Stimulant Medication for ADHD and Tics - Understanding Response versus Non-stimulants (SATURN): a randomised trial of the clinical and cost-effectiveness of methylphenidate versus guanfacine for ADHD in children and young people with a co-existing tic disorder

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SYNOPSIS

Title	Stimulant Medication for ADHD and Tics - Understanding Response versus Non-stimulants (SATURN): a randomised trial of the clinical and cost-effectiveness of methylphenidate versus guanfacine for ADHD in children and young people with a co-existing tic disorder
Acronym	SATURN
Short title	Stimulant Medication for ADHD and Tics - Understanding Response versus Non-stimulants
Chief Investigator	Professor Chris Hollis
Objectives	**Aim**: To understand whether stimulant (Modified-Release Methylphenidate) or non-stimulant (Guanfacine Extended-Release) medication is most effective for treating children and young people who are experiencing both Attention Deficit Hyperactivity Disorder (ADHD) and tics. **Primary objective**: To test whether Modified-Release Methylphenidate (MR-MPH) compared with Guanfacine Extended-Release (Guanfacine XR) is: 1. superior for ADHD symptoms at 12 weeks post randomisation: MR-MPH should result in a clinically important improvement in ADHD symptoms. 2. non-inferior for tics at 12 weeks post randomisation: MR-MPH should not result in a clinically important worsening with respect to tics. **Secondary objectives:** i. To determine the effect of MR-MPH compared with Guanfacine XR on ADHD symptoms and tic severity at 24- and 52-weeks post randomisation ii. To assess the relative effectiveness of MR-MPH compared with Guanfacine XR on the global measure of clinical functioning and physical measures iii. To compare the relative cost-effectiveness of the two medications iv. To assess adherence to the interventions

	v. To compare the safety of the interventions
Trial Configuration	Two-arm parallel group randomised controlled trial.
Setting	NHS Children and Adolescent Mental Health Services (CAMHS) and community paediatric clinics in England. Recruitment will take place within three regional hubs.
Sample size estimate	***Tics*** Based on a non-inferiority margin in tic symptoms on the Yale Global Tic Severity Scale (YGTSS) Total Tic Severity Scale (TTSS) [1] of 0.4 standard deviations (SDs) (~2.6 units on TTSS, assuming SD=6.6) with 90% power, 1:1 allocation ratio, and one-sided 2.5% significance level, 133 participants per arm are required for analysis. Allowing for missing primary outcome data of up to 15%, 314 randomised participants are required in total. ***ADHD*** 133 participants per group for analysis achieves 90% power to detect a minimum clinically important difference of 0.4 SDs (equivalent to a between-group difference in mean rating-per-item score of 0.28, assuming item SD of 0.7) on Swanson, Nelson and Pelham questionnaire SNAP-IV 18 item scale [2].
Number of participants	314 participants (157 per arm)
Eligibility criteria	***Inclusion criteria for the child or young person*** • Aged ≥6 years up to <17 years at randomisation. • Confirmed diagnosis of ADHD at point of randomisation (ADHD DSM-5) (following review of all available information including the DAWBA). • Mild-moderate tics: Score >5 on the Yale Global Tic Severity Scale (YGTSS) Total Tic Severity Score (TTSS) [1] . • Referred to CAMHS or paediatric services taking part in the trial. • Parent/carer and Child/Young Person (CYP) seeking medication for ADHD (either ADHD medication naïve or seeking medication change). • Willing to adhere to the trial procedures. • If currently or recently on a different medication for ADHD or tics willing to go through or complete the appropriate wash-out period (as per standard care) to be able to receive the allocated trial IMP. • Able to give valid, informed assent (aged <16) or consent (aged 16). • Able to understand and complete assessments in English. • Eligible parent/carer willing and able to participate alongside the CYP. ***Inclusion criteria for the parent/carer*** • Individual with parental responsibility. • Individual with sufficient knowledge of CYP's medical history to be able to complete the relevant assessment tools. • Access to reliable internet connection and email.

	• Able to give valid, informed consent. • Able to speak, understand and complete assessments in English. **Exclusion criteria for the child or young person** • Current pharmacotherapy for tics and unwilling/unable to discontinue to begin trial medication. • Current pharmacotherapy for ADHD and unwilling/unable to discontinue to begin trial medication • A documented history of prolonged QTc or risk factors for torsade de pointes. • Abnormal cardiovascular examination (e.g., BP>95th percentile, tachycardia). • Diagnoses of alcohol/substance dependence, psychosis or mania (as per clinician judgement). • Suicidal tendency and risk (assessed by the referring clinician). • Intellectual disability (clinical estimate of IQ<70) (confirmed by Child and Adolescent Intellectual Disability Screening Questionnaire; CAIDS-Q [3] or alternative full cognitive assessment e.g. WISC). • Contraindications to MR-MPH and/or Guanfacine XR. • Immediate risk to self or others. • Individual who is, or is planning to become, pregnant. • Individual who is breastfeeding. ***Exclusion criteria for the parent/carer*** • Local authority representative of CYP.
Description of interventions	**Intervention:** Stimulant medication (once daily MR-MPH). **Comparator:** Non-stimulant medication (once daily Guanfacine XR).
Duration of trial	The recruitment period for the trial is scheduled for 24 months. The treatment period (from randomisation to end of follow-up) is 52 weeks (approximately 12 months). The overall duration of the trial is 50 months.
Randomisation and blinding	Eligible patients who consent (age under 16: parental consent, young person's assent; age 16+: parental consent, young person's consent) will be randomly assigned a treatment with a 1:1 allocation ratio. Dynamic randomisation will use a probabilistic minimisation algorithm to balance across groups by site, tic severity (based on the YGTSS-TTSS 0–50 scale minimal-mild symptoms <20 vs moderate-severe symptoms ≥20) and previous treatment for ADHD (vs treatment naïve). Interventions will be prescribed open-label. Participants, their parents/carers and research clinicians will be aware of treatment allocated. Follow-up assessors will be blinded to allocation throughout the trial.
Outcome measures	***Primary***

	ADHD symptoms measured using SNAP-IV [2] at 12 weeks, and tic severity measured using YGTSS (TTSS) [1] at 12 weeks are joint primary outcomes ***Secondary*** *Clinical* • ADHD symptoms measured using SNAP-IV [2] at 24 and 52 weeks • Tics severity measured by YGTSS (TTSS) [1] at 24 and 52 weeks • Global measure of clinical functioning: CGI-I at weeks 4, 8, 12, 24 and 52 and, CGI-S [4] at 1), 4, 8 12, 24 and 52 weeks • Tic subscale scores (Total Phonic and Total Motor) measured by YGTSS [1] at 12, 24 and 52 weeks *Safety* • Medication adverse events at 1–12, 24 and 52 weeks via Hill and Taylor questionnaire *Quality* of life • Child health-related quality of life: CHU-9D [5], EQ-5DY [6] at 12, 24 and 52 weeks • Parent health-related quality of life: EQ5D-5l [7] at 12, 24 and 52 weeks
Statistical methods	Each primary outcome comparison will be analysed without multiplicity adjustment since the success of the intervention will be concluded only if the stimulant medication is shown to be superior for ADHD symptoms and non-inferior for tic severity. For SNAP-IV, the between group difference at 12 weeks will be calculated using mixed-effect model, adjusting for site as a random effect and baseline score and other minimisation factors as fixed effects. Primary between-group comparisons for this outcome will be based on intention-to-treat (ITT), analysing participants in the groups to which they were randomised. For tic symptoms (TTSS), a two-sided 95% confidence interval (CI) (equivalent to a one-sided 97.5% CIfor the difference in TTSS score at 12 weeks between the two groups will be constructed using mixed-effect model, adjusting for site as a random effect and baseline TTSS score and other minimisation factors as fixed effects. Non-inferiority of MR-MPH for tic worsening will be inferred if the lower bound of this interval lies within the non-inferiority margin of 2.6 points. Both ITT and per-protocol analyses will be performed for this outcome, with primary inference based on ITT, and per-protocol results used to check consistency. Between-group comparison of secondary outcomes will be based on an appropriate regression for the outcome adjusted for the minimisation factors and baseline outcome measure for continuous variables, if available. A full statistical analysis plan will be developed and approved with the Trial Steering Committee (TSC) prior to database lock.

Health economics	Outcome Child/young person health-related quality of life. Parent/carer health-related quality of life. Resource Use Data will be collected on health care resource use, including education and social care. Analysis: The costs and benefits will be analysed using Marginal Net Benefit approach and Cost Effectiveness planes. Cost effectiveness acceptability curves will be determined between the control and the intervention group.

ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
BNF	British National Formulary
CAMHS	Child and Adolescent Mental Health Services
CEAC	Cost Effectiveness Acceptability Curve
CI	Chief Investigator
CRF	Case Report Form
CYP	Child and Young Person
DAP	Data Analysis Plan
DAWBA	Development and Well-Being Assessment
DIRUM	Database of Instruments for Resource Use Measurement
DMC	Data Monitoring Committee
DMP	Data Management Plan
DSUR	Development Safety Update Report
EAGG	European ADHD Guideline Group
EOT	End Of Trial
GCP	Good Clinical Practice
HTA	Health Technology Assessment
ICF	Informed Consent Form
MHRA	Medicines and Healthcare products Regulatory Agency
MR-MPH	Modified-Release Methylphenidate
NCTU	Nottingham Clinical Trials Unit
NHS	National Health Service
NIHR	National Institute for Health Research
NMB	Net Monetary Benefit
OCBP	(Referring to participants) Of Child Bearing Potential
PI	Principal Investigator
PIC	Patient Identification Centre
PIS	Participant Information Sheet
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-Adjusted Life-Years
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development department
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SIL	Summary Information Leaflet (for parent/carer)
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
XL	Extended-Release (it refers to commercial names of MR-MPH medication)
XR	Extended-Release (it refers to Guanfacine)

1. TRIAL BACKGROUND INFORMATION AND RATIONALE

Approximately 3-5% of children and young people (CYP) in the UK have ADHD [8]. CYP with ADHD find that they struggle to pay attention, have higher than usual levels of energy and restlessness and their behaviour can be impulsive or unpredictable. This can sometimes lead to a young person with ADHD finding it difficult to achieve and fit in at school or to maintain and find employment. This may result in dependence on drugs, alcohol, other substances as well as crime and anti-social behaviour as an expression of how they are feeling [9]. This can lead to further mental health struggles as well as other consequences of their actions.

Around 1 in 5 CYP with ADHD also experience chronic tics [10], which consists of uncontrolled, sudden movements and sounds. This may sometimes lead to the person feeling isolated and hopeless, and with many experiencing bullying or social exclusion. These feelings can sometimes result in self-harm and the person may start to experience more mental health struggles [10]. Prompt treatment is crucial to help the person cope and reduce the burden on the family and wider social and healthcare systems.

Medication for ADHD is highly efficacious, at least in the short term [11]. NICE guidelines (NG87) [8] recommend that the first-line medication in children and adolescents is methylphenidate, which is a stimulant. However, there is concern amongst clinicians that using stimulant medication to treat young people with ADHD and tics may make the young person's tics worse. As a result of this, many clinicians avoid using stimulants and prefer to prescribe non-stimulant medication, which may be less effective for treating the ADHD symptoms [11].

A recent Cochrane systematic review [12] found eight randomised controlled trials (RCTs) (n=510) of pharmacological treatments for ADHD with tics. There was low/very low quality evidence that methylphenidate, clonidine, guanfacine, desipramine and atomoxetine reduced ADHD symptoms in children with co-existing ADHD and tics. The quality of the evidence was rated as low/very low due to concerns around unclear or selective reporting and imprecision. These concerns will be addressed in the SATURN trial by reporting all the Cochrane Risk of Bias items in a transparent way and according to a pre-established protocol and by using a powered sample. The authors of the Cochrane review noted that although stimulants have not been shown to worsen tics in most people with tic disorders, they may exacerbate tics in individual cases. In these circumstances, they suggested alternative treatments with alpha agonists (clonidine or guanfacine) or atomoxetine. In summary, there was no conclusive trial evidence that stimulants increase tics any more than placebo [12]. However, based on the information available to the trial team at the point of writing, there are no adequately powered head-to-head trials that have directly compared the effects of stimulant with non-stimulant medication in CYP with co-existing ADHD and tics.

Methylphenidate (MPH) is the most commonly prescribed stimulant medication and the first-line choice recommended by the National Institute for Health and Care Excellence (NICE) for ADHD in CYP [8]. However, there remains clinical uncertainty, and equipoise, regarding the best choice of medication (i.e. methylphenidate or guanfacine) in CYP with both ADHD and tics. The rationale of the trial is to answer this clinical question and provide treatment guidance specific to CYP with co-morbid ADHD and tics.

The risk/ benefit analysis for participants entering the trial is favourable. All participants will receive a NICE [NG87] recommended and licenced treatment for ADHD in line with dose guidelines set out in the BNF. The risk of potential adverse effects with these licenced medications is low is has been deemed as acceptable by both regulators and NICE. In this trial, all participants will receive routine monitoring for adverse events at a frequency

comparable to, or greater than, that which occurs in standard clinical practice [13] .In SATURN, once-daily modified release (MR) is preferred to immediate release, multiple day, dose regimens for convenience and adherence. In standard clinical practice, supported by national guidelines [14] extended-release methylphenidate preparations are generally preferred to immediate release during the initiation and titration phase as extended-release allows once daily dosing (lasting between 6-10 hours) which is more convenient than multiple immediate release doses (lasting only up to 4 hours). Extended-release also ensures better adherence and avoids the difficulties of taking a controlled drug into school for midday and afternoon doses, which are required with an immediate release (short acting) preparation. While there is no difference in the risk of adverse effects between extended- and immediate release preparations, immediate release preparations do carry a greater risk of drug diversion and misuse. Hence, the preference of clinicians, parents and children in this trial is to use extended-release methylphenidate. Participants and clinicians will be offered a choice of MR-MPH formulation to closely mirror NICE Guidance (NG87) [8].

Guanfacine XR is recommended by NICE for ADHD treatment in CYP [8] and as a first-line treatment for tic disorder – when medication needs to be used [10]. Other non-stimulants include clonidine and atomoxetine.

Atomoxetine, a non-stimulant noradrenergic reuptake inhibitor, is recommended as a second-line treatment for ADHD [8], but there is less evidence compared to guanfacine or clonidine that it improves tics [10]. Because Atomoxetine has different pharmacodynamics to clonidine and guanfacine – results for atomoxetine may not be generalisable to either clonidine or guanfacine. In contrast, results for either clonidine or guanfacine would be more easily generalizable to each other.

Both guanfacine and clonidine are alpha-2 noradrenergic agonists and improve ADHD symptoms and tics. Clonidine is used principally as the first-line drug treatment for tics [10] but is not recommended by NICE [8] as an ADHD treatment and hence, remains an ‘off-label’ treatment for ADHD with co-existing tics. Furthermore, clonidine requires twice or three-times daily dosing which necessitates complex titration and may reduce adherence compared to a once-daily intervention with MR-MPH or Guanfacine XR. Due to the above, Guanfacine XR will be the active ingredient of the medication prescribed to the non-stimulant group.

The SATURN trial aims to compare the clinical and cost effectiveness of stimulant medication (MR-MPH) with nonstimulant medication (Guanfacine XR) (both of which are NICE recommended ADHD treatments [8]), in children and young people with co-existing ADHD and tics to ascertain whether MR-MPH can control ADHD without exacerbating tics.

2. DETAILS OF INVESTIGATIONAL MEDICINAL PRODUCTS

In standard practice, titration of methylphenidate and guanfacine would normally take between 4 to 6 weeks. In this trial we would expect the optimum dose to be reached by 8 weeks at the latest. With methylphenidate and guanfacine, there is no lag effect between dosing and clinical effects therefore, we would expect to see maximal clinical benefit at 12 weeks. Therefore, the primary endpoint will be 12 weeks from randomisation. In order to assess long-term outcomes, the treatment and assessment period (from randomisation to end of follow-up) will be 52 weeks (approximately 12 months).

After the 12-week primary end-point, prescribing management is handed back to the local clinical service. Researchers will follow-up participants up to 52 weeks with an intention to treat parallel-group analysis to assess long-term outcomes. However, the research team are not

requiring participants stay on the IMPs for 52 weeks or longer. The decision to remain on the allocated treatment IMP or to change, or stop treatment, is made by the local clinician in accordance with standard NICE Guidance. Hence, any decision to discontinue mediation as part of evaluating ongoing treatment effectiveness after 12 weeks, will be made by the local clinician (usual care team), not the by the research team and therefore is not part of the protocol.

2.1. Stimulant Medication – Modified-Release Methylphenidate (Intervention)

2.1.1. Description

MPH is the most commonly prescribed stimulant medication and the first-line choice recommended by NICE for ADHD in CYP [8].

Participants randomised to stimulant medication will be prescribed once-daily modified-release methylphenidate (MR-MPH). The dose (mg) is not fixed, and the titration schedule will be tailored to each participant based on clinician judgement of all available information (baseline and/or follow-up measurements and medical history). Dosing for all brands of methylphenidate will follow BNF guidelines.

The commercial names of a few of the most commonly prescribed MR-MPH (active ingredient) medication are, Equasym XL, Medikinet XL and Concerta XL.

Please refer to the Concerta XL SmPC, provided as an example, for detailed information on the drug's chemical and pharmacological properties.

2.1.2. Manufacture

Formulation: Concerta XL, Equasym XL, Medikinet XL or generic equivalent; stepped-dose titration to optimum dose.

Concerta XL has been selected out of the most commonly prescribed medications to be used in this protocol as an example. Other brands, some examples of which have been provided above, may be used. The IMP is defined by its active substance only and all available brands and forms of MR-MPH can be prescribed.

Concerta XL's marketing authorisation holder is Janssen-Cilag Pharma GmbH Ltd, Pfarrgasse 75 A-1232 Wien.

2.2. Non-Stimulant Medication – Guanfacine Extended-Release (Comparator)

2.2.1. Description

Guanfacine XR is recommended by NICE for ADHD treatment in CYP [8] and as a first-line treatment for tic disorder requiring medication [10]. Participants randomised to non-stimulant medication will be prescribed once-daily Guanfacine XR. The dose (mg) is not fixed, and the titration schedule will be tailored to each participant based on clinician judgement of all available information (baseline and/or follow-up measurements and medical history). Dosing for guanfacine extended-release will follow BNF guidelines.

Guanfacine is an alpha-2 noradrenergic agonist and improves ADHD symptoms and tics.

Please refer to the Intuniv™ SmPC, provided as an example, for detailed information on the drug's chemical and pharmacological properties.

2.2.2. Manufacture

Formulation: Intuniv™ stepped dose titration to optimum dose.

Intuniv™'s marketing authorisation holder is Takeda Pharmaceuticals International AG Ireland Branch. The IMP is defined by its active substance only and all available brands and forms of Guanfacine XR can be prescribed.

2.3. Known Side Effects – Intervention (MR-MPH)

Common/Very Common side effects include: Aggression (or hostility); alopecia; anxiety; appetite decreased; arrhythmias; arthralgia; behaviour abnormal; cough; depression; diarrhoea; dizziness; drowsiness; dry mouth; fever; gastrointestinal discomfort; growth retardation; headaches; hypertension; laryngeal pain; mood altered; movement disorders; nasopharyngitis; nausea; palpitations; sleep disorders; vomiting; weight decreased.

Uncommon side effects include: Chest discomfort; constipation; dyspnoea; fatigue; haematuria; hallucinations; muscle complaints; psychotic disorder; suicidal behaviours; tic; tremor; vision disorders.

Rare or very rare include: Anaemia; angina pectoris; cardiac arrest; cerebrovascular insufficiency; confusion; gynaecomastia; hepatic coma; hyperfocus; hyperhidrosis; leukopenia; mydriasis; myocardial infarction; neuroleptic malignant syndrome; peripheral coldness; Raynaud's phenomenon; seizures; sexual dysfunction; skin reactions; sudden cardiac death; thinking abnormal; thrombocytopenia.

Frequency not known: Delusions; drug dependence; hyperpyrexia; intracranial haemorrhage; logorrhea; pancytopenia; vasculitis

Detailed side effects of the different medication containing MR-MPH as their active substance can be found in their SmPC and for participants in the leaflet inside the medication packet.

Reference Safety Information: Refer to the submitted Concerta XL SmPC (used as an example of MR-MPH medication) for the detailed list of side effects. Section 4.8 of the Concerta XL SmPC date of last revision 04 September 2023 will act as the reference safety information for this IMP.

2.4. Known Side Effects – Comparator (Guanfacine XR)

Common/Very Common side effects of guanfacine include: Anxiety; appetite decreased; arrhythmias; asthenia; constipation; depression; diarrhoea; dizziness; drowsiness; dry mouth; gastrointestinal discomfort; headache; hypotension; mood altered; nausea; skin reactions; sleep disorders; urinary disorders; vomiting; weight increased.

Uncommon side effects include: Asthma; atrioventricular block; chest pain; hallucination; loss of consciousness; pallor; seizure; syncope

Rare or very rare include: Hypertension; hypertensive encephalopathy; malaise

Frequency not known: Erectile dysfunction

Reference Safety Information: Refer to the submitted Intuniv™ SmPC for the detailed list of side effects. Section 4.8 of the Intuniv™ SmPC date of last revision 23 February 2022 will act as the reference safety information for this IMP.

2.5. Packaging and Labelling

The Investigational Medicinal Product (IMP)s, have marketing authorisation and will be used in accordance with their authorisation. Therefore, labelling and packaging details are not required as standard pharmacy/clinic supplies will be used.

The allocated IMP will be dispensed to a trial participant in accordance with a prescription given by an authorised healthcare professional and labelled in accordance with the requirements of Schedule 5 to the Medicines for Human Use (SI 1994/31 94) (Marketing Authorisations etc.) Regulations 1994 that apply in relation to relevant dispensed medicinal products.

2.6. Storage, Dispensing and Return

The trial IMPs should be stored appropriately as per the conditions specified in the SmPC of the prescribed medication and should only be accessible to authorised pharmacy/clinic staff. Sites should follow their own local policies for storage and dispensing of medication.

Following randomisation and treatment allocation, trial treatment will be dispensed to participants from standard clinic stocks or their local pharmacy in accordance with the usual dispensing procedures at each site. For trial purposes the medication prescribed, and titration schedule will be recorded on the trial database.

Home storage conditions: Participants should store the IMP they have been allocated to according to the instructions in the enclosed leaflet.

Participants who reach the end of their participation in the trial will be asked to speak to their treating clinician, who will advise whether they should continue on the medication or return it to a local pharmacy for disposal.

3. TRIAL OBJECTIVES AND PURPOSE

3.1. Purpose

To evaluate the clinical and cost-effectiveness of MR-MPH compared with Guanfacine XR medication for CYP with ADHD and co-existing tics.

3.2. Primary Objective

ADHD symptoms and tics at 12-weeks post-randomisation are designated joint primary outcomes. The trial aim is to test whether, in CYP with ADHD and co-existing tics, stimulant (MR-MPH) compared with non-stimulant (Guanfacine XR) medication is:

1. superior for ADHD symptoms: MR-MPH should result in a clinically important improvement in ADHD symptoms.

2. non-inferior for tics: MR-MPH should not result in a clinically important worsening with respect to tics.

3.3. Secondary Objectives

The secondary objectives are:

- To determine the effect of MR-MPH compared with Guanfacine XR on ADHD symptoms and tics
- To assess the relative effectiveness of MR-MPH compared with Guanfacine XR on the global measure of clinical functioning and physical measures
- To compare the relative cost-effectiveness of the two medications
- To assess adherence to the interventions
- To compare the safety of the interventions

3.4. Outcome Measures

3.4.1. Primary outcomes

1. *ADHD symptoms measured using the SNAP-IV at 12 weeks post-randomisation*

The SNAP-IV rating scale is an abbreviated version of the full SNAP-IV Rating Scale [2], and it consists of just the 18 items that closely parallel (in wording) the diagnostic symptoms for ADHD as they appear in the DSM-5. The parent and teacher versions contain the same items and wording. For each item on the SNAP, the respondent indicates whether the behavioural symptom describe the child “not at all” (0), “just a little” (1), “quite a bit” (2), or “very much” (3). The score for the 18-item SNAP is calculated by deriving an average rating per item. An average rating-per-item score less than or equal to 1.0 is considered to represent behaviour within the normal range. In participants with ADHD, the mean SNAP-IV-ADHD score is typically 1.7–1.8 (SD 0.7) [2].

2. *Tics severity measured by YGTSS (TTSS) at 12 weeks post-randomisation*

The Yale Global Tic Severity Scale (YGTSS) [1] will be administered by a blinded assessor as an investigator-based semi-structured interview focussing on motor and vocal tic frequency, severity, and tic related impairment.

The YGTSS symptom checklist lists 46 tic disorder symptoms, including simple motor tics (e.g., eye blinking), complex motor tics (e.g., facial expressions), simple vocal tics (e.g., coughing), and complex vocal tics (e.g., words). The YGTSS produces a total tic severity score (TTSS) [1] in the range from 0–50.

The TTSS score is made up from 5 sub-scale domains:

1) Number (how many tics)
2) Frequency (how often are the tics happening)
3) Intensity (how noticeable are the tics)
4) Complexity (how many different types of muscle groups are involved in the tics)
5) Interference (how much do they stop the person doing things)

Each sub-scale has a score ranging from 0–5, which is scored once for motor tics and once for vocal tics.

3.4.2. Secondary outcomes

Secondary outcomes will be assessed up to 52 weeks post-randomisation.

For a full description of all outcome measures please see Section 20.2. Appendix B.

Clinical

- ADHD symptoms measured using SNAP-IV [2] at 24 and 52 weeks
- Tics severity measured by YGTSS (TTSS) [1] at 24 and 52 weeks
- Global measure of clinical functioning: CGI-I & CGI-S [4] at 4, 8-12, 24 and 52 weeks
- Tic subscale scores (Total Phonic and Total Motor) measured by YGTSS [1] at 12, 24 and 52 weeks

*Safety**

- Medication adverse events at 1–12, 24 and 52 weeks measured via modified Hill and Taylor side-effects questionnaire

Health Economics

- Child health-related quality of life: CHU-9D [5], EQ-5DY [6] at 24 and 52 weeks
- Parent health-related quality of life: EQ5D-5I [7] at 24 and 52 weeks

***Safety Endpoint**

Adverse events will be recorded from consent to the end of the 52-week follow-up period on a modified version of the side effects scale developed by Hill and Taylor [15]. This consists of a 17-point scale and a free text part at the end to capture any other event/s not included in the scale. An adverse event within the modified Hill and Taylor questionnaire is defined as: a score equal to or greater than 2 for any individual category **and** a total score greater than baseline.

Serious adverse events will be recorded and reported in a timely fashion (within 24 hours of awareness of the event) following the procedure outlined in section 13.4 and will only be collected for the first 12 weeks.

Cardiovascular examination (blood pressure and pulse) will be conducted as part of routine safety monitoring as required. Physical measures and monitoring will be adjusted depending on treatment route; a decision based on individual risk factors and the baseline examination. See section 9 “Trial Treatment and Regimen” for further details on the different treatment routes and the data collection time points.

4. TRIAL DESIGN

4.1. Trial Configuration

Multi-centre, two-arm, parallel-group, randomised controlled trial of MR-MPH or Guanfacine XR for the treatment of ADHD and tics.

The co-primary outcomes (ADHD symptoms and tics) will be compared at 12 weeks. The treatment period (from randomisation to end of follow-up) is 52 weeks (approximately 12 months). Participants wishing to stop, pause or change their allocated medication will be free to do so, with any changes recorded. Clinicians may also decide to stop, pause or change medications based on their clinical judgement. All participants, whether continuing

with allocated medication or not, will be followed up for 52 weeks unless they withdraw consent. Participants' medication will be monitored by the SATURN team during the 52-week follow-up period to determine if they are still taking their assigned medication.

4.2. Trial Setting

NHS CAMHS and community paediatric clinics in England. Target population: CYP with ADHD and coexisting tics.

4.3. Stopping Rules and Discontinuation

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the TSC and the funder (NIHR HTA) as appropriate in making this decision.

4.4. Internal pilot

An internal pilot phase has been built into the trial to allow a feasibility assessment which will examine recruitment and retention. The stop-go criteria (shown in Table 1 below) will be used to determine the progression of the trial 10 months after the first site opening (unless agreed otherwise with the funder).

Pilot recruitment will be assessed against the overall recruitment target. Retention will be determined by the percentage of participants that are enrolled in the trial (i.e. not marked as lost-to-follow-up) at the end of the 12-week titration period.

Table 1. Recruitment and retention progression guidance for internal pilot

Progression guidance	Recruitment at 10 months	Retention at 12 weeks
Continue: no action	>85%	>80%
Continue: action required	50%–85%	45%–80%
Stop trial	<50%	<45%

The above criteria to aid decision making about progression of the trial has been proposed by the trial team and agreed with the Trial Management Group (TMG), TSC, Data Monitoring Committee (DMC) and funder (NIHR).

The TMG, TSC and DMC will continue to meet to monitor progress and review any proposed corrective measures, both during this internal pilot phase and beyond, should the trial progress into the main phase.

5. RANDOMISATION AND BLINDING

Eligible patients who consent (age <16: parental consent, young person's assent; aged 16: young person's consent, parental consent) will be allocated in a 1:1 ratio to receive either MR-MPH or Guanfacine XR.

Treatment will be assigned randomly using a minimisation algorithm using a probabilistic element, balancing across groups on site, tic severity (based on the YGTSS-TTSS 0–50 scale minimal-mild symptoms <20 vs moderate-severe symptoms ≥20) and previous treatment for ADHD (vs treatment naïve). Allocation will be concealed using a web-based randomisation

system developed and maintained by the Nottingham Clinical Trials Unit (NCTU) and hosted on a secure server, accessed via a secure website.

Interventions will be prescribed open-label. Participants, their parents/carers and research clinicians will know which treatment has been allocated.

Investigator-based measures, including the primary outcome for tics (YGTSS TTSS) [1] will be recorded (via face-to-face, online, video conference interview) by researchers who will be blinded to allocation (as far as possible) throughout the trial. 'Researchers' in this protocol refers only to the blinded research assistants/follow-up assessors and no other member of the research team.

The researchers will remind families not to disclose their treatment allocation at the start of every session. In instances of assessor unblinding, a different (blinded) researcher will continue all further assessments for this participant, where possible.

All instances of researcher unblinding will be recorded on the trial database.

Table 2. Blinding status per role in trial

Role	Status	Justification
Participants	Not blinded	Interventions will be open-label therefore participants will know what treatment they are taking.
Research clinicians / Hub leads deputising for Research clinicians	Not blinded	Interventions will be open-label therefore clinicians will be aware of treatment allocation.
Researcher	Blinded	Investigator-based measures, including the primary outcome for tics, will be completed by researchers blinded to allocation throughout the trial.
Principal Investigators	Not blinded	The PIs will be aware of the treatment allocation.
Trial management staff at NCTU	Not Blinded	The Trial Management team will have access to participant data with the potential to unblind until after database lock when this is not required to perform their role.
Data Management staff at NCTU	Not blinded	The Data Management team will have access to all database information in order to maintain the database and manage queries.
Trial statistician	Blinded	The trial statistician will not have access to any participant data with the potential to unblind them until after database lock. Provision of any unblinded disaggregated data, e.g., for the DMC, will be carried out by an independent unblinded statistician.
Chief Investigator (CI)	Blinded	The CI will not have access to any participant data with the potential to unblind until after database lock, with the exception of SAEs. In this case, the CI/medical monitor will become unblinded in order to complete the SAE causality assessment.

TMG	Blinded	Except in the specified roles, noted in this table, members of the TMG will not have access to any participant data with the potential to unblind until after database lock.
DMC	Not blinded	The independent members of the DMC will be provided with data presented by treatment group in order to perform their oversight role.
TSC	Blinded	Except in the case of a specific recommendation from the DMC, independent members of the TSC will not have access to any participant data with the potential to unblind until after database lock.

Maintenance of randomisation codes and procedures for breaking code

Only researchers will be blinded (as far as possible) to treatment allocation. Interventions will be open-label, and both participants and research clinicians will be aware of the treatment allocation, therefore there is no requirement for blind-breaking procedures.

The researcher role refers specifically to NHS research assistants, support officers etc. who will be part of the hub research team and supervised by the hub lead.

In this protocol, where the 'research team' is referenced, this refers **only** to the NHS research clinician and (NHS) researcher(s) undertaking all hub related trial activities (e.g., data collection procedures and follow-up contacts). Where this team is referenced throughout this protocol, it should be assumed that they are NHS-employed personnel.

6. Trial Management

The trial is funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme. The Sponsor is the University of Nottingham. The trial will be managed and co-ordinated by the NCTU.

The CI has overall responsibility for the trial and shall oversee all trial management. The data custodian will be the CI.

Trial Management Group

The TMG will meet on a regular basis (approximately monthly) and will be responsible for the day-to-day management of the trial. The full co-applicant team and NCTU staff responsible for the day-to-day management of the trial will form the TMG.

The TMG will ensure high quality trial conduct, to time and within budget, 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 integrity of trial itself. The TMG will also be responsible for ensuring project milestones are achieved.

Trial Steering Committee

The role of the TSC is to maintain oversight of the trial, monitor progress and provide advice to the trial team. The TSC will consist of an independent chair, and other independent members with clinical and research expertise including parent representatives. The CI will also be a member of the TSC.

The TSC will operate in accordance with a trial-specific charter, the funder's guidelines and the relevant NCTU Standard Operating Procedure (SOP).

The TSC will meet at least once a year during the trial, including following completion of a 10-month internal pilot period to review the results of the internal pilot and decide on recommendations regarding trial progression. Additional meetings may be called and the TSC may, at their discretion, request to meet more frequently.

The TSC will consider and act, as appropriate, upon the recommendations of the DMC.

Data Monitoring Committee
The role of the DMC is to give advice on whether the accumulated data from the trial, together with the results from other emerging research, justifies the continuing recruitment of participants.

Members of the DMC will be independent of the trial and consist of a statistician, a clinician and an academic with experience of clinical trials.

The DMC will operate in accordance with a trial-specific charter, the funder's guidelines and the relevant NCTU Standard Operating Procedure (SOP).

The DMC will meet at least once a year during the trial, including following completion of a 10-month internal pilot period to review the results of the internal pilot and make recommendations to the TSC on trial progression. Additional meetings may be called, 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 will report directly to the Chair of the TSC who will convey the findings of the DMC to the TSC, TMG and Sponsor as applicable.

7. DURATION OF THE TRIAL AND PARTICIPANT INVOLVEMENT

7.1. Participant Involvement Duration

The trial period is 52 weeks from randomisation, taking place at the end of baseline data collection. A screening call will be made with each participant before the start of baseline data collection.

All participants, whether continuing with allocated medication or not, will be followed up for 52 weeks from randomisation.

7.3. End of the Trial

The end of the trial is defined as the date of the final database lock. NCTU will notify the MHRA and REC that the trial has ended within 90 days of the end of trial.

If the trial has terminated early, NCTU will inform the MHRA and REC within 15 days of the end of trial.

8. SELECTION AND WITHDRAWAL OF PARTICIPANTS

8.1. Recruitment

Within this protocol, the terms "usual care team" and "treating clinician" refer to the CAMHS/paediatric clinic team/patient's usual care doctor/clinician at the recruiting/PIC site.

Family Identification and Approach:
CYP and their parent/carer will be approached through NHS CAMHS clinics, paediatric and hospital clinics. A positive ADHD diagnosis and confirmation of tics is not required in order to approach a family about the trial. Families can be approached in face to face or telephone consultations or be invited through a mailout by their local paediatric ADHD service (e.g. CAMHS). Invitation leaflets will be sent by sites to families on ADHD treatment and those on ADHD diagnostic/assessment waiting lists.

Completion of the Consent to Contact Form:
The Family invitation leaflet contains a QR code that the family can scan to access and complete a consent to contact form (C2C) form. The C2C form contains pre-screening questions around identification of tics in the CYP and a link to read the summary information leaflet (SIL). The SIL contains information on the trial outline, potential required assessments, reimbursements, data handling and the potential requirements for medication washouts. The C2C provides the research team with permission to contact the family and discuss the trial and send the family the Development and Wellbeing Assessment (DAWBA) for completion and for an ADHD assessment (if required) to be carried out by a clinician that may not be part of the child or young person's usual care team. Only the parent or carer can provide this consent.

Verbal Consent to Contact:
Families that have discussed the trial with their usual care team can give consent for the usual care team to complete the EOI form on their behalf. The same details are provided irrespective of who completes the EOI form. Where verbal consent to complete the form on behalf of the family has been obtained, this will be recorded in the medical notes by the referring member of the usual care team.

Confirmation of ADHD diagnosis and review of DAWBA:
Where required, the hub research clinicians, will coordinate with the local care team to complete an ADHD diagnostic assessment, consent for this is provided by the parent or carer as part of the C2C form. The requirements for this assessment are determined by local practice. ADHD assessments will only take place for families that submit a C2C linked to a participating centre (site or PIC), where the child or young person is on an ADHD diagnostic waitlist and whose parent or carer has identified tic symptoms.

Irrespective of the outcome the results of any ADHD diagnostic evaluations will be discussed with the family and shared with the family and the CYP usual care team.

If the family are potentially eligible for the trial on review of the previously-completed DAWBA, then the Hub research team will notify the family and send the appropriate patient information sheets by email. Any ineligible families will be notified, and it will be explained that their CYP's treatment or next steps will be decided by their usual care team. Their usual care team will be notified by the hub research team providing as much clinical detail as required in local practice.

Scheduling of Baseline Appointment(s)

For eligible patients, the hub research team will phone the family and provide the opportunity for them to ask questions. If the family are willing, the baseline visit(s) will be scheduled. This appointment will factor in any required medication washout periods. Medication will only be changed if there is clear clinical indication for doing so. The washout for existing medication will be determined by the research clinician, in collaboration with the hub lead clinician and/or site PI or another suitably trained and delegated clinician.

It will be explained to the family that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time. In the event of withdrawal following informed consent, it will be explained that the data collected up to that point will be retained and will be used in the final analysis.

Pregnancy

Any CYP that are, or are planning, to become pregnant will be excluded. The research clinician will discuss the risk of pregnancy and the importance of contraception with participants of child bearing potential during the baseline visit. In line with the Clinical Trials Facilitation and Coordination Group (CTFG) guidelines [16], forms of contraception that will be considered effective are:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation 1 - route of administration oral, intravaginal or transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation 1 - route of administration oral, injectable, implantable
- sexual abstinence

Sexually active participants who the research clinician is concerned are not taking adequate contraceptive measures will be required to have a negative pregnancy test at the face-to face baseline data collection visit. Participants will be asked when completing the trial consent form to confirm they understand that pregnancy is inadvisable during the trial and they will be required to use contraception if they are sexually active. The hub research team and clinicians in this discipline cannot be responsible for prescribing contraception. If a participant becomes pregnant during the trial, they will be discontinued from trial medication however they may continue to complete questionnaires if willing and management will be handed back to their usual care team. In these circumstances following withdrawal, the decision whether to stop or change the trial medication will be made collaboratively between the former participant, their parent/carer and usual care team/treating clinician.

Oversight

Sites may have a local Principal Investigator (PI) who will have the overall responsibility for trial activities at their site.

Hubs may also choose to operate a Hub & Spoke model in some or all of the sites in the hub. In this model, a PI oversees activity across more than one site and delegates responsibility as needed to local site leads.

Lead hub sites can also have PICs that identify cases and are willing to keep the CYP's medical notes open to the hub clinicians for the duration of their participation in the trial (52 weeks post randomisation) to facilitate safety monitoring of SAEs.

All PIs will be reporting to the hub lead who will oversee trial activities across all sites under their hub. The hub lead will be responsible for representing PIs at the TMG and reporting on site set-up and recruitment progress.

8.2. Eligibility Criteria

The target population is children and young people with ADHD and co-existing tics.

Only **one** child or young person (CYP) will be recruited per family. If more than one CYP is eligible for entry into the trial, the choice of who should take part will be made by the family and communicated to the research team by the parent(s)/carer(s). This decision has been made to prevent accidental confusion of trial treatments for people living in the same household.

Both CYP and parent/carer need to be eligible for the CYP to be enrolled in the trial.

A parent/carer for SATURN is defined as the person with parental responsibility who can be:

- the child's mother or father,
- the child's legally appointed guardian,
- a person with a residence order concerning the child.

8.2.1. Inclusion criteria

Inclusion criteria for the child or young person

- Aged ≥6 years up to <17 years at randomisation.
- Confirmed diagnosis of ADHD at point of randomisation (ADHD DSM-5) (following review of all available information including the DAWBA).
- Mild-moderate tics: Score >5 on the Yale Global Tic Severity Scale (YGTSS) Total Tic Severity Score (TTSS) ;
- Referred to CAMHS or paediatric services taking part in the trial
- Parent/carer and CYP seeking medication for ADHD (either ADHD medication naïve or seeking medication change).
- Willing to adhere to the trial procedures.
- If currently or recently on a different medication for ADHD or tics willing to go through or complete the appropriate wash-out period (as per standard care) to be able to receive the allocated trial IMP.
- Able to give valid, informed assent (aged <16) or consent (aged 16).
- Able to understand and complete assessments in English.
- Eligible parent/carer willing and able to participate alongside the CYP.

Inclusion criteria for the parent/carer

- Individual with parental responsibility.
- Individual with sufficient knowledge of CYP’s medical history to be able to complete the relevant assessment tools.
- Access to reliable internet connection and email.
- Able to give valid, informed consent.
- Able to speak, understand and complete assessments in English.

8.2.2. Exclusion criteria

Exclusion criteria for the child or young person

- Current pharmacotherapy for tics and unwilling/unable to discontinue to begin trial medication.
- Current pharmacotherapy for ADHD and unwilling/unable to discontinue to begin trial medication.
- A documented history of prolonged QTc or risk factors for torsade de pointes.
- Abnormal cardiovascular examination (e.g., BP >95th percentile, tachycardia).
- Diagnoses of alcohol/substance dependence, psychosis or mania (as per clinician judgement).
- Suicidal tendency and risk (assessed by the referring clinician).
- Intellectual disability (clinical estimate of IQ<70) confirmed by Child and Adolescent Intellectual Disability Screening Questionnaire; CAIDS-Q [3] or alternative full cognitive assessment e.g. WISC.
- Contraindications to MR-MPH and/or Guanfacine XR.
- Immediate risk to self or others.
- Individual who is, or is planning to become, pregnant.
- Individual who is breastfeeding.

Exclusion criteria for the parent/carer

- Local authority representative of CYP.

If the participant is taking part in another trial, they will not be invited or be able to continue with their participation in this trial. We will, however, ask participants for consent to be contacted about future, relevant trials. Maintenance of a participant contact database will be full adherent with GDPR guidelines.

8.3. Expected Duration Of Participant Participation

Participants will be in the trial for 52 weeks from randomisation (baseline visit).

8.4. Withdrawal of Participants from Therapy or Assessments

Participants may be withdrawn from the trial either at their own request or at the discretion of the Investigator (after consultation with the Site PI/Lead). The participants will be made aware that this will not affect their future care.

If a participant wishes to discontinue the trial intervention or comparator, they may do so. The research clinician will support them to do this safely, avoiding abrupt withdrawal.

- Where the parent/carer decides to withdraw from the trial, their CYP (6-17 years old) will be discontinued from the trial intervention or comparator.
- Where the young person (16-year-old) chooses to withdraw consent from the trial or the CYP (≥ 6 to <16 years old) chooses to withdraw assent, their parent/carer may continue completing any parent/carer reported measures (See section 20.1. Appendix A for further details).

The trial follow-up schedule (which includes questionnaires and assessments) will continue in accordance with the protocol unless the participant **and** their parent/carer choose to withdraw from the trial completely.

Participants will be made aware (via the information sheet and consent form) that should they withdraw, data collected to date cannot be erased and will still be used in the final analyses.

8.5. Informed Consent

The Investigator research team member or other delegate will explain the details of the trial and provide an age-appropriate PIS, ensuring that the patient and their parent/carer have sufficient time to consider participating or not. The Investigator (or delegate) will answer any questions that the patient and their parent/carer have in relation to the trial.

Informed consent (and assent depending on the patient's age) will be obtained from patients and their parent/carer either electronically on the trial database or on paper where the former is not possible.

Patients will be assured that they may withdraw from the trial at any time, without giving a reason and without any impact upon any treatment they are currently receiving or any prejudice towards their future care.

For young people aged under 16, parental consent will be obtained and the young person's assent.

For those aged 16, the young person's consent will be obtained as a requirement of being recruited to the trial. Consent will also be sought from the parent/carer participating alongside the young person aged 16 for their own involvement.

Due to the nature of the assessments and the population under investigation consent will be sought from **both** parent/carer and young person aged 16.

In the event of any discordance between the parent and CYP (6-16 years old) the CYP will **not** enter the trial. In the event of discordance in optional items on the consent and assent forms, the parent's consent will be needed as a requirement for any relevant data to be collected.

Consent/Assent Forms will be signed and dated by the person providing consent/assent before they enter the trial. If completed electronically, signatures may be obtained in the form of an 'e-signature' online. An e-signature will be drawn by the person giving consent/assent on an electronic signature pad (a REDCap feature). Where electronic completion is not an option, paper forms may be completed and signed. Signatures will not be collected from children aged 6-10. CYP aged 11-16 may sign with their name if they do not have a signature. Regardless of the completion method chosen (online or paper), consent/assent will be taken at the baseline visit. Consent may be taken remotely where the parent/CYP preference is for a remote baseline visit a copy of the consent form can then be emailed to the participant.

Informed consent/assent (depending on the participant's age) will be collected from each participant and their parent/carer before they undergo any trial-related interventions (including physical examination and history taking) related to the trial. One copy of the researcher verified (econsent) or researcher countersigned (paper) consent form will be shared with the patient, one will be kept by the Investigator (stored on the trial database if electronic, or in the Investigator Site File (ISF) if taken on paper), and a third will be retained in the patient's medical notes. Along with the completed consent form, the version number and date of the PIS provided to the participant and the date the consent was obtained should also be recorded on the participant's medical notes.

Participants entering the trial at age 15 and who turn 16 during follow-up will be re-consented.

9. TRIAL TREATMENT AND REGIMEN

9.1. Trial Regimen

9.1.1 Screening Metrics

Primary reason for non-participation or exclusion will be captured in the database by the research team between the consent to contact step and confirmation of eligibility.

9.1.2 Expression of Interest

If a CYP has an existing diagnosis of ADHD:

Direct approach through usual care team

Families can be approached by their usual care team directly or they may see a SIL, poster or other advert in a waiting area or clinic room and choose to refer themselves to their usual care team/treating clinician.

Mailout through usual care team

The usual care team can perform a waiting list search for CYP aged 6-16, with a diagnosis of ADHD who are medication naïve or seeking a medication change. A leaflet explaining the trial and inviting families to express an interest through the C2C form will be posted or emailed to identified families. This form is accessed by scanning a QR code on the leaflet.

The C2C form contains tic screening questions, a copy of the SIL, a contact details section and provides consent for the hub research team to send the family the Development and Wellbeing Assessment (DAWBA) and contact the family about the trial.

If a CYP does not have an existing diagnosis of ADHD:

Mailout through usual care team

The usual care team can perform a search for CYP on ADHD assessment/diagnostic waitlists and complete a mailout. The usual care team can send a leaflet in the post or via email to parents/carers of CYP aged 6-16 inviting families to express an interest through the consent to contact form.

As above, the consent to contact form contains tic screening questions, a copy of the SIL, a contact details section and provides consent for the hub research team to send the family the Development and Wellbeing Assessment (DAWBA) and contact the family about the trial.

Additionally, as part of the consent to contact form the parent or carer will be asked to provide their permission for their CYPs ADHD assessment to be completed by another clinic or clinical team (outside of their usual care team) and to relevant information being shared between clinics for that purpose.

For all potential families:

Advertising the trial directly to the Public Online or via Social Media

The trial will also be advertised online using social media (X, LinkedIn, Facebook etc.) and on site/trust websites. Any enquiries from those living within the catchment areas of participating centres (Sites and PICs) will be considered for joining the trial and be forwarded to hub research teams as potential participants. Parents/carers of potentially eligible patients will be given a SIL and C2C, which will include a link to the trial website where the full PIS will be available.

For all families that are interested in participating:

Parents/carers will be asked to complete the C2C form and DAWBA on behalf of their CYP (≥6 to <17 years old).

Reminders will be sent to the parent/carer to complete the DAWBA following receipt of the completed C2C form.

9.1.3 Screening

Initial contact will be made by the hub research team to the family by telephone when a consent to contact is received. The researcher will provide further information on the trial including the appropriate PISsand answer any questions the parent/carer and/or patient may have. Any additional contact details, not already provided via the C2C, will be obtained during the screening contact to help facilitate the baseline visit appointment (e.g., phone number, best contact time/method for reminders). The hub research team will send a link and password to complete the DAWBA, and arrange any required assessments for ADHD diagnosis.

Those who are found ineligible following review of the DAWBA or because the CYP is not diagnosed with ADHD will be notified of the assessment outcome. Ineligible families will be reminded that this will have no impact on their current or future standard of care. The family and the usual care team will be offered a copy of the complete DAWBA assessment, and the outcomes of the ADHD assessment, and their usual care team will be notified that they were not able to join the trial.

If the family wish to proceed, the research team will confirm eligibility as far as possible by completing a brief screening questionnaire with the parent/carer over the phone, the CYP may also wish to contribute, and will then book their baseline visit appointment.

This appointment should be booked considering the need for an appropriate washout period of existing medications for ADHD and tics where applicable. The washout for existing medication will be determined by the research clinician, in collaboration with the hub lead clinician and/or site PI or another suitably trained and delegated clinician.

The parent/carer may receive an appointment confirmation and further reminders via email or phone regarding their baseline visit appointment.

9.1.4 Baseline Data Collection: Eligibility, Consent, Baseline data collection and Randomisation

Baseline data will be collected following consent and prior to randomisation. Baseline data will be collected either at one face to face visit where possible or across multiple visits, as deemed appropriate to support participation. Visits can be conducted in person or as a combination of in-person and online. A breakdown of which measures can be collected via a virtual appointment is provided in Table 3 (pg 35).

Following consent, the research team will confirm eligibility by conducting the relevant assessments including the CAIDS-Q [3] or equivalent method (to detect intellectual disability) and YGTSS [1] (to assess tics).

Eligibility criteria for the trial will be collected by the research team from patient medical notes, including:

i) if there are diagnoses of alcohol/substance dependence, psychosis or mania
ii) if the participant poses an immediate risk to themselves or others

iii) any medication the CYP is currently taking

Ultimately, eligibility for the trial must always be confirmed by a medically qualified doctor.

If eligible, the researcher will support participants and/or parents/carers (see section 20.1. Appendix A for a detailed table of people responsible for completion of each of the trial measures) to complete the following measures:

- SNAP-IV [2]
- CHU9D [5]
- EQ5DY [6]
- EQ5D-5l [7]
- (modified) Hill & Taylor side-effects scale [15]

The research team will conduct the cardiovascular exam (blood pressure and pulse), record physical measurements (height and weight), relevant medical history and ascertain cardiovascular risk factors as set out by the European ADHD Guidelines Group (EAGG) guidance (i.e., personal or family history of cardiac disease). Additionally, they will review the concomitant medication list on the trial database and update it if needed as per the participant's medical record. Although there are no prohibited concomitant medications for both IMPs some cautions are advised for co-prescribing. Guidance from the SmPC will be followed in regard to this.

Following baseline data collection, eligible patients will be randomised, an appropriately trained and delegated authorised health professional will prescribe the trial medication according to the allocated treatment group. Depending on local arrangements, participants will collect the prescription from the clinic or a local pharmacy. Prescription arrangements will be confirmed by each site.

In the event that randomisation cannot take place within 4 weeks of collection of primary outcome measures the primary outcome measures (YGTSS [1] and SNAP-IV [2]) these will be repeated and subsequent scores entered into the database

The participant's GP will be notified about their patient's participation in the trial and the treatment they have been allocated to. Additionally, they may be given access to the parent/carer's consent and CYP's consent/assent (depending on age). The GP will continue to be updated on the participants progress throughout the trial. Where a site holds a shared care agreement with the participants GP, the GP will be asked to issue repeat prescriptions at the end of the titration period as per standard practice. If a site does not have shared care agreements with participants GPs, the local treating clinicians will be taking over prescribing from the research doctor at the end of the titration period. The research team will recommend that participants stay on their allocated medication after the titration period if it is effective and well tolerated, however, decisions regarding treatment changes should be made by the local treating clinician.

A brief summary of the screening (DAWBA) and baseline assessments will be shared with the usual care team who will also be asked that the participant's concomitant medication and treatments remain stable (as far as possible) while they are in the trial. If any changes are made, the GP or local treating clinician will be advised to refer to the appropriate SmPC and the BNF for guidance on co-prescribing.

A brief summary of the baseline assessment (e.g. consent, allocated IMP) should be documented in the participant's medical record.

9.1.5 12-Week Titration Phase

The titration schedule in both monitoring groups will be guided by the medication's SmPC with maximum dosing following BNF guidance. In addition, two treatment pathways are proposed for the 12-week titration phase of the trial: 'Routine physical monitoring' or 'Enhanced physical monitoring'. The pathway of monitoring is informed by the outcome of the physical measures taken at baseline and a short series of questions to ascertain medical history and risk factors as set out by the EAGG guidance [17, 18].

There will be 12 weekly visits, during the titration phase, regardless of monitoring pathway. The monitoring pathway only indicates the frequency of data collection of blood pressure and pulse measurements as well as whether a participant needs to be seen in person to have these taken.

Routine monitoring: Participants allocated to this group will receive a level of monitoring during the titration period that is equivalent to standard care. Visits may be conducted face-to-face or remotely by teleconference (e.g. Teams) or telephone, this will depend on the policies in place at each site. The hub team will notify the participant of how their monitoring visits will take place. Participants allocated to this route are those who do not meet any of the risk criteria set out by the EAGG therefore no further routine physical measures (height, weight) are required during the titration period. Blood pressure and pulse measures will be advised to be taken and shared with the research team at weeks 4, 8 and 12 following randomisation. Participants allocated to this group may be moved to the enhanced monitoring group should new information/measures become available that would lead the research clinician to make this decision.

Enhanced monitoring: Participants who meet the risk criteria set out by the EAGG guidance will have their blood pressure and pulse taken on an as-needed-basis during the 12 weeks of the titration period. It will be up to the research clinician to decide at which titration period visits these measures should be collected. The research clinician will also decide whether these measures are collected during face-to-face clinic visits, or remotely (e.g. by participants completing blood pressure and pulse measurements at home, or in a community setting such as GP practices or their referring CAMHS service or paediatric clinic).

The type (remote or in-person) and frequency of monitoring will be a clinical judgement, based on individual risk factors and circumstances. For example, some participants may only need blood pressure and pulse measures during the first couple of weeks of titration whereas others may have these measures taken throughout the 12-week titration period.

9.1.6 Trial Visits (Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11)

The following measures will be completed weekly (See section 20.1. Appendix A for details on people responsible for completion of outcome measures). The measures will be completed online (or on paper if required). Reminders for completion and for the contact (phone or online) with the research team may be sent via email or phone.

- Adherence CRF
- Concomitant medications and treatments CRF (modified)

- (modified) Hill and Taylor side-effects scale (used to record adverse events) [15]
- CGI-I and CGI-S [4] (only at weeks 4 and 8)
- Blood pressure and pulse (collected as indicated according to the monitoring schedule set out by the research clinician).
- Medication will also be reviewed and any further prescriptions, or changes to prescriptions will be raised. Prescriptions can also be raised by appropriately trained and delegated local staff under the supervision of the treating clinician. Participants will need to collect any new prescriptions from the clinic, their local pharmacy or as per the relevant local arrangements (which may differ per site).

9.1.7 Trial Visits 12 (Week 12), 13 (Week 24) & 14 (Week 52)

The following measures will be completed at weeks 12, 24 and 52 from randomisation. The measures will be completed online (or on paper if required). Reminders for completion and for the contact (phone or online) with the research team may be sent via email or phone.

- SNAP-IV [2]
- (modified) Hill and Taylor side-effects scale (adverse events) [15]
- EQ5D-5l [7]
- CHU9D [5]
- EQ5DY [6]
- YGTSS [1]
- Health Resource Use pro forma
- Adherence CRF
- Concomitants medications and treatments CRF
- Height, weight (at the 12-week visit only)
- Blood pressure and pulse (collected as indicated according to the monitoring schedule set out by the research clinician).
- CGI-I and CGI-S [4]
- Medication will also be reviewed and any further prescriptions, or changes to prescriptions will be raised. Prescriptions can also be raised by appropriately trained and delegated local staff. Participants will need to collect any new prescriptions from the clinic, their local pharmacy or as per the relevant local arrangements (which may differ per site).

Following the 12 week titration period the decision to discontinue or continue treatment will be made by the local treating clinician in collaboration with the family and young person following NICE guidance [8] which includes a regular evaluation (at least every 12 months) of on-going treatment effectiveness.

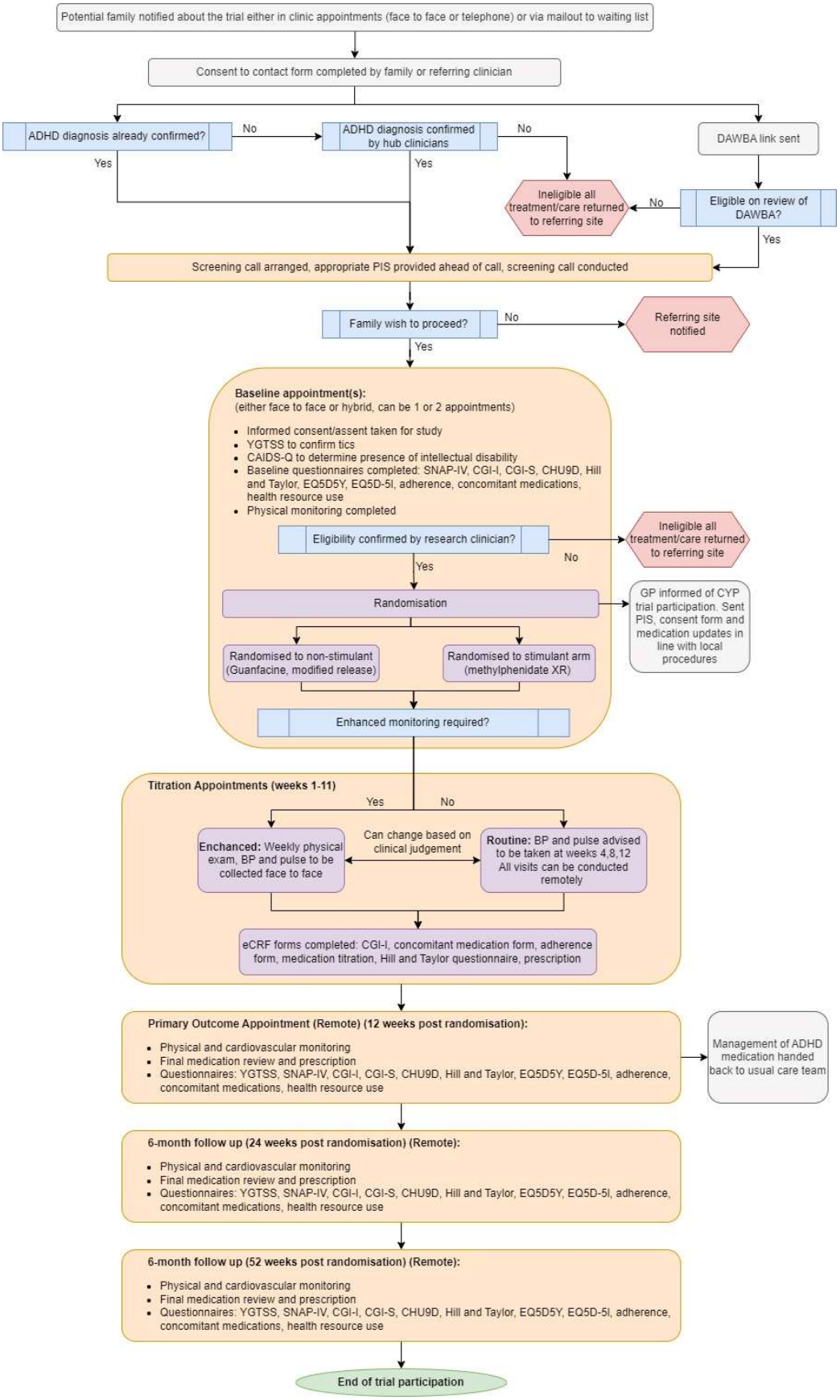
Please see a detailed list of CRFs and assessments in table 3 below.

Table 3. Trial activities

	Expression of Interest	Screening Contact	Baseline Data Collection	Follow-up Visit 1,2,3,4,5,6, 7,8,9,10, 11 (Weeks 1,2, 3, 4,5,6, 7, 8,9,10, 11)	Follow-up Visit 12 (Week 12) (Primary Outcome)	Follow-up Visits 13 (Week 24) & 14 (Week 52)
Consent to Contact	X					
Screening Call		X				
DAWBA	X					
Eligibility Assessment			X			
Pregnancy test where applicable (see section 8.1)			X			
Informed Consent			X (V)			
CAIDS-Q or alternative			X (V)			
Randomisation			X			
Demographics			X (V)			
Physical monitoring			X		X	X**
Medical history			X (V)			
Cardiovascular examination*			X	X	X	X**
Medication review and prescription			X	X	X	
CGI-I & CGI-S			X***	X (Weeks 4 and 8)	X	X
YGTSS			X		X	X

Health Resource Use			X [V]		X	X
SNAP-IV			X		X	X
CHU9D			X [V]		X	X
EQ5DY			X [V]		X	X
EQ5D-5l			X [V]		X	X
(Modified) Hill and Taylor side-effects scale			X [V]	X	X	X
Concomitant medications	X		X [V]	X	X	X
Adherence				X	X	X
** As indicated according to the monitoring schedule and individual risk factors.* ***Collected only if the participant is still taking trial medication and only if indicated (see above *).* ****CGI-S only* *[V] – may be collected during a virtual appointment*						

Figure 1. Participant pathway



9.2. Concomitant and Rescue Medications and Treatments

Concomitant medications and treatments will be recorded on the relevant electronic Case Report Forms (eCRFs).

Participants will be advised to avoid making any changes to their medications and treatments during the 12-week titration phase unless it is clinically required.

Any changes in treatments and dosage throughout their participation should be reported to the research team and logged on the trial database as appropriate.

9.3. Compliance

Adherence to allocated treatment will be assessed through parent/carer (and young person if appropriate) report. Questions about adherence will be asked during routine trial follow-up (weekly contacts with the research team during the titration phase and at the 24-week and 52-week follow-ups) and logged on the trial database.

Adherence levels will be monitored and reported regularly to the TMG. If poor adherence is observed, appropriate training and guidance will be given to the research team, and materials may be provided to the participants to aid with compliance.

Guidance as to what constitutes poor adherence will be provided to the research team.

Satisfactory adherence for the trial is defined as participants having taken 80% of allocated medications as intended during the 12-week titration phase [19].

Treatment-switching and other types of non-adherence are likely to increase after 12 weeks and will therefore reduce the generalisability of later outcomes to the effects of either MR-MPH or Guanfacine XR. However, for the estimated treatment effect at 12 weeks, the majority of participants are expected to still be taking the allocated medication and will therefore most usefully inform clinical practice.

9.4. Accountability for Drug & Placebo

As the trial IMPs have marketing authorisation, clinic/pharmacy stocks will be used. Therefore, site and local pharmacies will follow their own local procedures for recording medication dispensed to trial participants.

Details of the trial medication prescribed e.g., commercial name, dose and number of tablets will be recorded on the participant's eCRF and updated as needed if adjustments are made.

Participants who are advised to stop taking the trial medication will be asked to return it to a local pharmacy for destruction.

9.5. Management of Trial Drug Overdose

Trial participants will be advised of the appropriate dose by their research clinician. Advice will also be given to follow the guidance on the enclosed leaflet.

Any incidents will be recorded as part of safety monitoring and reporting.

9.6. Urgent Safety Measures

Both trial IMPs have marketing authorisation and well characterised safety profiles thus urgent safety measures are not likely to be needed.

However, if an urgent safety measure is adopted, the MHRA will be notified in writing immediately and in any event no later than 3 days from the date the measures are taken. The sponsor and the relevant Research Ethics Committee (REC) will also be notified of the measures taken within the same time period. If needed, the sponsor will contact the MHRA Clinical Trials Unit and discuss the event with a safety scientist.

The DMC, in accordance with their charter, will be reviewing safety data at regular intervals throughout the trial and report any safety concerns as appropriate.

9.7. Protocol Deviations and Violations

Protocol non-compliance will be monitored via central monitoring of eCRF data. All protocol deviations and violations will be recorded on the trial database and reviewed by the NCTU.

Where the outcome of the initial assessment is a serious breach or other serious protocol violation, it will be reported immediately to the CI and further investigated following the relevant NCTU SOPs.

The CI will notify the Sponsor if a deviation or violation has an impact on participant safety or integrity of the trial data. The Sponsor will advise on appropriate measures to address the occurrence which may include reporting of a serious Good Clinical Practice (GCP) breach, conduct of an internal audit of the trial, and seeking counsel of the trial committees and the REC/MHRA.

The following violations will trigger retraining of relevant staff:

- Enrolment in the trial (e.g., medication prescription, randomisation or any measures administered) without consent
- Enrolment in the trial (randomisation) of an ineligible participant
- Lack of participant-level pre-screening data (e.g., ADHD diagnosis confirmation) needed to proceed with screening contact
- Lack of reporting of serious adverse events

9.8. Criteria for Terminating Trial

On the recommendation of the TSC, the sponsor (in collaboration with the TMG) may stop the trial if emerging evidence of efficacy or major safety concerns arise, or if there are significant concerns regarding trial conduct. There should be proof beyond reasonable doubt for overall efficacy or major safety concerns (internal or external evidence) for the TSC and TMG to recommend the trial is stopped.

Stopping at one site or hub will reflect unacceptable performance in recruitment or poor compliance with the protocol. In the case where a site closure has been decided due to inability to meet its recruitment target or due to poor compliance, the TMG may make this decision without consultation with the TSC.

10. DATA MANAGEMENT

10.1. Data Management Plan

Full details about data management will be provided in the Data Management Plan (DMP).

10.1.1. General

The DMP will include the agreed validation specification, roles and responsibilities for the trial data and user access. Additional manual and electronic reviews may also be conducted, and data queries / clarifications may arise from such reviews.

The trial database to be used is REDCap. It is a validated secure web-based platform which allows for data tracking via date stamped audit logs. SATURN participants will be identified on REDCap only by a unique participant identifier (their trial/participant ID) to protect from bias and ensure confidentiality.

Data will be held on secure servers. These servers are located within The University of Nottingham data centres, which are managed and monitored regularly. Security is both physical (secure limited role-based access) and electronic (behind firewalls, access via user accounts (username and password) on encrypted connections, restricted access e.g. site staff only have access to their site patient data, and by user type/role). All access and data transactions will be logged in a full audit trail.

The DAWBA will be completed on a secure encrypted online platform [20]. Access is restricted by user accounts and will therefore be via a unique ID number and password. The DAWBA team will provide the requested number of DAWBA IDs and passwords. Each DAWBA respondent will be sent their own unique logins by the trial team. The link between participants' unique trial IDs and their DAWBA logins (ID and password) will only be known to the trial team, which includes the local hub research teams. Neither the DAWBA platform team nor anyone else outside the trial team will have access to this information.

Personal information collected on the DAWBA are the CYP's age, gender and their first name (should the parent/carer wish to provide it). Full name, contact address, IP address or any other sensitive data is not collected on the platform.

Forms will be locked once the DAWBA has been completed so the information cannot be modified or re-entered at a later date.

10.1.2. Data Capture and Data Queries

Data will be collected directly from the parent/carer and the participant as appropriate (depending on measure and age of participant) and entered directly onto the secure trial database. Some measures (e.g. YGTSS, CGI-I) will be completed by the research team based on their judgement and the responses provided by the parent/carer and, if appropriate, trial participant.

Only staff listed on the delegation log will be given access to the relevant sections of the trial database e.g. site 1 staff will only have access to site 1 trial participants while the trial team including the hub research teams will have access to the wider database. Individual trial and research team member access will vary depending on role and associated blinding status.

Relevant regulatory authorities will also be permitted access onto the database.

Data reported on each eCRF will be checked for missing data or discrepancies and will be queried. Staff delegated to complete eCRFs will be trained to adhere to relevant aspects of GCP associated with data entry.

Data queries will not be raised on participant or parent/carer completed questionnaires.

10.1.3. Description of Data Entry Validation

Programmed validation and manual checks will be used to identify data anomalies. All programmed validation checks are documented in the data dictionary and data quality rules on the REDCap database.

Programmed validation checks will automatically flag discrepancies at the point of data entry or will be executed by data management at the point of data cleaning. Data identified as missing or having discrepancies, may require a manual data query to be raised within REDCap by the Data Management team at NCTU.

10.1.4. Data Cleaning and Database Lock

Once all data has been collected and is cleaned and signed off by the PI, the trial database will be locked.

The database will be hard locked as per the relevant NCTU SOP using the associated checklist. All user rights will be removed, and it will be read only. Further details will be included in the trial DMP.

10.1.5. Monitoring

Monitoring will be carried out as required, following a risk assessment, and as documented in the trial monitoring plan. Any onsite monitoring activities will be reported to the Sponsor and any issues noted will be followed up to resolution.

The NCTU will be in regular contact with the hubs to monitor recruitment progress and address any queries they may have.

11. STATISTICAL CONSIDERATIONS

11.1. Sample Size and Justification

The sample size calculation is based on the co-primary outcomes of ADHD symptoms and tics. The success of the intervention will be concluded only if the stimulant medication is shown to be superior for ADHD symptoms and non-inferior for tic severity, hence we have not made any multiplicity adjustment to the statistical significance level.

Tics: Based on a non-inferiority margin (= maximum clinically unimportant difference) in tic symptoms on the YGTSS Total Tic Severity Scale (TTSS) [1] of 0.4SDs with 90% power, 1:1 allocation ratio, and 1-sided 2.5% significance level, 133 participants per group are required for analysis. Allowing for missing primary outcome data of up to 15%, 314 randomised participants are required. A difference of 0.4 SDs equates to 2.6 units on TTSS, assuming SD=6.6 [10], which would be achieved for example by a shift of 1 category on each of 2–3 of the 5 domains in either motor or phonic tics. The proposed non-inferiority margin of 0.4 SDs

was chosen to be *smaller* than the lowest minimally clinically important difference (MCID) for YGTSS-TTSS reported in the literature which is a 4 to 5 points or 25% reduction [21].

ADHD symptoms: 133 participants per group for analysis achieves 90% power to detect a minimum clinically important difference of 0.4 SDs (equivalent to a between-group difference in mean rating-per-item score of 0.28, assuming item SD of 0.7 [2] on Swanson, Nelson and Pelham questionnaire (SNAP-IV) 18-item scale. This difference can be achieved, for example, if 5 out of 18 ADHD symptom items change from “very much” to “quite a bit”, or from “quite a bit” to “just a little”.

11.2. Analysis of Outcome Measures

The reporting of the trial will be in accordance with CONSORT guidelines [22]. Further details about the statistical analysis will be provided in the Statistical Analysis Plan which will be finalised prior to completion of data collection, database lock and unblinding of trial data. This will be developed and approved with the TSC prior to database lock.

Descriptive statistics will be used to summarise the baseline and outcome data by treatment group. Each primary outcome will be analysed without any multiplicity adjustment.

For the SNAP-IV [4], the between group difference in means at 12 weeks will be calculated using a mixed-effect model, adjusting for site as a random effect and baseline score and other minimisation factors as fixed effects. Primary between-group comparisons for this outcome will be based on intention-to-treat (ITT), analysing participants in the groups to which they were randomised.

For the tic symptoms (TTSS) [23, 24], a two-sided 95% CI(equivalent to a one-sided 97.5%CI) for the difference in mean TTSS score at 12 weeks between the two groups will be constructed using a mixed-effect model, adjusting for site as a random effect and baseline TTSS score and other minimisation factors as fixed effects. Non-inferiority of the stimulant medication (MR-MPH) for tic worsening will be inferred if the lower bound of this interval lies within the non-inferiority margin of 2.6 points.

Both ITT and per-protocol analysis will be performed for the tic outcome as protection against possible increased risk of type I error associated with ITT in a non-inferiority analysis. The primary inference will be based on the ITT analysis, with per-protocol analysis used to check consistency. Non-adherence is expected to be minimal at primary follow-up point, but efforts will be made to maximise adherence with allocated treatment throughout follow-up.

A sensitivity analysis will be performed for the primary outcomes to examine the impact of missingness using multiple imputation with the imputation model also including auxiliary variables not adjusted for in the primary model.

Between-group comparison of secondary outcomes will be based on an appropriate regression for the outcome adjusted for the minimisation factors and baseline outcome measure for continuous variables, if available.

11.3. Planned Interim Analysis

There is no planned formal interim statistical analysis of treatment effectiveness. However, as part of continuous oversight, the DMC will be provided with confidential reports by trial group, containing information on recruitment, protocol compliance, safety, and interim assessments of outcomes (between-group estimates of differences in efficacy and/or safety outcomes), as

agreed. The funder will also be provided with reports on recruitment, retention and adherence during the internal pilot phase and after the implementation of the supplementary recruitment recovery strategy as described in Section 4.4 (internal pilot).

11.4. Planned Final Analyses

Final analyses will be performed once the database has been locked.

11.5. Planned Subgroup Analyses

Subgroup analyses for the primary outcomes will be performed according to tic severity (based on the YGTSS-TTSS 0–50 scale: minimal-mild symptoms <20 vs moderate-severe symptoms ≥20), ADHD severity (using a cut off score of 2) and previous treatment for ADHD/tics (has had treatment vs treatment naïve) by including appropriate interaction terms in the regression models. The trial is not powered to detect any interactions, hence the subgroup analyses will be treated as exploratory.

11.6. Assessment of Safety

Analysis of safety data will be presented descriptively using frequency counts and percentages in each allocated group.

11.7. Procedures for Missing, Unused and Spurious Data

Analysis of the primary outcomes will be via ITT using maximum likelihood estimation with data from all participants included in the analysis. Every effort will be made to follow up all participants up to the primary endpoint, however, as missing data is inevitable, we will employ statistical techniques for handling missing data for the primary outcomes. As a sensitivity analysis for the primary outcomes, multiple imputation, based on multivariate imputation by chained equations (MICE), will be used to generate at least 15 multiply-imputed datasets of each missing outcome, under the Missing At Random assumption.

11.8. Definition of Populations Analysed

For the primary analysis of ADHD symptoms, all participants will be analysed according to allocated treatment group regardless of adherence to the allocated treatment.

For tics, both ITT and per-protocol analysis, which excludes individuals who fail to adequately adhere to the assigned treatment protocol as defined in Section 9.3, will be used.

12. HEALTH ECONOMICS ANALYSIS

12.1. Aim

The primary economic analysis will take an NHS and personal social services cost perspective in accordance with NICE guidance of the effects of MR-MPH versus Guanfacine XR.

The secondary aim will take a wider societal perspective to capture the broader effects of MR-MPH versus guanfacine. It will establish potentially broader effects on families and society by establishing time lost from work because of care of children with ADHD and co-existing tics and out-of-pocket expenses for the families. The combination of resource use and subsequent

calculation of health service and societal cost will be combined with outcome and child/young person and parent/carer quality of life data to provide a measure of the cost effectiveness and cost utility of the effects of MR-MPH versus Guanfacine XR.

12.2. Health Care Resource Use, Including Education and Social Care

A purposely designed health economic resource collection proforma drawing on expertise gained in previous ADHD and tic studies will be created and used in this trial [25-27] The team will work closely with the PPI to ensure the measure captures the economic consequences and costs of the treatment alternatives that are important to families. The measure will collect data on treatment effects such as inpatient and outpatient hospital visits and primary and community care use as well as societal and education costs. Whilst minimising patient burden it is important this measure is fit for purpose. To aid better research in resource collection the measure developed will be submitted to the health economics professional database for resource costing; the Database of Instruments for Resource Use Measurement (DIRUM).

Within the secondary analysis, data collection methods will be designed to quantify the effect of time off work for parents/carers (including friends and family) and the implications for productivity. In addition, the plan is to measure effects on time lost from education or training for the child/young person because of their ADHD and co-existing tics. One of the key cost drivers of the health intervention and usual care in this trial will be medication. It is important to record and as such cost this accurately.

12.3. Outcome Measures

The health economic analyses will utilise the following outcomes as defined in the Synopsis.

- Child/young person quality of life – EQ5DY[6] and CHU-9D [5]
- Parent/carer quality of life – EQ5D-5l [7]
  The above measure enables cost utility analysis to be undertaken.
- SNAP-IV [2]
  This will be used, if feasible, for a cost effectiveness analysis.

Health economic outcome data for children/young people will be collected using the EQ5DY and the CHU-9D. Use of both measures will enable comparative analysis to be performed of the validity and acceptability of these two measures within the patient group. The two represent the most frequently used preference-based measures in children/young people [28, 29]. Eliciting comparative use of the two measures will provide a valuable resource for investigators going forward, who are seeking to incorporate an outcome-based preference measure into their research. Use of both measures will be evaluated during the pilot phase and if this is considered to impose too great a burden on respondents, the decision will be taken to continue with the collection of one measure only.

Whilst there is currently controversy around the EQ5D-5l tariff, we will map the EQ5D-5l values back to the EQ-3D using the Crosswalk Index Value Calculator [7] to provide consistency with current NICE requirements [8].

12.4. Analysis

The quality-of-life data will be constructed using area under the curve analysis to construct the Quality-Adjusted life years (QALYs) for parents and children over the course of the trial.

The resource use data and subsequent calculation of health service and societal cost will be combined with child [6] and carer [5] quality of life data to provide a measure of the cost effectiveness and cost utility of the use of MR-MPH versus Guanfacine XR.

The net monetary benefit (NMB) framework will be used. The NMB framework estimates the extent to which, and the probability that, the use of MR-MPH versus Guanfacine XR is cost effective at a range of threshold values (i.e. from £0 to £30,000) for the willingness to pay per QALY. Non-parametric probabilistic sensitivity analysis (PSA) will be employed to calculate realised values; subsequently generating Cost Effectiveness Acceptability Curves (CEACs), which indicate the probability of being cost effective at the range of threshold values.

Although first analysis will be on a complete case basis, the team will examine the level of data missingness and consider the use of methods such as multiple imputation analysis missing at random assuming data quality is good.

This may include methods such as bootstrap analysis, complete consideration can be given towards examining key cost drivers through sensitivity analysis [26].

13. ADVERSE EVENTS

13.1. Definitions

An adverse event is any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the trial.

An AE does include a / an:

1. exacerbation of a pre-existing illness.

2. condition detected or diagnosed after medicinal product administration even though it may have been present prior to the start of the trial.

3. continuous persistent disease or symptoms present at baseline that worsen following the start of the trial.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) as per NCTU standard practice.

An AE does <u>not</u> include a / an:

1. medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that led to the procedure is an AE.

2. pre-existing disease or conditions present or detected at the start of the trial that did not worsen.

3. situations where an untoward medical occurrence has not occurred (e.g., hospitalisations for cosmetic elective surgery, social and / or convenience admissions).

4. disease or disorder being studied, or sign or symptom associated with the disease or disorder unless more severe than expected for the participant's condition.

5. overdose of concurrent medication without any signs or symptoms.

The known side effects listed as common or very common in sections 2.3 and 2.4 'Known side effects – Intervention (MR-MPH)' and 'Known side effects – Comparator (Guanfacine XR)' respectively of this protocol will not be classed as adverse events and do not require reporting. As these medications are licenced for use in this population and are commonly prescribed, risks are comparable to usual practice.

The source used to define the known side effects and therefore those events that do not require reporting is for:

- MR-MPH - The Concerta XL SmPC section 4.8, date of last revision 04 September 2023.

- Guanfacine XR - The Intuniv ™ SmPC section 4.8, date of last revision 23 February 2022.

A **Serious Adverse Event (SAE)** is any adverse event occurring following trial mandated procedures, having received the intervention or comparator IMP that results in any of the following outcomes:

1. Death.

2. A life-threatening adverse event.

3. Inpatient hospitalisation or prolongation of existing hospitalisation.

4. A disability / incapacity.

5. A congenital anomaly in the offspring of a participant.

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

All adverse events will be assessed for seriousness, expectedness and causality.

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

13.2. Causality

Not related or improbable: a clinical event including laboratory test abnormality with temporal relationship to trial treatment administration which makes a causal relationship incompatible or for which other drugs, chemicals or disease provide a plausible explanation**.** This will be counted as "unrelated" for notification purposes.

Possible: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, but which could also be explained by other drugs, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Probable: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and is unlikely to be due to other drugs, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Definite: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as "related" for notification purposes.

An AE whose causal relationship to the trial IMP is assessed by the CI or PI as "possible", "probable", or "definite" is an Adverse Reaction. The CI will assess relatedness and will be able to upgrade an assessment (from unrelated to related) but cannot downgrade an assessment (from related to unrelated).

With regard to the criteria above, medical and scientific judgment shall be used in deciding whether prompt reporting is appropriate in that situation.

13.3. Expectedness

Expectedness will be determined by the CI or their delegate according to the SmPC of the trial IMPs. An AE that is listed in the approved SmPC will be characterised as 'expected' whereas one that is not listed, or if the nature or severity of the event is not consistent with the SmPC will be considered 'unexpected'.

13.4. Reporting of Adverse Events

Reporting timelines

AEs will be reported regularly by the participant and/or their parent/carer as per the schedule outlined in section 9 'Trial Treatment and Regimen' of this protocol.

In the event of a SAE, the site/usual care team should inform the research team immediately/within the day upon becoming aware of the event. The research team will be responsible for the timely reporting of the SAE via the relevant SAE form to the trial team at NCTU for attention of the CI.

The completed, signed and dated form should be sent to the NCTU using the following email address: nctu-sae@nottingham.ac.uk

Please note this email address is used for SAE monitoring only and should not be used for any trial queries or any other trial-related communications.

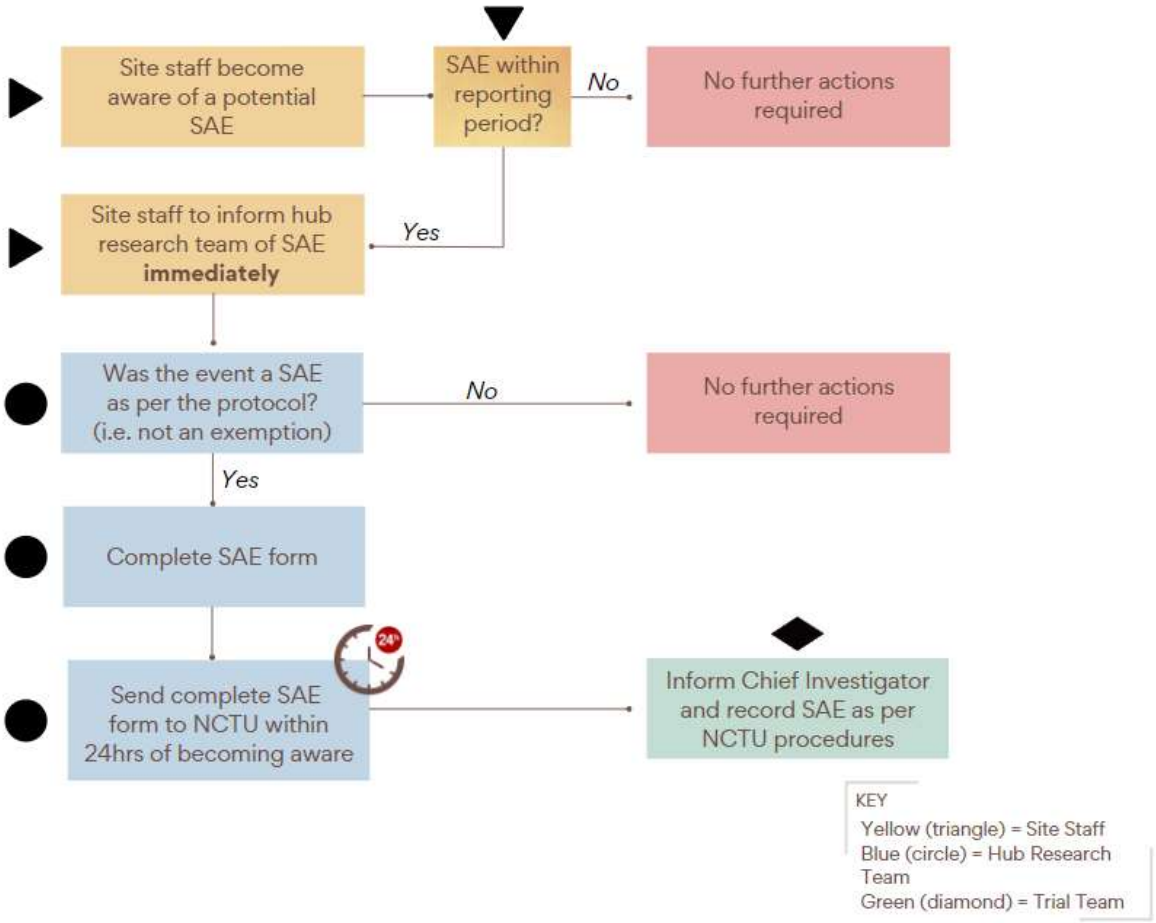
The research team should send the completed SAE form to the trial team within 24 hours of becoming aware of the event. The NCTU will confirm receipt of the SAE form and follow the appropriate procedure for processing as per the relevant NCTU SOP.

Related SAEs will be collected from the day of randomisation until either the end of trial participation (52 weeks) or when the hub team are notified of the discontinuation of trial medication.

Related SAEs will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the trial medication or treatment is not the cause.

The CI (delegated responsibility by the Sponsor) shall be informed immediately of any serious adverse events and shall determine seriousness and causality in conjunction with any treating medical practitioners.

Figure 2. SAE Reporting Process



See figure 2 above for the detailed SAE reporting process. Please note that shapes (triangle, circle, diamond) refer to the shapes outside the boxes and are there in case the document is printed in black and white.

13.5. SAEs Exempt from Reporting

SAEs that do not need to be reported immediately are routine hospitalisations for pre-existing conditions, admissions lasting less than 24 hours and hospitalisations for social reasons.

Pregnancy

In the event of a pregnancy occurring in a trial participant or their partner, monitoring shall occur during the pregnancy and after delivery to ascertain any trial related adverse events in the mother or the offspring.

13.6. Reporting to Regulatory Bodies

All related SAEs and SARs (including SUSARs) will be recorded and reported to the MHRA and REC as part of the annual Development Safety Update Report (DSUR). SUSARs will be reported within the statutory timeframes to the MHRA, and REC as stated below. The Sponsor shall be responsible for adverse event reporting.

13.7. SUSARs

A serious adverse event whose causal relationship is assessed by the CI as "possible", "probable", or "definite" will be regarded as a Serious Adverse Reaction (SAR).

A serious adverse event that is either sudden in its onset (e.g. anaphylaxis), unexpected in its severity and seriousness or not a known side effect of the IMP *and* related or suspected to be related to the IMP is classed as Suspected Unexpected Serious Adverse Reaction (SUSAR) and requires expedited reporting as per the clinical trials regulations.

All serious adverse events that fall or are suspected to fall within these criteria shall be treated as a SUSAR until deemed otherwise.

The event shall be reported immediately (within 24 hours) of knowledge of its occurrence to the CI.

The CI will:

- Assess the event for seriousness, expectedness and relatedness to the trial IMP.
- Be able to upgrade an assessment (from unrelated to related) but cannot downgrade an assessment (from related to unrelated)
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action.
- If the event is deemed a SUSAR, enter the required data on the MHRA's eSUSAR website within seven days.
- Inform the REC using the reporting form found on the HRA web page within seven days of knowledge of the event.
- Send any follow-up information and reports to the MHRA and REC within a further eight days.
- Make any amendments as required to the trial protocol and inform the ethics and regulatory authorities as required.

13.8. Trial Treatment Related SAEs

A serious adverse event that is unexpected in its severity and seriousness *and* deemed directly related to or suspected to be related to the trial treatment but not the IMP shall be reported to the ethics committee that gave a favourable opinion as stated below.

The event shall be reported immediately of knowledge of its occurrence to the CI.

The CI will:

- Assess the event for seriousness, expectedness and relatedness to the trial treatment.
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action.
- If the event is deemed related to the trial treatment shall inform the REC using the reporting form found on the HRA web page within 7 days of knowledge of the event.
- Shall, within a further eight days send any follow-up information and reports to the REC.
- Make any amendments as required to the trial protocol and inform the REC as required.

Participant removal from the trial due to adverse events

Any participant who experiences an adverse event deemed as serious may be withdrawn from the trial at the discretion of the research clinician but would continue to be followed-up in accordance with the protocol unless they withdraw consent.

14. ETHICAL AND REGULATORY ASPECTS

14.1. Ethics Committee and Regulatory Approvals

The trial will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval / favourable opinion from the Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics Committee (REC), the respective National Health Service (NHS) or other healthcare provider's Research & Development (R&D) department, and the Health Research Authority (HRA). Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and (if appropriate) revised informed consent forms, PISs etc. have been reviewed and received approval/favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the MHRA, R&D and REC are notified as soon as possible, and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, in accordance with the Medicines for Human Use Regulations, Statutory Instrument 2004, 1031 and its subsequent amendments and the UK Department of Health Policy Framework for Health and Social Care, 2017.

14.2 Informed Consent and Participant Information

The process for obtaining participant informed consent or assent and parent / guardian informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant (parent carer/CYP as appropriate) shall sign and date the Consent Form before the person can participate in the trial.

The participant will receive a copy of the signed and dated forms, and the original will be retained in the trial database (for econsent) or in the ISF if completed on paper. A second copy will be filed in the participant's medical notes and a signed and dated note made in the notes that informed consent was obtained for the trial.

The decision regarding participation in the trial is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding trial participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be done before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the trial, and will discuss with them, whether they wish to continue with the trial. If applicable they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the trial, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

14.3. Records

14.3.1. Drug accountability

There are no trial-specific accountability requirements; sites and/or local pharmacies will follow their own local procedures for recording treatments dispensed.

Drug supplies will be kept in a secure, limited access storage area under the storage conditions specified by each pharmacy.

Accountability logs will not be required as trial IMPs will be obtained via standard prescriptions dispensed by local pharmacies/clinic stocks. Prescriptions raised (i.e., titration schedule) however will be recorded on the trial database.

14.3.2. Electronic Case Report Forms (eCRFs)

Each participant will be assigned a trial identity code number, allocated at randomisation for use on eCRFs, other trial documents and the electronic database. The documents and database will use the CYP date of birth (dd/mmm/yyyy), name and NHS number.

eCRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial in accordance with regulatory requirements and for follow-up as required.

eCRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.'

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled, and dated.
The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the eCRF.

14.3.3. Source documents

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, current medical records, laboratory results and pharmacy records. An eCRF may also completely serve as its own source data. Only trial staff as listed on the Delegation

Log shall have access to trial documentation other than the regulatory requirements listed below.

14.3.4. Direct access to source data / documents

The eCRF and all source documents, including progress notes and copies of laboratory and medical test results shall made be available at all times for review by the CI, Sponsor's designee and inspection by relevant regulatory authorities (MHRA).

14.4. Data Protection

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 2018. The eCRF will only collect the minimum required information for the purposes of the trial. Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one-way encryption method).
Information about the trial in the participant's medical records will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

15. QUALITY ASSURANCE & AUDIT

15.1. Insurance and Indemnity

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff with both public liability insurance and clinical trials insurance in respect of claims made by research subjects.

15.2. Trial Conduct

Trial conduct will be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting.

The Trial Coordinator, or where required, a nominated designee of the Sponsor, shall carry out a site systems audit at least yearly, and an audit report shall be made to the TSC.

15.3. Trial Data

Monitoring of trial data shall include confirmation of informed consent, source data verification, data storage and data transfer procedures, local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Trial Coordinator, or where required, a nominated designee of the Sponsor, shall carry out

monitoring of trial data as an ongoing activity. Further details are included in the Monitoring Plan.

Entries on eCRFs will be verified by inspection against the source data. A sample of eCRFs (10% or as per the trial risk assessment) will be checked on a regular basis for verification of all entries made. In addition, the subsequent capture of the data on the trial database will be checked. Where corrections are required, these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by the regulatory authority as required.

15.4. Record Retention and Archiving

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Code of Research Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the trial. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the trial records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the CI on behalf of the Sponsor shall be finally archived securely in the Microsoft cloud which has multiple redundant systems and backup services. This archive shall include all trial databases and associated meta-data encryption codes. Access to files once archived (e.g. for inspection purposes), will be managed by the NCTU archivist and will only be accepted on approval of the University of Nottingham sponsor.

15.5. Discontinuation of the Trial by the Sponsor

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the TSC and DMC as appropriate in making this decision.

15.6. Statement of Confidentiality

Individual participant medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted above.

Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare. If information is disclosed during the trial that could pose a risk of harm to the participant or others, the research team will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

16. PUBLICATION AND DISSEMINATION POLICY

Results from the trial will be published in peer reviewed scientific journals and may be disseminated to relevant user groups. Results may also be published on relevant websites and presented at conferences. Participants will not be identified in any publications or presentations. Publications and presentations will typically happen after the end of the trial.

17. USER AND PUBLIC INVOLVEMENT

The perspectives of young people and their parents are key to this research. PPI will be embedded throughout the project to ensure impact and value to the research.

A PPI panel consisting of parents and children will be involved in the research at all stages. This panel will contribute to the trial design and implementation including development of participant information, recruitment strategies, data collection, retention.

Members of the panel will be invited to attend TMGs or meet separately with the trial manager (if that is their preference) to discuss trial updates. This will include updates on recruitment, strategies, and retention. They will also be contacted on an ad-hoc basis outside these scheduled meetings as-and-when issues with recruitment arise. We will also have two lay members of the public as part of our TSC (who will also be independent of our PPI panel).

There will also be a range of flexible opportunities for participating in project feedback and dissemination activities including co-facilitating and presenting at the interactive dissemination workshop/consensus meeting, publication authorship and presenting at conferences to highlight the project findings.

Panel members will be reimbursed accordingly, with appropriate remuneration and recognition being established for each group as per guidance from NIHR Involve, especially with regard to PPI with young people. A budget has been allocated for PPI training and learning events to ensure our PPI group are supported in gaining the necessary skills, which may include learning about research design and good clinical practice.

A webpage will be created which will host short blogs to inform the public about our research. Some of these blog entries may include videos of our PPI children/young people talking about the trial. Members of the Panel will also be invited to co-present the trial findings with the research team, both to academic and lay audiences.

18. TRIAL FINANCES

18.1. Funding source

This trial is funded by the NIHR, Health Technology Assessment programme; Project Reference Number: NIHR128472. The funder is not involved in the conduct, analyses interpretation or reporting of the trial.

18.2. Participant stipends and payments

Participants will not be paid to participate in the trial. However, families will be offered a total of £30 in e-vouchers as a token of appreciation for their involvement in the trial. The e-vouchers will be given at different timepoints in the trial. Families will also be entered into a number of

prize draws (up to six expected to be scheduled during follow-up) for an electronic tablet or equivalent.

Travel expenses will be offered for any clinic visits in excess of usual care.

19. SIGNATURE PAGE

Signatories to Protocol:

Chief Investigator: Chris Hollis

Signature:_____

Date:

Trial Statistician: Reuben Ogollah

Signature:_____

Date:

20. REFERENCES

1. WALKUP JT, Rosenberg LA, Brown J, Singer HS. The validity of instruments measuring tic severity in Tourette's syndrome. Journal of the American Academy of Child & Adolescent Psychiatry. 1992;31(3):472-7.
2. Swanson JM, Kraemer HC, Hinshaw SP, Arnold LE, Conners CK, Abikoff HB, et al. Clinical Relevance of the Primary Findings of the MTA: Success Rates Based on Severity of ADHD and ODD Symptoms at the End of Treatment. Journal of the American Academy of Child & Adolescent Psychiatry. 2001;40(2):168-79.
3. McKenzie K, Paxton D, Murray G, Milanesi P, Murray AL. The evaluation of a screening tool for children with an intellectual disability: The Child and Adolescent Intellectual Disability Screening Questionnaire. Research in Developmental Disabilities. 2012;33(4):1068-75.
4. Guy W. ECDEU assessment manual for psychopharmacology: US Department of Health, Education, and Welfare, Public Health Service; 1976.
5. Stevens K. Valuation of the child health utility 9D index. Pharmacoeconomics. 2012;30(8):729-47.
6. Wille N, Badia X, Bonsel G, Burström K, Cavrini G, Devlin N, et al. Development of the EQ-5D-Y: a child-friendly version of the EQ-5D. Quality of Life Research. 2010;19(6):875-86.
7. Van Hout B, Janssen M, Feng Y-S, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value in health. 2012;15(5):708-15.
8. The National Institute for Health and Care Excellence (NICE). Attention deficit hyperactivity disorder: diagnosis and management NICE guideline [NG87]. 2018.
9. Faraone S, Asherson P, Banaschewski T, Biederman J, Buitelaar J, Ramos-Quiroga J, et al. Attention-deficit/hyperactivity disorder. Nature Rev. Dis. Primers 15020. 2015.
10. Hollis CP. Clinical effectiveness and patient perspectives of different treatment strategies for tics in children and adolescents with Tourette syndrome: a systematic review and qualitative analysis. 2016.
11. Cortese S, Adamo N, Del Giovane C, Mohr-Jensen C, Hayes AJ, Carucci S, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. The Lancet Psychiatry. 2018;5(9):727-38.
12. Osland ST, Steeves TD, Pringsheim T. Pharmacological treatment for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders. Cochrane Database of Systematic Reviews. 2018(6).
13. Yemula C, Cope K. 1808 An audit of our ADHD service to review assessments before and after starting ADHD medication and to check compliance with NICE guidelines. Archives of Disease in Childhood. 2021;106(Suppl 1):A497-A8.
14. Canadian ADHD Resource Alliance. Canadian ADHD Practice Guidelines [Available from: https://adhdlearn.caddra.ca/purchase-guidelines/.
15. Hill P, Taylor E. An auditable protocol for treating attention deficit/hyperactivity disorder. Archives of disease in childhood. 2001;84(5):404-9.
16. Clinical Trials Facilitation and Coordination Group (CTFG). Recommendations related to contraception and pregnancy testing in clinical trials 2020 [Available from: https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-

About_HMA/Working_Groups/CTFG/2020_09_HMA_CTFG_Contraception_guidance_Version_1.1_updated.pdf.
17. Cortese S, Holtmann M, Banaschewski T, Buitelaar J, Coghill D, Danckaerts M, et al. Practitioner review: current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents. Journal of Child Psychology and Psychiatry. 2013;54(3):227-46.
18. Graham J, Banaschewski T, Buitelaar J, Coghill D, Danckaerts M, Dittmann RW, et al. European guidelines on managing adverse effects of medication for ADHD. European child & adolescent psychiatry. 2011;20(1):17-37.
19. Morrison A, Stauffer ME, Kaufman AS. Defining medication adherence in individual patients. Patient preference and adherence. 2015;9:893.
20. Youthinmind. DAWBA. Information for researchers and clinicians about the Development and Well‐Being Assessment. 2012.
21. Jeon S, Walkup JT, Woods DW, Peterson A, Piacentini J, Wilhelm S, et al. Detecting a clinically meaningful change in tic severity in Tourette syndrome: a comparison of three methods. Contemporary clinical trials. 2013;36(2):414-20.
22. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. Journal of Pharmacology and pharmacotherapeutics. 2010;1(2):100-7.
23. Leckman JF, Riddle MA, Hardin MT, Ort SI, Swartz KL, Stevenson J, et al. The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. Journal of the American Academy of Child & Adolescent Psychiatry. 1989;28(4):566-73.
24. McGuire JF, Piacentini J, Storch EA, Murphy TK, Ricketts EJ, Woods DW, et al. A multicenter examination and strategic revisions of the Yale Global Tic Severity Scale. Neurology. 2018;90(19):e1711-e9.
25. Hollis C, Hall CL, Guo B, James M, Boadu J, Groom MJ, et al. The impact of a computerised test of attention and activity (QbTest) on diagnostic decision‐making in children and young people with suspected attention deficit hyperactivity disorder: single‐blind randomised controlled trial. Journal of Child Psychology and Psychiatry. 2018;59(12):1298-308.
26. Hall CL, Walker GM, Valentine AZ, Guo B, Kaylor-Hughes C, James M, et al. Protocol investigating the clinical utility of an objective measure of activity and attention (QbTest) on diagnostic and treatment decision-making in children and young people with ADHD—'Assessing QbTest Utility in ADHD'(AQUA): a randomised controlled trial. BMJ open. 2014;4(12):e006838.
27. Hall CL, Davies EB, Andrén P, Murphy T, Bennett S, Brown BJ, et al. Investigating a therapist-guided, parent-assisted remote digital behavioural intervention for tics in children and adolescents—'Online Remote Behavioural Intervention for Tics'(ORBIT) trial: protocol of an internal pilot trial and single-blind randomised controlled trial. BMJ open. 2019;9(1):e027583.
28. Peasgood T, Bhardwaj A, Biggs K, Brazier JE, Coghill D, Cooper CL, et al. The impact of ADHD on the health and well-being of ADHD children and their siblings. European Child & Adolescent Psychiatry. 2016;25(11):1217-31.
29. Rowen D, Keetharuth AD, Poku E, Wong R, Pennington B, Wailoo A. A review of the psychometric performance of selected child and adolescent preference-based measures used to produce utilities for child and adolescent health. Value in Health. 2021;24(3):443-60.

30. Goodman R, Ford T, Richards H, Gatward R, Meltzer H. The Development and Well-Being Assessment: description and initial validation of an integrated assessment of child and adolescent psychopathology. The Journal of Child Psychology and Psychiatry and Allied Disciplines. 2000;41(5):645-55.
31. Goodman A, Heiervang E, Collishaw S, Goodman R. The 'DAWBA bands' as an ordered-categorical measure of child mental health: description and validation in British and Norwegian samples. Social psychiatry and psychiatric epidemiology. 2011;46(6):521-32.

20. APPENDICES

20.1. Appendix A

Participant Age	6–10 years old	11–15 years old	16+ years old
Primary Contact	Parent/carer	Parent/carer and CYP*	Parent/carer and CYP*
Screening call contact	Parent/carer (CYP may be present and contribute should they wish)		
Consent	Parent/carer		Parent/carer and CYP
Assent	CYP	CYP	Not applicable
Questionnaire/ Scale			
DAWBA	Parent/carer report on CYP	Parent/carer report on CYP (CYP may wish to provide input)	Parent/carer report on CYP (CYP may wish to provide input)
YGTSS	Researcher with CYP and parent/carer	Researcher with CYP and parent/carer	Researcher with CYP and (optional) parent/carer
CAIDS-Q or alternative	Parent/carer report on CYP	Parent/carer report on CYP	Parent/carer report on CYP
SNAP-IV	Parent/carer report on CYP	Parent/carer report on CYP	Parent/carer report on CYP
CHU9D	CYP self-report**	CYP self-report**	CYP self-report
EQ-5DY	CYP self-report**	CYP self-report**	CYP self-report
EQ5D-5l	Parent/carer self-report	Parent/carer self-report	Parent/carer self-report
Health Economics	Parent/carer report on CYP	Parent/carer and CYP***	Parent/carer and CYP***
Hill & Taylor Side Effects Scale (modified)	Parent/carer report on CYP	Parent/carer and CYP***	Parent/carer and CYP***
CGI-I & CGI-S	Researcher report on CYP	Researcher report on CYP	Researcher report on CYP
Adherence	Parent/carer report on CYP	Parent/carer and CYP***	Parent/carer and CYP***

*Parent/carer as a requirement. CYP 11-16 can be included in relevant communications should they wish and only following consent from the parent/carer to do so.
**with the help of the parent/carer as needed.
***should they wish to provide input

20.2. Appendix B

Description of Outcome Measures

Child and Adolescent Intellectual Disability Screening Questionnaire (CAIDS-Q)[3] or alternative

The CAIDS-Q is a valid and reliable tool to help identify children and adolescents who are likely to have an intellectual disability. It is a 7-item scale which can be completed with or by the individual or someone who knows him/her well. A total score is calculated which is converted to a percentage score. A cut-off by age group indicates if the child/young person is likely to have an intellectual disability or not. The CAIDS-Q in SATURN is utilised to determine intellectual disability at baseline.

Child Health Utility 9D (CHU9D) [5].

The CHU9D is a paediatric generic measure of health-related quality of life developed for children and young people. It consists of a short questionnaire with 9 items (worried, sad, pain, tired, annoyed, schoolwork/homework, sleep, daily routine, and activities) with 5-level response categories per question (scored 1–5) and is self-completed by the child/young person (with parent/guardian help for younger children).

Clinical Global Impressions Scale (CGI) [4].

The Clinical Global Impressions (CGI) Scale is a brief, individual assessment of the clinician's view of the patient's global functioning prior to and after starting a trial medication. The CGI provides an overall clinician-determined summary measure that considers all available information, including knowledge of the patient's history, psychosocial circumstances, symptoms, behaviour, and the impact of the symptoms on the patient's ability to function. The CGI comprises two one-item measures evaluating the following: (a) severity of psychopathology from 1 to 7 and (b) change from the initiation of treatment on a similar seven-point scale. For the purpose of SATURN only the CGI-Improvement (CGI-I) & CGI-Severity (CGI-S) will be used.

The Development and Well-being Assessment (DAWBA) [24,25].

The DAWBA is a structured package of questionnaires designed to generate ICD-10 and DSM-IV psychiatric diagnoses on 5-16 year olds. The DAWBA computer algorithm estimates the probability of having a psychiatric disorders in bands of <0.1%, 0.5%, 3%, 15%, 50% and > 70% based on large community-based population studies [30], the top two levels have been shown to reliably indicate presence of a clinician-rated diagnosis and can be used as an alternative to clinician-rated diagnoses in research studies [31]. The DAWBA has established validity and reliability [30] and will be completed online, via the DAWBA platform, prior to baseline appointment to ascertain patient eligibility. A trial team area is created for each trial specifically and can be accessed only with unique login details provided to the trial team. The information collected from parents/carers online is immediately available to the trial team (hub research team in SATURN) for review or rating online. The reports summarising the

symptoms and diagnoses on each child/young person can be downloaded as a .pdf file and printed or stored in electronic form. The database for the entire research project can be downloaded as csv files for statistical analysis in Excel, SPSS etc.

Parent health-related quality of life questionnaire (EQ5D-5l) [7].

A self-report questionnaire to measure health-related quality of life according to 5 dimensions i.e., mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The recipient is asked to rate their own current level of function in each dimension into one of three degrees of disability (severe, moderate or none). The combination of these with the conditions “death” and “unconscious” enables description of 245 different health states. Each health state is ranked and transformed into a single score called the utility. The utility score is an expression of the QALY and is commonly used to make evidence-based decisions in analyses of cost-effectiveness.

Child and adolescent health-related quality of life questionnaire (EQ-5DY) [6].

The EQ-5DY is a generic, self-report tool which measures health-related quality of life in children and adolescents. It comprises of the following five dimensions: mobility, looking after myself, doing usual activities, having pain or discomfort and feeling worried, sad or unhappy. Each dimension has 3 levels: no problems, some problems and a lot of problems. The recipient is asked to indicate their health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient’s health state.

Swanson, Nolan, and Pelham Questionnaire (SNAP-IV) [2].

The SNAP-IV is a rating scale used to screen for Attention Deficit Hyperactivity Disorder. Originally, the SNAP-IV had 90 items but has now been revised to an 18-item scale; items from the DSM-IV criteria for attention-deficit/hyperactivity disorder (ADHD) are included for the two subsets of symptoms: Inattention and Hyperactivity/Impulsivity. The measure is based on a 0 to 3 rating scale: Not at All = 0, Just A Little = 1, Quite A Bit = 2, and Very Much = 3. Sub-scale scores on the SNAP-IV are calculated by summing the scores on the items in the subset and dividing by the number of items in the subset. The score for any subset is expressed as the Average Rating-Per-Item. The SNAP-IV is completed by the parent/carer at various timepoints in the trial (including baseline and the 12-week follow-up visit).

Yale Global Tic Severity Scale (YGTSS) [1] .

The Yale Global Tic Severity Scale (YGTSS) [1]is a tool used to measure the severity of tic symptoms in individuals aged 6–17. It is made up of a semi-structured interview, followed by a questionnaire where individuals are asked to rate the severity of their tic symptoms (both motor and vocal) in domains such as: number, frequency, intensity,

complexity, interference and an impairment scale, where the individual rates how the tic impacts on their daily life and activities. The overall score incorporates ratings in 5 domains: Total Motor Tic Score, Total Verbal Tic Score, Total Tic Score (Motor + Verbal), Overall Impairment Rating, and Global Severity Score. When calculating the Global Severity score, it is found by adding together the total motor, verbal and impairment scores. The Total Tic Severity Score (TTSS) has a range of 0–50, and the Global Severity Score has a range of 0–100. A higher score on all scales suggests more severe tics, or a greater impact that tics have on the person's life. The baseline assessment will be conducted face-to-face. When possible, the follow-up assessments will be conducted by the same blinded assessor via video-conference call or telephone.

(Modified) Hill and Taylor side-effects scale [15].

The (modified) Hill and Taylor [15] consists of 17 short items relating to common side effects (such as headaches, anxiety, sleep, and low mood). The participant is asked to respond on a 5-point scale ranging from "not at all" to "all the time" to describe the presence of each item. Item 17 asks if the patient has tics, this has been modified to read "increased tics" as tics will be present in our sample. This will be completed and all subsequent follow up visits. It will be used for the purposes of adverse event reporting.