECAP-A (capability wellbeing) at specific time-points. See Section 8.0 for further details.

5.5. Covid-19 and trial process resilience

Visits throughout the informed consent process and beyond will take place in person at the clinic or participant's home, or by telephone or video call as per local practice where patient and/or public health circumstances dictate. Where visits are in the participant's home, or by telephone or video call, due care will be paid to ensure the participant is in a suitably safe and confidential environment before proceeding.

6. IDENTIFICATION, SCREENING, RANDOMISATION AND BLINDING

6.1. Identification

Potentially eligible participants 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 minutes either at a face-to-face appointment or by the patient at home and returned to the clinician.

NHS research staff may assist clinicians with caseload screening, use of electronic record searches or research registers to help identify patients on their caseloads, according to local permissions as appropriate, for any of the methods described.

6.1.1. Participant Identification Centres

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 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.

6.1.2. Social media by way of patient forums, Facebook, Twitter, etc.

The study will be advertised widely for purposes of recruitment using ethically approved material via websites and social media platforms related to ADHD, psychosis and bipolar disorder (Facebook, Twitter, Instagram etc.). Direct advertisements to the membership of national ADHD, psychosis and bipolar disorder charities, and on charity websites will also be developed for promoting and supporting the study for recruitment. Potential patients will be asked to contact the SNAPPER Trial Office for further information. The Trial Office will direct the patient to the nearest site open for the trial or inform the patient how to be referred to an open site.

Patient targeted posters in clinical areas, research invitation letters and newsletters based on centrally ethically approved material will be used to promote the trial locally at Sites. Whichever method of identification is used, the patient will be asked if they are willing to speak to a study researcher to find out about the study in more detail and to further check eligibility. Screening and Enrolment

Screening of potential participants will be conducted by the clinical team and/or a member of the local research team as indicated above. Eligibility will be confirmed by a medically qualified doctor.

Those that consent for screening will complete the following screening assessments to confirm full eligibility criteria:

- DIVA-5 to confirm a DSM-5 diagnosis of ADHD
- MINI to confirm a DSM-5 diagnosis of psychosis (schizophreniform disorders) or bipolar disorder
- If female of childbearing potential (fertile, following menarche and until becoming post-menopausal unless permanently sterile), a spot urine pregnancy test to confirm patient is not pregnant

If all the eligibility criteria are met and the participant confirms they are still willing to take part in the study, they will be asked to formally consent to participate in the main trial and to randomisation. After consent has been obtained, the full baseline battery of questionnaires and Case Report Forms (CRFs) will be completed and they will then be randomised into the trial. Anonymised details of all participants approached about the trial will be recorded on the SNAPPER **Participant**

Screening and Enrolment Log which will be kept in the ISF, and should be available to be sent to the Trials Office upon request.

6.2. Randomisation

6.2.1. Randomisation Method

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.

Full details of the randomisation specification will be stored in a confidential document at BCTU.

6.2.2. Randomisation Process

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. Randomisation Forms will be provided to collate the necessary information prior to randomisation. All questions and data items on the Randomisation Forms must be answered prior to a participant being randomised into the trial and given a treatment allocation. During randomisation, the participant details including date of ADHD diagnosis, full name, full date of birth, gender, NHS/CHI number (CHI number applicable to sites based in Scotland only) and name of hospital Trust/ Health Board will be collected. The name of the clinician who confirmed eligibility and the date consent for main entry to the trial was taken will also be recorded.

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). Unique usernames and passwords will be provided to those who have been delegated the role of randomising participants as detailed on the SNAPPER **Site Delegation Log**. These unique login details must not be shared with other staff and in no circumstances should staff access the randomisation process using another person's login details. The online randomisation system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance. A telephone toll-free back up randomisation service (0800 953 0274) is available Monday to Friday, 09:00 to 17:00 UK time, except for bank holidays and University of Birmingham (UoB) closed days.

When all questions have been answered on the Randomisation Form, a unique sequential trial number (TNO) for each participant randomised will be issued which, going forwards, will be used for all correspondence relating to the participant between the site and the Trial Office.

6.2.3. Randomisation Records

Following randomisation, a confirmatory email will be sent to the research team with details of the randomisation, with the participant's trial number and treatment allocation. As per Site preference, the confirmatory e-mail will also be sent to the local PI and/or the clinician who confirmed eligibility.

PI's will keep their own file which links participants with their trial number and allocated treatment in the **Participant Recruitment and Identification Log**. PI's (or their delegates) must maintain this document securely, which is **not** for submission to the Trials Office. The **Participant Recruitment and Identification Log** should be held in strict confidence. PI's (or their delegates) will also keep the **Participant Screening & Enrolment Log** which will be kept in the ISF and should be available to be sent to the Trial Office upon request.

For participants who are seen at a research clinic and who are not in contact with services at that centre, a notification of the participant's entry to the trial will be sent to their GP, consultant psychiatrist and care co-ordinator.

6.3. Blinding

This is an observer-blind trial.

6.3.1. Blinded Personnel

It is not feasible to blind the prescriber or participant as:

- the effects of Lisdexamfetamine are immediate and wear off by the end of the day, unlike Atomoxetine that has slow onset and longer duration of effect;
- dosage schedules are different for Lisdexamfetamine (once/day in the morning AM) and Atomoxetine (once or twice/day);
- for Atomoxetine the aim is usually a fixed daily dose target of 80-100mg regardless of clinical effect, whilst Lisdexamfetamine dose is titrated against clinical and adverse effects.

However, blinded assessors will complete all outcome measures at 6, and 12 months, to include the CAARS-O, WRAADS-Interview, LIFE, PANSS and FAST assessments. The assessors will be the study funded researchers who will complete these assessments for participants outside of their centres. It will be feasible to conduct video-assessments where travel to another site is not convenient. Whilst the CAARS-O has not been formally validated for use by video-assessment, the clinical assessment is no different to that which takes place face to face. Participants will be reminded not to disclose any information regarding their allocated trial medication to the blinded assessors.

6.4. Informing the Participant's GP and Other Parties

The participant's General Practitioner (GP) will be notified that they are taking part in the SNAPPER trial, using the approved SNAPPER **GP Notification Letter.** This will be sent to the participant's GP directly from the randomising site. The participant's Consultant Psychiatrist and care co-ordinator will also be copied into this letter.

6.5. Supporter registration

As described in section 5.4, the participant's supporter, if the supporter consents to join the trial, will be asked register to participate in the trial after the participant has been randomised. The short online Self-Registration Form will be used for the collection of their details required to register them on the SNAPPER trial database. To link the supporter with the participant, the supporter will be registered against the TNO of the participant to whom they are the supporter. During registration,

the supporter's details including initials, age category (categories ranging from 18 to 71+ years), gender, relation to participant and whether they cohabit with the participant will be collected.

Following registration, the supporter will be sent a confirmatory email with the local research team and Consultant Psychiatrist copied in. A notification of supporter participation will also be sent to the supporter's participant via the participant's e-mail or mobile number.

7. TRIAL INTERVENTION

7.1. Trial Interventions and Dosing Schedule

Participants will be randomised to receive either:

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

Starting doses will be amended (typically reduced), and dose escalation will be slower as clinically indicated consistent with good quality routine care.

7.2. Medication titration protocol post randomisation

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.

Participants will be monitored more closely than if they didn't have comorbid bipolar or psychosis, consistent with the current NICE and British Association of Psychopharmacology (BAP) guidelines [13], [36]. In week 1-2, there will be face to face contact (in person or via a video-call) with the participant's clinical care team; then 2-weekly face-to-face or telephone contact as clinically necessary, aiming for a maintenance dose by 4 months of no more than 70mg daily of Lisdexamfetamine and no more than 100mg daily of Atomoxetine. As per routine practice, participants will have their BP and pulse measured at baseline before medication for ADHD is commenced, after 1-2 weeks of starting medication and after dose increases. This may be conducted by a clinician or via a blood pressure and heart rate monitor provided to study participants to take readings where their assessments are done. Clinicians will record self-reported or clinically assessed readings in the participant's medical notes. Any large changes in readings will be managed as per standard practice.

As is routine practice for this patient population prescribed ADHD medication, this monitoring and any additional visits will not be part of the protocol requirements and should be managed locally. Prescribing should be guided by the standard approach of titrating dose against clinical effects, while keeping adverse effects to a minimum, using repeated measurement of ADHD symptoms and adverse events, which sites will document in the participant medical records.

7.3. Drug Interaction or Contraindications

7.3.1. Permitted medications

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, from the perspective of

their psychosis or bipolar. Usual practice of dose changes or change 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.

7.3.2. Prohibited medications

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.

7.4. Intervention Modification or Discontinuation

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 (as defined by the clinical care team), 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 (such as adverse events) for temporary and permanent discontinuation of Lisdexamfetamine or Atomoxetine will be documented in the participant's medical record and transcribed onto the IMP Medication Stop/Re-Start Form.

7.5. Continuation of Intervention after the Trial

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 licenced as indicated for use and available under an NHS prescription.

7.6. Intervention Supply and Storage

Participants will be provided with a prescription for their allocated intervention every 1- 2 weeks during initial titration and monthly thereafter. This will be prescribed and dispensed as per routine local practice from NHS stock. No clinical trial specific pharmacy requirements of the drug intervention including supply, storage, labelling, drug accountability and destruction will be needed.

7.7. Adherence

Adherence to trial medication will be assessed using 2 methods:

- **Adherence during the previous week at 6 and 12 months** post-randomisation, measured using the Medication Adherence Rating Scale (MARS) [37]. This is a short 10 item self-report, reliable and valid scale specifically designed for psychotropic medications providing an overall score describing behaviour during the previous week. A higher score indicates greater adherence.

- **Self-report adherence during the previous 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 they have taken their psychosis/bipolar medication 0-24%, 25-49%, 50-74%, 75-99 or 100% of the time will be asked.

8. OUTCOME MEASURES AND TRIAL PROCEDURES

8.1. Trial Outcomes

All outcomes will be collected in all participants at 6 months (the primary endpoint), and at 12 months in those who reach 12 months before the trial end (which will be when the last randomised participant reached 6 months).

8.1.1. Primary Outcome

ADHD symptoms at 6 months post-randomisation, as measured by the Conners Adult ADHD Rating Scale-Observer (CAARS-O) total score [38]. The CAARS-Observer questionnaire comprises 18 investigator-rated items corresponding to the 18 DSM-5 ADHD symptoms and provides a total score ranging from 0-54, where a low score indicates fewer symptoms.

8.1.2. Secondary Outcomes

Secondary outcomes will be collected only on those participants recruited 12 months or more from end of all trial follow up .

8.1.2.1. Clinical

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 randomisation. This will be measured using the Longitudinal Interval Follow-up Evaluation (LIFE) [39], 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 by the Positive and Negative Symptoms Scale (PANSS) positive symptom subscale [40], 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. This will be 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) [41]. 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) [42], 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.

8.1.2.2. Quality of life (QOL)

ADHD specific QOL at 6 and 12 months post-randomisation assessed by the Adult ADHD QOL Measure (AADHD QOL) [43]. 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 [44] 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 [45-47]. 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).

8.1.2.3. Occupational and functional

Occupational and daily functioning at 6 and 12 months post-randomisation, measured using the Functioning Assessment Short Test (FAST) [48]. The overall score, which ranges from 0-72 will be used where a higher score indicates severe difficulty in functioning

Employment (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.

8.1.2.4. Substance misuse

Problem drug use at 6 and 12 months post-randomisation measured using the Drug Abuse Screening Test-(DAST)10 [49]. 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) [50]. A score of 8 and above will be used to indicate problem drinking as indicated by the instrument authors.

8.1.2.5. Adherence

Adherence during the last week at 6 and 12 months post-randomisation, measured using the Medication Adherence Rating Scale (MARS) [37] 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.

8.1.2.6. Concomitant medication

Type and dose of concomitant medication, start date and stop date (duration) will be recorded at 6 and 12 months post-randomisation, using the electronic patient record, and presented descriptively.

8.1.2.7. Process outcomes

All cause discontinuation of randomised treatment.

8.1.2.8. Resource use

Measured by the modified Client Service Receipt Inventory (CSRI) at 6 and 12 months. We will use an adapted version of the CSRI [51] to measure service users' health and social care resource use, as well as wider societal costs to informal carers, employment, and criminal justice sectors [52].

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 Section 5.4, 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.

8.1.3. Schedule of Assessments

Following consent for screening, the local research team will undertake a urine pregnancy test for females of child-bearing potential. They will complete the DIVA-5 and MINI **diagnostic screening assessments** as described in section 5.1. with participants. Participants will also be provided the Supporter's Pack to hand to their nominated supporter.

All assessment visits will be carried out in person either at the clinic or participant's home, or by telephone or video calls as per local practice where participant and/or public health circumstances dictate. Supporter questionnaires will be completed online via links sent directly to the email address/mobile number provided by the supporter.

At the **baseline visit (i.e., pre-randomisation)**, following confirmation of diagnosis for eligibility (by the Consultant Psychiatrist or a medically qualified doctor) and consent for randomisation into the main trial, the local research team will undertake a urine pregnancy test for females of child-bearing potential if randomisation is not done on the same day as the screening assessments. The participant's contact details (email address or mobile number), medical history, current medications and demographic information including age, gender, marital status, ethnicity, mother tongue, country of birth and employment status will be recorded. Participants will also be asked about a history of trauma using the Childhood Trauma Questionnaire (CTQ) [53]. All baseline assessments will also be completed as follows:

- AADHD QOL, AUDIT, DAST-10, DERS-16, EQ-5D-5L and ICECAP-A self-report measures will be completed by the participants themselves.
- Adverse Events Scale, CAARS-O, LIFE, PANSS, FAST, WRAADS-Interview and CSRI will be completed by the researcher with the participant.

After collection of all baseline data, participants will be randomised as described in section 6.3.

Following randomisation (at either the screening and/or baseline visit), the Consultant Psychiatrist or medical prescribing team will arrange the participant prescription according to the participant's trial treatment allocation. Participants should aim to start their allocated treatment as soon as they have

received their prescription and no later than 28 days from randomisation. Prescriptions will be reviewed on a 1-2 weekly basis during medication titration and monthly thereafter as per standard practice.

The participant's supporter will complete the EQ-5D-5L and ICECAP-A soon after the participant has been randomised (and will be reminded to complete these again at 6 and 12 months post randomisation).

At the **3 and 9 month follow-up visits**, the Adverse Events Scale, LIFE and PANSS assessments will be completed. These will be unblinded assessments completed by the Research Assistants (RA) at the participant's randomising site.

At the **6 and 12 month follow-up visits,** assessments will be completed as follows:

- Participant self-reports/questionnaires to include the AADHD QOL, AUDIT, DAST-10, DERS-16, EQ-5D-5L, ICECAP-A, MARS and medication self-report will be completed by the participants themselves.
- Unblinded assessments to include the Adverse Events Scale, CSRI andconcomitant medications will be completed by the local research team at the participating site.
- Blinded assessments to include the CAARS-O, LIFE, PANSS, FAST and WRAADS-Interview will be completed by blinded assessors, i.e. the study funded Research Assistants (as described in section 6.4 above) from other participating centres.
- Supporter completed questionnaires to include the EQ-5D-5L and ICECAP-A.

Adverse events (AEs), Serious Adverse Events (SAEs) and pregnancies should be monitored throughout the AE reporting period and reported as per section 9.

Table 2: Schedule of assessments

VISIT	Screening	Baseline*	Month 3	Month 6	Month 9	Month 12

			±21 days	±21 days	±21 days	±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.

8.2. Withdrawal and Changes in Levels of Participation

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process and participants should be asked about their ongoing willingness to continue participation at all visits.

Participants should be aware from the beginning that they can freely withdraw (cease to participate) from the trial at any time. A participant may wish to cease to participate in a particular aspect of the trial. The changes in levels of participation within the trial are categorised in the following ways:

No trial intervention: The participant would no longer like to receive the trial intervention, but is willing to be followed up in accordance with the schedule of assessments and if applicable using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected and used in the trial analysis).

No trial related follow-up: The participant does not wish to attend trial visits in accordance with the study schedule of assessments, but is willing to be followed up at standard clinic visits and if applicable using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected at standard clinic visits and used in the trial analysis, including data collected as part of long-term outcomes).

No further data collection: The participant is not willing to be followed up in any way for the purposes of the trial AND does not wish for any further data to be collected (i.e. a full withdrawal; only data collected prior to any changes of levels in participation can be used in the trial analysis).

The details of changes in levels of participation in the trial (date, reason and category of change) will be clearly documented in the source documents and transcribed onto the Participant Change of Status Form. Participants can change their level of participation without giving a reason.

8.2.1. Supporter withdrawal

Supporters will be made aware (via the information sheet) during consent that they can freely withdraw (cease to participate) from the trial at any time. For supporters, withdrawal will be in the form of no further completion of the health-related quality of life and capability wellbeing questionnaires. Supporters can choose to withdraw participation by using the 'OPT-OUT' weblink that will be sent to them as part of the reminder to complete the questionnaires.

If the participant who is related to the supporter withdraws from trial related follow-up or from further data collection, prior to the 6 or 12 month assessments, the supporter will be notified of this via their chosen method of contact and will no longer be required to participate in the study.

9. ADVERSE EVENT REPORTING

9.1. Definitions

Table 3: Definitions of severity for Adverse Events

Severity	Definition
Mild	Awareness of signs or symptoms that do not interfere with the participant's usual activity or are transient and resolved without treatment and with no sequelae.

Moderate	A sign or symptom which interferes with the participant's usual activity.
Severe	Incapacity with inability to do work or perform usual activities (including life threatening events and fatality).

Table 4: Definitions for Adverse Events

Term	Abbreviation	Definition
Adverse Event	AE	Any untoward medical occurrence in a participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.
Adverse Reaction	AR	All untoward and unintended responses to an IMP related to any dose administered. An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.
Serious Adverse Event	SAE	Any untoward medical occurrence or effect that: Results in death Is life-threatening* Requires hospitalisation or prolongation of existing hospitalisation Results in persistent or significant disability or incapacity Is a congenital anomaly/birth defect Or is otherwise considered medically significant by the Investigator**
Serious Adverse Reaction	SAR	An AR which also meets the definition of an SAE.
Unexpected Adverse Reaction	UAR	An AR, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator Brochure for an unapproved IMP or (compendium of) Summary of Product Characteristics (SPC) for a licensed product). When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.

Suspected Unexpected Serious Adverse Reaction	SUSAR	A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information. A SUSAR should meet the definition of an AR, UAR and SAR.

* The term life-threatening is defined as diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted.

** Medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definitions above.

9.2. Adverse Event Recording – General

The recording and reporting of Adverse Events (AEs) will be in accordance with the UK Policy Framework for Health and Social Care Research, the Principles of GCP as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments), and the requirements of the Health Research Authority (HRA) and The Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments thereof.

Definitions of different types of AEs are listed in the table of definitions in table 4.

It is routine practice to record AEs in the participant's medical notes and it is also recommended that this includes the documentation of the assessment of severity and seriousness and also of causality (relatedness) in relation to the intervention in accordance with the protocol.

9.3. Adverse Event Reporting in SNAPPER

Since the screening visit will be minimally invasive, the reporting period for AEs in SNAPPER will start from the day of randomisation 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) (as detailed below) will be reported as SAEs.

9.4. Serious Adverse Advent (SAE) Reporting in SNAPPER

For SAEs the PI or delegate must do one of the following:

Record safety reporting-exempt SAEs in the medical notes but **not report** them to the Trials Office on an SAE form (9.4.1 below).

Report SAEs to the Trial Office in a non-expedited manner. This can only be done for the pre-defined subset of SAEs as per section 9.4.2 below.

Report SAEs to the Trial Office in an expedited manner (within 24 hours of the site research team becoming aware of the event). All SAEs not covered by the above 2 categories must be reported as per section 9.5 below.

Note: when an SAE occurs at the same hospital at which the participant is receiving trial intervention or is being followed up for trial purposes, processes must be in place to make the trial team at the hospital aware of any SAEs, regardless of which department first becomes aware of the event, in an expedited manner.

9.4.1. Serious Adverse Events not requiring reporting to BCTU

During the SAE reporting period, the following will not be considered to be critical to evaluations of the safety of the trial:

- Pre-planned hospitalisation;
- General hospital attendance lasting less than 24 hours, unrelated to a mental health event;
- Hospitalisation for routine treatment or monitoring of the studied indication, not associated with any deterioration in condition or trial procedures;
- Treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study, and did not worsen;
- Admission to a hospital or other institution for general care (not related to ADHD or mental health condition), not associated with any deterioration in condition or trial procedures;

All events which meet the definition of serious must be recorded in the participant notes, including the causality and severity, throughout the participant's time in the trial but for trial purposes these events do not require reporting. Such events are "safety reporting exempt".

9.4.2. Serious Adverse Events requiring non-expedited reporting to BCTU

Where the safety profile is well established, the causal relationship between the intervention (or the participant's underlying condition) and the SAE may be known. That is, such events are protocol-defined as "expected" (see Section 9.5.2). Such events should still be recorded by the trial team in the participant's notes and reported to the Trial Office on the trial specific SAE form within 4 weeks of becoming aware of the event. However, these events do not require expedited reporting (i.e. immediately on the site becoming aware of the event) since the assessment of expectedness for the specified events has been pre-defined. These include:

- Attendance at A&E for a mental health related reason
- Referral to mental health crisis team
- Referral to liaison psychiatry

9.4.3. Serious Adverse Events requiring expedited reporting to BCTU

All SAEs not listed in Sections 9.4.1. and 9.4.2 must be reported to BCTU on a trial specific SAE form within 24 hours of the site research team becoming aware of the event.

9.5. SAE Reporting process

On becoming aware that a participant has experienced an SAE which requires reporting on an SAE form, the PI or delegate should report the SAE to their own Trust in accordance with local practice and to the Trial Office as per the requirements of sections 9.4.2 and 9.4.3 above.

To report an SAE to the BCTU trials office, the PI or delegate must complete, date and sign the trial specific SAE form. The completed form together with any other relevant, appropriately anonymised data should be scanned and emailed to the Trial Office using the information below in accordance with the timelines given in sections 9.4.2 and 9.4.3.

To report an SAE:

Email the SAE Form to: SNAPPER@trials.bham.ac.uk

Where an SAE Form has been initially completed by someone other than the PI, the original SAE form will need to be countersigned by the PI to confirm agreement with the causality and severity assessments.

On receipt of an SAE form, the Trial Office will allocate each SAE a unique reference number and notify the site via email to the site as proof of receipt. The site and the Trial Office should ensure that the SAE reference number is quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the ISF.

If the site has not received confirmation of receipt of the SAE or if the SAE has not been assigned a unique SAE identification number within 1 working day of reporting, the site should contact the Trial Office.

9.5.1. Assessment of causality of an SAE

When completing the SAE form, the PI (or, throughout this section 9.5.1, a medically qualified delegate) will be asked to define the causality (relatedness to the intervention) and the severity of the AE.

In defining the causality, the PI must consider if any concomitant events or medications may have contributed to the event. Where this is so, these events or medications should be reported on the SAE form. It is not necessary to report concomitant events or medications which did not contribute to the event.

As per table 5 below, all events considered to be 'possibly', 'probably', or 'definitely' related to the intervention will be reported to the Trial Office as 'related'; all events considered at site to be 'unlikely' or 'unrelated' to the intervention will be reported to the Trial Office as 'unrelated'. The same categorisation should be used when describing AEs and safety reporting exempt SAEs in the source data.

Table 5: SAE causality and relatedness

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.	Related
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.	
Possibly	There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant events or medication)	
Unlikely	There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant events or medication).	Unrelated
Not related	There is no evidence of any causal relationship.	

On receipt of an SAE form, the Trials Office will forward the SAE form to the Chief Investigator (CI) or delegate who will independently* review the causality of the SAE. An SAE judged by the PI or CI or delegate to have a reasonable causal relationship ("Related" as per table 5) with the intervention will be regarded as a related SAE (a SAR). The severity and causality assessment given by the PI will not be downgraded by the CI or delegate. If the CI or delegate disagrees with the PI's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

*Where the CI is also the reporting PI an independent clinical causality review will be performed.

9.5.2. Assessment of Expectedness of an SAE by the CI

The CI or delegate(s) will also assess all related SAEs for expectedness with reference to the criteria in table 6 below:

Table 6: SAE expectedness

Category	Definition
Expected	An adverse event that is consistent with known information about the trial related procedures or that is clearly defined in the reference safety information (RSI).
Unexpected	An adverse event that is not consistent with known information about the trial related procedures and is not listed in the RSI.

The RSI will be the SmPCs for the studied drugs with reference to Section 4.8 Undesirable effects of the studied drugs.

If the event is unexpected (i.e. it is not defined in the approved version of the RSI) it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

The CI will undertake review of all SAEs and may request further information from the clinical team at site for any given event to assist in this.

9.5.3. Provision of SAE follow-up information

Following reporting of an SAE for a participant, the participant should be followed up until resolution or stabilisation of the event. Follow-up information should be provided using the SAE reference number provided by the Trial Office. Once the SAE has been resolved, all critical follow-up information has been received and the paperwork is complete, a copy of the final version of the completed SAE form must be submitted to the Trial Office and a copy kept in the ISF.

9.6. Reporting SAEs to third parties

The independent Data Monitoring Committee (DMC) may review any SAEs at their meetings.

BCTU will report details of all SARs (including SUSARs) to the MHRA, Research Ethics Committee (REC), and UoB Research Governance Team (RGT) annually from the date of the Clinical Trial Authorisation, in the form of a Development Safety Update Report (DSUR).

Additionally, BCTU will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the MHRA, REC and RGT within 7 days of being notified. Detailed follow-up information will be provided within an additional 8 days.

All other events categorised as non-life threatening SUSARs will be reported within 15 days of being notified.

The REC and RGT will be notified immediately if a significant safety issue is identified during the course of the trial.

Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to PIs. A copy of any such correspondence should be filed in the ISF and Trial Master File (TMF).

9.7. Urgent Safety Measures

The Clinical Trials Regulations make provision for the Sponsor and PIs to take appropriate Urgent Safety Measures (USMs) to protect a research participant from an immediate hazard to their health and safety. This measure can be taken before seeking approval from the MHRA and REC.

If the PI (and not the Sponsor) has instigated the USM, the Sponsor should be notified immediately so that they can assess and report the USM within the timelines required.

If any urgent safety measures are taken, the Trial Office shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the REC and MHRA of the measures taken and the reason why they have been taken.

9.8. Follow-up of pregnancy outcomes for potential SAEs

Any participant that becomes pregnant between the start of protocol-defined treatment until 30 days after the last dose will be followed up to outcome of the pregnancy. The outcome of these pregnancies will be recorded via the Pregnancy Notification Form, which will be completed by the site (providing the participant's details) with basic information of when the participant became pregnant and returned immediately to the Trials Office. Further information on the pregnancy will only be collected if the participant consents to provide their details via the Pregnancy Release of Information. Once consent has been obtained, further details of the pregnancy will be provided on the Pregnancy Notification Form. Information on the outcome of the pregnancy will be collected on the Pregnancy Outcome Form. If a congenital abnormality/birth defect or neonatal death (occurring within 28 days of delivery) is observed, then an SAE Form must also be completed in compliance with the SAE reporting procedure (as per section 9.5 above).

The participant will be withdrawn from trial treatment, but not from follow-up. Follow-up will be as described in the protocol.

10. DATA HANDLING AND RECORD KEEPING

10.1. Source Data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. In order to allow for the accurate reconstruction of the trial and clinical management of participants, source data will be accessible and maintained at the study sites.

Source data is kept as part of the participants' medical notes generated and maintained at site. This will include notes made by local research team and also notes made by the blinded assessors, the latter which should be scanned and sent to the participant's site for retaining in the participant's medical notes. For this study, the participant electronic completed questionnaires will also be regarded as source data.

Table 7: Source data in SNAPPER

Data	Source
Participant Self-Reported Forms	The original participant-completed electronic form is the source data and will be entered directly into the Trial database.

(AADHD QOL, AUDIT, CTQ, DAST-10, DERS-16, EQ-5D-5L, ICECAP-A, MARS and medication self-report)	
Clinical Reported Forms (Adverse Event Scale, CAARS-O, modified CSRI, FAST, LIFE, PANSS, WRAADS-Interview)	The original completed electronic form is the source data and entered directly into the Trial database.
Supporter Self-Reported Forms EQ-5D-5L and ICECAP-A	The original participant-completed electronic form is the source data and will be entered directly into the Trial database.
Clinical event data including AEs	The original clinical annotation is the source document. This may be found on clinical correspondence, or electronic or paper participant records. Clinical events reported by the participant, either in or out of clinic (e.g. phone calls), must be documented in the medical records.
Health Economics	Often obtained by interview directly with the participant in addition information obtained from the participant's medical record for transcription onto the CRF. The CRF is source data.
Recruitment	The original record of the participant's randomisation is the source. It is held on BCTU servers as part of the randomisation and data entry system.
Registration	The original record of the supporter's registration is the source. It is held on BCTU servers as part of the data entry system.
Participant withdrawal	Where a participant expresses a wish to change their level of participation, the conversation must be recorded in the medical records.
Supporter withdrawal	The supporter's 'OPT-OUT' notification is the source. It is held on BCTU servers as part of the data entry system.

10.2. Case Report Form (CRF) Completion

The CRFs will include (but will NOT be limited to) the following forms (Table 8).

Table 8: 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 & 9 Month Assessments: Clinical Form	At 3 & 9 month assessments	As soon as possible after completion	Site
(F5A) 6 & 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 & 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 & 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 section 8.3)	Site
(F8) Serious Adverse Event CRF	On becoming aware of an SAE	If expedited: emailed within 24 hours 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 & 12 Month Form	After registration at baseline and then at the 6 & 12 month time-points	As soon as possible after completion	Supporter

An electronic CRF is required and relevant forms should be completed for each individual participant. All electronic forms must be completed, signed and dated and submitted online to the Trials Office by the research team (as delegated on the SNAPPER **Site Delegation Log**) within the timeframe listed above.

It is the responsibility of the PI to ensure the accuracy of all data entered in the CRFs. This will be evidenced by the signature of the PI on each completed CRF. The **Site Delegation Log** will identify all those personnel with responsibilities for data collection.

The delegated staff completing the CRF should ensure the accuracy, completeness and timeliness of the data reported. This will be evidenced by signing and dating the CRF.

Data reported on each form will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried. Staff delegated to complete CRFs will be trained to adhere to SNAPPER working instructions.

The following guidance applies to data:

- Only those paper CRFs provided by the Trial Office should be used as a guide to complete the electronic forms.
- Time format and unknown times – all times should be in accordance with the 24hr clock.
- Rounding conventions – rounding should be to the nearest whole number: If the number you are rounding is followed by 5, 6, 7, 8, or 9, round the number up. **Example**: 3.8 rounded to the nearest whole number is 4. If the number you are rounding is followed by 1, 2, 3 or 4, round the number down. **Example**: 3.4 rounded to the nearest whole number is 3.
- Trial-specific interpretation of data fields – where guidance is needed additional information will be supplied.

- Entry requirements for concomitant medications (generic or brand names) – generic names should be used where possible.
- Missing/incomplete data – should be clearly indicated – all blank fields will be queried by the Trial Office.
- Repeat laboratory tests – the data used to inform clinical decisions should always be supplied. If a test is repeated it is either to confirm or clarify a previous reading. Confirmatory tests should use the original test values.
- Protocol and GCP non-compliances should be reported to the Trials Office on discovery.
- For all changes made, an explanation must be given next to the change in the space provided

In all cases it remains the responsibility of the PI to ensure that the CRF has been completed correctly and that the data are accurate. This will be evidenced by the electronic signature of the PI on the CRF.

A member of the local research team will complete the assessment schedules with participants by using a tablet computer provided by the Trial Office for data entry. This eCRF will facilitate data entry into the trial database. Supporter QOL data will be collected via a link sent to the supporter's email or mobile phone number, unless a face-to-face meeting is requested.

10.3. Participant Completed Questionnaires

The CTQ, AADHD QOL, AUDIT, DAST-10, DERS-16, EQ-5D-5L, ICECAP-A and MARS are participant reported and will be completed by the participant electronically online either in their own setting, or at clinic using the tablet computer with the local research team overseeing completion and providing support if necessary. Prompts for missing data will be built into the electronic questionnaires encouraging participants to complete all missing fields. Checks for missing data will also be done at the visit by the local research team reviewing the questionnaire for completeness.

10.4. Data Management

Processes will be employed to facilitate the accuracy and completeness of the data included in the final report. These processes will be detailed in the trial specific Data Management Plan and include the processes of data entry, data queries and self-evident corrections on trial data.

Data entry will be completed electronically by the sites in addition to the participants and supporters via a bespoke BCTU trial database (except for SAEs which will be completed on paper and entered by the Trial Office). 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 data clarification forms (DCFs) via the trial database, with the expectation that these queries will be completed by the site within 30 days of receipt. Overdue data entry and data queries will be requested at a frequency and intensity stipulated in the Data Management Plan. The participant completed questionnaires are patient reported outcomes and therefore, a data query process cannot be implemented. However, the questionnaires should be checked by the research staff for completeness and to ensure participants are asked to fill in any missing data items.

All data will be handled in accordance with the Data Protection Act 2018.

CRFs may be amended and the versions updated by the Trial Office, as appropriate, throughout the duration of the trial. Whilst this may not constitute a protocol amendment, new versions of the CRFs must be implemented by Investigator sites immediately on receipt.

10.5. Self-evident corrections

The following self-evident corrections will be permitted by the Trial Office:

- **Contingent fields:** When a response to a question determines, to a degree, the response required by a second question, then conflicts in the responses can be resolved by the data entry clerk. E.g. Has the person had procedure "x"? If yes, state type. If the response to the first question is "no", yet the type of procedure is stated, it is self-evidently true that the initial response was incorrect.
- **Changes to administrative notes and reference numbers:** when new information becomes available such that a reference number does not accurately reflect the sequence of CRFs received e.g. an SAE form is received for an incident which occurred prior to an already reported incident, then it is appropriate to change the reference number provided no DCFs have been raised using the original number. Similarly, any notes relating to the patient care which have an impact on the administration process, but not the data fields themselves, can be changed as appropriate.

10.6. Data Security

The University of Birmingham (UoB) has policies in place, which are designed to protect the security, accuracy, integrity and confidentiality of Personal Data.

The trial will be registered with the Data Protection Officer at UoB and will hold data in accordance with the Data Protection Act (2018 and subsequent amendments). The Trial Office has arrangements in place for the secure storage and processing of the trial data which comply with UoB policies.

The Trial Database System incorporates the following security countermeasures:

- Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.
- Logical measures for access control and privilege management: including restricted accessibility, access-controlled servers, separate controls of non-identifiable data.
- Network security measures: including site firewalls, antivirus software and separate secure network protected hosting.
- System Management: the System will be developed by the Programming Team and will be implemented and maintained by the Programming Team.
- System Design: the System will comprise of a database and a data entry application with firewalls, restricted access, encryption and role based security controls.
- Operational Processes: the data will be processed and stored within BCTU.
- System Audit: the System will benefit from the following internal/external audit arrangements:
    - Internal audit of the System
    - Periodic IT risk assessment
- Data Protection Registration: UoB's Data Protection Registration number is Z6195856.

10.7. Archiving

It is the responsibility of the PI to ensure all essential trial documentation and source documents (e.g. signed ICFs, ISFs, participants' hospital notes, CRFs etc.) at their site are securely retained for at least 25 years. Archiving will be authorised by BCTU on behalf of UoB following submission of the

end of trial report. No documents should be destroyed without prior approval from the BCTU director or their delegate.

The TMF will be stored at BCTU under controlled conditions for at least 3 years after the end of the study. Long-term offsite data archiving facilities will be considered for storage after this time; data will be stored for at least 25 years. BCTU has standard processes for both hard copy and computer database legacy archiving.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Site Set-up and Initiation

All PIs will be asked to sign the necessary agreements including a **Site Delegation log** between the PI and BCTU/Sponsor and supply a current CV and GCP certificate. All members of the site research team are required to sign the **Site Delegation Log**, which details which tasks have been delegated to them by the PI. The **Site Delegation Log** should be kept up to date by the PI. It is the PI's responsibility to inform the Trial Office of any changes in the site research team.

Prior to starting recruitment, each recruiting site will undergo a process of site initiation, either a meeting or a teleconference, which key members of the site research team are required to attend, covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an ISF containing essential documentation, instructions, and other documentation required for the conduct of the trial.

11.2. Monitoring

The central and on-site monitoring requirements for this trial have been developed in conjunction with the trial specific risk assessment and are documented in the trial specific monitoring plan.

11.2.1. Onsite Monitoring

For this trial we will monitor all sites in accordance with the trial risk assessment and monitoring plan. Any monitoring activities will be reported to the Trial Office and any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered, for example by poor CRF return, poor data quality, low SAE reporting rates, excessive number of participant withdrawals or deviations (also defined in the monitoring plan). PIs and site research teams will allow the SNAPPER trial staff access to source documents as requested. The monitoring will be conducted by BCTU/UoB staff.

11.2.2. Central Monitoring

The Trial Office will check incoming ICFs and CRFs for compliance with the protocol, data consistency, missing data and timing at a frequency and intensity determined by the Data Management Plan. Sites will be sent DCFs requesting missing data or clarification of inconsistencies or discrepancies.

Sites will be requested to send in copies of signed ICFs and other documentation for central review for all participants providing explicit consent for this. This will be detailed in the monitoring plan.

11.3. Audit and Inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site and provide direct access to source data/documents. The Investigator will comply with these visits and any required follow up. Sites are also requested to notify the Trial Office of any relevant inspections or local audits.

11.4. Notification of Serious Breaches

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments, the Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of the conditions and principles of GCP in connection with the trial or of the protocol relating to the trial within 7 days of becoming aware of that breach.

For the purposes of this regulation, a "serious breach" is a breach which is likely to affect:

- the safety or physical or mental integrity of the participants of the trial;
- the scientific value of the trial.

Sites are therefore requested to notify the Trial Office of any suspected trial-related serious breach of GCP and/or the trial protocol as soon as they become aware of them. Where the Trial Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Trial Office in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment.

12. END OF TRIAL DEFINITION

The end of trial will be the date of the last data capture including resolution of DCFs. This will allow sufficient time for the completion of protocol procedures, data collection and data input. The Trial Office will notify the REC, MHRA and the Sponsor within 90 days of the end of trial. Where the trial has terminated early, the Trial Office will notify the MHRA and REC within 15 days of the end of trial. The Trial Office will provide the REC, MHRA and the Sponsor with a summary of the clinical trial report within 12 months of the end of trial.

13. STATISTICAL CONSIDERATIONS

13.1. Sample size

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 [54], [55], the sample size required would be182 ($(1-0.3^2)*200$). Accounting for 25% loss to follow-up [56], [57], 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 [54], and is considered to represent a clinically meaningful difference between stimulants vs. non-stimulant for ADHD symptoms.

13.2. Analysis of outcomes

There is no specific target sample size for supporters since the supporter outcomes are being used in the economic analysis, where power calculations are not used. Nevertheless, the more supporters that are recruited, the greater the precision of our estimates and the more we reduce any potential bias due to sample unrepresentativeness.Analysis of outcomes

A separate Statistical Analysis Plan will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of these analyses is given below.

The primary comparison groups will be composed of those randomised to stimulant medication versus those randomised to non-stimulant medication. In the first instance, all analyses will be based on the intention to treat principle, i.e. all participants will be analysed in the treatment group to which they were randomised irrespective of compliance or other protocol deviation.

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. P-values from two-sided tests will be provided for the primary outcome only. Intervention effects will be adjusted for the baseline value (if applicable), and the minimisation and stratification variables listed in section 6.3.1 where possible. All variables will be treated as fixed effects, apart from centre which will be treated as a random effect. No adjustment for multiple comparisons will be made.

13.3. Primary outcome

The primary outcome is ADHD symptoms at 6 months post-randomisation measured by the CAARS-O. Mixed effects linear regression methods will be used if the outcome is sufficiently normally distributed (or where data can be suitably transformed). Adjusted mean differences and 95% confidence intervals will be presented.. The p-values from the associated tests of the final models will be presented.

13.4. Secondary outcomes

Analysis will be performed as per the primary outcome for all continuous secondary outcomes (e.g. emergence of hypomania/mania measured using LIFE, ADHD specific quality of life assessed by Adult ADHD QOL) at each time-point.

For binary outcomes (e.g. education (yes/ no), employment (yes/ no)), the number and percentage of participants reporting each outcome will be reported by group. A logistic regression model, using a logit link function will be used, followed by the marginal standardisation approach for covariate adjustment [58] to calculate an adjusted risk ratio and an adjusted risk difference (and their corresponding 95% confidence intervals). If the event rate is zero in one strata of a covariate used in the model adjustment, this covariate will be excluded from the model.

13.5. Planned Subgroup Analyses

Subgroup analyses will be limited to the primary outcome only and undertaken to investigate any differential treatment effect forfor the following: whether the participant had a history of bipolar or psychosis; and based onon the number of previous acute care episodes (as used in the minimisation algorithm). Tests for statistical heterogeneity (e.g. by including the treatment group by subgroup interaction arameter in the regression model) will be presented alongside the effect estimate and 95% confidence interval within subgroups. The results of subgroup analyses will be treated with caution and will be used for the purposes of hypothesis generation only.

13.6. Missing Data and Sensitivity Analyses

Every attempt will be made to collect full 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 methods such as multiple imputation. Full details will be included in the SAP.

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 each of the three adherence measures given in section 7.7. Details regarding the definition of adherence will be included in the SAP.

13.7. Interim analysis

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 SAP. Further details of DMC arrangements are given in section 15.5.

13.8. Planned final analyses

The primary analysis for the trial will occur once all participants have completed the 12 month assessment and corresponding outcome data has been entered onto the trial database and validated as being ready for analysis. This analysis will include data items up to and including the 12 month assessment and no further.

14. ECONOMIC EVALUATION

A separate Health Economic Analysis Plan will be produced and will provide a more comprehensive description of the planned economic analyses. A brief outline of these analyses is given below.

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, if there is sufficient 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.

14.1. Within-trial economic evaluation

Reduction in ADHD symptom severity is the primary outcome of the clinical trial, and therefore we will evaluate the cost-effectiveness in terms of the cost per case of a reduction in the CAARS-O [38] measure of 4 points. The use of QALYs as an outcome allows the comparison of the results across different diseases and interventions using a common threshold value for cost per QALY. Participants will be given the EQ-5D-5L [59] to complete at baseline and 6 months. As changes in patients' symptoms may affect carer wellbeing [60], we will ask trial participants to nominate a supporter and

collect EQ-5D-5L outcomes from those individuals too. EQ-5D 5L responses will be converted to utility scores using the crosswalk algorithm [61] as recommended by NICE [62] unless guidance on the most appropriate value set is updated before analysis is undertaken. Healthcare resource use will be collected at follow-up assessment, when patients will be asked to recall visits to health professionals, medications and admissions. This will be recorded on a modified version of the Client Service Receipt Inventory (CSRI) [51], as is common in mental health evaluations. The information provided will be checked by the RAs who will search patients' electronic patient records. Resource use will be costed using national sources (i.e. PSSRU for healthcare contacts) [63].

Mean costs and outcomes will be estimated for both trial arms and non-parametric bootstrapping will be used to estimate 95% confidence intervals around differences in mean costs, EQ-5D scores and QALYs. In the base case, where there is missing cost and outcome data, multiple imputation will be used. EQ-5D-5L scores will be used to generate QALYs using the area under the curve approach. Imbalances in baseline utility (EQ-5D-5L scores) between trial arms will be controlled for using a regression approach. Incremental cost-effectiveness ratios (ICERs) will then be calculated. Cost-effectiveness acceptability curves will be used to plot the probability of each intervention being cost-effective at different thresholds of willingness to pay per additional unit of outcome.

Methodological sensitivity analysis will be conducted, to improve the rigour and value of the economic analysis. In view of US panel recommendations that economic analyses adopt a two-perspective approach [64], we will broaden the perspective to society. In view of the limits of the EQ-5D-5L in mental health [65] and for carers [60], we will additionally consider capability-wellbeing, rather than health as the unit of outcome. To take a societal perspective, non-healthcare related resource use additionally collected as part of the CSRI (employment and criminal justice costs [52]) will be included and valued using published sources. To analyse cost-effectiveness in terms of improving wellbeing, we will replace cost-per-QALY with cost-per-YFC (year of full capability) [46] as the metric for assessing cost-effectiveness. Years of full capability will be based on ICECAP-A capability data [45] collected from patients and their supporter, alongside the EQ-5D-5L data.

14.2. Model-based economic evaluation

If there is evidence from the trial that differences between the two drugs exist in terms of symptom reduction for ADHD as well as other outcomes that may have significant cost or outcome implications beyond the trial period, a model-based economic evaluation will also be conducted. The model structure will be informed by reviewing previous modelling studies and also consulting clinical experts within the team.

To parameterise the model, we will utilise clinical and economic evidence collected as part of the trial and other secondary sources. The cost-utility (cost per QALY) analysis will be conducted from the NHS/PSS perspective, using a lifetime horizon and discount rates of 3.5% for costs and outcomes [66]. Deterministic and probabilistic sensitivity analyses will be conducted to explore the robustness of the results to plausible variations in key assumptions and variations in the analytical methods used, and to consider the broader issue of the generalisability of the results. Cost-effectiveness acceptability curves will be used to reflect sampling variation and uncertainties in the appropriate threshold cost-effectiveness value. All methods and analyses will be reported as recommended by the CHEERS reporting guidelines [67].

15. TRIAL ORGANISATIONAL STRUCTURE

15.1. Sponsor

The Sponsor for this trial is University of Birmingham (UoB).

15.2. Coordinating Centre

The trial coordinating centre (Trial Office) is Birmingham Clinical Trials Unit, based at UoB.

15.3. 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. The TMG are listed at the front of the protocol. Their 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.

15.4. 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, health economist and a patient representative.

The TSC will operate in accordance with a trial specific TSC Charter. Membership and duties/responsibilities will be outlined in the TSC Charter. In summary, the TSC will provide overall oversight of the trial including the practical aspects of the trial and ensure the trial is run in a way which is both safe for the participants and provides appropriate data to the Sponsor and funder. The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee.

The TSC will meet at the start of the trial, prior to recruitment of any patients and then will aim to meet at least bi-annually thereafter by tele/video-conference, at face-to-face meetings or via e-mail communication of updates of reports.

15.5. Data Monitoring Committee

Data analyses will be supplied in confidence to an independent Data Monitoring Committee (DMC), which will meet prior to trial commencement to agree 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.

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC may consider recommending the discontinuation of the trial if any issues are identified which may compromise participant safety. The DMC may recommend early stopping of the trial if the interim analyses shows differences between treatments that are deemed to be convincing to the clinical community. Further details on the trial stopping guidelines will be outlined in the DMC Charter and the Statistical Analysis Plan.

15.6. Finance

The research costs of the trial are funded by a National Institute for Health Research (NIHR) Health Technology Assessment (HTA) grant, reference NIHR129817, awarded to Professor Steven Marwaha at UoB. The trial has been designed to minimise extra 'service support' costs for participating hospitals as far as possible. Additional costs, service support costs and excess treatment costs associated with the trial, e.g. gaining consent, are estimated in the Statement of Activities. These costs should be met by accessing the Trust's Support for Science budget via the Local Comprehensive Research Network.

16. ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and applicable UK Acts of Parliament and Statutory Instruments (and relevant subsequent amendments), which include, but are not limited to, the Medicines for Human Use (Clinical Trials) Regulations 2004 and the Data Protection Act 2018.

This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use (Clinical Trials) Regulations and according to the Principles of GCP as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments).

The protocol will be submitted to and approved by the REC, MHRA and Health Research Authority (HRA) prior to circulation and the start of the trial. All correspondence with the REC, MHRA and HRA will be retained in the TMF/ISF, and an annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given by the REC, and annually until the trial is declared ended. A trial-specific risk assessment and monitoring plan will be developed before submission to the REC and will be reviewed regularly during the trial.

Before any participants are enrolled into the trial, the PI at each site is required to obtain the necessary local R&D approval. Sites will not be permitted to enrol participants until written confirmation of R&D approval/assurance is received by the Trials Office.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

17. CONFIDENTIALITY AND DATA PROTECTION

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 (and subsequent amendments).

Participants will only be identified by their unique trial identification number and initials on CRFs and on any correspondence with the Trial Office. For all participants full name, full date of birth, gender and NHS/CHI number will be collected on the Randomisation Form. The participant's full name will also be collected on the participant consent forms in addition to their email address and/or mobile number. For supporters, their full name and email and/or mobile number will be collected on the Supporter ICF. Their initials, age category (categories between 18 to 71+ years), gender, will be collected on the Self- Registration Form. Participants and supporters will give their explicit consent

for the storage of their consent form, on the trial database at BCTU. This will be used to perform in-house monitoring of the consent process.

The PI must maintain documents not for submission to the Trial Office (e.g. **Participant Recruitment and Identification Logs**) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

BCTU will maintain the confidentiality of all participant 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.

18. FINANCIAL AND OTHER COMPETING INTERESTS

There are no financial or other competing interests related to the results of this trial. Members of the TSC and DMC are required to provide declarations on potential competing/conflicts of interests as part of their membership of the committees. Authors are similarly required to provide declarations at the time of submission to publishers.

19. INSURANCE AND INDEMNITY

UoB has in place Clinical Trials indemnity coverage for this trial which provides cover to UoB for harm which comes about through UoB's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at UoB's discretion, provide cover for non-negligent harm to participants.

With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

UoB is independent of any pharmaceutical company and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

20. POST-TRIAL CARE

The intervention will stop at 6 months after randomisation. Whether to continue with the Lisdexamfetamine or Atomoxetine at this stage will be a decision made collaboratively between the participant and their clinical team.

21. ACCESS TO FINAL DATASET

The final dataset will be available to members of the Trial Management Group 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) any of the following: The Trial Sponsor, the relevant Trial Management Group (TMG), and independent TSC.

A formal Data Sharing Agreement (DSA) may be required between respective organisations once release of the data is approved and before data can be released. Data will be fully de-identified (anonymised) unless the DSA covers transfer of patient identifiable information. Any data transfer will use a secure and encrypted method.

22. PUBLICATION POLICY

Any abstracts and presentations will be circulated to the TMG members for comment prior to submission to NIHR. These will be discussed at the TMG meetings or via written communication, e.g. email.

On completion of the trial, the data will be analysed, and a Final Study Report will be prepared. Results of this trial will be submitted for publication in a peer reviewed journal which will be accessible via the trial website. Manuscripts will be prepared by the writing group as defined in the trial publication plan. Any secondary publications and presentations prepared by Investigators must be reviewed and approved by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of NIHR HTA, UoB and BCTU. Intellectual property rights will be addressed in the Clinical Trial Site Agreement between Sponsor and site.

Results will also be sent to all participating centres who will notify the participants recruited from their site. Participants will be invited to discuss the study results with the local research team.

23. APPENDIX 1

Reproduced below are the details of the commissioned call 19/34 from the NIHR HTA Programme, *Medication for ADHD in adults with a history of psychosis or bipolar disorder*.

Research Question:

What is the clinical and cost-effectiveness of stimulant compared with non-stimulant medication for adults with attention deficit hyperactivity disorder (ADHD) and a history of psychosis or bipolar affective disorder?

1. Intervention: ADHD stimulant medication - to be defined and justified by applicants, including dose and regimen.

2. Patient group: Adults with ADHD and a history of psychosis or bipolar affective disorder - exact inclusion criteria to be defined and justified by applicants. Consideration should be given to any concurrent psychiatric medication.

3. Setting: Appropriate setting/s to be defined by applicants.

4. Comparator: ADHD non-stimulant medication - to be defined and justified by applicants, including dose and regimen.

5. Study design: Randomised controlled trial(s). The study/studies should be powered to examine the effect of stimulant vs non-stimulant medication on each of the comorbid populations. Applicants to decide whether 1 or 2 protocols are required. There should be an internal pilot phase to test ability to recruit and randomise, and clear stop/go progression criteria to the full trial(s).

6. Important outcomes: ADHD symptoms.

Other outcomes: Adverse effects including emerging psychotic/manic/hypomanic symptoms as appropriate; health related quality of life, occupational and functional outcomes, substance misuse, cost-effectiveness of ADHD medication.

7. Minimum duration of follow-up: One year.

Longer-term follow up: If appropriate, researchers should consider obtaining consent from participants to allow future follow up through efficient means (such as routine data) as part of a separately funded study.

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