PROTOCOL FULL TITLE:

Randomised controlled trial of the short term effects of OROS-methylphenidate on ADHD symptoms and behavioural outcomes in young male prisoners with attention deficit hyperactivity disorder

Protocol Short Title/Acronym:

CIAO-II

Trial Identifiers:

EudraCT Number – 2015-004271-78

REC Number – 16/EE/0117

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1. Study Synopsis

Title of clinical trial	Randomised controlled trial of the short term effects of OROS-methylphenidate on ADHD symptoms and behavioural outcomes in young male prisoners with attention deficit hyperactivity disorder
Protocol Short Title/Acronym	CIAO-II
Study Phase if not mentioned in title	Phase IV study
Sponsor name	King's College London
Chief Investigator	Prof Philip Asherson
EudraCT number	2015-004271-78
REC number	16/EE/0117
Medical condition or disease under investigation	Attention-Deficit/Hyperactivity Disorder (ADHD)
Purpose of clinical trial	The overall aim of the trial is to investigate the effects of OROS-MPH in young male prisoners (age 16-25) meeting DSM-5 diagnostic criteria for ADHD. We address the following study questions: (1) What is the efficacy of OROS-MPH in reducing inattention and hyperactivity-impulsivity in young male prisoners meeting diagnostic criteria for DSM-5 ADHD? (2) What is the efficacy of OROS-MPH in reducing secondary outcomes that are key indicators of behavioural and functional impairments used in the management of young prisoners in the UK? These include emotional dysregulation, antisocial behaviour in the prison, violent attitudes (a measure linked to aggression) and reports of behaviour from prison staff. (3) Are improvements in secondary behavioural outcomes mediated by improvements in ADHD symptoms or emotional dysregulation?
Primary objective	To establish the efficacy of OROS-MPH in reducing ADHD symptoms (inattention and hyperactivity-impulsivity) in young male offenders aged 16-25, meeting diagnostic criteria for DSM-5 ADHD.

Secondary objective (s)	To investigate the efficacy of OROS-MPH in young male offenders aged 16-25, meeting DSM-5 diagnostic criteria for ADHD, on reducing secondary outcomes that are indicators of behavioural and functional impairments used in the management of young prisoners in the UK. These include emotional dysregulation, antisocial behaviour in the prison, violent attitudes (a measure linked to aggression) and reports of behaviour from prison staff. To investigate the hypothesis that improvements in secondary behavioural outcomes are mediated by improvements in ADHD symptoms or emotional dysregulation?
Trial Design	An 8-week parallel arm randomised placebo controlled trial of an extended release formulation of MPH (OROS-MPH), on ADHD symptoms, behaviour and functional outcomes in young male offenders aged 16-25, meeting DSM-5 criteria for ADHD. Participants will be randomised to 8-weeks treatment with either OROS-MPH or placebo, titrated over 5 weeks to balance ADHD symptom improvement against side effects. 200 participants will be recruited with 1:1 ratio of drug to placebo. Randomisation will be conducted by the King's CTU with blinding of both investigators and participants. OROS-MPH will be offered to both the OROS-MPH and placebo treated groups as part of their clinical care once the 8-week trial is completed.
Endpoints	The primary outcome measure is the level of ADHD symptoms measured on the investigator rated Connors Adult ADHD rating scale (CAARS-O) to address the question of efficacy of OROS-MPH on ADHD symptoms in young offenders meeting DSM-5 diagnostic criteria for ADHD. Secondary outcomes address important exploratory questions about the effects on comorbid symptoms and behavioural impairments that are commonly seen in offenders with ADHD. These include: emotional dysregulation (Wender-Reimherr Adult ADHD Diagnostic Scale, WRAADS) [18]. The number of adjudications for antisocial behaviour and rule breaking in the previous 8-weeks. Ratings of aggressive behaviour by prison staff and educational staff using the prison officer and education staff versions of the Modified Overt Aggression Scale (MOAS) [19]; and classroom behaviour report cards Attitudes towards violence (Maudsley Violence

	Questionnaire, MVQ) [20]. CORE Outcome Measure (CORE-M) [21], a self-rated scale of subjective well-being, problems/symptoms, life functioning and risk/harm, designed to measure psychological distress before and after treatment. In addition we will include: the mind excessively wandering scale (MEWS) [22], comorbid symptoms using the BSI scale [23], rating scale for irritability (ARI-S) [24] and a clinical global impression using the CGI [25].
Sample Size	A total of 200 participants will be randomised to Concerta XL or placebo in a 1:1 ratio.
Summary of eligibility criteria	Males aged between 16 and 25 years who provide fully informed consent and have a clinical and research diagnosis of ADHD following assessment with the DIVA clinical interview for DSM-5 ADHD.
IMP, dosage and route of administration	Over-coated Concerta XL capsules, taken orally, at doses of 18, 36, 54 and 72 mg.
Active comparator product(s)	There is no active comparator.
Maximum duration of treatment of a subject	The treatment duration for the trial (and primary endpoint) is for 8-weeks
Version and date of final protocol	Version 2.0 30.08.18
Version and date of protocol amendments	v.1.1 22.03.2016 v.1.2 05.07.2016 v.1.3 29.03.2017 v.1.4 03.05.2017

Version and date	Author	REC /HRA approved date	Reason for change
v.1.1 22.03.2016	P Asherson	31.05.2016	First approved version
v.1.2 05.07.2016	P Asherson	11.07.2016	Remove Gough SO scale (Section 6.1)
v.1.3 29.03.2017	P Asherson	06.04.2017	1) Typo regarding visit (Section 3.3) 2) Add IQ clarification (Section

			5.3)
v.1.4 03.05.2017	P Asherson	26.05.2017	Remove RPAQ from week 5 and 8 table and text since only baseline measure (Section 6.1 and 7.1.2)
v.2.0 30.08.2018	P Asherson		1) Update sponsor details. 2) Update co-applicant details. 3) Add previous versions and protocol amendments and a description of the changes. 4) Page number amendments. 5) Amendment to referencing throughout the protocol. 6) Amendment to trial objectives not looking at positive Incentives and Earned Privileges (IEP) but rather reports of behaviour from prison staff (Session 3.1). 7) Amendment to secondary endpoints. IEPs are no longer recorded in Scottish prisons. The secondary outcomes using

			IEPs are replaced by prison rated behaviour report cards. (Session 3.1.2). 8) Amendment to 3.3 flowchart and to table 1, clarifying the process when a participant is invited into the study and that there is a detailed summary table on page 25 (Section 3.3). 9) Clarification in the table p.17 that it is only a repeat of outcome measures at week 8 (Section 3.3). 10) Amendment to text to state that participants transferred to another prison will be followed up for study assessment but not supplied with study medication. (Section 4.4.1) 11) Added two exclusion criteria and clarification of other exclusion and inclusion criteria (Section 5.1 and 5.2).

			12) Clarification that Rochester will only be used if recruitment targets are not met and other procedures (Section 5.3). 13) Potential participants who are visually impaired- IQ based on clinical judgement only and for those unable to complete the assessment (Section 5.3). 14) Clarified arrangements to maintain blinding until after primary analysis (Section 5.4). 15) Added instruction to stop study medication if participants disclose using “spice” (Section 5.5). 16) Clarification that trial ends at database lock (Section 5.6). 17) Clarification in the table 2 p.26 that full details are in another table. Also, visit 3 and 4 procedures have been

			clarified (Section 6.1). 18) Baseline measures: clarification regarding adjudication, IEP and behaviour report cards. Typo error Brief symptom inventory rating scale and amendment regarding the data from the prison records form (Section 6.1). 19) Changes to summary of measures and procedures table 3. All baseline measures moved to visit 3, IEP and report cards clarified and ZAN-BPD only at visit 3. 20) Secondary Efficacy Parameters- amended and clarified (Section 7.1.2) 21) Amended USAR to SUSAR (Section 8.2) 22) Adverse events will be reported at each site and verified by clinician who is part of research

			team, by medical colleagues who are part of prison healthcare or by the CI (Section 8.2.2). 23) Clarifications that all AEs are recorded and all SAEs reported (Section 8.2.2). 24) Explanatory analyses paragraph amended (Section 9.3.2). 25) TSC and DMEC members details updated (Section 10 and 11). 26) Local Trial Management details updated (Section 12). 27) Clarified that all research records are to be securely transferred to King's College London at the end of the study (Section 18).

Contents

2. Background & Rationale

2.1 Rationale for the current study: Attention-deficit/hyperactivity disorder (ADHD) is characterised by developmentally inappropriate levels of inattentive, hyperactive and impulsive behaviours. The disorder is often accompanied by mood instability and leads to clinical and psychosocial impairments culminating in long-term negative outcomes and comorbid conditions. ADHD is a common childhood disorder affecting 3-5% of children in the UK [1, 2]. The disorder persists in two-thirds of cases by the age of 25 years, with an estimated adult prevalence of 2-4% [3-4]. Individuals meeting diagnostic criteria for ADHD occur at disproportionately high rates in forensic populations with an estimated prevalence rate between 25-30% in young offender institutes and prison populations [6].

Both the National Institute of Health and Clinical Excellence (NICE) and Scottish Intercollegiate Guidelines Network (SIGN) recommend methylphenidate (MPH) for treating ADHD with severe impairment in children, adolescents and young adults [6-8]. Nevertheless it is uncommon to diagnose and treat ADHD in young offenders because the common occurrence of mental health, neurodevelopmental and psychosocial problems might provide a better explanation for impulsive, overactive and inattentive states in young offenders, or might interfere with the treatment response in cases of ADHD . For these reasons NICE (2008) recommended that drug treatment efficacy trials are needed in offender populations (Page 134 of the full guideline, section 5.18.1.4) and repeated this recommendation in 2013 [9]. The guideline states that “there should be an assessment of efficacy in these groups (i.e. forensic and drug abuse populations) of the ADHD treatments already recommended for treatment in the community. Randomised controlled trial design is recommended”. Clinical trials of ADHD treatments have yet to be conducted in young offenders and the efficacy of MPH treatment for ADHD remains unknown in this group. A letter of support explaining the rational for this recommendation from the chair of the NICE guideline committee is appended to this protocol (see section 20).

There are two main reasons why response of ADHD symptoms to stimulant medications may be different for young offenders compared to previous studies in community ADHD samples. First, offenders present with an array of complex mental health problems that may better explain states of inattentive, overactive restless and impulsive behaviours, used to define ADHD. This includes problems commonly seen in offenders such as personality disorder, anxiety, post-traumatic stress, general and specific learning difficulties and substance abuse. Secondly, previous treatment trials of ADHD have generally been conducted in carefully selected samples with low levels of co-occurring psychosocial and mental health comorbidities. However, the co-occurrence of mental health disorders might interfere with the efficacy of drug treatments in ADHD. One example is comorbid drug abuse. Meta-analysis of treatment trials found no effect of MPH on ADHD symptoms in ADHD cases comorbid with drug abuse ($d=0.08$, $p=.59$) whereas there was a medium effect in non-comorbid samples ($d=0.51$, $p<.00001$) [10]. This may be relevant to prison populations where a history of drug abuse is common. Nevertheless, preliminary data suggests moderate to large effects of MPH on ADHD in offender populations.

2.2 Previous studies: Previous community studies demonstrate the efficacy of MPH and the study drug, OROS-MPH, in children, adolescents and adults with ADHD [6,7]. However there is no trial data-

for the treatment of ADHD in young offenders presenting with a more complex mix of psychosocial, mental health and behavioural problems. To date there is only one randomised controlled trial of MPH in a forensic population, consisting of a sample of 30 Swedish prisoners with ADHD which showed a large effect (Cohen's d=2.1) [11]. While this study supports the treatment of ADHD in offenders, it cannot be considered definitive for the treatment of young offenders because of the small sample size, older age group and selection of severe ADHD cases with long term sentences treated in a special prison unit in Sweden. Additional support comes from the pilot open label study for this proposal that investigated the effects of MPH in 121 young offenders in HMP Isis meeting DSM-5 diagnostic criteria for ADHD (unpublished data). A large effect was observed (d=2.75) suggesting that clinically significant effects will be observed in a randomised placebo controlled trial.

The benefits of treatment are expected to extend to a range of secondary outcomes beyond the core symptoms of ADHD and their associated impairments. An epidemiological study indicated the potential benefits of treating ADHD among offenders. This large survey of 25,656 Swedish patients with ADHD found a 6-fold higher rate of criminal convictions in ADHD patients compared to controls and a 32% reduction during periods of drug treatment for ADHD with either MPH or atomoxetine; but not when antidepressants were prescribed, suggesting the specificity of these findings to the treatment of ADHD [12]. In our own prevalence study of ADHD in prison we found a 6-fold increase in critical incidents among prison inmates even after controlling for antisocial personality disorder [13]. Other studies have also reported significant effects of MPH on emotional dysregulation in adolescents and adults with ADHD, including problems with temper control, mood lability and emotional over-reactivity [14]. Hence, treatment of offenders with ADHD might lead to significant reductions in emotional dysregulation and potentially aggressive or violent behaviour. The symptoms of ADHD are also known to interfere with education and employment due to a combination of restlessness, reduced attention span, forgetfulness and problems with planning and organisation [15]. Treatment might therefore lead to greater positive engagement with educational and rehabilitation programs within prison. In our open label pilot study at HMP Isis we also found significant effects on all the secondary outcomes proposed for this study (all $p<.001$) including measures of emotional dysregulation, critical incidents and engagement with the education and rehabilitation program.

2.3. Potential benefits: Potential benefits of treatment include improvement in the primary and secondary clinical and behavioural outcomes including ADHD symptoms, emotional dysregulation, attitudes towards violence, critical incidents and engagement with the educational and rehabilitation programs. Demonstrating efficacy and safety of OROS-MPH on ADHD symptoms and associated impairments will provide the data needed to develop effective healthcare pathways, including the use of MPH, for a significant group of young offenders. Establishing efficacy of MPH in this population will provide the foundation needed to establish long term effectiveness studies with the potential for demonstrating significant reductions in criminal behaviour and improved health-economic outcomes.

2.4 Potential risks: The main concern with use of MPH in offenders with high rates or substance abuse is the potential for abuse of stimulant medications. Abuse of stimulants is usually by crushing short acting formulations such as Ritalin, which can then be insufflated (snorted) or injected, leading to a rapid entry of drug into the brain and the experience of euphoria. When taken orally, the slow pharmacokinetic profile does not lead to euphoria [16]. This is important because it is not possible to crush the study drug (Concerta XL) or easily extract the MPH for injection. Risk of diversion or abuse is therefore reduced in this study by the use of OROS-MPH which is difficult to abuse. In our pilot study we did not observe drug seeking behaviour. The offenders being treated for ADHD in HMP ISIS were generally cautious about increasing the dose of medication and used modest doses, comparable to community samples (18% used 18mg; 37% used 36mg; 14% used 54mg; 26% used 72mg; and only 4% use 90mg). There are standard operating procedures for the delivery of controlled drugs within the prisons.

Other potential risks are the usual range of adverse effects observed when treating ADHD with OROS-MPH (see Assessment of safety, section 8.2).

3. Trial Objectives and Design

3.1 Trial Objectives

The overall objective is to investigate the effects of OROS-MPH in young offenders (age 16-25) meeting DSM-5 diagnostic criteria for ADHD: We address the following study questions:

(1) What is the efficacy of OROS-MPH in reducing inattention and hyperactivity-impulsivity in young offenders?

(2) What is the efficacy of OROS-MPH in reducing secondary outcomes that are key indicators of behavioural and functional impairments used in the management of young prisoners in the UK? These include emotional dysregulation, antisocial behaviour in the prison, violent attitudes (a measure linked to aggression) and reports of behaviour from prison staff.

(3) Are improvements in secondary behavioural outcomes mediated by improvements in ADHD symptoms or emotional dysregulation?

3.1.1 Primary endpoint: The primary endpoint is the level of ADHD symptoms measured on the investigator rated Connors Adult ADHD rating scale (CAARS-O) [17] to address the question of efficacy of OROS-MPH on ADHD symptoms in young offenders meeting DSM-5 diagnostic criteria for ADHD. Investigator rated CAARS scores is a common outcome measure used in previous treatment trials of ADHD in the community; and measures the same list of 18 symptoms used as the primary outcome in nearly all other studies of ADHD.

3.1.2 Secondary endpoints: Secondary outcomes address important exploratory questions about the effects on comorbid symptoms and behavioural impairments that are commonly seen in offenders with ADHD. These include: emotional dysregulation (Wender-Reimherr Adult ADHD Diagnostic Scale, WRAADS) [18]. The number of adjudications for antisocial behaviour and rule breaking in the previous 8-weeks. Ratings of aggressive behaviour by prison staff and educational staff using the prison officer and education staff versions of the Modified Overt Aggression Scale (MOAS) [19]; and classroom behaviour report cards rated by the prison staff and education staff. Attitudes towards violence (Maudsley Violence Questionnaire, MVQ) [20]. CORE Outcome Measure (CORE-M) [21], a self-rated scale of subjective well-being, problems/symptoms, life functioning and risk/harm, designed to measure psychological distress before and after treatment.

In addition we will include: the mind excessively wandering scale (MEWS) [22], comorbid symptoms using the BSI scale [23], rating scale for irritability (ARI-S) [24] and a clinical global impression using the CGI [25].

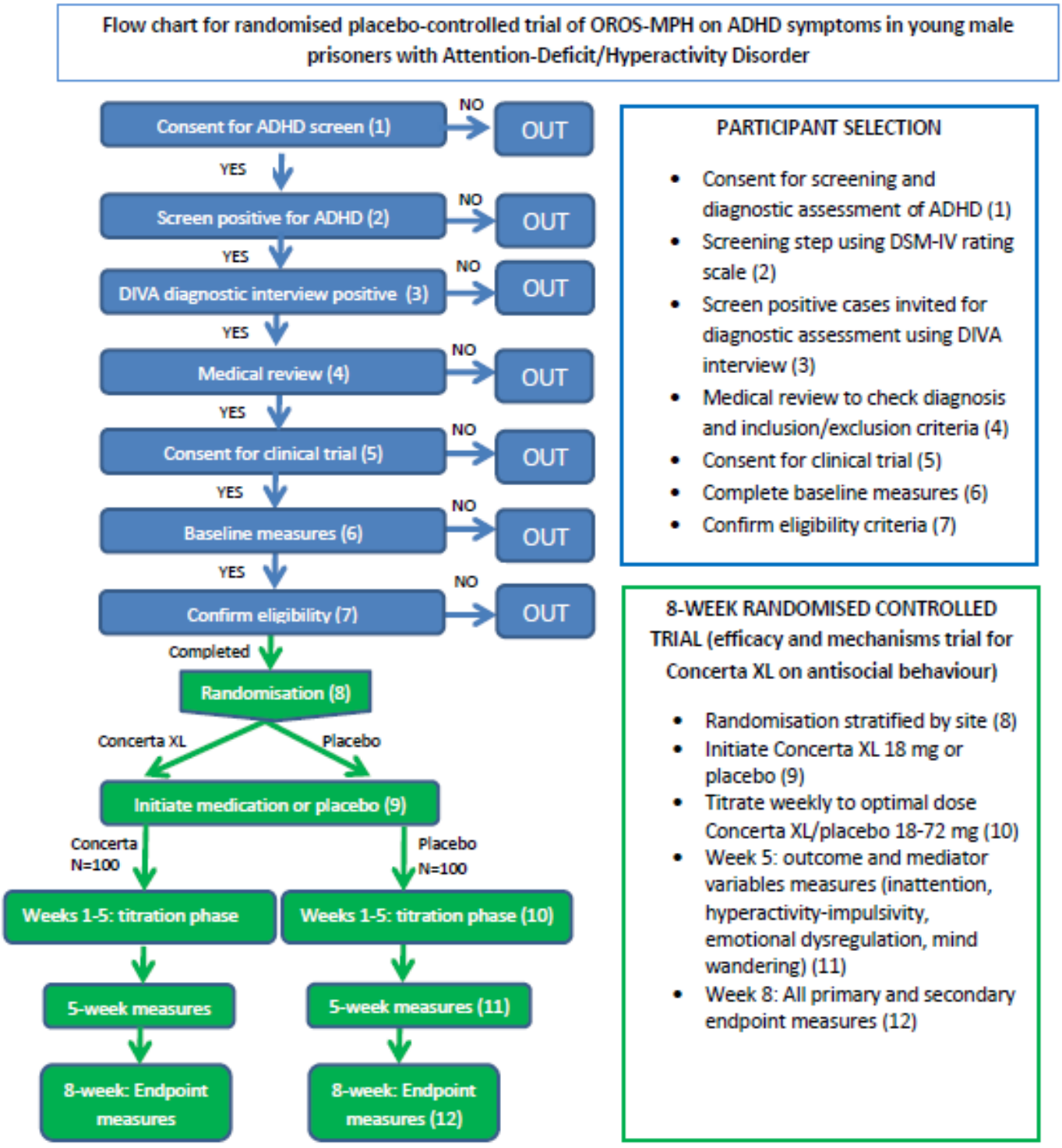
The WRAADS has been used in previous treatment trials of ADHD to demonstrate the effects of MPH on emotional dysregulation [14,26]. The measures of prisoner behaviour were used successfully in the previous open label pilot study.

Further explanatory analyses explicitly test the mediation hypothesis that change in symptoms of ADHD or emotional dysregulation mediate change in critical incidents and engagement with educational activities measured using the MOAS and behaviour report cards completed by prison and educational staff.

3.2 Trial Design

An 8-week parallel arm randomised placebo controlled trial of an extended release formulation of MPH (OROS-MPH) on ADHD symptoms, behaviour and functional outcomes in young male prisoners aged 16-25, meeting DSM-5 criteria for ADHD. Participants will be randomised to 8-weeks treatment with either OROS-MPH or placebo, titrated over 5 weeks to balance ADHD symptom improvement against side effects. 200 participants will be recruited with 1:1 ratio of drug to placebo. Randomisation will be conducted by the King's CTU with blinding of both investigators and participants. OROS-MPH will be offered to both the OROS-MPH and placebo treated groups as part of their clinical care once the 8-week trial is completed.

3.3 Trial Flowchart



This is a randomised placebo controlled clinical trial of OROS-MPH in young adult offenders with ADHD. There are two stages of consent. Initial consent (screening and diagnostic step) allows for the use of screening questionnaires for ADHD, followed by a diagnostic assessment using the DIVA interview for adult ADHD. Individuals that meet diagnostic criteria are invited to take part in the clinical

trial, at which stage informed consent is requested (clinical trial). A summary of the visits and decision points delineated in the flow diagram are described in more detail below (see table 2 on p.23 for full trial visit details (post consent for trial):

Table 1:

During the pre-trial steps (2,3 and 4) patients who fail eligibility criteria will not be invited to continue and will not be asked to provide consent for trial. The eligibility criterion which they are identified as failing will be noted.

Screening and Diagnostic Step (pre-trial research)	
Consent for screening (1)	Consent will be requested for use of screening and diagnostic data in addition to prison mental health records.
Screening step (2)	ADHD screening measure (Barkley) completed by prison mental health team or study research staff. Used for initial identification of potential cases of ADHD. Individuals that screen positive for ADHD will be invited to take part in a diagnostic interview for ADHD.
Diagnostic interview (3)	Diagnostic assessment completed using the Diagnostic Interview for ADHD (DIVA interview).
Medical review (4)	For those that meet DIVA diagnostic criteria for ADHD, a psychiatrist with training in the diagnosis of ADHD will review the diagnostic information and eligibility for the trial. Patients who are thought to meet eligibility criteria for the study will be invited to take part in the clinical trial.
Clinical trial (start of the clinical trial)	
Visit 1	Information sheets given to participants who wish to consider taking part in the clinical trial. The content of the information sheet will be discussed and explained.
Visit 2	Review of information sheets and consent forms signed for the clinical trial.
Visit 3	Baseline data collected from participants (including physical health checks), prison records and prison and education staff behaviour report card.
Visit 4	Once baseline data has been collected and eligibility checks confirmed, participants will be randomised to treatment with placebo or OROS-MPH (Concerta XL). Trial prescriptions will be completed and given to the pharmacy. Medication should be started within 1-week of Visit 4.
Visit 5	1-weeks (±2 days) after start of medication to complete CAARS-O, and adjust medication. Pulse, blood pressure and Adverse Events Scale. Further 1-week prescription.
Visit 6	2-weeks after weeks (±2 days) after start of medication to complete CAARS-O, and adjust medication. Pulse, blood pressure and Adverse Events Scale. Further 1-week

	prescription.
Visit 7	3-weeks (±2 days) after start of medication to complete CAARS-O and adjust medication. Pulse, blood pressure and Adverse Events Scale. Further 1-week prescription
Visit 8	4-weeks (±2 days) after start of medication to complete CAARS-O and adjust medication. Pulse, blood pressure and Adverse Events Scale. Further 1-week prescription.
Visit 9	5-weeks (±2 days) after start of medication to complete CAARS-O, WRAADS and MEWS. Pulse, blood pressure, weight and Adverse Events Scale. Further 3-week prescription.
Visit 10	8-weeks (±2 days) after start of medication to repeat outcome measures as listed for visit 10 in table 3: Summary or measures/procedures for the trial p.25.

4. Trial Medication

4.1 Investigational Medicinal Product

Overview: OROS-MPH is supplied as 18 mg capsules and placebo to match. Capsules will be over-encapsulated and packaged in bottles of 46. Each bottle will be assigned a unique randomisation number and the randomisation system will allocate the right bottle to each patient. Over-encapsulation has been successfully adopted in previous studies to generate matched placebo to OROS-MPH. Prisoners will be observed taking trial medication.

Piramal Healthcare UK Ltd. will supply IMP, placebo to match manufacture, clinical trials packaging, QP Certification and distribution for 200 patients for a randomised clinical trial involving Concerta 18mg tablets and placebo. The Sponsor has arranged the supply of Concerta 18mg tablets from the Marketing Authorisation (MA) holder, Janssen. Janssen will provide the SmPC, updated throughout the duration of the study.

Dispensing: Prescriptions will be completed by the trial psychiatrist or nurse prescriber. Each patient will be allocated a kit (labelled carton) containing four labelled bottles each containing 46 active or placebo tablets. These four bottles will suffice for the entire patient's treatment duration under consideration of the dosing titration. Each kit and its bottles will be labelled according to Annex 13 guidelines and have its own randomisation/treatment pack number. The centralised randomisation system will allocate the correct treatment pack/kit to each patient during the trial.

Shelf-life and trial duration: The over-encapsulated active tablets will be re-packed in HDPE bottles and take over the remaining shelf life of the study without the need for a stability program as Concerta 18mg has a marketing authorisation for both HDPE and blister packaging. Placebo tablets will be manufactured once. Trial medication over-encapsulation and packaging will be undertaken in 2 campaigns in order to accommodate a trial duration of up to 3.5 years. Concerta 18mg tablets typically has a maximum shelf-life of 3 years from the date of manufacture, however, by the time the product is repacked for the clinical trial, the remaining shelf life is likely to be under 2.5 years.

Dosage: Both active medication and placebo will be titrated weekly for 5 weeks and then kept at stable maintenance dose for 3 weeks. The maximum titrated dose (or matching placebo) is as follows: Daily

dose titrated as follows (or matching placebo): Week 1 = 18 mg (1 tablet); Week 2 = 36 mg (2 tablets); Week 3 = 54 mg (3 tablets); Week 4 = 72 mg (4 tablets); Week 5 = 72 mg (4 tablets); Week 6 = 72 mg (4 tablets); Week 7 = 72mg (4 tablets); Week 8 = 72mg (4 tablets).

Over-encapsulation will use 'DBcaps' capsules which are designed specifically for the blinding of clinical trial medication. We have to over-encapsulate the Concerta tablets with lactose capsule placebo, rather than make a matching placebo tablet because Concerta tablets have printing on them and are of a distinct shape that would be difficult to manufacture and might infringe copyright. We have sought advice on this from previous investigators using OROS-MPH and from companies who provide drug and placebo supplies for studies. Studies on the use of DBcaps have shown that encapsulation of tablets results in a lag time of 2–3 min in disintegration compared with the unencapsulated tablets (http://pharmtech.findpharma.com/pharmtech/article/articleDetail.jsp?id=664328&sk=&date=&pageID=3).

The pharmacokinetic (absorption) properties of Concerta XL 18mg prolonged release capsules indicate release over several hours: following oral administration of Concerta XL to adults the drug overcoat dissolves, providing an initial maximum drug concentration at about 1 to 2 hours. The methylphenidate contained in the two internal drug layers is gradually released over the next several hours. Peak plasma concentrations are achieved at about 6 to 8 hours, after which plasma levels of methylphenidate gradually decrease." (Section 5.2 of the SPC: https://www.medicines.org.uk/emc/medicine/8382).

4.2 Dosing regimen

Titration of dose is conducted by the study psychiatrist or nurse prescriber. Both the trial investigators and participants are blinded. The titration protocol is followed in the same way for both active medication (IMP) and placebo. Treatment will start at an initial dose of 18 mg (1 tablet) for 1 week, and be increased weekly in 18 mg increments to a maximum of 72 mg (4 tablets) (i.e. 18 mg (1 tablet), 36 mg (2 tablets), 54 mg (3 tablets) and 72 mg (4 tablets)). Medication will be reduced by 18 mg (1 tablet) if there is a limiting adverse event, in which case there will be no further increase in medication for the duration of the trial. Medication may be provided either once or twice daily up to the maximum daily dose. Titration upwards will be stopped if all 18 ADHD symptoms are scored as negligible (score of 0 or 1 on the CAARS) or absent. Unacceptable levels of adverse effects on the lowest dose of 18mg might lead to a cessation of treatment in a few cases; if this occurs we will ask participants to remain in the trial for the remaining trial assessments.

A maximum dose of 72 mg is included for this trial because previous clinical trials have indicated that a proportion of adults respond better at higher doses without unacceptable levels of adverse events; and because current licensing for Concerta XL up to 54 mg is based on dose levels for children and adolescents, rather than adults. NICE recommend a daily dose of MPH in adults to a maximum of 100 mg per day [6,7] and for Concerta XL the British National Formulary (No 62, September 2011) recommends doses up to a maximum of 108 mg in adults.

4.3 Drug Accountability

All aspects of treatment and accountability for managing the medication storage and delivery are managed locally by the prison pharmacies and mental health teams, as per standard HMPYOI practice for this. IMP accountability will be recorded and verified.

4.4 Subject Compliance

All aspects of treatment compliance and recording of treatment administration/refusal are managed by the prison mental health teams and locally by healthcare staff as per standard practice for these sites. Patients are observed when they are given medication and checked to ensure the capsules have been

swallowed. This information is then recorded (signed off) by nursing staff who delivered the medication on prison pharmacy record sheets or digital records.

4.4.1 Missing data: In the pilot study 10% left the prison unexpectedly. Missing data was loss at random because transfers out of the prison (to other prisons or the community) were unrelated to recent behaviour that might be influenced by the trial protocol, such as pending court cases, transfers to prisons nearer home or early probation based on longstanding behaviour. In this study we will limit this source of missing data by retaining participants who leave the prison in the trial, whenever possible. For HMP Isis, those transferred to another prison will usually be in the London area, and should be available for follow-up visits. Outcome measures will be collected wherever possible on those participants who transfer to another local prison. We will not follow-up those who are released from prison or transferred out of the local area. Polmont is the only young offender's prison in Scotland, so transfers to other prisons are not envisaged. The study medication will not be given to participants following release or transfer but participants will be given a letter from clinician confirming diagnosis and providing advice regarding future clinical management. Loss to follow-up may rarely arise following problems with adherence to the trial medication; however we expect nearly all such cases to continue in the trial by completing assessment sessions.

4.4.2 Adherence to medication: This will present a challenge for around 20% of participants. Some offenders may not feel motivated to take the trial medication, if they experience adverse effects or do not feel they are improving. They may also take medication intermittently because of the strict prison regime that allows for only a short time-window for leaving their cells to obtain medication from the medicine hatch on the prison wings. These cases are not expected to contribute to missing data.

In our pilot study we accrued considerable experience in managing the expectation of offenders and providing the support needed to help participants adhere to the trial protocol. The following steps will be adopted to maximise adherence to medication:

(1) In the pilot, minor adverse effects (13%) were the most common reason for non-adherence to medication. This was linked to the observation that this population may be more sensitive to minor adverse effects, particularly changes in appetite, than community samples; perhaps reflecting the importance of meal times to prisoners. To maximise adherence to the protocol and minimise this as a potential source of missing data, we will take care to identify the early signs of minor adverse effects such as appetite loss and adjust the medication dose accordingly.

(2) Seven percent of the pilot sample did not wish to take medication in the mornings (08:00), which was the initial protocol followed in the pilot study. We then adjusted the protocol to allow for 12:00 medication for those that got up later in the day, worked mainly in the afternoons or had a strong preference for a 12:00 dosing, which resolved the problem. This flexibility in dosing time more accurately reflects dosing decisions in the community and provides a better match to patient's daily routines.

(3) During the pilot study, prison staff did not always let patients out of their cells to receive medication or remind participants to get up on time. To resolve this problem we initiated the use of research staff to assist in the delivery of medication by checking that prisoners were always out of their cells on time to receive trial medication.

(4) In the pilot study, treatment was disrupted for the Ramadan festival for several participants. We will take care to check that participants are not started on trial medication where religious customs might interfere with adherence to the trial protocol.

(5) In the pilot study, daily adherence to the trial medication reduced when participants were not reviewed weekly. One of the findings in the pilot study was the importance that prisoners gave to the weekly follow-up meetings when they are able to discuss their ADHD and response to the treatment process, in addition to completing study assessments. We will therefore offer weekly meetings with offenders throughout the 8-week trial.

(6) Nurse support in addition to a research assistant and medical staff will ensure that offenders are given the support they need to adhere to the protocol.

4.5 Concomitant Medication

All concomitant medications will be recorded. Use of the following medications in the 4-weeks prior to the start of treatment with Concerta XL will lead to exclusion from the clinical trial, based on potential adverse drug interactions:

- Clonidine
- Coumarins
- Monoamine oxidase inhibitors
- Moclobemide
- Rasagline

5. Selection and Withdrawal of Subjects

5.1 Inclusion Criteria

- Male, aged between 16 and 25 years (at consent for screening)
- English speaking (defined as sufficient to complete study assessments)
- Able to provide informed consent (understand the information sheet and make an informed decision taking into account pros and cons of study participation)
- Meet clinical diagnostic criteria for DSM-5 ADHD.
    - 5 or more symptoms of ADHD in either the inattentive or hyperactive-impulsive symptom domains
    - 6 or more symptoms of ADHD in either the inattentive or hyperactive-impulsive symptom domains before the age of 12 years.
    - Where it is not possible to gain sufficient clinical information to score childhood symptoms of ADHD, the operational criteria will be adapted to include evidence of several ADHD symptoms with impairment starting before the age of 12 years, and 5 or more symptoms currently with moderate to severe impairment
    - Persistent trait like (non-episodic) course of symptoms
    - Impairments in two or more clinical or psychosocial domains and two or more settings from symptoms of ADHD
    - Onset of symptoms before the age of 12 years.

5.2 Exclusion Criteria

- Lack capacity to give informed consent
- Moderate or severe learning disability, defined as IQ<60
- Serious risk of violence to the researcher
- Current major depression, psychosis, mania or hypomania
- Past history of bipolar disorder or schizophrenia (exclude those with clear history of episodic mania/hypomania or psychosis unrelated to acute drug intoxication. Do not exclude on the basis of chronic emotional dysregulation i.e. irritability, frustration, anger or emotional-mood instability)
- Medical contraindications to the use of stimulants (e.g. glaucoma, hypertension, cardiovascular disease or structural heart problem)
- Is taking a contraindicated medication (e.g Clonidine, Coumarins, Monoamine oxibase inhibitors, Moclobemide, Rasagline) during the 4 week prior to randomnisation.
- Drug seeking behaviour or craving (defined as drug seeking behaviour that is unusually severe and likely to affect the titration protocol due to unusual and excessive demands for drugs; or where there is a current withdrawal syndrome from an addiction disorder with drug dependency)
- Participant receiving any ADHD medication between consent for screening and randomnisation.

5.3 Selection of Participants

Participants will be recruited from HMYOI Isis (London) and HMYOI Polmont (Falkirk). HMP Rochester (Kent) is a third site that will be used if sufficient numbers of participants cannot be recruited from ISIS and Polmont. Following consent to be screened for ADHD (consent 1), screening questionnaire data will be collected by the prison mental health teams using a DSM-IV ADHD symptom rating scale (25). Patients who screen positive will be invited to complete the Diagnostic Interview for Adult ADHD (DIVA) [27]. This will be followed by a clinical review by a psychiatrist trained in the diagnostic assessment of ADHD, including collateral information obtained from an informant whenever feasible. Following clinical review patients who meet diagnostic criteria for ADHD and meet the other eligibility criteria for the trial, will be invited to take part in the clinical trial.

Eligibility for the study will be further checked and recorded once the consent form (consent 2) has been signed and baseline assessments have been completed, prior to randomisation. Using an algorithm that applies the DSM-5 criteria to the DIVA interview data, cases will be checked to ensure they meet diagnostic criteria for DSM-5 ADHD. A clinical review by a psychiatrist trained in the diagnostic assessment of ADHD, will review all inclusion and exclusion criteria. The exclusion criteria of IQ less than 60 will be based on the 95% confidence interval for the IQ estimate from the WASI-II including IQ of 60, in combination with a clinical assessment by the psychiatrist to confirm that the participant has the ability to understand the rating scale and interview assessment questions, understand the information sheet and the study procedures and risks, and the ability to provide sufficiently detailed accounts of ADHD symptoms and behaviours, consistent with an IQ score greater than 60. Since there are no validated IQ tests for the visually impaired, including WASI-II, this criterion will be based on clinical judgement alone for participants with this impairment. This will also be the

procedure for anyone unable to complete the WASI-II assessment due to severity of their ADHD symptoms or other mental health problems.

5.4 Randomisation Procedure/Code Break

Randomisation will take place once informed and signed consent has been obtained, eligibility checks have been completed and recorded, and before the treatment is started. We will use the King's Clinical Trials Unit's Independent Randomisation Service, ensuring reliability and credibility in the randomisation process. Random block sizes will be used to control the numbers of subjects allocated to each group, stratified by site and in a 1:1 drug-placebo ratio. Patient characteristics will not be taken into account in the randomisation process, but we expect a balanced ratio of cognitive ability, ADHD symptom severity and co-occurring psychosocial and mental health problems across the drug treatment and placebo groups.

Emergency unblinding will follow the standard operating procedures for the Kings Health Partners Clinical Trials Office. In circumstances where unblinding is deemed necessary, the first port of call will always be the local investigating team. Whenever possible the decision to unblind will be made the chief investigator, the principal investigator or clinically qualified staff working on the project. Out of hours, if clinically qualified members of the research team are not available, then the 24 hour emergency system will be used (ESMS). The ESMS system consists of a call centre which is manned around the clock by Information Scientists who have a minimum qualification of a life science degree to include toxicology or pharmacology. These Information Scientists are always available and are the direct line of communication to the number on the patient card. The Information Scientists will be trained in the specific details of this study and have direct access to one of the ESMS Consultant Physicians should clinical advice be required. Our Consultant Physicians practice general and internal medicine and specialise in clinical pharmacology and toxicology, ensuring clinical advice is available night and day. To maintain the overall quality and legitimacy of the clinical trial, code breaks will occur only in exceptional circumstances when knowledge of the actual treatment is absolutely essential for further management of the patient. The Investigator will always maintain the blind as far as possible.

Investigators will be unblinded after the primary analysis is complete. We intend to use linear mixed modelling (see section 9) which assumes that only variables included in the model predicts missingness. We will assess empirically whether this particular missing at random (MAR) assumption is reasonable, using an independent statistician to maintain blinding if necessary. The primary analysis dataset will not include any trial medication dosage data to ensure that the statistician remains blinded. If the MAR assumption is not reasonable -multiple imputation will be used to complete missing outcomes and the statistician will be unblinded at this point but investigators will remain blind until the primary analysis is complete. The Investigator must report all code breaks (with reason) as they occur on the case report form.

5.5 Withdrawal of Subjects

Participants have the right to withdraw from the study at any time for any reason. Healthcare staff has the right to withdraw patients from the trial if they consider the trial is having an adverse effect on the participants. However, where the problem is restricted to taking trial medication we will invite participants to remain in the study to complete trial assessments, thereby minimising loss of data. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible. Anyone withdrawn from the clinical trial will be reviewed by the prison healthcare team to ensure their safety. All participants will be informed that they have the right to withdraw from the study at any time.

Due to potential concerns about the interaction of trial medication with unknown psychoactive substances, if a participant disclosed to any member of the research team that they have used "spice"

i.e. synthetic cannabis or other unknown psychoactive substance, while participating in the study, a clinical evaluation will be made. If it is current use (defined as within the last two days) the study medication will be stopped. If it happened earlier in the study and this is considered an isolated incident the trial medication can continue. If the trial medication is stopped, the participant will remain in the study and will be asked to complete trial assessments. A clinical assessment will be made on a case by case basis as to the safety of restarting the trial medication after 48 hours from the time of stopping the trial medication.

5.6 Expected Duration of Trial

For each individual, active trial participation will continue for 8-weeks unless the patient withdraws prematurely from the trial. Following the last visit of the last patient, data will be verified for all participants, corrected where necessary and the database will be locked before data extraction. The trial ends at database locking.

6. Trial Procedures

6.1 By Visit (see page 28 for a detailed list of all measures and procedures) Table 2:

Visit 1	Following confirmation of the diagnosis of ADHD and eligibility by a psychiatrist trained in the assessment of ADHD, information sheets and consent forms will be provided and discussed with potential participants.
Visit 2	Information sheets reviewed and informed consent obtained for clinical trial. There is no limit on the time taken between visits 1 and 2 within the timeframe of the project. Potential participants will be encouraged to take as much time as they need to reach a fully informed decision about participation in the trial.
Visit 3	Baseline data collected from participants (including physical health checks), prison records and members of staff.
Visit 4	Once baseline data has been collected and eligibility confirmed following medical review by a psychiatrist to check diagnosis and all inclusion and exclusion criteria- participants will be randomised to treatment with placebo or OROS-MPH (Concerta XL). Trial prescriptions will be completed and given to the pharmacy. Medication should start within 1-week of Visit 4.
Visit 5	1-weeks after start of medication to complete CAARS-O, and adjust medication. Pulse, blood pressure and Adverse Events Scale. Further 1-week prescription.
Visit 6	2-weeks after start of medication to complete CAARS-O, and adjust medication. Pulse, blood pressure and Adverse Events Scale. Further 1-week prescription.
Visit 7	3-weeks after start of medication to complete CAARS-O and adjust medication. Pulse, blood pressure and Adverse Events Scale. Further 1-week prescription
Visit 8	4-weeks after start of medication to complete CAARS-O and adjust medication. Pulse, blood pressure and Adverse Events Scale. Further 1-week prescription

Visit 9	5-weeks after start of medication to complete CAARS-O, WRAADS and MEWS. Pulse, blood pressure, weight and Adverse Events Scale. Further 3-week prescription.
Visit 10	8-weeks after start of medication to complete final outcome measures as shown for visit 10 in table 3.

Baseline measures: The following baseline data will be collected from participants:

(1) Barkley ADHD self-rating scale for DSM-IV ADHD symptoms (pre-trial screening data)

(2) Diagnostic Interview for DSM-IV ADHD (DIVA) (pre-trial screening data)

(3) Diagnostic interview for comorbid mental health disorders (MINI 7.0: baseline moderator variable)

(4) Connors Adult ADHD Rating Scale for ADHD symptoms (CAARS-O: baseline and outcome variable)

(5) Emotional Dysregulation from the Wender-Reimherr Adult ADHD Diagnostic Scale (WRAADS: baseline and outcome variable)

(6) Rating scale for irritability (ARI-S: baseline and outcome variable)

(7) Mind Excessively Wandering Scale (MEWS: baseline and outcome variable)

(8) Clinical Global Impression scale (CGI: baseline and outcome variable)

(9) *Number* of adjudications for antisocial behaviour and rule breaking (HMP ISIS and HMP/YOI Polmont); and negative IEPs (HMP ISIS only) (baseline and outcome variable)

(10) Ratings of aggressive behaviour by prison staff (Modified Overt Aggression Scale)

(11) Ratings of behaviour by prison staff (behaviour report cards by prison officers) (baseline and outcome variable)

(12) Ratings of aggressive behaviour by education staff (Modified Overt Aggression Scale – education staff) (this item is optional, depending on whether prisoners are attending education sessions or not: baseline and outcome variable)

(13) Classroom behaviour report card (HMP ISIS and HMP/YOI ISIS) (this item is optional, depending on whether prisoners are attending education sessions or not: baseline and outcome variable)

(14) Number of positive IEPs for positive engagement in education, occupational and rehabilitation programs (HMP ISIS only)(baseline and outcome variable)

(15) Brief symptom inventory (BSI) - self-rating scale for comorbid symptoms (baseline and outcome rating scale)

(16) Attitudes towards violence - Maudsley Violence Questionnaire (MVQ: baseline and outcome variable)

(17) CORE Outcome Measure (CORE-M). A self-rated scale of subjective well-being, problems/symptoms, life functioning and risk/harm, designed to measure psychological distress before and after treatment (baseline and outcome variable)

(18) The Reactive-Proactive Aggression Questionnaire (RPAQ) (baseline moderator variable only)

(19) Weiss conduct disorder subscale (baseline moderator variable only)

(20) ZAN Borderline personality disorder (ZAN-BPD) (baseline moderator variable)

(21) Drug use (in year prior to current prison sentence) (baseline moderator variable)

(22) Childhood trauma questionnaire (baseline moderator variable)

(23) Adverse events scale (AES) (baseline and outcome variable)

Data from prison records and prison staff: Data will be collected from case/prison records and prison nursing and educational staff, relating to behaviour in the 8-weeks before the collection of the baseline measures. For cases of individuals new to custody presenting with significant behavioural problems linked to ADHD, the retrospective baseline reporting period will be reduced to their reception date at HMP/YOI Isis to baseline. This will be a period of 1 month or more to allow for initial behavioural problems that may arise when people first enter prison.

- Number of critical incident records (adjudications)
- Number of educational sessions attended (events scheduled and attended over the preceding 56 days)
- Prison and educational staff ratings of aggressive behaviour (using Modified Overt Aggression Scale (MOAS) and the classroom behaviour report cards) (incidents and behaviour recorded over the week preceding the baseline collection)
- Number of positive and negative IEPs (HMP ISIS only)

Summary of measures/procedures for the trial (not including initial diagnostic screening steps) Table 3:

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10

Patient information sheet (given to patient)	X									
Informed consent (signed consent obtained)		X								
Eligibility checks				X						
Barkley (taken from pre-trial clinical records)			X*							
DIVA (taken from pre-trial clinical records)			X**							
MINI 7.0 interview for comorbidity			X							
MINI 7.0 cross disorder symptom checklist			X							X
ZAN-BPD (borderline personality disorder)			X							
CAARS-O (ADHD item subscale)			X		X	X	X	X	X	X
WRAADS (motional dysregulation)			X						X	X
ARI-S (Irritability)			X						X	X
MEWS (mind wandering)			X						X	X
RPAQ (réactive/proactive agression)			X							
CTQ (Child trauma questionnaire)			X							
Drug and alcohol use			X							
WASI-II (IQ)			X							
Prison officer behaviour report cards			X							X
Demographic data			X							
MVQ (Maudsley violence questionnaire)			X						X	X
BSI (Brief symptom inventory)			X						X	X
CGI (clinical global impression scale)			X						X	X
Weiss-CD (conduct disorder scale)			X							
AES (Adverse Events Scale)				X	X	X	X	X	X	X
Blood pressure and pulse			X		X	X	X	X	X	X

Weight			X						X	X
N Critical Incidents (adjudications from prison records)			X							X
Prison officer reports (MOAS)			X							X
Education staff reports (MOAS) [optional]			X							X
Class behaviour report card [optional]			X							X
Educational engagement (N sessions attended)			X							X
Positive and negative IEPs (from HMP ISIS prison records only)			X							X
CORE-M			X							X
Concomitant medications and compliance (taken from prescription records)			X	X	X	X	X	X	X	X
Prescribed dose of trial medication and compliance (taken from prescription records)					X	X	X	X	X	X

DIVA: diagnostic interview for adult ADHD; WRAADS: Wender-Reimherr Adult ADHD Diagnostic Scale; CAARS-O: observer rated DSM-IV ADHD: MEWS: Mind Excessively Wandering Scale; RPAQ: reactive proactive aggression questionnaire; WASI-II: Wechsler Abbreviated Scale of Intelligence-II; ; Wechsler abbreviated scale of intelligence;; MVQ: Maudsley violence questionnaire; BSI: Brief symptom inventory; MOAS: modified overt aggression scale; AES: adverse events scale; IEPs: Incentives and Earned Privileges; CORE-M: the CORE outcome measure; ZAN-BPD: Zan borderline personality disorder scale; MINI-7.0: MINI international psychiatric interview for common mental health disorders; ARI: Irritability scale; Barkley-CD: Weiss conduct disorder scale; CGI: clinical global impression scale; CTQ: childhood trauma questionnaire; MEWS: mind wandering excessively scale;

*** Barkley-CD score is recorded at Screening step (Table 1- 2).**

**** DIVA is recorded at the Diagnostic interview (Table 1- 3).**

6.2 Laboratory Tests

None.

7. Assessment of Efficacy

This is an efficacy trial with the primary outcome of investigator rated ADHD symptoms using the CAARS.

7.1.1 Primary Efficacy Parameters

The primary outcome parameter will be the investigator rated ADHD symptom scores from the Conners Adult ADHD rating scale (CAARS).

7.1.2 Secondary Efficacy Parameters

These include the following:

- 1)Modified Overt Aggression Scale(MOAS) from prison staff
- 2) Modified Overt Aggression Scale (MOAS) from education staff
- 3) Behaviour report cards from prison staff- reports of behaviour over the previous week
- 4) Number of critical incidents (adjudication) – from prison records
- 5) Maudsley Violence Questionnaire (MVQ)
- 6) Comorbid symptoms (BSI)
- 7) Mind Excessively Wandering Scale (MEWS)
- 8) Engagement with education activities over the previous week measured at 8-weeks: number of sessions scheduled, number of sessions attended: reports of disruptive behaviour in educational sessions using the classroom behaviour report cards from education staff over the previous week.
-
- 9) Symptoms of Emotional Dysregulation (WRAADS)
- 10) Symptoms of Emotional Dysregulation (ARI)
- 11) Clinical global impression scale (CGI)
- 12) CORE-M outcome measures

7.2 Procedures for Assessing Efficacy Parameters

The WRAADS, the CAARS and the Clinical Global Impression scale (CGI) are investigator rated scales, rated by investigators following an assessment interview. This will take around 20- minutes.

Other data from participants will be collected using self-rated rated assessment scales. The self-rated questionnaires take around 40 minutes to complete.

Other data is collected from prison or educational staff or from prison records

8. Assessment of Safety

Patients are monitored daily by the prison mental and healthcare teams. Safety checks will be conducted in line with NICE Guidelines (2009):

1. Checks before commencing treatments: pulse and blood pressure; and review of pre-study health checks.

2. Any evidence of cardiovascular abnormalities will be evaluated for risk and if necessary an opinion obtained from a cardiologist prior to commencing treatment.

3. The clinical team will check pulse and blood pressure once a week for the first 5 weeks and at the end of the 8-week trial.

4. Other safety checks will include monitoring of adverse events during assessments. In addition, participants will be monitored daily by prison staff and any potential adverse events will be reported to the prison healthcare and mental healthcare teams.

8.1 Specification, Timing and Recording of Safety Parameters

With regards to the research aspect of the study (i.e. obtaining follow-up data) there is little risk to participant safety. Participants will be aware that should they wish to withdraw from the study they may do so. Participants who become upset or distressed by the questions in the research (this is unlikely as the questions are similar to those asked regularly in the context of their clinical care) will be offered support by the researchers and by the prison mental health team.

The healthcare team will follow national guidelines on safety, which is predominantly related to monitoring of cardiovascular function. More specifically the clinical care will follow these procedures:

1. Checks before commencing treatments pulse and blood pressure and review of healthcare records.
2. Potential cardiovascular abnormalities will be evaluated for risk and if necessary an opinion obtained from a cardiologist prior to commencing treatment.
5. The clinical team will check pulse and blood pressure once a week for the first 5-weeks and at the end of the 8-week trial.
6. Other safety checks will include monitoring of adverse events during assessments. In addition, participants will be monitored daily by prison staff and any potential adverse events will be reported to the prison healthcare team.

8.2 Procedures for Recording and Reporting Adverse Events

Safety will remain the responsibility of the prison mental healthcare team. Adverse events of any medical or non-medical intervention identified or recorded by the research team at each site, will be verified by the clinician who is part of the research team, or an assigned medical colleague at specialist registrar grade or above who is a member of the prison healthcare team, or the clinical lead for the project (Asherson).. The decision to stop treatment following an adverse event will remain the responsibility of the clinical team. Minor adverse events that do not come under official reporting procedures will be reported to the clinical team, e.g. include sleep disturbance, minor levels of anxiety or dysthymia, small increase in pulse and blood pressures, reduced appetite and other minor physical symptoms that do not endanger patients or cause more than minor distress. All other adverse events from medication will be recorded and reported in line with The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 as follows:

Adverse Event (AE): Any untoward medical occurrence in a subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR): Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Unexpected Adverse Reaction (UAR): An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in: The summary of

product characteristics (SmPC) for that product (for products with a marketing authorisation)

Serious adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR): Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

- Results in death;
- Is life-threatening;
- Required hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability or incapacity;
- Consists of a congenital anomaly or birth defect
- Important Medical Events (IME) – defined as an event that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above..

8.2.1 Reporting Responsibilities

The research team acting on behalf of King's College London as sponsors have delegated the delivery of the Sponsor's responsibility for Pharmacovigilance (as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004) to the King's Health Partners Clinical Trials Office (KHPCTO).

Reporting of SAEs will continue until last patient last dose has been completed. For each individual, the reporting period will be from the time of first dose of the trial medication, to the end of their involvement in the trial (last dose at the end of 8-weeks).

All SAEs, SARs and SUSARs and IMEs (excepting those specified in this protocol as not requiring reporting) will be reported immediately by the Chief Investigator or designated site investigators to the KHPCTO in accordance with the current Pharmacovigilance Policy. We will copy this information to Janssen-Cilag at the same time.

The KHPCTO will report SUSARs and other SARs to the regulatory authorities (MHRA), competent authorities of other EEA (European Economic Area) states in which the trial is taking place.

The Chief Investigator will report to the relevant ethics committees. Reporting timelines are as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction.
- The Chief Investigator and KHP-CTO (on behalf of the co-sponsors), will submit a Development Safety Update Report (DSUR) relating to this trial IMP, to the MHRA and REC annually.

8.2.2 Adverse events that do not require reporting

All AEs are being recorded and all SAEs reported for this trial.

8.3 Treatment Stopping Rules

The trial may be prematurely discontinued by the Sponsor, Chief Investigator or Regulatory Authority on the basis of new safety information or for other reasons given by the Data Monitoring and Ethical Committee/Trial Steering Committee, regulatory authority or Ethics Committee concerned. Trial discontinuation for safety reasons is not envisaged given the successful pilot study. If the study is prematurely discontinued, active participants will be informed and no further participant data will be

collected.

9. Statistics

Statistical analysis will be conducted by Sabine Landau or a junior statistician working under her supervision. Professor Landau will be responsible for implementation of the analysis plan.

9.1 Sample Size

The primary outcome is ADHD symptoms, measured using CAARS. The results of a single arm open label pilot study of young prisoners with ADHD who were given MPH showed a mean decrease of 25.0 points with a standard deviation of 9.1. This suggested a standardised effect size of d=2.75. It could reasonably be assumed that 20% of this effect might be attributed to the effects of MPH. On this basis, this study is powered to detect a standardised effect size of d=0.55. Assuming a standard deviation of 9.1, this would translate into a treatment difference of 5.0 points. This effect size is consistent with the results of a recent meta-regression analysis (29), which estimated the effect of treatment to be d=0.49 (95% CI 0.08, 0.64). The sample size calculation used G*Power version 3 and was based on the use of a t-test to compare the means of the treatment groups. In order to have 90% power at the 5% significance level to detect a standardised effect of d=0.55, this study would need to collect outcome data on 142 participants. Inflating for the expectation that loss to follow-up may be as high as 25%, a minimum of 190 participants should be recruited, with the target for the study set at 200.

25% loss is expected to be easily achievable since in the pilot 10% left the prison due to unexpected transfers from the prison and problems with adherence to trial medication was rarely followed by problems completing trial assessments. We will minimise unexpected loss by arranging continued follow-up of participants so they can remain in the trial.

9.2 Randomisation

Randomisation will take part once informed consent has been agreed and before the treatment trial is initiated. We will use the King's Clinical Trials Unit's Independent Randomisation Service, ensuring reliability and credibility in the randomisation process. Random block sizes will be used to control the numbers of subjects allocated to each group, stratified by site and in a 1:1 drug-placebo ratio. Patient characteristics will not be taken into account in the randomisation process, but we expect a balanced ratio of cognitive ability, ADHD symptom severity and co-occurring psychosocial and mental health problems across the drug treatment and placebo groups.

9.3 Analysis

9.3.1 Efficacy analyses: All statistical analyses will follow the intention-to-treat principle. Efficacy will be assessed by comparing primary and secondary outcomes between OROS-MPH and Placebo arms. Repeatedly measured primary and secondary outcomes (e.g. CAARS, WRAADS) will be analysed using linear mixed models. Secondary count outcomes at 8 weeks (e.g. number of critical incidents) will be compared between treatment arms using Poisson regressions to estimate incidence rate ratios (after conditioning on baseline counts and randomisation stratifiers). These models will contain outcomes from the two post-randomisation time points as the dependent variables and trial arm, time (5 and 8 weeks) and interaction terms as explanatory variables. Models will condition on baseline values and randomisation stratifiers. Random effects that vary at the subject level will be used to model the covariance structure between the repeated measures. Parameters will be estimated using maximum likelihood and inferences will remain valid in the presence of missing data provided that the missing data generating mechanism is missing at random (MAR). The primary analysis dataset will not include medication dosage information to ensure that the statistician remains unblinded.

Here this means that we can allow variables measured and included in the model (e.g. previously observed values of the outcome including baseline values, trial arm, stratifiers and post-treatment time point) to predict attrition. If necessary we will further expand our modelling to allow observed variables that do not form part of the analysis model (e.g. treatment withdrawal or side effects in the model for CAARS) to predict missingness. An independent statistician will be asked to determine the need for this step. This can be achieved either by considering such variables as auxiliary variables in a structural equation model or by including then as predictors in the imputation step of a multiple imputation approach.

The assumption of MAR is a reasonable one since loss to follow-up was largely related to measured outcomes (ADHD or adverse effects) or was the consequence of unexpected events that were not related to study outcomes. For example, in the pilot study transfers out of the prison were due to court cases for outstanding convictions, moving prison to be nearer home, change in category of prison or early release. However, in each case the decisions made were related to the index offence and long standing aspects of behaviour, unrelated to changes in recent behaviour during the recruitment or participation phases of the trial.

When reporting the findings, we will conduct formal sensitivity analyses to check robustness of the conclusions regarding assumptions about the missing data generation process (30).

9.3.2. Explanatory analyses: We will conduct explanatory analyses to investigate potential mediating effects of ADHD symptoms (CAARS inattention and hyperactivity-impulsivity subscale) and emotional dysregulation (WRAADS) on improvements in secondary behavioural outcomes. Our prior hypothesis is that reductions in the hyperactive-impulsive scores and emotional dysregulation scores will mediate reductions in the number of adjudications and reports of antisocial behaviour measured by behaviour report cards from prison staff and education staff. We will carry out mediation analyses to partition total treatment effects into mediated and non-mediated components. Mediation hypothesis will be investigated using structural equation modelling (Baron and Kenny approach (31) to partition the total treatment effect on number of adjudications or behavioural report scores into components that operate via the putative mediators (hyperactive-impulsive scores, emotional dysregulation scores or inattention) and non-mediated effects. Baseline confounders of the relationship between mediators and behavioural outcomes will be recorded and adjusted for in the modelling. These include age, IQ, educational level; in addition to baseline severity of ADHD symptoms and emotional dysregulation. Such analyses rely on the assumption of hidden confounding; instrumental variables methods will be considered to relax this assumption.

10. Trial Steering Committee (TSC)

A TSC will be convened to provide overall supervision of the trial and ensure the trial is conducted to the rigorous standards set out in the MRC guidelines for Good Clinical Practice. The TSC will monitor progress, adherence and safety. The TSC chair is Professor Jenny Shaw (Consultant Forensic Psychiatrist), University of Manchester,DrYlva Ginsberg (Consultant Psychiatrist specialising in ADHD in prisoners, Stockholm, Sweden), Peter Mason (Forensic Psychiatrist and specialist in ADHD, Cheshire and Wirral), Anthony Davis, R&D Manager, Oxleas NHS Foundation Trust, Dr Ulrich Muller-Sedgwick, Barnet, Enfield and Haringey Mental Health NHS Trust, Beverley Nolker, POA learning and a and user representative. (2) Non-independent members: The lead applicants in London and Edinburgh (Philip Asherson and Lindsay Thomson). Other members of the research management group will attend as observers and to report to the steering committee. It is envisaged that the TSC will meet before the start of the project and every 6-months, alternating between telephone conference and face to face meetings.

11. Data Monitoring Committee (DMEC)

A DMEC will be convened to monitor the safety, efficacy, ethical conduct and quality of the data. The committee will consist of three members experienced in clinical trials including an independent statistician. The DMEC chair is Professor Seena Fazel, University of Oxford (an experienced Forensic Psychiatrist). Other members are Professor Chris Hollis, University of Nottingham (an expert on the Clinical Management of ADHD) and Adrian Cook (a Trial Statistician) DMEC meetings will be timed to occur prior to TSC meetings to report to the TSC.

12. Local Trial Management

The project will be led by Professor Asherson in London supported by a Trial Manager. The Trial Manager will liaise with the trial monitors and ethical board where required and support for completion of interim reports as well as the ongoing management of the project. The Research Psychiatrist at YOI ISIS will coordinate all daily activities on site. Principal Investigator Thomson will lead the project in Edinburgh and will be supported by the local RA who will conduct similar day to day coordinating tasks in HMYOI Polmont.

13 Project Management Group

The project will be led by Chief Investigator Asherson in London. The program manager in London will liaise with the Edinburgh study coordinator weekly throughout the project, monitor progress and maintain communication about successes and barriers to progress and report back to the lead applicants. Asherson and Thomson will hold a weekly telephone conference to review progress with the data collection teams. A meeting of all investigators and co-applicants will review progress on a monthly basis.

14. Direct Access to Source Data and Documents:

The Investigator(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsor(s), Regulators and REC direct access to source data and other documents (e.g. patients' case sheets, blood test reports, X-ray reports, histology reports etc).

15. Ethics & Regulatory Approvals

15.1 General considerations: The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of Good Clinical Practice (GCP) and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments. This protocol and related documents will be submitted for review to London South East Research Ethics Committee (REC), and to the Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trial Authorisation. Annual progress and safety reports and a final report at conclusion of the trial will be submitted to the KHPCTO (on behalf of the Sponsor), the REC and the MHRA within the timelines defined in the Regulations. We previously received ethical approval and MHRA registration for the current open label trial of OROS-MPH in HMP ISIS and will follow the same recruitment and consent procedures as the previous study.

15.2 Ethical issues specific to this project: OROS-MPH is only licensed for first time use in young people with ADHD and severe impairment under the age of 18, although NICE also recommend MPH as the first line treatment for ADHD in adults. The 8-week trial includes a placebo group, so we will be denying a recommended treatment for ADHD during this period. However, currently prisoners with ADHD are rarely treated because of uncertainty over validity of the ADHD diagnosis, efficacy of treatment and concerns about potential drug abuse and diversion in prison populations. To address

the issue of equal access to treatment, we will offer treatment to all participants once the trial is completed. Care will be taken to ensure that no coercion is involved in recruiting prisoners into the study. Initial consent will be obtained by members of the prison mental health team. Following procedures in the pilot study, informed consent will be obtained at the screening and diagnostic steps as well as the start of the trial. All participants will have the mental capacity to make informed decisions. It will be made very clear that taking part in the study will have no impact, negative or positive, on their time in the prison or the prison regime. However some participants may benefit (and show improvements in behaviour) from the treatment that is offered as part of the clinical trial. Taking part in the study will not lead to loss of earnings. The study medication is a controlled substance. There are however standard operating procedures in place for the prescription of controlled drugs from the prison pharmacy.

16. Quality Assurance

Monitoring of this trial will be to ensure compliance with Good Clinical Practice and scientific integrity will be managed and oversight retained, by the King's Health Partners Clinical Trials Office Quality Team.

17. Data Handling

The Chief Investigator (Philip Asherson) will act as custodian for the trial data. Data will be stored on a database to be set up by the Clinical Trials Unit at Kings College London. The following guidelines will be strictly adhered to:

Patient data will be anonymised:

- All anonymised data will be stored on a password protected computer.
- All trial data will be stored, handled, processed and archived in line with the Data Protection Act; and the Medicines for Human Use (Clinical Trials) Amended Regulations 2006.

18. Data Management

Data will be stored on a trials database to be set up by the Clinical Trials Unit at Kings College London. This allows for full audit information and allows for checks on data entry that will be used to ensure the integrity of the data collection and monitoring of the study progress. At the end of the study all research records will be transferred by secure courier service to Social, Genetic and Developmental Psychiatry (SGDP) centre, King's College London.

19. Publication Policy

It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals. Additionally we will disseminate through internal reports to the prisons services and through relevant online forums such as UKAAN (UK Adult ADHD Network).

20. Insurance/Indemnity

Clinical Trial insurance is provided by the King's College London Clinical Trials Insurance Policy.

21. Financial Aspects

Funding to conduct the trial is provided from two sources: (1) Research costs from Efficacy and Mechanism Evaluation (EME) Programme (National Institute of Health Research and Medical Research Council); (2) Commercial stocks of OROS-MPH will be

provided by Janssen-Cilag. Note that over-encapsulation of OROS-MPH and manufacture of matched placebo will be conducted by Piramal Healthcare UK Ltd, funded from the EME programme grant.

22. Signatures

_____ _____

Chief Investigator Date

Print name

_____ _____

Statistician Date

Print name: Sabine Landau

REFERENCES

1. Ford T, Goodman R, Meltzer H: **The British Child and Adolescent Mental Health Survey 1999: the prevalence of DSM-IV disorders**. *Journal of the American Academy of Child and Adolescent Psychiatry* 2003, **42**(10):1203-1211.
2. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA: **The worldwide prevalence of ADHD: a systematic review and metaregression analysis**. *The American journal of psychiatry* 2007, **164**(6):942-948.
3. Fayyad J, De Graaf R, Kessler R, Alonso J, Angermeyer M, Demyttenaere K, De Girolamo G, Haro JM, Karam EG, Lara C *et al*: **Cross-national prevalence and correlates of adult attention-deficit hyperactivity disorder**. *The British journal of psychiatry : the journal of mental science* 2007, **190**:402-409.
4. Simon V, Czobor P, Balint S, Meszaros A, Bitter I: **Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis**. *The British journal of psychiatry : the journal of mental science* 2009, **194**(3):204-211.
5. Young S, Moss D, Sedgwick O, Fridman M, Hodgkins P: **A meta-analysis of the prevalence of attention deficit hyperactivity disorder in incarcerated populations**. *Psychological medicine* 2014:1-12.
6. NICE: **Attention Deficit Hyperactivity Disorder: The NICE guideline on diagnosis and managment of ADHD in children, young people and adults**: The British Psychological Society and The Royal College of Psychiatrists; 2008.
7. NICE: **Diagnosis and management of ADHD in children, young people and adults**. London The British Psychological Society and The Royal College of Psychiatrists; 2018.
8. SIGN: **Management of attention deficit hyperactivity and hyperkinetic disorders in children and young people: A national clinical guideline**. Edinburgh, Scotland: Scottish Intercollegiate Guidelines Network; 2009.
9. **Attention deficit hyperactivity disorder: evidence update 45** [file:///C:/Users/Philip%20Asherson/Downloads/Attention+deficit+hyperactivity+disorder+Evidence+Update+July+2013.pdf]
10. Koesters M, Becker T, Kilian R, Fegert JM, Weinmann S: **Limits of meta-analysis: methylphenidate in the treatment of adult attention-deficit hyperactivity disorder**. *Journal of psychopharmacology* 2009, **23**(7):733-744.
11. Ginsberg Y, Lindefors N: **Methylphenidate treatment of adult male prison inmates with attention-deficit hyperactivity disorder: randomised double-blind placebo-controlled trial with open-label extension**. *The British journal of psychiatry : the journal of mental science* 2012, **200**(1):68-73.
12. Lichtenstein P, Larsson H: **Medication for attention deficit-hyperactivity disorder and criminality**. *The New England journal of medicine* 2013, **368**(8):776.
13. Young S, Gudjonsson G, Wells J, Asherson P, Theobald D, Oliver B, Scott C, Mooney A: **Attention deficit hyperactivity disorder and critical incidents in a Scottish prison population**. *Personality and individual differences* 2008, **46**(3):265-269.
14. Moukhtarian TR, Cooper RE, Vassos E, Moran P, Asherson P: **Effects of stimulants and atomoxetine on emotional lability in adults: A systematic review and meta-analysis**. *Eur Psychiatry* 2017, **44**:198-207.
15. Asherson P, Buitelaar J, Faraone SV, Rohde LA: **Adult attention-deficit hyperactivity disorder: key conceptual issues**. *Lancet Psychiatry* 2016, **3**(6):568-578.

16. Volkow ND, Swanson JM: **Variables that affect the clinical use and abuse of methylphenidate in the treatment of ADHD**. *The American journal of psychiatry* 2003, **160**(11):1909-1918.
17. Conners CK, Erhardt D, Sparrow E: **Adult ADHD Rating Scales (CAARS). Technical Manual**. New York: Multi Health Systems Inc.; 1999.
18. Rosler M, Retz W, Retz-Junginger P, Stieglitz RD, Kessler H, Reimherr F, Wender PH: **[Attention deficit hyperactivity disorder in adults. Benchmarking diagnosis using the Wender-Reimherr adult rating scale]**. *Der Nervenarzt* 2008, **79**(3):320-327.
19. Alderman N, Knight C, Morgan C: **Use of a modified version of the Overt Aggression Scale in the measurement and assessment of aggressive behaviours following brain injury**. *Brain injury : [BI]* 1997, **11**(7):503-523.
20. Walker J, Bowes N: **The evaluation of violent thinking in adult offenders and non-offenders using the Maudsley Violence Questionnaire**. *Criminal behaviour and mental health : CBMH* 2013, **23**(2):113-123.
21. Evans C, Connell J, Barkham M, Margison F, McGrath G, Mellor-Clark J, Audin K: **Towards a standardised brief outcome measure: psychometric properties and utility of the CORE-OM**. *The British journal of psychiatry : the journal of mental science* 2002, **180**:51-60.
22. Mowlem FD, Skirrow C, Reid P, Maltezos S, Nijjar SK, Merwood A, Barker E, Cooper R, Kuntsi J, Asherson P: **Validation of the Mind Excessively Wandering Scale and the Relationship of Mind Wandering to Impairment in Adult ADHD**. *J Atten Disord* 2016.
23. Derogatis LR, Melisaratos N: **The Brief Symptom Inventory: an introductory report**. *Psychological medicine* 1983, **13**(3):595-605.
24. Stringaris A, Goodman R, Ferdinando S, Razdan V, Muhrer E, Leibenluft E, Brotman MA: **The Affective Reactivity Index: a concise irritability scale for clinical and research settings**. *Journal of child psychology and psychiatry, and allied disciplines* 2012, **53**(11):1109-1117.
25. Guy W: **Clinical Global Impressions (CGI) Scale, Modified**. In: *Task Force for the Handbook of Psychiatric Measures Handbook of Psychiatric Measures* edn. Edited by In Rush JA. Washington, DC: American Psychiatric Association 2000.
26. Rosler M, Retz W, Fischer R, Ose C, Alm B, Deckert J, Philipsen A, Herpertz S, Ammer R: **Twenty-four-week treatment with extended release methylphenidate improves emotional symptoms in adult ADHD**. *The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry* 2010, **11**(5):709-718.
27. Kooij JJS: **Adult ADHD: diagnostic assessment and treatment**, 3rd edn. London: Springer Healthcare LTD; 2012.

1. 59(2):120-129.