ADDUCE Report Summary

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Final Report Summary - ADDUCE (Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects)

Executive Summary:
Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders in children, affecting approximately 5% of children in Europe. Methylphenidate (MPH), a central nervous system stimulant, is the most commonly prescribed medication for children suffering from ADHD; it is also increasingly used to treat ADHD in adults. In 2007 the European Commission requested a referral to the Committee for Medicinal Products for Human Use (CHMP) under Article 31 of Directive 2001/83/EC, as amended, for MPH because of possible safety concerns. The CHMP concluded that a study of the long term effects of MPH on growth, sexual development, neurological system, psychiatric states and cardiovascular system was needed. In response to the concerns of the CHMP, the ADDUCE (Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects) research team was formed by a consortium of experts in the fields of ADHD, drug safety, neuropsychopharmacology and cardiovascular research.
The ADDUCE project was an EU funded programme focusing on the safety of treatment of ADHD with MPH in children and adolescents, more specifically, the long-term effects of MPH on growth, the neurological system, psychiatric states and the cardiovascular system.
The key objectives of the study were:

1. To perform a series of pharmacovigilance studies that will lead to innovative knowledge with respect to the long-term adverse effects of methylphenidate that constitutes major public health concerns as specified by the EMA.

2. To address scientific questions about prevalence, clinical significance, development and moderating and/or mediating factors of four specific classes of long-term adverse effects of methylphenidate; growth, neurological, psychiatric and cardiovascular.

3. To develop new research tools and to identify new safety issues for future pharmacovigilance research for the treatment of ADHD.

4. To promote public health by disseminating the innovative knowledge acquired by the proposed studies to regulatory authorities, scientific community, medical and mental health professionals, to patients and their families, policy makers and to society in general, in order to promote the safer use of methylphenidate.

Project Context and Objectives:
2. Project Description
2.1.1 Symptoms and Diagnosis of ADHD
Whilst attention deficit hyperactivity disorder (ADHD) remains a controversial condition that continues to receive significant levels of coverage within both the medical and general press it is far from being a “new” condition. In an article in The Lancet over a century ago, George Still, an English paediatrician, described a condition where patients had “marked inability to
concentrate and sustain attention”. The diagnostic criteria for ADHD are described in the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders. There are three core symptom domains: inattention, hyperactivity and impulsivity. In order to meet the diagnostic criteria symptoms must be pervasive, persistent and impairing. Whilst the DSM system allows hyperactive/impulsive, inattentive and combined presentations, the International Classification of Diseases – Version 10 (ICD-10) diagnosis of hyperkinetic disorder (HKD), a disease of the, describes a more severe form of ADHD which requires the presence all three symptom domains and higher degrees of pervasiveness and impairment.

2.1.2 Aetiology of ADHD
ADHD is a disorder with multiple overlapping causal pathways that include, both genetic and environmental components. The precise mechanisms by with these interact and exert their effects is not known. Genetic factors are clearly important in ADHD. Family, twin and adoption studies have estimated a heritability of ADHD of around 0.80 but little is known about the mechanisms by which their influence is exerted. Candidate gene studies have produced a number of replicated associations, especially for polymorphisms of dopamine genes, e.g. the D4 and D5 receptors (DRD4 & DRD5) and the Dopamine Transporter (DAT1) and more recently GWAS studies have indicated several potentially important areas of interest. There are structural changes in the brain compared to typically developing children and young people: Total brain volumes of children with ADHD are reduced by up to five percent with effects on both grey and white matter and larger reductions apparent in the right hemisphere. Correspondingly, there are functional brain changes, with reduction of activation in areas controlling inhibition and executive function, and several neurocognitive impairments including impairments in tests of memory, inhibition, decision making, delay aversion, timing and response variability.

2.1.3 Epidemiological Data on ADHD
The prevalence of ADHD depends on a number of factors; the diagnostic criteria used (whether a DSM-IV diagnosis of ADHD or an ICD-10 diagnosis of hyperkinetic disorder is made); the diagnostic measures used (such as rating scales for parents/ teachers or interviews); the number of informants involved in the diagnostic process (parents only, teachers only or both); the age of the population (school-aged children and/or adolescents/adults) and the area from which the population was sampled (inner city or rural areas). A difference also exists as to the way in which the term prevalence used; ‘administrative prevalence’ refers to the numbers clinically diagnosed in the population while ‘true prevalence’ refers to the number of people in the population with the condition (whether recognised clinically or not). There has been debate as to whether the prevalence of ADHD truly differs among different countries, particularly whether the rate in the US is significantly higher than that reported elsewhere (as is reported in the literature). Whilst it is difficult to compare the rates reported in various studies from different settings and countries due to those factors described above the most recent meta analyses suggest that from an epidemiological perspective when ADHD is measured using the same type of instruments and information and using the same criteria the prevalence of ADHD, at around 5%, is very similar across the globe and has not changed in recent times. Thus differences in administrative prevalence found both between and within countries are probably a consequence of variations in recognition and clinical practice. The prevalence of ADHD in school-aged children in England and Wales is estimated at 3-5% whereas the prevalence of HKD in the same population is approximately 1%. ADHD is more common in males (ratios ranging from 2:1 to 9:1 depending on subtypes used) and in primary school-aged children compared to adolescents.

2.1.4 Treatment of ADHD
There are a number of different interventions used in the treatment of patients with ADHD including psychological, behavioural, social and pharmacological interventions. The former interventions are beyond the scope of this study which has focussed on the medications currently available for the treatment of the condition and in particular on methylphenidate.

2.1.5 European Guidelines for the treatment of ADHD in Children
The European Network for Hyperkinetic Disorders (EUNETHYDIS) produced the first upgrade of the European clinical guidelines for hyperkinetic disorder in 2004 and have added to these over time with guidance on long acting medications, adverse effects, quality of life and non-pharmacological treatments. These guidelines provide recommendations on the diagnosis and
management of ADHD and include information on the presence of comorbid conditions, differential diagnoses, patient evaluation, and various modes of treatment. In summary, this group recommends that a comprehensive assessment is required before a diagnosis of ADHD or HKD is made. This includes a clinical interview with the parents, and the child and information from the child’s school. Behavioural observations are made during the clinical examination are also taken into account. The ADHD symptoms are considered taking into account the developmental level of the child and any alternative possible explanations and/or comorbid conditions. A physical examination is also advised to exclude any underlying medical conditions which may either mimic ADHD symptoms or contraindicate drug treatment; hearing should be checked, and any history of epilepsy determined. Only after these examinations have been completed can treatment be initiated. In terms of pharmacological treatment, the consensus recommendation of the group is that initial medication is given as a trial, and that methylphenidate is usually the first choice.

Methylphenidate
Methylphenidate, the most common first-line therapy for ADHD in Europe. It has been used in the treatment of ADHD for over 50 years and has been well studied with regards short term efficacy and safety. Methylphenidate is a controlled drug. It is licensed as part of a comprehensive treatment programme for ADHD in children aged 6 years and above. Methylphenidate as the immediate release formulation is normally started at a dose of 5mg twice or three times a day at breakfast, lunchtime and late afternoon (after school). Dosage and frequency can be titrated slowly over time according to symptom response to a maximum recommended daily dose of 60mg.

The long-acting stimulants are as effective as the immediate-release formulation and also have a similar side-effect profile. The most common side-effects experienced with methylphenidate include sleeplessness, nervousness, reduced appetite, headache, abdominal pain, tachycardia, changes in blood pressure and heart rate. Rarer effects include reduced weight gain and growth reduction occurring with prolonged use. It is thought many of these effects are transient and can be managed by reduction in dose. Whilst there are some data regarding long term adverse effects of methylphenidate these are relatively lacking and to date none have included control data from either un-medicated ADHD or healthy controls.

Safety Issues proposed by the Committee for Medicinal Products for Human Use (CHMP) for further research.

In 2007, the European Commission requested a referral to the Committee for Medicinal Products for Human Use (CHMP) under Article 31 of Directive 2001/83/EC, as amended, for all methylphenidate containing products because of safety concerns. During the procedure, the main potential safety areas evaluated concerned cardiovascular risks, cerebrovascular risks, psychiatric disorders, carcinogenicity, effect on growth and effects of long-term treatment.

In January 2009 the CHMP concluded that the benefit risk of methylphenidate in the authorized indication remains favourable but that additional data was needed on long-term effects in children, adolescents and young adults with a particular focus on:
1. Design of appropriate tools to study developmental effects
2. Study of long-term developmental effects including growth
3. Study of long-term neurological effects including cognitive function
4. Study of long-term psychiatric outcomes (including mood disorders, hostility and psychotic disorders)
5. Study of long-term effects on sexual development and fertility
6. Cardiovascular effects in adults who are either currently taking methylphenidate or who have a history of use in childhood.

The CHMP emphasized that the specific research outputs should be the generation of data that allow for the comparison of exposed children with suitable control groups bearing in mind that ADHD covers a broad spectrum of inappropriate behaviour and may be associated with other disorders. Pre-clinical data show that methylphenidate causes behavioural changes in animal models manifesting as hyperactivity and stereotyped behaviour, so control of confounding was an important issue in study design. The European Commission referred to Article 31 of Directive 2001/83/EC and defined long-term as “more than 1 year”.

2.2 Project Objectives
In line with the CHMP’s concerns and advice on the safety of methylphenidate, the key objectives of the ADDUCE Research
Key Objective 1: To perform a series of pharmacovigilance studies that will lead to innovative knowledge with respect to the long-term adverse effects of methylphenidate that constitutes major public health concerns as specified by the EMA.

Key Objective 2: To address scientific questions about prevalence, clinical significance, development and moderating and/or mediating factors of four specific classes of long-term adverse effects of methylphenidate; growth, neurological, psychiatric and cardiovascular.

Key Objective 3: To develop new research tools and to identify new safety issues for future pharmacovigilance research for the treatment of ADHD.

Key Objective 4: To promote public health by disseminating the innovative knowledge acquired by the proposed studies to regulatory authorities, scientific community, medical and mental health professionals, to patients and their families, policy makers and to society in general, in order to promote the safer use of methylphenidate.

Key objective 1 includes the following specific aims:
Aim 1. To identify and acquire appropriate and high quality retrospective data to investigate the long term safety of methylphenidate for the treatment of ADHD.
Aim 2. To conduct a 24-month prospective open-label observational cohort pharmacovigilance study with 2 control groups (untreated ADHD patients and healthy siblings), to investigate the long-term safety of methylphenidate for the treatment of ADHD.
Aim 3. To ensure that when performing these pharmacovigilance studies due consideration is paid to medical ethical issues.

Key objective 2 includes the following specific aims:
Aim 4. To determine whether methylphenidate treatment for ADHD is associated with a statistically significant increase in long-term (> 1 year) risk of negative effects on: the rate of growth (i.e. height and weight) and of pubertal maturation.
Aim 5. To determine whether methylphenidate treatment for ADHD is associated with a statistically significant increase in long-term (> 1 year) risk for the following neurological outcomes: Seizures, Sleep problems and Dyskinesia.
Aim 6. To determine whether methylphenidate treatment for ADHD is associated with a statistically significant increase in long-term (> 1 year) risk for the following psychiatric outcomes: Mood disorder, Suicidal behaviour, Psychotic symptoms, Substance misuse, Tics/ Tourette’s disorder.
Aim 7. To determine whether the long-term use (≥ 3 years) of methylphenidate increases the blood pressure and causes left ventricular hypertrophy (LVH) identified by echocardiography in late adolescent (≥15 years) and young adults with ADHD.
Aim 8. To determine whether the increases in blood pressure and pulse rate seen in children with ADHD identified with short term exposure to methylphenidate persist in the long-term (> 1 year).
Aim 9. To explore the moderating and/or mediating factors of the long-term safety of methylphenidate in children, adolescents and adults with ADHD. Moderators identify in whom and under which circumstances treatment has different effects. Mediators identify why and how adverse effects occur.
Aim 10. To determine whether methylphenidate treatment for ADHD is associated with a statistically significant increase in long-term (> 1 year) risk for other adverse effects as assessed by a semi-structured interview addressing all major body systems.

Key objective 3 includes the following specific aims:
Aim 11. To explore the application of intensive monitoring of bone age as a tool to study adverse developmental effects of methylphenidate.
Aim 12. To develop validated reliable tools for the evaluation of negative cognitive effects including: reduced cognitive flexibility, reduced motivation and increased or decreased sensitivity to reward.
Aim 13. To identify and propose new research areas to enhance the safety of long-term use of methylphenidate in patients with ADHD

Key objective 4 includes the following specific aims.

Aim 14. To directly interact with the EMA to ensure the protocols and results are able to aid the EMA in making regulatory decisions regarding the marketing authorization of methylphenidate including the product information warnings for doctors and patients.

Aim 15. Publish the results of these studies as peer-reviewed papers in international journals and in leading national medical and mental health journals.

Aim 16. Present the data in national and international meetings in the form of symposia, workshops and clinical training sessions. We will pay particular attention to knowledge transfer to new EU states and associated and candidate states.

Aim 17. To translate the results of the proposed studies into evidence for developing new and updating existing clinical guidelines and practice parameters for the treatment of ADHD.

Project Results:

3.1 Project Overview

Methylphenidate was introduced and licensed in the 1960s, before modern standards of clinical trials and pharmacovigilance were established. Recent developments, as summarised below, have resulted in increased levels of public concern and several reviews by professionals working in the field have attacked the widespread prescribing of methylphenidate on these and other grounds further increasing public disquiet.

3.1.1 Recent developments:
(i) A rapid increase in the diagnosis of ADHD and in the use of medication treatments for ADHD, in some European countries (including Germany, Netherlands, Belgium, Ireland and UK) has created a large number of children exposed to potential hazards.
(ii) Adults with ADHD are now being diagnosed and treated. The drug is therefore being given to a group that is more at risk for certain adverse events, such as hypertension, heart disease, depression and psychosis that could be exacerbated by stimulants.
(iii) It is now commonplace for children to receive the medication for many years – often until the age of 16 and sometimes into adulthood. By contrast, long-term data on safety and effectiveness are lacking. Much of our knowledge about treatment periods of longer than a year comes from following up one study, the Multimodal Treatment of ADHD study (MTA) that did not include untreated controls.
(iv) Medications more recently introduced into the marketplace have been identified as having the potential for unexpected harm, [e.g. a potential for suicidal thinking from atomoxetine] – raising the possibility that this adverse outcome may also apply to methylphenidate.
(v) Reports of frequent illicit use by college students and associations with increased substance misuse have reinforced concern about the potential of methylphenidate (which is a controlled drug) for generating misuse of both legal (e.g. alcohol and nicotine) and illegal substances.
(vi) Cases of potentially very serious cardiovascular adverse events have been reported in the literature by the United States Food and Drugs Administration (FDA). Some of these, such as sudden death is too rare to have occurred in controlled trials. Other more common adverse events, such as hypertension have been poorly documented in the available study reports and publications. However, the occurrence of these adverse events influenced the FDA in America to attach warnings to the use of methylphenidate.
(vii) Laboratory studies of the pharmacological effects of methylphenidate have demonstrated its actions to inhibit the dopamine transporter and thereby to increase synaptic levels of dopamine. The consequence of this in the brain can therefore be expected to include (i) known dopaminergic effects such as appetite suppression and motor tics; (ii) long-term changes in brain neurotransmission. Whether or not such changes are associated with actual negative patient outcomes and if so how common these occur, is not known.
Together these concerns and unresolved questions regarding the safety of methylphenidate resulted in the EMA request that the safety of methylphenidate be rigorously evaluated. The ADDUCE project was designed on the basis of the EMA’s recommendations as the current lack of information on various safety issues makes it possible that vulnerable children are being exposed to unreasonable hazard, and/or that some children are being denied the benefit of a safe effective medication if perceived risks are being exaggerated. The purpose of this programme of work was to provide some answers to these important questions to ensure that a better understanding is available to the regulators, clinicians, patients and their parents in order to promote safe and effective high quality, evidence-based care for those with ADHD.

3.1.2 ADDUCE approach
In order to obtain a clearer idea of the scale of the risk, the project analysed the data from the Vigibase™ which is developed and maintained by the World Health Organisation’s (WHO) Programme for International Drug Monitoring. The Vigibase™ contained more than three million ADR reports in 2004 from 86 countries. This dataset was used to compare the rates of ADRs for methylphenidate with those for all other drugs using a statistical modelling approach. The results showed disproportionally high signals of certain ADR reports with methylphenidate. The 21 most frequent ADRs signals for methylphenidate are given in the table below.

The ADDUCE consortia used this list to prioritise the research questions. Some of the above “adverse reactions” are confounded by the presence of each other (e.g. muscle twitching, tics and Tourette Disorder). Others are confounded because they are part of the symptomatology of ADHD itself (e.g. impulsive behaviour).

**Most frequent ADRs signals for methylphenidate in Vigibase™ (2009)**
17. Obsessive-compulsive disorder 18. Personality disorder

Using our clinical judgement and accounting for confounding those remaining ADRs were included as important signals for the investigation.

The ADDUCE consortia convened as part of the EUNETHYS programme, for a series of meetings to review the existing evidence on the safety of drugs for ADHD. Child psychiatrists, adult psychiatrists, psychologists, paediatricians, cardiologists and laboratory scientists made a critique of the literature on drug safety to date. The goal of these meetings was to describe: the frequency of adverse reactions, their latency and seriousness, the strength of their association with methylphenidate, the evidence for causality, factors influencing the level of risk, and how they should be managed. This process clearly identified that there were many gaps in the existing literature, some topics yet to be systematically reviewed, some databases not fully exploited for this purpose, and that for some topics new research was urgently required.

The knowledge at the start of this project was largely derived from published trials of drug against placebo (which have relied almost exclusively on children rather than adolescents and which last only for a few weeks or months and from observational follow-up of those exiting these trials into either open-label extension studies or unrestricted observational follow-up which generate databases over longer periods, but lack suitable controls and consequently it is difficult to draw conclusions from these studies. As a result, there are several types of uncertainty to be resolved, each of which requires a somewhat different approach:

- A long time-span is needed for problems that are expected to emerge only after years of therapy (e.g. left ventricular hypertrophy)
- A broad age range is required as some adverse outcomes are likely to appear only when children reach a certain age (e.g. psychosis, substance misuse). Adolescent and adult subjects therefore need to be investigated as well as younger children
• Suitable controls are required in order to assess whether adverse outcomes occur more frequently or at greater severity as a result of the medication. The preferred controls are children and/or adults with ADHD who have not been treated with methylphenidate – these are essential for examining outcomes that are associated with untreated ADHD, such as substance misuse. Untreated subjects with ADHD are, however not appropriate for some other outcomes because of the likelihood of systematic bias in those who are not treated (such as the presence of risk factors for adverse outcomes that have deterred clinicians from prescribing). Individuals without ADHD are therefore also needed to establish the population risk – but need to be matched for possible social adversity because of its effects on outcomes such as hypertension (via obesity), psychiatric disorders, and substance misuse.

• Appropriate measures that investigate risks are required. Systematic recording is usually only provided for short-term studies but has not been universally adopted in these studies, as most industry funded randomised controlled trials depend on spontaneous reporting by patients/parents rather than structured assessment of potential adverse effects. This reliance on spontaneous reporting has in all probability resulted in a general underestimate of the frequency of hazards to health associated with these medications. For certain aspects of functioning such as cognition, it is not yet clear which measures have adequate sensitivity, specificity, reliability and validity to identify changes in cognition that are often subtle in nature but are reported by patients being significantly impairing. Furthermore, some modern methods for monitoring adverse events have scarcely been used. The concerns about the possible cardiac dangers raise a special need for greater use of tests of cardiac function such as 24-hour monitoring of blood pressure and ultrasound measurements of cardiac structure and function.

• Very large numbers of patients are required when the adverse outcome is rare. Liver failure with the non-stimulant drug atomoxetine and sudden death in people taking methylphenidate have been reported, but on closer inspection the rates appear to be similar or even lower than those expected in the general population. To further investigate the occurrence of such rare adverse events, population databases with extraordinary large sample sizes are needed which is out with the scope of the ADDUCE project.

As the nature of the existing uncertainties varies for different adverse outcomes, it was apparent that it was necessary to conduct a range of investigations to detect different forms of risk. The ADDUCE project was designed to bring together these complementary lines of work into a cohesive programme.

3.2 Key Objective 1:
To perform a series of pharmacovigilance studies that will lead to innovative knowledge with respect to the long-term adverse effects of methylphenidate that constitutes major public health concerns as specified by the EMA.

3.2.1 Aim 1. To identify and acquire appropriate and high quality retrospective data to investigate the long term safety of methylphenidate for the treatment of ADHD.

The ADDUCE project aimed to investigate the long-term adverse effects of methylphenidate (MPH) on growth, neurological systems, psychiatric states and the cardiovascular system in children and adults. One approach to address these questions was to conduct retrospective studies using existing databases (WP2). On this purpose an extensive assessment of available databases has been performed. Results have been published as ADHD data source inventory. Based on the results the most appropriate high quality data sources, i.e. CPRD, KiGGS, ALSPAC databases, were chosen and utilized for the retrospective studies in the ADDUCE project. Unfortunately, it was not possible to combine these data from different databases. A brief description of each of them is given below:

1) The Clinical Practice Research Datalink (CPRD) is a large database of primary care medical records. With about 11 million total patients (5.25 million active) from 639 general practices in the United Kingdom, the database contains anonymised, validated data on prescriptions, diagnoses, demographics, as well as the results of laboratory tests at individual patient visit level. The Read Clinical Terms classification is used to code specific diagnoses and signs and symptoms, and a drug dictionary based on data from the Multilex classification (First DataBank Europe Ltd) is used to code drugs. The database also includes reports on episodes of secondary care (e.g. emergency care, hospital admissions and discharge) as well as information on referral to specialists. However, it does not code prescriptions issued by specialists but information on drug treatment may be
available as free-text comments in the database. The CPRD provides a longitudinal record of care for each patient. It is nationally representative and has been used in several published studies of chronic conditions including ADHD and epilepsy.

2) The German Health Interview and Examination Survey for Children and Adolescents (KiGGS) is a nationwide, representative cross-sectional health interview and examination survey with a total of 17641 examined children and adolescents aged 0-17 years. The sampling procedure in this survey was based on a two-stage protocol developed in co-operation with the Centre for Survey Research and Methodology (ZUMA), Mannheim, Germany. The survey was conducted between May 2003 and 2006 in 167 sample points all over Germany. Participants of the survey were medically and physically examined and tested. In addition, parents and children older than 11 years completed self-administered questionnaires that included psychological and social testing. The data set is nationally representative and has been used in a variety of analysis. The core data set is available to the scientific community as a “public use” file. Additional information such as medication use can be used by research co-operation with the RKI in order to jointly answer defined scientific questions.

3) The Avon Longitudinal Study of Parents and Children (ALSPAC) is a prospective population-based study in the South West of England. All pregnant women resident in the Avon area with an expected delivery date between April 1991 and December 1992 were invited to participate. Around 85% of all eligible women participated, providing a cohort of 14,541 pregnancies. ALSPAC participants were broadly representative of the local population of mothers with infants and comparable against national census data although they were slightly more likely to be Caucasian, married or cohabiting, home owner-occupiers, and have a car in the household (http://www.alspac.bris.ac.uk). Detailed information on the whole sample (mothers and children) has been obtained at regular intervals during the pregnancy and since the birth. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Advisory Committee and the Local Research Ethics Committees. Psychiatric disorder at age 7 years (91 months) was based on the reliable and well-validated Development and Well-Being Assessment (DAWBA) which consists of a structured combined package of parent and teacher questionnaires and incorporates open questions allowing free-text answers. Questions focus on current symptoms and impairment. To emulate the clinical diagnostic process as closely as possible, experienced clinicians independently reviewed all available symptom and impairment information obtained from parents and/or teachers in assigning DSM-IV psychiatric diagnoses reflecting externalising and internalising disorders. ADHD diagnostic information was obtained on 8,242 children, of whom 175 met criteria for ADHD (8,067 are non-ADHD controls). Follow-up data are available through to age 17 years.

Additionally, we conducted a study with University of Hong Kong, which was only partly funded by the ADDUCE project, to investigate the association between MPH use and psychotic events in the Hong Kong Clinical Data Analysis and Reporting System (CDARS), an electronic health record database developed by the Hong Kong Hospital Authority, a statutory body which manages all public hospitals and their ambulatory clinics in Hong Kong. Data from CDARS have proved to be a reliable database for research and have been used for various pharmacoepidemiological studies, including MPH prescribing trends in Hong Kong, and the association between MPH treatment and risk of trauma. Patient-specific clinical data include diagnosis, prescription and information on admission and discharge which are recorded by trained clinicians. Other patient-specific data such as demographics, payment method, prescription and pharmacy dispensing information are entered by other trained staff. CDARS contains the records of all in-patient, out-patient and emergency room admissions in Hospital Authority clinics and hospitals since 1995. Records are anonymised to protect patient confidentiality. Detailed descriptions of CDARS can be found elsewhere.

3.2.2 Aim 2. To conduct a 24-month prospective open-label observational cohort pharmacovigilance study with 2 control groups (untreated ADHD patients and healthy siblings), to investigate the long-term safety of methylphenidate for the treatment of ADHD.

Introduction
In January 2009 an investigation into medicines containing methylphenidate by the Committee for Medicinal Products for
Human Use (CHMP) concluded that overall the benefits of methylphenidate outweigh the risks when prescribed to children with ADHD aged 6 years and over. However, the Committee made recommendations to standardise prescribing and provision of safety information across all EU member states. Importantly, the report also stated that more data are required on the long-term effects of methylphenidate on children and adolescents and concluded that further research should be carried out to investigate long-term effects of methylphenidate on (1) growth and development, (2) neurological health, (3) psychiatric health, (4) sexual development and fertility and (5) cardiovascular effects in adults who have taken/are taking methylphenidate. ADDUCE Work Package 3 (WP3) was a 2-year prospective cohort study that compared children and adolescents newly started on methylphenidate with two separate control groups (children and adolescents with ADHD not treated with medication and a health control group) which was designed to provide new data to specifically answer these questions about long-term methylphenidate safety in children and adolescents with ADHD.

Aim
The aim of this study was to determine the long-term effects of methylphenidate on growth and development, neurological, psychiatric and cardiovascular health. The primary outcome measure, on which the sample size was based, was the height velocity standard deviations score (SDS). Height velocity SDS indexes how quickly a child is growing, compared with an average child of the same age and gender. We also collected data on several other key secondary outcomes in the fields of growth, cardiovascular system, as well as psychiatric and neurological health.

Cohort
The original design was to recruit three groups of children and adolescents (aged 6-17) from child and adolescent mental health services in the UK, Germany, Italy and Hungary:

Group 1: Medicated ADHD: participants diagnosed with ADHD who have not yet been treated with any ADHD medication and are about to start methylphenidate treatment for the first time. We aimed to recruit 800 participants to this group.

Group 2: Unmedicated ADHD: participants diagnosed with ADHD who have never been treated with ADHD medication and are not intending to start treatment. We aimed to recruit 400 participants to this group.

Group 3: Non-ADHD: participants who do not have ADHD, but have siblings who do have ADHD and are in either Group 1 or 2. We aimed to recruit 400 participants to this group.

Due to difficulties in recruiting into Group 3 the inclusion criteria for this group were changed to allow unrelated healthy controls without ADHD to be included.

Study design
The study was a 2-year naturalistic three group longitudinal prospective pharmacovigilance multicentre study. There were 5 study visits in total with participants in all 3 groups underwent identical assessments at baseline and then at 6 monthly intervals for 2 years, (Figure 1).

Participants in the medicated ADHD group (Group 1) had their first assessment before they began methylphenidate treatment. The study visits were carried out during an eight week period four weeks either side of the actual date that the visit was due. This was don’t to maximise the opportunity for the visit to take place. All primary and secondary measures were assessed at each study visit, with the exception of the visit at 18 months at which only height, weight, blood pressure, vital signs and pubertal maturation were assessed, and medication history updated.

Study set up
The UK was the lead country for the study, with Sponsorship provided by Tayside Medical Science Centre (TASC), a joint partnership of NHS Tayside and the University of Dundee. Initial ethical approval for the study was obtained from the East of
Scotland Research Ethics Service (reference 11/ES/0016). Patient information leaflets and consent forms were translated (and checked by back translation) as necessary for each country and submissions were then made by each of the other three countries to secure ethical permission at their own sites. Overall management of the trial was provided jointly by the Division of Neuroscience, University of Dundee and the Tayside Clinical Trials Unit (TCTU), a UK Clinical Research Collaboration (UKCRC)-registered clinical trials unit study-specific training was given to lead representatives of all countries at an initial set-up meeting. A training package was developed based on this meeting and then distributed to all researchers working on the study via their site. The design of the project enables the study to be run with some flexibility (e.g. in terms of recruitment strategy and number of participating sites) within each of the four participating countries, whilst remaining within the boundaries of the study protocol. Each country had a lead site which coordinated and supported the other recruiting sites within that country. The study had a total of 27 recruiting sites: 6 in the UK led by the University of Dundee; 1 in Hungary at Vadaskert Hopital, Budapest; 6 in Italy led by the University of Cagliari and 12 in Germany led by the Central institute of Mental Health in Mannheim.

Training and quality control across sites
To ensure that the data collected from the study are of the highest quality, the ADDUCE study was conducted to standards that are in line with GCP guidelines. A number of measures were put in place to ensure the data are of highest quality possible and are collected in as consistent a way as possible across all sites. These included a comprehensive training package which included audio and video records of the initial training meeting and needed to be completed by all researchers before they began work on the study. Additionally, training meetings were held in each country for which there is more than one site, to ensure that information was disseminated from the lead sites to their satellite sites, and that there was good communication between sites in each country. Similar levels of communication were maintained throughout the study period through regular teleconferences, emails and face-to-face meetings. Finally, the trial manager located in Dundee oversaw the work and progress at all sites, ensuring that all sites adhered to the research governance regulations, collected good-quality data, and entered those data into the electronic data management system correctly.

Data collection and management
Data collected at each study visit was entered into a paper case report form (CRF). The data was then entered into an electronic version of the CRF (eCRF) at each site. The eCRF was developed by the Health Informatics Centre (HIC) at the University of Dundee using Openclinica open source software. Primary outcome data entered into the database were verified against source data in the paper CRFs. A proportion of secondary outcome data were also be verified with the level dependent on the available resources.

Sample size calculation
A variation in instantaneous height velocity SDS of 0.25 is equivalent to a reduction in height velocity of around 0.5 cm/year. In a sample of 600 treated patients and 300 untreated patients, such a variation can be detected with a power of 94% (type 1 error=0.05). Further power calculations for the secondary outcomes confirmed that 600 medicated patients with ADHD (group 1) and 300 non-medicated patients with ADHD (group 2) will produce sufficient power to determine the adverse effects of MPH. To calculate the sample size needed for each group, the likely attrition rate due to dropouts over the 24-month follow-up period was anticipated to be around 25% based on experience from a previous longitudinal study of a similar population (ADORE study, personal communication D. Coghill). Thus, the initial target size was 800 for group 1, 400 for group 2 and 400 for group 3. Recruitment targets were divided among the four countries so that each country was required to recruit 200 to group 1 and 100 to group 3. Since the population of unmedicated children with ADHD is much larger in Italy and Hungary compared with that in the UK and Germany, Italy and Hungary were to recruit 200 children each to group 2, with the UK and Germany having no target for this group.

Analysis plan
Description at baseline
Characteristics of participants included in the study will be presented using the ‘five number summary’ (minimum, maximum,
lower and upper quartiles and median) for the quantitative variables, and percentages for categorical variables. The whole sample and each of the three groups will be presented in this way. Traditional trivariate/bivariate comparisons will be carried out to compare the groups (e.g. analysis of variance (ANOVA), \( \chi^2 \) tests or non-parametric tests, according to their conditions of validity).

Graphical representations will be used to characterise distributions (histograms, density plots, box plots) or to explore patterns of association of covariates (multidimensional exploratory graphical methods). When participants change their status, their data will be censored for analyses.

Longitudinal description
The evolution of data with time will be graphically and numerically presented. This part is essential, in particular to design the mixed models used to analyse the primary end point (see below).

Incidence rates and relative risk
These will be estimated according to the number of participant-years available in the study at the time of analysis. For a given participant, only the first occurrence of a side effect will be considered. Incidence rates will be estimated in each of the three groups.

Bivariate analysis
The association with the primary and secondary end points will be statistically tested with all potential covariates of interest (including time on drug and dose and duration of treatment) using traditional procedures (e.g. correlations, ANOVA, \( \chi^2 \) tests or non-parametric tests according to conditions of validity). These tests will be regarded as strictly exploratory.

Analysis of primary end point
The child’s height velocity will be estimated from all available data using a simple linear regression of height with time (one linear regression for each participant). Child’s height velocity and child’s height velocity SDS will thus be available only for participants having at least two visits. The distribution of height velocity SDS will be carefully examined (density plot with standardised normal plot). If this distribution is normal, a mixed model for normal outcome will be used. The primary predictor variable will be ‘group’ (medicated ADHD, un-medicated ADHD, non-ADHD controls). The covariates will be:
1) Three propensity scores contrasting each of the three pairs of group categories (i.e. medicated vs un-medicated, medicated vs non-ADHD, un-medicated vs non-ADHD). These propensity scores will be estimated from a logistic regression incorporating all available data (at the condition of convergence of the maximum likelihood estimator). A regression spline between height velocity SDS and each of the three logistic scores will help to determine how these propensity scores will be introduced in the model (linear, polynomial, deciles, etc). The propensity scores will be estimated after imputing missing data using a Gibbs sampler.
2) Family’ as a random effect (to take into account the pairing of groups medicated ADHD and non-medicated sibling).
3) ‘Country’.
4) ‘Duration of treatment’.

Additional adjustment for potential confounders, or adjustment by inclusion of variables (measured at baseline) that are considered essential (because of their clinical relevance, because of the bivariate analysis or because the propensity scores were unsuccessful in suppressing the imbalance between groups for a given covariate), may also be necessary. No adjustment of \( p \) values for inclusion of multiple covariates will be carried out, since the primary hypothesis concerns the effect of the ‘group’ variable, and since in a pharmacovigilance study statistical power is at least as important as type one error. The effect of the ‘group’ variable will be assessed globally, then with planned contrasts comparing medicated versus un-medicated, and medicated versus non-ADHD. Missing data in adjustment covariates will be imputed using a Gibbs sampler (simple imputation because inferential statistics especially concern the variable ‘group’) Regression diagnostics will be performed. Interaction terms, for example, age and sex, will be tested one at a time to look for specific populations at risk. If the height velocity SDS is not normally distributed, linearizing transformations will be tried (log, box-cox, etc). If no transformation is possible, a bootstrap procedure will be used. Finally, sensitivity analyses will be conducted to test the robustness of the results, for example, removal of patients who switch treatment and patients with concurrent psychotropic drugs.

Ethics
The study was conducted according to the principles of the Declaration of Helsinki, in accordance with the Research
Governance Framework Scotland and other appropriate guidelines and regulations in each country. Since the study was purely observational, there were no anticipated extra risks to participants.

Recruitment
Recruitment rates were slower than anticipated for all groups, in particular for Group 3. To improve rates we:
• Increased the number of sites in the UK from one to six
• Increased the recruitment period from 8 to 15 months
• Broadened the eligibility criteria to include; younger children (from age 5) and, in group 3, we dropped the requirement of being related to a child with ADHD in order to include all healthy controls who did not have ADHD nor have taken ADHD medication
• Included reward voucher payments to compensate children for their time
• Displayed posters and leaflets at clinics, schools, sports clubs and other areas frequented by families

When recruitment finished in August 2014 we had enrolled 1370 children into the study, 86% of our target. This included 722/800 into Group 1, 376/400 into Group 2 and 272/400 into Group 3.

Retention
Retention rates are described in Table 3. This shows the number of primary outcome (height) measurements recorded at each visit. As expected, the number of participants attending their study visits declined as the study progressed so that the number attending the final visit was around 50% of those attending the baseline visit.

During the study several measures were taken to improve retention rates:
• Families were offered study visits conducted at home
• Children were given a thank you voucher if they attended all visits
• Visits of siblings who were enrolled in the study had their visits combined to reduce the time burden on the family

452 participants attended all scheduled study visits (Table 4).

Primary and secondary outcomes
These will be reported separately for growth, neurological, psychiatric and cardiovascular under aims 4, 5, 6 and 8 respectively.

3.2.3 Aim 3. To ensure that when performing these pharmacovigilance studies due consideration is paid to medical ethical issues.

WP9, the ethics work package, was tasked with supporting the various studies undertaken as part of the ADDUCE project with respect to medical ethical issues. There were a number of tasks assigned to WP9, each of which is discussed below.

Task 1: Discussion of the ethical aspects in the proposed project. A number of different study designs were utilised in this project including a retrospective cohort derived from existing datasets, the development of a prospective cohort and consensus meetings. These various methods have both common and unique ethical issues which have been addressed.

The ADDUCE study comprised of a number of different study designs; WP2 was concerned with the analyses of retrospective studies using data from the CDARS (Hong Kong), ALSPAC (UK) and KiGGS (Germany). These data were available to the ADDUCE researchers already anonymised, however prior to the start of each of the studies, the ethical aspects of the study were discussed by members of WP2 and appropriate approval was sought and granted. WP 3 involved the recruitment of participants to a 24-month open-label observational cohort of patients with ADHD and two control groups. Prior to the initiation of the study, the ethical aspects of the study were discussed by all members of the ADDUCE consortium at the annual meeting. WP6 included a qualitative study which involved patient recruitment along with recruitment of parents,
physicians and teachers. Prior to the initiation of the study, the ethical aspects of the study were discussed by all members of the ADDUCE consortium at the annual meeting. WP8 was concerned with the long-term effects of MPH on blood pressure and pulse and involved patient recruitment; again prior to the initiation of the study, the ethical aspects of the study were discussed by all members of the ADDUCE consortium at the annual meeting.

Task 2: Design of a guideline for protecting the confidentiality and privacy of patients’ data. Where existing datasets are used, the appropriate measures will be taken to ensure that these data are obtained in accordance with the data sharing agreements of the database. Ethical permission was sought where necessary. Where new data have been gathered, in particular for the prospective cohort study, issues to be considered included (but were not limited to) the types of data collected, including what personal identifiers or sensitive information has been held, how data has been collected and held, also how long data will be retained, database security, access to identifiable data, withdrawal of consent and conditions for releasing data to external researchers.

A guideline was developed with regards to patient confidentiality and privacy of data and was made available to researchers. With regards to retrospective data used within the ADDUCE study, data were obtained in agreement with the database controllers and appropriate ethical approval was sought and granted when necessary. With respect to the prospective studies, the study protocols provide in detail information relating to the data collected, the nature of these data, the protocol for withdrawal of participants, database security etc. The handling of personal data complied with relevant Personal Data Protection Acts or each participating nation state. See Deliverable Number: (D 9.1) Guideline for protecting confidentiality and data privacy for ADDUCE.

Task 3: Collate information surrounding the issue of informed consent in each of the partner EU countries. It is necessary to ascertain the level of variance of informed consent procedures in order to determine to what extent harmonisation is possible. Data, relevant to the participating ADDUCE countries, were retrieved and collated on the following issues: national provisions for consent of children, specific national provisions for child’s assent, age of assent etc, specific national provisions for adolescents, age etc.

Task 4: Preparation of informed consent and assessment forms. Based on the information garnered in Task 3, informed consent and assent forms will be prepared by the partners in the WP2 and WP3 in association with this WP. As this project seeks to recruit children, older adolescents and adults, age-appropriate consent and assent forms will also be prepared. These will then be tailored according to the language, the legal and the ethical framework of the individual participating country.

Informed consent and assessment forms were prepared by researchers from WP9 and the individual WPs involved in participant recruitment i.e. WP3, WP6 and WP8.

Task 5: Preparation of information sheets. Consent can only be given once the participant and/or their representative have been informed of the nature, significance, implications and risks of the study. The participants of the proposed studies will vary in age (children through to adulthood) and in cognitive ability and may also present with various comorbid conditions such as Autistic Spectrum Disorder. Due to the nature of this vulnerable patient group, it is important that age and developmentally-appropriate leaflets are devised.

In addition, studies have shown that parents of ADHD children are at a higher risk of the condition compared to parents of non-ADHD children and so this will need to be considered when developing information leaflets for parents. Information sheets detailing the nature of the projects will also be prepared for teachers, where appropriate. Information sheet will be prepared by the partners in WP3 in association with this WP.

Participant information sheets were prepared by researchers from WP9 and the individual WPs involved in participant recruitment i.e. WP3, WP6 and WP8.

Task 6: Training of study site personnel in GCP-informed consent procedures. This will be done in conjunction with WP10 (Training and Dissemination).

It was essential that study site personnel were appropriately trained in GCP-informed consent procedures. If personnel had undergone this training prior to the ADDUCE study and this training was still valid, that was considered to be sufficient for consenting participants onto the ADDUCE study. For individuals who had not received training, then online GCP training was provided (http://www.onlinegcp.com/) and an assessment was conducted.

Task 7: Discussions with the Independent International Advisory Committee on the ethical components of the studies, including on the relationship between the project team, ethics committees, regulatory agencies, media and industry
Discussions took place with the IAC on a number of occasions with respect to all aspects of the WPs in the ADDUCE study. Task 8: Assistance will be given to individual countries principal investigators in the preparation of annual progress reports to the Ethics Committee. Also, notifying any substantial amendments to study protocol or safety reports to ethics committees. End of study and final report preparation.

WP9 has worked with each of the WPs involved in the submitting documentation to ethics committees.

3.3 Key Objective 2: To address scientific questions about prevalence, clinical significance, development and moderating and/or mediating factors of four specific classes of long-term adverse effects of methylphenidate; growth, neurological, psychiatric and cardiovascular.

3.3.1 Aim 4. To determine whether methylphenidate treatment for ADHD is associated with a statistically significant increase in long-term (> 1 year) risk of negative effects on: the rate of growth (i.e. height and weight) and of pubertal maturation.

Issues

According to international guidelines, treatment for ADHD is based on a multimodal approach that combines behavioural and pharmacological treatment. The first choice medication for ADHD and the most frequently used treatment for ADHD in Europe is methylphenidate. Positive effects of stimulants are supported by numerous studies with clear improvements in the core symptoms of hyperactivity, impulsivity and inattention. However, these improvements can be accompanied by common mild and transient different side effects (sleeplessness, nervousness, reduced appetite, headache, abdominal pain, changes in blood pressure and heart rate) and several less common effects including reduced weight gain and growth reduction with prolonged use. Although many studies have monitored changes in growth and weight during medication, they have not provided definite results as to whether the reported growth and weight suppression are caused by medication or not. Such effects on growth are usually reported as minor, but there is substantial variability with some children being completely unaffected and others reporting significant growth suppression. There are many methodological limitations with these published studies and as a consequence it has not been possible to draw firm conclusions and poor growth has therefore remained a common public concern about the treatment of ADHD. Considering these gaps in our understanding and those expressed by the European Medicine Agency that we need more data about the long term effects of methylphenidate, the ADDUCE programme aimed to address scientific questions about the potential long term (“more than 1 year”) adverse effects of Methylphenidate on growth and pubertal maturation in ADHD children and adolescents. The primary objective of the study, aimed to investigate the possible developmental adverse effects by stimulant medication in the long term has been achieved by a broad programme of work including:

1. A systematic review of evidence in the published literature: a systematic review has been performed and extensively updated up to August 2015 on the human literature focusing on the impact on growth and pubertal maturation of chronic MPH and stimulants exposure in children and adolescents affected by ADHD.

2. The retrospective analysis of previously collected cohorts: data extracted from existing datasets including data on growth and ADHD medication were analysed and discussed

3. The prospective analysis of three newly established cohorts: data collected within the 24 month prospective open-label naturalistic observational pharmacovigilance study comparing methylphenidate-treated ADHD patients and controls (un-medicated ADHD and non ADHD subjects) have been collected, analysed, interpreted and discussed

Systematic review

The systematic review was restricted to human studies focusing on the impact of MPH exposure on growth in ADHD children and adolescents diagnosed according to DSM criteria. Studies were eligible if they examined the effects of methylphenidate as
a mono-therapy or, when it was not possible to distinguish between two medications, associated with other stimulant medication. Studies were excluded if the effects on growth were related exclusively to amphetamines or other psycho-stimulants. Studies involving only adults were also excluded. The search was performed by using the three most relevant databases (Ovid Medline, Embase and Psychinfo) and updated up to August 2015. The search strategy, included the following medical terms and free text words: “Methylphenidate” or synonymous or trend medication; “Side effects” or synonymous; “ADHD” or synonymous; “Growth” OR “growth velocity” OR “growth spurt; AND “height” or “stature” AND “adult height” OR “adult stature” OR definitive stature”.

Thirty-nine eligible studies were identified covering a total of 6395 children and adolescents (range= 10-1758; mean= 168.02; SD= 287.2) 81% were males. Quantitative analysis of the impact of methylphenidate on growth was conducted on 3799 subjects.

The selected studies were heterogeneous in terms of design, sample characteristics, duration of follow up, variables and main outcomes, allowing us mainly to perform a qualitative description of the results rather than a precise and powerful statistical analysis.

Nineteen of the studies did not find an association between stimulant use and a growth deficit while the other twenty studies (n = 2118) did identify significant changes on the standardized parameters of height, weight and BMI z scores. Impact on weight and BMI were more evident during the first months of treatment, mainly within the first 6-12 months. Height deficit was around 1 cm/year during the first three years of treatment with a subsequent normalization.

Seven studies for height and six studies for weight met inclusion criteria for a quantitative meta-analysis (a statistical analysis). In order to perform a meta-analysis, we selected the studies that clearly reported Z scores for height and weight (mean ± Standard Deviation) at baseline and after stimulant treatment at follow up times. For each study we considered a follow up of 36 months, or the closest one where the 36th month was not present. For these studies we calculated the effect size (ES) as the measure of the possible impact of stimulants on height and weight.

The analysis of the pre-post difference standardized parameters for height appeared to be statistically insignificant with an effect size of 0.27 (SMD = 0.27 95% CI 0.16-0.42 p = 0.28; I²= 20%).

The analysis of the pre-post difference standardized parameters for weight evidenced a small but statistically significant pre-post differences with a large heterogeneity between studies (SMD = 0.19 95% CI 0.03-0.35 p = 0.01; I²= 65%).

The combined findings of the qualitative and quantitative analysis of our review suggest a minor impact of long term methylphenidate on height and weight ADHD in children and adolescents. These effects seem to be limited in time and of minimal clinical significance.

Very few studies examined potential effects on pubertal maturation related to the continuous stimulant medication use. Spencer et al showed no interference by methylphenidate in 124 boys with ADHD. A comparable study of 124 girls with ADHD also found no differences in growth or pubertal development between girls with ADHD and controls. A more recent study found a delay in pubertal maturation for adolescents aged between 14.00-15.99 years after three years of continuous treatment with stimulant medication. Of the 65 boys recruited for the study, the 22 aged 14.00-15.99 years reported significant delay in their pubertal development compared to control, with no significant correlation with the dose of medication. No significant difference in the stages of puberty was found at 12.00-13.99 years of age. These findings suggest that stimulant medication may delay the rate of maturation during puberty but not the onset of puberty. A recent publication from the MTA study further confirmed the absence of a significant impact on pubertal maturation by stimulant medication during a follow up of 36 months comparing ADHD medicated subjects, not medicated ADHD children and adolescents and a healthy control population. The time of follow up and the characteristics of medication (dose, drug holidays, length of treatment) appeared as possible important mediating factors correlated to a possible negative effect both on weight and height in several studies. Considering individual characteristics of subjects, the baseline auxological parameters appeared the major predictor for the magnitude of the effect on growth by prolonged stimulant treatment.

Retrospective cohort data analysis

We identified several existing high quality relevant datasets suitable for investigating the long term effects of methylphenidate exposure on growth outcomes in children and young people. In particular, we extracted and analysed the data in order to determine whether methylphenidate treatment for ADHD is associated with a statistically significant increase
in long-term (> 1 year) risk of negative effects on height and weight.

KiGGS
One of the selected databases was the German Health and Examination Survey for Children and Adolescents (KiGGS), within which data from a population-based German representative sample were collected that allowed examination of the association between MPH use, ADHD, and growth (height, body mass index) in boys. The outcome variables investigated within KiGGS were body mass index (BMI) and height. BMI data was available for 4229 boys aged 6 to 15 years, while data for height resulted available for 4242 boys same age.

Four groups of patients were identified for inclusion in the study as following:
Drug Cohort 1: subjects with an ADHD diagnosis and a record of current MPH use with a duration of treatment of less than 12 months.
Drug Cohort 2: subjects with an ADHD diagnosis and a record of current MPH use with a duration of treatment of 12 months or longer.
ADHD Control: subjects with an ADHD diagnosis and no record of current MPH use. These patients may have never taken medication or may have taken medication in the past.
Non-ADHD Control: Neither a code of an ADHD diagnosis nor a code of MPH use recorded.

Our results are summarised in Section B currently held in confidence as requested by the EMA prior to release.

ALSPAC
We also used data from the Avon Longitudinal Study of Parents and Children (ALSPAC) to investigate effects of MPH on growth trajectories in children from age 7 to 15 and body mass index (BMI). ALSPAC study is an ongoing study of a cohort of around 14,000 children born in the South West of England in the early 1990’s, and followed up at regular intervals since. At age 7, 8135 of these children were assessed for ADHD using the Development and Well-Being Assessment (DAWBA); with 175 of them meeting diagnostic criteria for ADHD. The DAWBA was repeated at age 15.

Data on medication usage, including methylphenidate (MPH) was collected at 8 time-points between the age of 7 and 16, four times via questionnaire which asked about all medication usage in the last 12 months, and four times during a research clinic which queried current medication use.
Height and weight were also recorded at ages 7, 9, 10, 11, 12, 13 and 15 years, with data being collected from an average of about 7000 children at each wave of data collection although the number declined from over 8000 at age 7 to around 5000 at age 15. We restricted our analyses to children from whom we had at least 4 measurements, including measurements at age 7 and age 15. As this left only four female participants for whom we had any record of MPH usage, and because growth trajectories were markedly different for girls than for boys, we also restricted our analysis to boys. This left a sample of 1995 boys, 19 of whom had a history of MPH use.

After fitting growth trajectories to each child’s growth data, we calculated growth velocity (speed of growth) for each of the MPH data collection time points, relative to the mean and variance of the whole sample at that time point (z scores of growth velocity). This enabled us to investigate whether growth velocity was affected by whether the child had taken MPH during the previous 12 months, relative to the growth velocity of other children at the same age, and also whether it affected the timing of the pubertal growth spurt. We used the height data together with the weight data to calculate body mass index (BMI), and again, investigated whether BMI was affected by whether the child had taken MPH during the previous 12 months.

3.3.2 Aim 5. To determine whether methylphenidate treatment for ADHD is associated with a statistically significant increase in long-term (> 1 year) risk for the following neurological outcomes: Seizures, Sleep problems and Dyskinesia.

Seizures
There has long been a concern that stimulant therapy may lower the seizure threshold. For example, in a study of over 200 non-epileptic children with ADHD with over 3 years of follow-up, four new seizure events were observed only in the MPH-treated group. Two studies also reported seizure events in patients who overdosed with antidepressants during MPH treatment. However, other studies reported higher seizure rates from never treated ADHD patients with epilepsy compared to...
ever-treated ADHD patients although it was unclear whether this was due to a reluctance to administer ADHD medication to
children at risk of epilepsy or to risk factors mitigated by ADHD treatment (e.g. substance abuse). However, these studies were
either uncontrolled or confounded by patient characteristics such as severity of underlying brain dysfunction between
individuals. Animal studies also provided inconclusive results so far with some studies showing prolonged duration of kindled
seizures after MPH treatment in rats but also increased or decreased seizure risk in animals after amphetamine treatment.
As seizures are relatively rare, very large sample sizes would have been needed in order to investigate the long-term impact
of MPH on seizures longitudinally, which was impossible within the ADDUCE prospective study. Thus, we used two different
methods in order to evaluate the long-term MPH effects on epilepsy by (1) systematically reviewing all published studies and
(2) by analysing appropriate exiting data sets to address this question.

(1) All studies published in English or Chinese language before 10/2015 were systematically reviewed. Overall 16 studies
reported information about seizures and/or EEG abnormalities. 5 studies including 147 children overall (67 with comorbid
epilepsy) reported no seizures during at least one year of MPH treatment: prospective cohort; prospective case series;
prospective cohort, prospective follow-up; prospective follow-up). One of these studies reported no increase in seizure
frequency in 23 comorbid children. A prospective cohort study including 119 comorbid children (62 with EEG abnormalities, 57
with seizures) reported no new seizures, 5 children with increased seizure frequency, and unchanged seizure frequency on the
group level. Two cases of study discontinuation due to seizures were reported, one in a prospective open-label extension of
previous trials including 140 children (suspected seizures possibly related to MPH) and one in a prospective cohort study
including 229 children (absence seizures with no relation between the receiving dose and time of the adverse event). New
seizures after at least 1 year of MPH administration were reported in 5 cases. Of these 5 cases, 2 had pre-existing rolandic
spike retrospective chart review including 205 children), and 3 reported case studies happened after starting additional
medication (high dose of bupropion; 75mg sertraline: higher-than-prescribed dose of venlafaxine. One prospective cohort
study (62 with EEG abnormalities, 57 with seizures) and a retrospective study (170 children without epilepsy) showed EEG
normalization. 3 retrospective chart reviews including overall 53 children with ADHD and abnormal EEG or epilepsy found no
cases with new seizures after one year of MPH treatment and in one of these studies in 17 children no new EEG alterations and
3 EEG normalizations were observed. A prospective case series including 20 children with comorbid epilepsy and 1 prospective
follow-up study including 24 ADHD only children showed no EEG change.

When we quantitatively integrated these studies within a small meta-analysis, we found that the percentages of study
discontinuations due to seizures ranged from 0-2.9 with a mean of 0.71% (95% confidence interval: -2.6-5.0). Five prospective
studies and three retrospective chart reviews in children with epilepsy or an abnormal EEG provided information about
seizures during at least one year of MPH administration: No seizures occurred in any of these studies. Taking into
consideration that epileptic disorders affect about 1% of the general population and that the risk for unprovoked seizures and
epilepsy is two to three times higher in ADHD patients compared to non-ADHD children, the fact that the mean percentage of
study discontinuations due to seizures in ADHD children without epilepsy was below 1% in the longitudinal studies that were
included in our review seems to indicate no increased seizure risk due to long-term MPH administration. Furthermore, eight
respective studies in comorbid children showed no new seizures at all, rendering the MPH administration in children with
epilepsy or EEG abnormalities as overall safe.

(2) Although in general 13 European databases of birth cohorts or electronic healthcare records were identified and included in
the ADDUCE data inventory as they might have potential value individually or pooled for the evaluation of the long-term safety
of MPH treatment in patients with ADHD, few of these could be used to investigate side effects on seizures. We were however
able to use two independent existing data sets to explore the risk of seizures during MPH treatment: Patients aged 6-19 years
who received MPH prescription were identified using the Hong Kong Clinical Data Analysis & Reporting System (2001-2013)
and the United Kingdom Clinical Practice Research Datalink linked with Hospital Episode Statistics (1996-2011). The
underlying risks of seizure among MPH users and non-users are likely to be different due to ADHD and its comorbidities, which
is difficult to control in many observational study designs. Therefore, we conducted a self-controlled case series study in which
participants act as their own controls to reduce confounding between individuals. The seizure event rates during periods
exposed and not exposed to MPH within an individual were compared to assess the association between MPH exposure and
seizures. Among 27,500 (17,381 in HK, 10,119 in UK) patients prescribed MPH, 308 (183 in HK, 125 in UK) had incident seizure
within the study period. No significant difference was observed in the rate of seizure during exposed compared to non-exposed
periods in both settings (Incidence-rate-ratio [IRR]=1.02 95% confidence interval [CI]=0.65-1.61 for HK; IRR=1.04 95%CI=0.63-1.73 for UK). The pooled estimate was similar (IRR=1.03 95%CI=0.73-1.45). Thus, this data analysis does not support the association between the use of MPH and risk of seizure58.

Thus, to summarize, no increased seizure risk due to long-term MPH administration and no increase in seizure frequency in children with ADHD and comorbid epilepsy was found within the systematic review and by the analyses of existing data sets.

Sleep problems
Short-term effects of MPH on sleep appear to be rather mixed and variable and a review indicated that no clear conclusions could be drawn. With respect to long-term MPH effects on sleep previous findings are even more unclear. Thus, we studied sleep in our prospective study by applying the “Children's Sleep Habits Questionnaire” (CSHQ) to all subjects. Results from the prospective study are included in the confidential part of the final report.

In addition, we systematically reviewed all published studies on MPH long-term effects on sleep behaviour in children with ADHD. In total, 19 studies were identified which provided information about insomnia and/or other sleep disorders after long-term MPH treatment. Negative effects of MPH on sleep was described in a prospective study including 687 treated children, two prospective open-label extension of previous trials including overall almost 300 participants and a retrospective case control study including 22 children.

No effect on sleep was reported by a prospective study including almost 300 children, a prospective follow-up study including 12 children, three prospective open-label extensions of previous trials including overall >300 children, a retrospective case control study including almost 300 children, and a retrospective chart review including 12 children. Neutral reports on sleep-related side effects (incidence rates between 0.4-26%) were given in 3 prospective studies including more than 200 children overall 5 open-label extensions of previous trials including overall >600 participants and a retrospective chart review including 240 children.

Summarized within a meta-analysis, eight out of 10 prospective studies in children with sample sizes ranging from 34-293 children provided explicit information about the number of children presenting with insomnia. The percentages ranged from 2.3-14.8 with a mean of 6.9% (95% confidence interval: 3.6-10.2). Five prospective studies in adults (n = 57-298) provided explicit information about the number of adults presenting with insomnia. The percentages ranged from 0-29, with a mean of 12.8% (95% confidence interval: 1.9-23.8).

A former meta-analysis comparing overall 722 unmedicated children with ADHD to 638 controls showed that the former had significantly higher bedtime resistance, more sleep onset difficulties, night awakenings, difficulties with morning awakenings, sleep disordered breathing and daytime sleepiness in comparison. Unmedicated ADHD children presented also with significantly worse outcomes on several objective measures such as number of stage shifts, sleep efficiency on polysomnography, and true sleep on actigraphy. Thus, taken together these data suggest that sleep problems are very common in unmedicated subjects with ADHD, however, MPH long-term treatment might have long-term effects on sleep in subjects with ADHD (in particular in adults) which needs further evaluation in prospective studies.

Dyskinesia
Although there are some case reports linking acute MPH treatment with dyskinesia and one case study describing dyskinesia (involuntary movements, difficulties in eating and initiating speech) after MPH long-term treatment, no systematic evaluation of MPH long-term effects on dyskinesia exists. Thus, within the ADDUCE prospective study we systematically explored the long-term impact of MPH on dyskinesia. Dyskinesia was assessed by the “Abnormal involuntary movement scale” (AIMS; Psychopharmacology Research Branch of the NIMH). The results of the study are presented in the confidential part of the final report.

3.3.3 Aim 6. To determine whether methylphenidate treatment for ADHD is associated with a statistically significant increase in long-term (> 1 year) risk for the following psychiatric outcomes: Mood disorder, Suicidal behaviour, Psychotic symptoms, Substance misuse, Tics/ Tourette’s disorder.
The fact that methylphenidate (MPH) is a drug used to treat the behavioural problems of ADHD, naturally raises concerns about possible unintended mental and behavioural effects.

At the outset of this study, research into possible adverse psychiatric effects had mostly focused on short term (less than 1 year) effects of MPH use. Relatively little was known about potential adverse psychiatric effects of long term (more than 1 year) MPH use, nor about any long-term adverse psychiatric effects (e.g. effects in the years following MPH use).

One objective of the ADDUCE project, therefore, was to address this knowledge gap. We considered five kinds of adverse psychiatric outcomes:

- Psychosis or psychosis-like experiences
- Mood disturbance or symptoms of depression
- Suicide, thoughts of suicide (suicidal ideation), or self-harming behaviour
- Substance abuse (including alcohol, smoking, and cannabis)
- Tics

We took three approaches to the investigation:

1. Systematic review: We systematically reviewed the existing literature for reports or studies of adverse psychiatric effects, as well as of adverse neurological effects (See Aim 5) of MPH treatment.
2. Retrospective data analysis: We analysed data from two existing datasets:
   - data collected at regular intervals from a group of children who have been followed since before birth (Avon Longitudinal Study of Parents and Children, ALSPAC)
   - data from patients aged 6-19 years who received at least one MPH prescription, identified using the Hong Kong population-based electronic medical records on the Clinical Data Analysis & Reporting System (2001-2014)
3. Prospective data analysis: We analysed data from a 24 month observational ‘pharmacovigilance study’ (See Aim 2) in which children with ADHD were followed up over a period of 24 months, to see whether psychiatric outcomes were different in children with ADHD who received MPH and children with and without ADHD who did not receive MPH. The results of these analyses are within the confidential part of the final report.

Retrospective data analyses

ALSPAC

The Avon Longitudinal Study of Parents and Children (ALSPAC) is an ongoing study of a cohort of about 14,000 children born in the South West of England in the early 1990’s, and followed up at regular intervals since. Pregnant women living in the Avon area with an expected delivery date between April 1991 and December 1992 were invited to take part in the study. This study design meant that ALSPAC participants were broadly representative of local people. Data were collected at regular intervals through questionnaires completed by mothers and teachers and direct face-to-face assessments with study children, and including, at age 8, a measure of IQ. Data were also collected regarding family psychiatric history (parents and grandparents), and socio-economic status.

At age 7, 8135 of the children were assessed for ADHD using the Development and Well-Being Assessment (DAWBA) and 175 of them met diagnostic criteria for ADHD. At approximately 12 month intervals, caregivers were asked what medication their children had been taking over the last year, including MPH. Of the 175 children who met criteria for ADHD, 35 were reported to have been treated with MPH at least one assessment, and of those who did not meet criteria, 15 were reported to have been treated with MPH at least one assessment. In addition, of those who missed the DAWBA at age 7, 15 had subsequent reports of MPH treatment. The DAWBA was repeated at age 15, this time in a form that allowed an estimate of the severity of any ADHD symptoms, rather than a simple yes/no diagnosis. In addition, at ages 12, 13, 15 and 16, assessments were made of specific symptoms or behaviours that might indicate adverse psychiatric outcomes. These were:

- Non-clinical psychotic-like symptoms” (PlikS), measuring experiences that can be associated with psychosis, at age 12.
- The Short Moods and Feelings Questionnaire (SMFQ), an index of depression, at age 13.
• Questionnaires about alcohol, tobacco and recreational psychotropic drug use at age 15.
• Questionnaires seeking evidence of self-harm at age 16.

Additionally, we collaborated with the University of Hong Kong (HKU) to investigate the association between MPH use and psychotic events in the Hong Kong hospital data. Over 20,000 patients aged 6-19 years who had received at least one MPH prescription were identified using Hong Kong population-based electronic medical records on the Clinical Data Analysis & Reporting System (2001-2014), an electronic health record database developed by the Hong Kong Hospital Authority (HA), a statutory body which manages all public hospitals and their ambulatory clinics in Hong Kong. The service is available to all Hong Kong residents (over 7 million) and covers about 80% of all hospital admissions in Hong Kong (2). Data from CDARS have proved to be a reliable database for research and have been used for various pharmacoepidemiological studies including MPH prescribing trends in Hong Kong, and the association between MPH treatment and risk of trauma. Patient-specific clinical data include diagnosis, prescription, and information on admission and discharge, which are recorded by trained clinicians. Other patient-specific data such as demographics, payment method, prescription and pharmacy dispensing information are entered by other trained staff. CDARS contains the records of all in-patient, out-patient and emergency room admissions in Hospital Authority clinics and hospitals since 1995.

Using a “self-controlled case series design”, in which each patient acts as their own “control”, the risk of psychotic events while patients were being treated with MPH was compared with the risk when they were not being treated with MPH. On average, each participant took MPH for just over two years, and psychotic events were recorded in 0.5% of patients in the study.

3.3.4 Aim 7. To determine whether the long-term use (≥ 3 years) of methylphenidate increases the blood pressure and causes left ventricular hypertrophy (LVH) identified by echocardiography in late adolescent (≥15 years) and young adults with ADHD.

The most commonly prescribed medications for people with ADHD are the psychostimulants methylphenidate and other amphetamines. The mechanism by which stimulants act in reducing symptoms in ADHD is not completely clear, however it is believed that they inhibit the reuptake of dopamine and noradrenaline into the presynaptic neuron and increase their release into extraneuronal space thus increasing intrasynaptic concentrations. However, as ADHD is a rather chronic condition, medication treatment typically will be extended over a long period of time, up to several years. The main goal of this aim is to examine the long-term effects of methylphenidate on the cardiovascular system and in particular on blood pressure and on left ventricular mass. We focus on methylphenidate because it is the most often prescribed psychostimulant.

Stimulants and heart rate and blood pressure
Stimulant medication is recognized to result in a small increase in heart rate averaging 1 - 2 beats per minute. Taking the average value in clinical studies hides a small proportion where the increment is larger; an increase of up to 50 beats per minute has been observed on rare occasions. Unfortunately, clinical trial data are rarely reported in a format that allows the incidence of clinically significant tachycardia to be quantified. In addition, there is a lack of data on the longer term impact of methylphenidate on heart rate and the lack of appropriate controls in such studies. Methylphenidate, like other stimulant drugs, is known to have small, short term effects on blood pressure. In clinical trials, children treated with methylphenidate have shown increases in systolic and diastolic blood pressure of 1-4 mmHg on average compared to those treated with placebo. A more relevant measure of risk, however, would be whether increases resulted in hypertension i.e. when blood pressure exceeds the 95th percentile, and if so how many children/young people are affected in this way. For this categorical measure, controlled trial data are not available for methylphenidate but data for atomoxetine (which has a comparable effect on mean blood pressure) suggested that elevations above the 95th percentile are seen in 6.8 % of patients (systolic) and 2.8% (diastolic) in comparison to 3% and 0.5% respectively in patients treated with placebo. There are inadequate data at any stage of therapy, not just in the long term and it remains to be established whether similar figures apply for methylphenidate. Because of the association between hypertension and socioeconomic status, studies will require socioeconomic status matched controls in addition to untreated ADHD controls.
Systematic review / meta-analysis

To obtain more information about the cardiovascular effects of ADHD medication, a literature review was performed. Articles about ADHD medication and cardiovascular effects, before May 2015, were obtained by systematic searches of electronic databases (PsychINFO, EMBASE, and Medline) to identify published trials which involved individuals who were 1) diagnosed with ADHD; 2) treated with methylphenidate, amphetamines or atomoxetine and 3) had their diastolic and systolic blood pressure and/or heart rate measured at baseline (pre) and the endpoint (post) of the study treatment. Studies of any duration were included. Statistical analysis involved calculating effect sizes (standardised mean differences SMD), i.e. calculating differences between pre- and post-treatment measurements for the various cardiovascular parameters divided by the pooled standard deviation at baseline. Further, we assessed the percentage of clinically relevant increased BP or HR, or documented arrhythmias.

Rationale of cross-sectional study of 24-hour blood pressure recordings

Children with ADHD are now being treated for longer than was previously the case and are increasingly likely to remain on methylphenidate into adolescence and adulthood. Furthermore, an increasing number of individuals are being diagnosed with ADHD in adulthood and methylphenidate is more frequently being started for the first time in adults who, as a group, are at greater risk of cardiovascular disorders than children. The possibility that long-term methylphenidate may result in left ventricular hypertrophy and increase the risk of myocardial infarction due to the increased blood pressure and heart rate response to this medication, is a concern for all patients. Premature onset of atherosclerotic disease leading to stroke is also a possibility.

A cross-sectional study design was used to differentiate between the cardiovascular risks associated with ADHD itself, and those associated with long-term methylphenidate treatment by comparing a large group of late adolescent and young adult subjects with ADHD, treated with methylphenidate for > 3 years (target group), to a similar group of late adolescent and adult subjects with ADHD who have not been treated with methylphenidate (control group). The study examined echocardiography and 24-hour blood pressure recordings to investigate the impact of long-term methylphenidate treatment on cardiac function.

Results from the cross-sectional study:

This cross-sectional study recruited in total 240 patients with ADHD, 171 who used methylphenidate for more than 2 years and 69 who were medication naïve and didn’t use any ADHD medication. They were all between 12-25 years old.

Inclusion criteria of study population

The target group (medicated group) included patients with ADHD according to DSM-IV criteria (any subtype), based on clinical diagnosis, and confirmed by a structured interview, aged between 12 and 25 years, any comorbidity was allowed. Co-medication was allowed except for dexamphetamine or atomoxetine, treated with methylphenidate (IR or ER preparations) for 3 years or longer, continuously.

The control group (unmedicated group) included patients with ADHD according to DSM-IV criteria (any subtype), based on clinical diagnosis, aged between 12 and 25 years, any comorbidity is allowed, any co-medication is allowed, never been treated with methylphenidate, dexamphetamine or atomoxetine.

Study parameters/endpoints

Blood pressure identified by a 24-hour blood pressure measurement: Blood pressure was measured by a 24-hour blood pressure recorder that measured systolic and diastolic blood pressure and heart rate.

Left ventricular hypertrophy (LVH) identified by echocardiography: Left ventricular mass was indexed by a partition. A partition value will be taken at the 95th percentile of measurements indexed to body size (whether, height, weight or body surface area). This has the attraction of simplicity and will be used as the primary outcome measure. This method essentially categorizes individuals into “normal” or “increased” left ventricular mass without conveying the degree to which the abnormal measurement differs from the reference population.
3.3.5 Aim 8. To determine whether the increases in blood pressure and pulse rate seen in children with ADHD identified with short term exposure to methylphenidate persist in the long-term (> 1 year).

Cardiovascular prospective study
See AIM 2 for the study design and study population of the prospective study.
All participants had comprehensive face-to-face assessments at baseline and thereafter at 6, 12, 18 and 24-months to assess effectiveness of treatment and potential adverse events. We had three groups of patients for this study 1) Patients with ADHD using methylphenidate, 2) Patients with ADHD with no medication, 3) Healthy controls (Non-ADHD sibling’s controls). Measurements of pulse, diastolic and systolic blood pressure were done at baseline, after 6 months, 12 months, 18 months and 24 months. The assessment for all three groups were identical. The results in this study were only from individuals that attended all visits. The norms used for blood pressure were the UK normative data. Results were corrected for age and gender.
As above the data has been reported elsewhere in the confidential report.

Cardiovascular results retrospective study
There were four groups of patients in the KiGGS database (Germany 2003-2006, age 6-15 years, all male participants): 1) Drug cohort 1: patients with ADHD who use methylphenidate for less than 1 year (n = 65), 2) Drug cohort 2: patients with ADHD who use methylphenidate for more than 1 year (n = 53), 3) ADHD control: patients with ADHD and no medication use (n=320), 4) Non-ADHD control: patients with no ADHD and no medication use (n=3806). We performed two cardiovascular measurements, two readings of systolic and diastolic blood pressure at 2-minute intervals.

The data of these cardiovascular studies is currently retained in confidence at the request of the EMA.

3.3.6 Aim 9. To explore the moderating and/or mediating factors of the long-term safety of methylphenidate in children, adolescents and adults with ADHD. Moderators identify in whom and under which circumstances treatment has different effects. Mediators identify why and how adverse effects occur.

I) Growth and Weight

A) Systematic Review
We performed a systematic review of human studies investigating adverse developmental (growth and pubertal maturation) effects of long-term MPH exposure (≥ 1 year). Studies were eligible if they examined subjects on MPH in monotherapy or associated with other stimulant medication when it was not possible to distinguish between the two drugs. Studies involving only adults were excluded. A Pubmed search and a centralized search using Ovid Medline, Embase and PsychInfo was carried out up to August 2015. The search strategy, involving medical subject headings [MeSH] and the terms as free text word as well, included: “MPH” or synonymous or trend medication; “Side effects” or synonymous; “ADHD” or synonymous; “Growth” OR “growth velocity” OR “growth spurt; AND “height” or “stature” AND “adult height” OR “adult stature” OR definitive stature”. Full details of the review can be found in Aim 4.

Thirty-nine eligible studies were identified covering a total of 6395 children and adolescents, 81% were males. Analysis of the impact of methylphenidate was performed in 3799 subjects. The reviewed studies indicated several possible factors that moderated the effects of methylphenidate, summarised below:
• Baseline auxological parameters: higher baseline weight and height resulted often associated with a greater impact of MPH, with the strongest correlation for weight. Subjects, with baseline parameters generally above the 50th centile, were in fact
more likely to show a significant weight loss. Three studies, on the contrary, did not find any significant correlation between basal height and weight and the effect of stimulant medication. The division of the sample in quartiles for height, weight and BMI Z scores revealed that the smallest children (shorter and slighter) were not necessarily the most affected by side effects on growth.

- **Age**: Age did not represent, in general, a significant mediating factor on MPH effects on growth: two studies, however, suggest that younger age group may be associated with wider growth (height) variations.
- **Gender**: We did not found evidence that longer MPH medication duration in childhood was associated with gender.
- **Dose of medication**: Several studies have shown that higher doses of methylphenidate are more predictive of height deficits. A dose related effect on growth parameters has been evidenced in 14 studies, seven reported a dose related effect on height, 8 on weight. The MTA study confirmed these results showing an effect on growth closely related to the dose (Swanson et al., 2007). Four of the studies that evidenced an impact of stimulant on height did not find however a correlation with the administered doses.
- **Time of follow up**: Five studies reported a significant height slowdown during the first 6-12 months of treatment with a subsequent normalization thereafter. Four other studies showed an impact on height at a later time generally after the 12th month of treatment or even after the 24th month; this effect, however, appears to decrease after the 30th month of treatment. Weight loss appeared to be more evident during the first few months of treatment with stimulants and up to 24 months of follow up. After 24 months of follow up changes in weight and BMI were generally not clinically significant anymore.
- **Length of treatment**: Only a few studies examined the total duration of exposure to treatment and the extent of growth impairment in terms of height and weight and only a few studies analysed growth data dividing the sample according to treatment (drug naive vs previously medicated children) finding a positive correlation.
- **Drug Holidays**: The most part of recent studies do not support the hypothesis of a rebound effect after suspension of treatment or do not confirm a positive correlation with “drug holidays”.

**B) Retrospective data analysis**

We used data from the Avon Longitudinal Study of Parents and Children (ALSPAC) to investigate effects of MPH on growth trajectories in children from age 7 to 15 and body mass index (BMI). For further details of this investigation, see Aim 4.

In addition to investigating whether MPH affected growth velocity or BMI (See Aim 4 for further details), we tested whether effects of MPH were mediated by ADHD itself, and whether the effects of MPH were moderated by age (different effects depending on age) or by ADHD.

While we found evidence that while growth velocity and BMI were slightly lower than otherwise expected when a child was reported to have taken MPH during the previous 12 months, we found no evidence that the effects of MPH were moderated by age, and thus no evidence for any effects of MPH on the timing of the pubertal growth spurt. We also found no effects of ADHD itself on growth velocity or BMI, nor any evidence that ADHD moderated the effects of MPH.

The German Health Interview and Examination Survey for Children and Adolescents (KiGGS) dataset was also used to examine associations between MPH use, ADHD, body mass index (BMI) and height. Two medication cohorts were included (Cohort 1 - ADHD & MPH<12 months’ duration; Cohort 2 - ADHD & MPH≥12 months), as well as ADHD control (ADHD, no MPH use) and non-ADHD control cohorts. Boys were categorised according to age 6-10 years and 11-15 years to account for pubertal maturation. Multivariable logistic regression was conducted to test for associations.

Full details of the above analyses can be found in the reports for Aims 1 and 4

II) Neurological and Psychiatric adverse events

A) Systematic Review
We undertook a review of studies investigating adverse psychiatric and neurological effects of long-term (greater than 1 year) MPH treatment. We searched English language databases (Embase, Medline, PsychInfo) as well as three Chinese databases [CNKI, WanFang, CBM] and then used the reference lists of these studies to identify further studies.

The reviewed studies indicated several possible factors that moderated the effects of methylphenidate, summarised below:

- **Seizures:** The reviewed evidence did not indicate that MPH treatment increased the risk of seizures, except for some evidence for increased risk of seizures in patients with pre-existing rolandic spikes.
- **Tics / Tourette Syndrome:** While we found no evidence for any overall effect of MPH on tics, there were some reports of a worsening of tics in those with pre-existing Tourette Syndrome.
- **Sleep disorders:** Quantitative summary of subjects presenting with insomnia during MPH long-term treatment were larger in studies including adults compared to those studies which only included children.
- **Psychosis:** We found some evidence that longer MPH medication duration in childhood was associated with fewer schizotypic features in adulthood.
- **Mood disorders:** Although there were some reports of irritability and mood swings associated with MPH treatment, children who had a better response to MPH tended to have lower depression scores in adulthood.
- **Suicide:** We found no research evidence for an effect of MPH in children, and a protective effect of MPH in young adults.

Full details of the findings from this review can be found in Aims 4 and 5.

**B) Retrospective data analysis**

We used data from the Avon Longitudinal Study of Parents and Children (ALSPAC) to investigate adverse psychiatric effects of MPH. For further details of this investigation, see Aims 1 and 6.

At ages 12, 13, 15 and 16, assessments were made of specific symptoms or behaviours that might indicate adverse psychiatric outcomes. These were:

- **Non-clinical psychotic-like symptoms** (PlikS), measuring experiences that can be associated with psychosis, at age 12.
- **The Short Moods and Feelings Questionnaire (SMFQ),** an index of depression, at age 13.
- **Questionnaires about alcohol, tobacco and recreational psychotropic drug use at age 15.**
- **Questionnaires seeking evidence of self-harm at age 16.**

Because MPH acts on the dopamine system, thought to be under-functioning in ADHD, there was reason to be concerned that MPH might have different psychiatric effects on children who did not show symptoms meeting criteria for ADHD than on children who did. We therefore investigated this, but found no evidence that ADHD symptoms moderated the effects of MPH on the psychiatric outcomes measured.

We did find that psychiatric effects that were associated with MPH use (PlikS, depression, substance abuse), were either substantially (in the case of depression), or solely (in the case PlikS and substance abuse) mediated by two factors that increased the likelihood that a child would receive MPH treatment. These were:

- **ADHD severity.**
  - Children with severe ADHD were more likely to have high scores on all four of psychiatric outcome measures, and were also more likely to have received MPH treatment, than other children.
- **Maternal depression:**
  - Children whose mothers had a history of depression were also more likely to have received MPH treatment, and these children were also more likely to show symptoms of depression at age 13, and score higher on the other psychiatric outcome measures.

**III Cardiovascular adverse events**

**A) Systematic Review**
We undertook a review of studies investigating effects of MPH treatment (and amphetamines and atomoxetine treatment) on diastolic (DBP) and systolic blood pressure (SBP) and heart rate. We searched English language databases (Embase, Medline, PsycINFO), then used the reference lists of these studies to identify further studies. The search strategy, involving medical subject headings [MeSH] and the terms as free text word as well, included all types of methylphenidate (amphetamines and atomoxetine) medication, all adverse events and ADHD. Full details of the review can be found in Aim 7. Eighteen studies were identified who met the inclusion criteria ten for MPH treatment, five for amphetamines treatment, and seven for atomoxetine treatment) with data from 5837 participants (80.7% boys) and average duration of 28.7 weeks (range 4-96 weeks).

Analysis of moderating and mediating factors revealed a significant effect of study duration on DBP following AMP treatment. Studies less than 18 weeks reported stronger effects on blood pressure and heart rate compared to longer duration studies. There was a significant effect of publication year on SBP for MPH treatment (F(1) = 5.346 p = 0.05). We were unable to establish significant effects of the following moderators: type of medication (e.g. MPH, AMP, ATX), doses, age, gender (male percentage), type of ADHD, and comorbidity.

B) Retrospective data analysis

We used data from the Avon Longitudinal Study of Parents and Children (ALSPAC) the German Health Interview and Examination Survey for Children and Adolescents (KiGGS). Full details of the analyses can be found in Aims 1 and 7

The German KiGGS dataset was used to examine associations between MPH use, ADHD, and blood pressure (systolic blood pressure (SBP) and diastolic blood pressure (DBP)). Two medication cohorts were included (Cohort 1 - ADHD & MPH<12 months’ duration; Cohort 2 - ADHD & MPH≥12 months), as well as ADHD control (ADHD, no MPH use) and non-ADHD control cohorts.

Due to the limitations of the ALSPAC22 data on pulse and blood pressure data, we were unable to draw meaningful conclusions as to the effects of MPH use, nor to evaluate moderating and/or mediating factors.

3.3.7 Aim 10. To determine whether methylphenidate treatment for ADHD is associated with a statistically significant increase in long-term (> 1 year) risk for other adverse effects as assessed by a semi-structured interview addressing all major body systems.

During the early stage of implementation of the project, the ADDUCE team identified a significant problem in using the semi-structured interview to obtain adverse effects of all major body systems. The time required for the ADHD subjects to be interviewed is very long. Subjects, particularly patients with severe ADHD, would find it difficult to take part. The use of the semi-structured interview would severely compromise the willingness of consent and participation of the project. It could lead to severe under-recruitment.

More importantly, the protocol of the prospective study covered all the important areas of adverse effects i.e. neurological, psychological, cardiovascular and growth. In the team’s opinion, the use of the semi-structured interview was unlikely to yield important information but very likely to severely jeopardize recruitment. Therefore, the ADDUCE team decided to drop the semi-structured interview from the protocol.

Key objective 3 includes the following specific aims:

3.4.1 Aim 11. To explore the application of intensive monitoring of bone age as a tool to study adverse developmental effects of methylphenidate.
Monitoring of growth changes with particular attention to height and weight during stimulant medication was a primary outcome of the project. Although several studies have been conducted on this topic the results provided were inconclusive.

Bone age is regarded as gold standard to evaluate the “growing power” of an individual and represents a major tool to calculate expected final height. Bone age is determined by comparing each of 20 bones of an X-ray of the left hand with the Tanner and Whitehouse atlas, and by giving a score to each one, then calculating an “age” from the score. Measurements of bone age at baseline allow calculation of the expected final height, subsequent yearly measurements allow calculation of the rate of bone maturation. The monitoring of bone age can give important information for the clinical practice: growing more slowly but having a bone maturation at the normal rate, can reflect the possibility of not reaching its own growth potential. An increase in the difference (bone age - chronological age) ≥ +/-6 months (+1SD) is deemed clinically significant because the child changed his growing potential.

Very few studies have investigated the rate of bone age as a measure of the impact of medication on height. Most of the studies that have included measures of bone age progression were cross-sectional design and in general reported no delay. Further very few studies have investigated whether bone mineral density and bone turnover are related to stimulant medication. Those that have report contrasting results. A pilot study compared 10 ADHD subjects treated with MPH for 12 to 24 months (mean 13 ± 4) with 10 controls. Laboratory data and bone mineral density did not differ between the two groups and no child deviated from his height percentile during the treatment period. A recent prospective study by examined 34 newly diagnosed ADHD children, aged 4.7-9.1 years, and treated with dexamphetamine or methylphenidate. They found significant reductions over 3 years in sex and height corrected Z scores for bone mineral content and bone mineral density compared to data from 241 healthy children. The same group also examined growth and bone age over the first 3 years of treatment in an enlarged sample of ADHD children (n=73) compared with healthy siblings (n=35;). Forty out of 73 patients, and 22 controls, completed the study. No significant growth differences were found at baseline between the two groups. Despite slower growth on treatment (5.1 cm/year, vs. 6.3 cm/year, p = 0.002) the patients showed no significant maturational delay.

3.4.2 Aim 12. To develop validated reliable tools for the evaluation of negative cognitive effects including: reduced cognitive flexibility, reduced motivation and increased or decreased sensitivity to reward

Currently, there are no validated and reliable tools to measure the cognitive adverse effects suspected by some to be associated with methylphenidate use. While there are several neuropsychological questionnaires and tasks available their clinical relevance as a measure of adverse effects are unknown. Previous studies of methylphenidate and cognitive functioning have focused on identifying the “positive effects” of methylphenidate on cognition; hence these data are not easily interpreted with respect to “adverse effects” nor are they useful in making sample size calculations for a prospective study. Consequently, we do not feel that the field is either well developed enough or has adequate tools, to conduct large-scale studies into the potential cognitive adverse effects associated with methylphenidate. We believe that the most important work in this field is the development and validation of a reliable instrument for identifying and monitoring cognitive adverse events that can be used in future clinical trials and pharmacovigilance studies.

In order to meet this deliverable, the team at Southampton conducted qualitative interviews with key stakeholders – parents, teachers, ADHD clinicians, and children and adults with ADHD about their experiences of medication. We selectively recruited individuals with experience (first or second hand) of adverse events of MPH to enrich the possibility of harvesting accounts of negative effects. This process enabled us to develop putative items for parent and child report versions of the Medication and Cognition Questionnaire (MCQ). Subsequently, the instrument was translated (and back translated) from English in to Italian, German and Hungarian so it could be implemented at the 18-month data collection point across WP3 prospective study sites. Unfortunately, the time and funding available from this call was only sufficient to develop and pilot this instrument and not to
conducted a large-scale study evaluation of the adverse cognitive effects associated with long-term methylphenidate use. This piloting of the instrument is complete, and data from all four sites have been returned to Southampton so that the psychometric properties of the MCQ can be evaluated (factor structure and reliability). This work has been published in the Journal of Child and Adolescent Psychopharmacology with gold-standard open access:


3.4.3 Aim 13. To identify and propose new research areas to enhance the safety of long-term use of methylphenidate in patients with ADHD

The major task of ADDUCE was to conduct a 24-month prospective open-label naturalistic observational cohort pharmacovigilance study in children and adolescents. While it was agreed by the European Medicines Agency and the European Commission 24 months follow-up is appropriate for this project. It is arguable many patients are prescribed MPH well over 24 months. Therefore, long-term follow-up studies beyond 24 months is needed.

The ADDUCE team has the following recommendations:
1) Further continuous follow-up study of the ADDUCE cohort from WP3 should be conducted.

A) Growth and sexual maturity: The children and adolescents should be follow-up to adulthood to determine the long-term effects of both short-term and long-term MPH exposure during childhood and adolescence.

B) Cardiovascular effects:
I) Repeating the 24-hour BPs measure at intervals of 2 years and comparing to the original measures. The study will be able to compare the BPs of patients with continued MPH use, patients with abandoned MPH use (from the original treatment cohort), patients who never used MPH (from the original control cohort) and new MPH users with baseline 24-hour BPs off medication (from the original control cohort). This study will be able to investigate the long-term effects of both short-term and long-term MPH exposure during childhood and adolescence.

II) Repeating the echocardiogram for after 5 years as we need to investigate whether sustained mild BP elevation translates into left ventricular mass increase in long-term.

III) A recently published pharmacoepidemiological study has reported an association between arrhythmias and MPH. The ADDUCE team is not aware of an ambulatory heart rate monitoring study that has been investigated previously (total beats in 24 hours, minimum and maximum heart rates, heart rate variability and number of ventricular extra-systoles). We recommend such study to evaluate the potential cardiac effects of MPH.

C) Psychological:
ADDUCE’s results does not support there is an association between the use of MPH and mood disorders or psychotic behaviour. However, as it is unclear whether patients with previous history of mood disorders and/or psychotic behaviour are at higher risk of recurrence/deterioration of mood disorders or psychotic behaviour. A prospective study can be conducted in patients with such history. Psychological states of these patients will be intensively monitored.

D) Validation and application of Medication and Cognition Rating Scale:
In accordance to application, the ADDUCE team has developed the Medication and Cognition Rating Scale. This Scale will now require testing in large, representative samples of ADHD patients both on and off MPH medication, with and without a positive adverse effect profile, to control for bias effects. Additional testing and refinement may also be required to ensure that the measure has good validity and developmental sensitivity for both younger children and adult populations.

2) The main focus of ADDUCE has been effects on MPH on children and adolescents. However, recent data has shown that many adults are prescribed MPH for treatment their ADHD.

A) The ADDUCE team believe a similar prospective study in adults is fully justified to evaluate the psychological, neurological and cardiovascular outcomes.

B) The ADDUCE team recommend retrospective data mining studies in adults with ADHD and treated with medication, as well exploitation of the Scandinavian case registries and the UK clinical databases for documenting risks for cardiovascular disease associated with ADHD and its treatments.

3.5 Key Objective 4: To promote public health by disseminating the innovative knowledge acquired by the proposed studies to regulatory authorities, scientific community, medical and mental health professionals, to patients and their families, policy makers and to society in general, in order to promote the safer use of methylphenidate.

3.5.1 Aim 14. To directly interact with the EMA to ensure the protocols and results are able to aid the EMA in making regulatory decisions regarding the marketing authorization of methylphenidate including the product information warnings for doctors and patients.

The ADDUCE team met with the EMA prior to the commencement of data collection to discuss the protocol and the project, then progress meetings with the Coordinator Prof David Coghill. The team also met with EMA on 15th April 2016 to present the preliminary analyses of the ADDUCE results.

One further meeting will be organized when the full statistical analyses have been conducted and the preliminary data has been verified and we will develop a plan:
1) The regulatory actions
2) Coordinated dissemination plan between the EMA and the ADDUCE team in order to achieve the best public health outcomes.

The EMA has expressed that they are pleased with the ADDUCE projects and will take the appropriate actions to use the information for regulatory purposes. At the last meeting, it has been agreed that Prof Ian Wong will take the lead to continue liaise between the EMA and the ADDUCE team beyond the official duration of ADDUCE project to ensure the best use of the ADDUCE results and a fully coordinated dissemination plan.

3.5.2 Aim 15. Publish the results of these studies as peer-reviewed papers in international journals and in leading national medical and mental health journals.

So far, the ADDUCE project resulted in three publications in leading international journals.


Two additional papers are ready to be submitted to highly valued international journals.


Further, several manuscripts are in preparation or are already committed to by the author groups.

Carucci et al. Long-term methylphenidate in children with ADHD. Effects on growth: a systematic review within the ADDUCE project.

Konrad et al. Long-term methylphenidate in children with ADHD. Neurological effects: a systematic review within the ADDUCE project.

Hollis and Liddle et al. Long-term methylphenidate in children with ADHD. Psychiatric effects: a systematic review within the ADDUCE project.

Häge et al. ADDUCE – Strategic planning and coordination of recruitment in a European multicenter pharmacovigilance study investigating methylphenidate in children and adolescents.

Carucci et al. Effects of methylphenidate on height in ADHD children. The monitoring of bone age within the ADDUCE project.

Van de Loo-Neus et al. Methylphenidate treatment for ADHD and long-term effects on the heart rate and blood pressure. A prospective multi-site European study.

Nagy et al. Adverse psychiatric effects of methylphenidate: results from ADDUCE, a 24-month observational study.

Coghill et al. Adverse effects of methylphenidate: results from a prospective observational multicenter European study.

Buyck et al. Practitioners’ review: how to deal with long-term adverse effects of methylphenidate.

Kovshoff et al. Validation paper on the MCQ.

3.5.3 Aim 16. Present the data in national and international meetings in the form of symposia, workshops and clinical training sessions. We will pay particular attention to knowledge transfer to new EU states and associated and candidate states.

The ADDUCE teams have already presented information in the following conferences and meetings:


4. The 3rd European Network of Hyperkinetic Disorders (EUNETHYDIS) International Conference on ADHD Haliç Congress.
The ADDUCE teams will continue to present our results in national and international conference and dissemination meetings, including:

4th Eunethydis International Conference on ADHD Berlin 16th - 19th October 2016
The first presentation of the data will be at the 3rd EUNETHYDIS International conference in Berlin in October 2016. This is one of the premier international ADHD conferences with a large clinical and scientific audience from Europe and further afield. ADDUCE will present one of the key symposia and a series of poster presentations. The topics that will be covered are: Difficulties with current data, Methodology Prospective study, Cardiovascular study, Growth including bone age, Psychiatric, Psychiatric 2, MCQ, Clinical implications

The National Attention Deficit Disorder Information and Support Service (ADDISS) will present ADDUCE results as our patient representative at different patients group meetings, the first of which is shown below
The Extra Ordinary: Change your life change the world - ADDISS & DUNDEE AND ANGUS ADHD CONFERENCE TUESDAY 21ST JUNE 2016 Dundee

Targeted Network Meeting Hot topics in ADHD across the life span research European College of Neuropharmacology conference 29th ECNP Congress – Vienna on 21 September 2016.

ECNP School of Child and Adolescent Neuropsychopharmacology, Venice, Italy 2-7 April 2017.
The ECNP School of Child and Adolescent Neuropsychopharmacology has been established to encourage and spread excellence in clinical neuropsychopharmacology among child and adolescent psychiatrists. A select number of participants were offered a week of interactive training with an international faculty of experts in basic and clinical paediatric neuropsychopharmacology. Participants were selected by the chair of the school, with two to three potential candidates per country, on the basis of their career potential. A maximum of 50 junior psychiatrists are accepted and their travel and accommodation costs were substantially covered by ECNP.

5. ADDUCE Personnel are contacting national organisations in developing EU countries to present the findings from the project. Already contacted Slovenia.

Local dissemination meetings:
1. Individual Partners in four countries will also organize local dissemination meetings:
   • Hungary
   • Germany
   • Italy
   • United Kingdom

Training

1. The Junior-EUNETHYDIS International Conference 2016 will take place at the Kaiserin-Friedrich-Haus in Berlin on Sunday afternoon, 16th October and Monday 17th October 2016 as training to the junior clinicians and researcher from different part of the world.

2. European College of Neuropharmacology training course 2017 as training to the junior clinicians and researcher from different part of the world. The College will specifically target professionals in new EU states and associated and candidate states.
3.5.4 Aim 17. To translate the results of the proposed studies into evidence for developing new and updating existing clinical guidelines and practice parameters for the treatment of ADHD.

The members of the ADDUCE team have been members of various guideline development groups including the European Guideline Group, German Guideline Group and the National Institute for Health and Care Excellence (NICE) ADHD Guideline Group. The members will disseminate the results of ADDUCE to various guideline groups to support these groups in the development and update of existing clinical guidelines.

1) European Guideline Group
As a member of European Guideline Group, David Coghill is liaising with Prof Emily Simonoff of the Chair of European Guideline Group and an initial meeting took place in London on April 19 2016 to initiate the guideline update.

2) German Guideline Group
As chair of the German ADHD Guideline Group, Tobias Banaschewski will disseminate information to the Group so that the evidence will be considered in the German ADHD Guideline update.

3) NICE Guideline Group
As a member of NICE Guideline Group Chris Hollis will disseminate information to the Group so that the Group can consider the evidence from ADDUCE for the next update in 2017.

Potential Impact:

Review of Impact

ADHD is a common and impairing condition that has a major impact on the health of children in Europe. It is associated with significant reductions in quality of life and impacts on educational and occupational performance of the individual and the health and wellbeing of their family and society in general.

Based on a meta-regression analysis of 32 European studies, the estimated prevalence of ADHD in children and young people is approximately 5% with rates in the European Union being similar to those in other parts of the world. Whilst ADHD is almost certainly over diagnosed and over treated across much of North America the situation is Europe is very different. Although rates of diagnosis have increased over the past 10 years ADHD remains under diagnosed in much of Europe. In the UK for example current rates of diagnosis are around 500 per 100,000 in children and young people aged 6 - 17 years and despite increased rates of diagnosis between 1998 and 2005 the rates remained did not increase between 2005 and 2009. Whilst there are higher rates of diagnosis in the Netherlands and some parts of Germany there are also countries such as France and Italy where the rates are much lower than those in the UK. There is clear evidence of considerable variation in diagnosis and treatment of ADHD within as well as between countries. In Scotland for examples the rate of diagnosis varied 10 fold across the 13 health boards.

European data does however confirm the heavy impact and burden associated with ADHD. With regards health related quality of life those with ADHD have consistently been found to have mean scores across most domains of functioning that are between 1.5 and 2 standard deviations below those for the general population. ADHD is consistently associated with poor educational outcomes with increased rates of dropping out early from school, increased behavioural difficulties in the classroom, increased lexical and arithmetical skill problems and by adulthood, hyperactive children have less education, achieve lower grades, fail more classes, and are more often held back or fail to graduate compared with typically developing children and adolescents.

Whilst for many years ADHD was considered a disorder of childhood and adolescence it is now recognised that many children
with ADHD continue to suffer into adulthood. Traditional figures, based on data from the USA, have indicated that whilst only 15% of those with ADHD in childhood continue to meet full diagnostic criteria at 25 years of age around 2/3rds continue to have impairing symptoms and significant functional impairments associated with ADHD. Recent data from the Netherlands has suggested that the rates of persistence may be even greater in that group of patients who receive a diagnosis and treatment in Europe. Van Lieshout et al reported that of their sample of more than 450 young adolescents with ADHD around 85% continued to meet diagnostic criteria six years later. A wide range of negative outcomes have been associated with ADHD in adults. These include; increased rates of criminality with a five-fold increase in prevalence of ADHD in youth prison populations and a 10-fold increase in the adult prison populations (26.2%); increased rates of substance misuse whereby 45–55% of ADHD patients misuse drugs and alcohol and 15–25% of substance abusers have symptoms of ADHD; poor quality of life and increased rates of mortality which for adults are 4 times those of adults without ADHD.

In addition to these very significant impacts on the lives of affected children and their families ADHD is associated with considerable economic burden. In addition to the direct costs associated with the use of healthcare there are also costs associated with the demands on specialist education, social care, and criminal justice services. The wider costs to society also reflect impacts on parental employment and mental health, family-borne expenses, and crime and offending.

A review of the US literature on the cost of illness related to ADHD has emphasised the considerable and persistent costs incurred at both the individual and societal level with annual costs estimated as between $143 billion - $266 billion. The majority of costs were attributable to family members of people with ADHD or to adults with ADHD; the economic impact being approximately three times greater for affected adults compared to children and adolescents.

The cost burden mainly related to healthcare and educational services for children and loss of income and productivity for adults.

Whilst there is no Pan-European data on the economic cost of ADHD treatment data from the UK, Germany and The Netherlands have confirmed that the economic impact of ADHD here also. Data from the nationally representative British Child and Adolescent Mental Health survey were assessed for resource use and estimated costings over a three-year follow-up period. Children with hyperkinetic disorder (using ICD-10) incurred greater costs than children with emotional disorders, mainly relating to the use of frontline and special educational services. In England and Wales, in 2006, basic National Health Service costs for ADHD (excluding medication) were estimated at £23 million for initial specialist assessment and £14 million annually for follow-up care. A study conducted in the UK estimated that the mean annual total healthcare costs for people of all ages with ADHD were higher than for people without, for example £1,327 per year in people with ADHD vs. £328 per year for people without in the first year of the study. Further UK data estimated resource use costs in relation to a sample of 12-18 year olds who were referred to specialist health services and received a clinical diagnosis of ADHD five years earlier. Based on 2010 prices, the estimated annual total costs to the NHS, social care, and education services were estimated at £670 million. The majority (76%) of the mental health-related costs fell to the education sector.

Evidence from long-term longitudinal studies about the long-term cost impacts of childhood attention and hyperactivity problems suggest that costs are substantial even if for sub-threshold cases who do not necessarily meet full ADHD diagnostic criteria. Over an 11-22 year follow-up period, when compared with controls, a community sample of preschool children at risk of ADHD had 17.6 times higher average costs per annum across most domains (apart from non-mental health costs). Attention and hyperactivity problems at the age of 10 are associated with lower levels of employment and earnings at age 30. Another community-based 20-year follow-up study highlighted the importance of comorbid conduct problems in childhood in terms of incurring recent costs related to receipt of benefits and use of general health and social care services. Delays in receiving a clinical diagnosis of ADHD also lead to greater long-term costs - recent research has shown that individuals with ADHD who were not diagnosed until adulthood cost 13,608 euros more per year than their same-sex sibling.

Treating ADHD
The significant financial and emotional costs of ADHD to the individual as well as to the healthcare system, educational
services, carers and families and society as a whole are therefore clear (NICE 2008). Providing effective treatment has been demonstrated to improve not only the symptoms of ADHD but also the quality of life of individuals with ADHD and that of their carers and families. At the same time treating ADHD has been demonstrated to reduce the broader economic and psychosocial burdens on society.

Whilst in North American guidelines medication treatments are generally considered first line for ADHD European guidelines tend to be more conservative in attitudes towards the use of stimulant and non-stimulant medications. Both NICE (NICE 2008) and the EAGG have suggested that medication should be reserved, as first line, for those with more severe ADHD. For those with mild to moderate ADHD behavioural parent training would be the first choice. Medications can still be used for these less severe cases but should not be considered first line. These decisions may be reconsidered in the near future subsequent to the publication of a series of systematic reviews and meta analyses by the EAGG that question the effectiveness of parent training approaches in reducing ADHD symptoms. These reviews support the efficacy of parent training at improving oppositional symptoms and general parenting but not in the reduction of ADHD. These findings may result in a shift of opinion such that medication in general, and stimulant medications specifically, are considered as the first line treatment for more of those with ADHD. Within countries like the UK, France, Spain and Italy and many others within Europe where ADHD is currently under recognised this may have little immediate impact as those cases that do get a diagnosis tend to be more severely affects and would therefore meet current criteria for medication as a first line treatment. However, as rates of recognition, in these countries, increase this will become an issue. In countries like Germany and The Netherlands where recognition rates are already higher such a change in guidance would have an immediate impact on treatment recommendations. This would result in increased numbers of being prescribed ADHD medications, primarily stimulant medications, at an earlier age and over longer periods of time. Clearly this indicates a need to fully understand the long term safety of these medications.

Whilst the evidence supporting the efficacy and effectiveness of non-pharmacological treatments for ADHD it is generally excepted that pharmacological treatments are effective and all systematic reviews and meta analyses have reported moderate to large effect sizes for ADHD symptoms and across a broad range of outcomes (e.g. NICE, 2008). Whilst some reviewers have been critical of the involvement of Big Pharma in clinical trials for ADHD and suggested that this should cast doubt on the findings of these studies this particular review has been heavily criticised and found to contain numerous errors of fact. There is also now considerable evidence to support a positive impact of ADHD medication on quality of life. It is however the case that, until recently the evidence to support efficacy and effectiveness of stimulant medications over the longer term was thin on the ground. In a large part this is a consequence of the inherent difficulties associated with conducting long term randomised placebo controlled trials in this field. It also however may be a consequence of inadequate monitoring and treatment adjustment during routine clinical practice which mitigate against good long term clinical outcomes. It has for example been demonstrated in a naturalistic observational study with prospectively collected data that, with careful monitoring and treatment adjustment excellent clinical outcomes can with methylphenidate be extended up to at least 10 years with no evidence of a drop off in effects over time. Recent advances in data management have allowed the linking of data from various databases in several countries. This has allowed researchers to investigate the more distil impacts of disease and treatment over long periods of time. In ADHD this has, for example, demonstrated that whilst ADHD is associated with increased rates of criminal convictions these are reduced during periods of exposure to ADHD medication. Man et al (2015) demonstrated that children and adolescents with ADHD were less likely to present to the Emergency Room with trauma related problems during the periods when they were taking ADHD medications than those when they were not. Data also supports longer positive effects on several disorders relevant to ADDUCE including; reduction of substance abuse and anxiety and depression.

Uncertainties and Controversies
Notwithstanding these significant short and long term beneficial effects there remain several key uncertainties and some controversy about the use of stimulant medications to treat ADHD and in particular the potential for long term adverse effects. Whilst many of the controversies relate to ideological debates about the validity of ADHD and general concerns about the ethics of giving medications to children with mental health disorders supported by media stories that emphasise sensation
over science others relate to very real gaps in the scientific literature. Perhaps the biggest of these relates to our knowledge and understanding about the potential long term adverse effect associated with ADHD medications in general and methylphenidate specifically. These uncertainties were highlighted by the review initiated in 2007 into the safety data on methylphenidate by the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP). In January 2009 following their investigation into medicines containing methylphenidate the CHMP concluded that overall the benefits of methylphenidate outweigh the risks when prescribed to children with ADHD aged 6 years and over. However, within the same document, the Committee made recommendations to standardise prescribing and provision of safety information across all EU member states. Importantly, the report stated explicitly that more data are required on the long-term (defined by CHMP as ≥ 1 year) effects of methylphenidate on children and adolescents. They concluded that further research should be carried out to investigate long-term effects of methylphenidate on;

- growth and development
- neurological health
- psychiatric health
- sexual development and fertility
- cardiovascular effects in adults who have taken/are taking methylphenidate.

New regulations were drafted and implemented by the EMA to guide the regulatory framework within which companies need to operate when developing new medications for ADHD. These include the use of active reference arms in initial short term efficacy studies, longer term extension studies with randomised withdrawal phases to demonstrate longer term efficacy and longer term post licencing studies that address the longer safety concerns described above. These have been fully implemented for lisdexamfetamine and extended release guanfacine both of which received marketing authorization for ADHD recently. Whilst atomoxetine was already licensed across much of Europe prior to the regulations taking effect many of the CHMPs requests have also been satisfied for this non-stimulant medication. Data on methylphenidate, which has been licensed for many years and which is the most frequently prescribed medication in the EU for ADHD, is however lacking.

Public health dilemma of the long-term effects of Methylphenidate:

Whilst the one hand, there are clear benefits in treating ADHD in both the short and long term there remain uncertainties about long term safety and adverse effects which makes it very difficult to give an accurate account of the longer term benefit risk ratios. Taken together with the ongoing public and media controversies about the use of stimulant medications it was agreed that there was an urgent public health matter for the European regulatory agencies and research community to address. Whilst initial approaches were made to ask the pharmaceutical companies who manufacture and market the various methylphenidate formulations to conduct the required studies these requests were apparently declined. The EMA therefore suggested to the European Commission that a call for investigation of the long term safety of methylphenidate in children and adults be included as a topic within the FP7 funding programme. The call was made and ADDUCE was chosen as the programme to address these important questions.

Impact of ADDUCE project on Public Health Assessment:

In response to these clear public health dilemmas, ADDUCE addressed specifically the issue of the long-term safety of methylphenidate answering specifically those questions posed by CHMP. ADDUCE has resulted in innovative knowledge with respect to the following important adverse effects of methylphenidate that constitute major public health concerns as specified by the EMA:

- long-term developmental effects including growth (WP5)
- long-term effects on sexual development (WP5)
- long-term neurological effects (WP6)
- long-term psychiatric outcomes (including mood disorders, hostility and psychotic disorders) (WP7)
- cardiovascular effects in adults who are either currently taking methylphenidate or who have a history of use in childhood (WP8).
These were addressed through a mixed methodologies approach that includes a systematic review of the existing published literature, identification and secondary analysis of relevant data from existing large scale databases and through the acquisition and analysis of data from: a newly recruited 2 year prospective longitudinal cohort study of children and adolescents with ADHD newly started on methylphenidate and two control groups (one with ADHD but no medication treatment and a healthy control group) (WP3); and a cross sectional study of cardiovascular health in older adolescents and adults with ADHD with long term exposure to methylphenidate compared to control subjects with ADHD but no methylphenidate exposure (WP8).

One very significant impact of these studies on our understanding of the adverse effects associated with methylphenidate is the inclusion of control groups as comparators in both the prospective WP3 study and the cross sectional WP8 study. Previous long term investigations into adverse effects of ADHD medications have failed to include comparison groups. This is significant as ADHD itself is associated with many comorbidities several of which overlap with the adverse effects of medication e.g. sleep problems, anxiety, depression, psychosis and substance misuse. Without the benefit of a contemporaneous comparison group it is not possible to identify which problems are associated with medication and which with the disorder itself. By including a comparison group with ADHD but not medicated as well as a health control group the three way between group as well as within group comparisons have allowed us to disentangle these effects.

In addition to the studies described above the ADDUCE project has also developed two new tools that can be implemented in future investigations of adverse drug effects. These are:

- The Medication and Cognition Rating Scale a new tool for detecting cognitive adverse effects
- A new application of existing tools to detect and utilize measures of bone maturation in order to identify and predict long-term growth retardation.

These tools both have the potential to be used not only for ADHD treatment but also for other CNS treatments in children and adolescents.

The project has had further spin-off potential in areas outside those primarily targeted:

Although some aspects of safety of methylphenidate may be rather specific to this molecule, other aspects may reflect the class effects of stimulants. As a consequence, although this project is exclusively focused on the use of methylphenidate, the new knowledge acquired will impact on the broader issue of the use of other stimulant (e.g. amphetamines and lisdexamfetamine) and non-stimulant ADHD medications (e.g. atomoxetine, guanfacine and clonidine) in both children and adults.

The findings from ADDUCE will impact directly on the development of clinical guidelines for ADHD and on the development of regulatory advice about the use of ADHD medications within the EU.

The study is utilizing the EUNETHYDIS network (a member of the European Networks for Paediatric Research at the EMA – ENPR-EMA steering group) and additional collaborating centres. This network will comprise academic centres and clinics with a high level of expertise and eminently capable of undertaking other collaborative studies. Collaborating together in the ADDUCE initiative has further strengthened the network, allowed it to grow in size through the incorporation of new research partners, served as a platform for developing our research infrastructure and facilitating the development of several further EU proposals. The EUNETHYDIS network, through its sister organization EUNETHYDIS International Conferences is responsible for the organization of largescale international ADHD conferences and coordinates EUNETHYDIS participation in other international conferences. The first public presentation of the main ADDUCE findings will be at the 3rd EUNETHYDIS International Conference in Berlin in October 2016. This will include a dedicated symposium as well as several oral and poster presentations.
ADDUCE partners also hold key roles on the European College of Neuropsychopharmacology (ECNP) Child and Adolescent Psychiatry and ADHD sections. This will facilitate dissemination of ADDUCE findings through ECNP sponsored meetings and in particular at the annual Child and Adolescent Psychopharmacology School which is attended by participants from across Europe including many from emerging nations. ADDUCE members hold key roles within several National Child and Adolescent Psychiatry representative bodies and associations as well as other organizations such as the British Association for Psychopharmacology. Through these contacts we are in an ideal position to ensure that the key messages from ADDUCE are widely disseminated. This will impact on clinical practice across Europe.

ADDUCE has also served to strengthen the links between the consortium, EUNETHYDIS and the European ADHD Guidelines Group (EAGG) and through this with the large National groups that are developing future ADHD guidelines. Members of the ADDUCE consortium currently sit on the UK, German, Dutch, Belgian and Spanish guidelines group. This facilitates the direct dissemination of the ADDUCE findings into National and International Clinical guidelines.

ADDUCE has had and will continue to have direct interaction with the EMA. The purpose of these meeting is to ensure that the EMA, as the regulators overseeing the licensing and indications for medications in the EU, are fully appraised of new information relating to safety of methylphenidate at an early stage allowing them to make appropriate regulatory decisions regarding the marketing authorization of methylphenidate including the product information warnings for doctors and patients, that may arise out of this information.

The public health of children and adults with ADHD will therefore be promoted and protected through more effective and safer use of methylphenidate with respect regulatory advice, advice from clinical guidelines and data disseminated at conferences and peer reviewed publications.

Impact of ADDUCE on health care professionals

The ADDUCE-project will have significant impact on the health care profession in many ways. The knowledge and tools produced by ADDUCE will guide everyday clinical practice for many health care professionals: GPs, psychologists, child and adolescent psychiatrists, (neuro)paediatricians, nurses and others, who are delivering assessment and treatment for children and adults with ADHD.

ADDUCE provides an exemplary comprehensive baseline assessment with clear standardized operating procedures to carry out a diagnostic and differential diagnostic work-up. Practical guidance in the measurement and appraisal of potential side-effects will be made available from the ADDUCE website. The Medication and Cognition Rating Scale, developed as part of the ADDUCE project, is a new tool to specifically assess potential cognitive side effects and will be open for use by clinicians to monitor these in a systematic way.

The knowledge produced by ADDUCE will serve as an important reference for clinicians to endorse currently existing guidelines in the treatment of ADHD and monitoring of side effects in everyday practice.

Educational material will be disseminated (published papers, reports, presentations at international, national and local symposia, slide-kits and e-books) when the results of ADDUCE are published, to serve in training programs for health care professionals. These materials will contain summaries of the literature reviews, results from the existing data base analyses and from the prospective and cross-sectional ADDUCE studies. They provide clinicians with evidence that the use of methylphenidate in general is safe and therefore should be considered for treatment of ADHD if deemed necessary. They will illustrate this with data on the small size of risks and their development over time. Of great clinical value is the fact that the data can differentiate between the effects of ADHD itself and the effects of the medication to treat the disorder. In light of current public controversy, the data will allow health care professionals to provide psychoeducation for patients and families, including longer term outcome data, in order to make a well-balanced treatment choice. At the same time, they will stimulate clinicians to properly monitor potential side-effects in order to identify the small minority of patients that does show clinically
significant adverse events, to delineate those with clinically significant risk and to develop a treatment plan to overcome them. The ADDUCE project outcome will provide health professionals with even greater trust in existing guidelines on stimulant treatment and more confidence in the general safety of this treatment.

For mental health professionals involved in research, the ADDUCE protocol may serve as a helpful example in setting up high quality studies. A useful set of guidelines has been developed to promote study compliance and retain subjects in the study program over long periods of time.

List of Websites:
Title: ADDUCE: Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects (GA no. 260576)

Principle Contact: Prof David Coghill, Formerly University of Dundee, United Kingdom, currently University of Melbourne

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THERA KIND LTD United Kingdom
GUY'S AND ST THOMAS' NHS FOUNDATION TRUST United Kingdom
ISTITUTO SUPERIORE DI SANITA Italy
UNIVERSITY OF SOUTHAMPTON United Kingdom

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Budget: EU contribution: 2,999,559.60 €

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Related information

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<thead>
<tr>
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</tr>
</thead>
<tbody>
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