Study title	Post-authorisation Safety Study to Evaluate the Long-term Safety of Dexamfetamine (Amfexa)	
Protocol version identifier	6.0	
Date of last version of protocol	01 June 2016	
EU PAS Register number	ENCEPP/SDPP/7782	
Active substance	Dexamfetamine	
Medicinal product	Amfexa	
Product reference	Not applicable	
Procedure number	UK/H/5007/01/DC EMEA/H/A-29/1375 (previous) EMEA/H/N/PSP/0018 (current)	
Marketing authorization holder (MAH) or sponsor company	MAH MEDICE Arzneimittel Pütter GmbH & Co. KG Kuhloweg 37 58638 Iserlohn Germany	Sponsor of the study MEDICE Arzneimittel Pütter GmbH & Co. KG Kuhloweg 37 58638 Iserlohn Germany
Joint PASS	No	
Research question and objectives	1. To assess the incidence proportion and incidence rate for cardiovascular, psychiatric, growth and sexual maturity-related adverse events in children with a diagnosis of ADHD who have been treated with dexamfetamine, methylphenidate or lisdexamfetamine as recorded in healthcare databases of three countries 2. To compare the risk of long-term cardiovascular, psychiatric, growth and sexual maturity-related adverse events of dexamfetamine versus methylphenidate or lisdexamfetamine in each database	
Countries of study	United Kingdom, Germany and the United States	
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1 List of abbreviations

Acronym	Definition
ADHD	Attention Deficit and Hyperactivity Disorder
AE	Adverse Events
ADR	Adverse Drug Reaction
ALSPAC	Avon Longitudinal Study of Parents and Children
AR	Assessment report
ATC	Anatomical Therapeutic Chemical Classification System
BNF	British National Formulary
CDR	Cause of Death Register
CHMP	Committee for Medicinal Products for Human Use
CMD	The Co-ordination group for Mutual recognition and Decentralised procedures
CMD(h)	The Co-ordination group for Mutual recognition and Decentralised procedures – human
CMS	Concerned Member States
CPT-4	Current Procedural Terminology, 4th Edition
DA	Disease Analyzer
DCP	Decentralised process
DUS	Drug Utilisation Study
EMA	European Medicines Agency
EMIF	European Medical Information Framework
EMR	Electronic medical records
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
HCP	Health Care Professional

Acronym	Definition
HCPCS	Healthcare Common Procedure Coding System
HIPAA	Health Insurance Portability Accountability Act
ICD	International Classification of Diseases
ICD-9-CM	International Classification of Diseases – 9TH Revision, Clinical Modification
IMI	Innovative Medicines Initiative
IQR	Inter Quartile Range
ISPE	International Society of Pharmacoepidemiology
LoOI	List of Outstanding Issues
LoQ	List of Questions
LSHTM	London School of Hygiene and Tropical Medicine
MAH	Marketing Authorisation Holder
MAR	Missing at Random
MREC	Multi-centre Research Ethics Committee
NHS	National Health Service
NPR	National Prescription Registry
PASS	Post-authorisation Safety Study
PCP	Primary Care Physicians
PIN	Personal Identification Number
PK	Pharmacokinetic
PRAC	Pharmacovigilance Risk Assessment Committee
PSRPH	Potential serious risk to public health
QMS	Quality Management System
RMP	Risk Management Plan
RMS	Reference Member State
RWD	Real World Data
RWES	Real World Evidence Solutions

Acronym	Definition
SAG	Special Advisory Group
SAP	Statistical Analysis Plan
SD	Standard Deviation
SRC	Scientific Review Committee
THIN	The Health Improvement Network
WHO	World Health Organisation

2 Responsible parties

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IMS is a partner centre of the ENCePP scientific network which is coordinated by the European Medicines Agency. IMS is dedicated to excellence in research by adhering to the ENCePP Guide on Methodological Standards and promoting scientific independence and transparency.

Project team: As team members are likely to change over the project duration of five years, no individual names are listed here.

3 Abstract

Title
Post-authorisation Safety Study to Evaluate the Long-term Safety of Dexamfetamine (Amfexa)

Rationale and background
Medice has submitted a marketing authorisation application for a dexamfetamine-containing medicine under Article 10a ('well-established use') of Directive 2001/83/EC using the decentralised procedure with the UK as Reference Member State. In line with the requirements for other medicines used in the treatment of ADHD, use of dexamfetamine for the treatment of children with ADHD must be initiated by a specialist in childhood and adolescent behavioural disorders. The important risks associated with the use of dexamfetamine are those common to other stimulant medicines used in the treatment of ADHD. The proposed RMP for dexamfetamine is considered to be generally in line with RMPs for compounds used in similar indications.

The PRAC agreed that additional information is needed on the areas of safety concern of the RMP and that a list of outstanding issues should be addressed to the MAH including consideration of the need for a PASS to further analyse the safety of dexamfetamine specifically targeting assessment of:

- Cardiovascular events
- Growth impairment
- Psychiatric disorders
- Sexual maturity disorders

Research question and objectives
The objectives of this study are to:

1. To assess the incidence proportion and incidence rate for cardiovascular, psychiatric, growth and sexual maturity-related adverse events in children with a diagnosis of ADHD who have been treated with dexamfetamine, methylphenidate or lisdexamfetamine in healthcare databases of three countries

2. To compare the risk of long-term cardiovascular, psychiatric, growth and sexual maturity-related adverse events of dexamfetamine versus methylphenidate or lisdexamfetamine in each database

Study design
Retrospective cohort study (new-user design)

Population
The study will select and pool patients from three representative electronic databases, one in the United Kingdom, one in Germany and one in the United States. The study population will consist of children with ADHD who are treated with a stimulant (i.e.,

dexamfetamine versus methylphenidate or lisdexamfetamine) for the first time in a 5-year period of which the start coincides with the launch of Amfexa in the UK (i.e., new users of ADHD therapy).

Variables

The three study databases include a wide range of parameters for quantifying exposure, adjusting for potential confounding, and characterising outcomes and adverse events: patient information (age, gender, diagnosis associated with the dexamfetamine prescriptions), prescription derived variables (average daily dose, co-prescriptions) co-morbidities and outcomes (refer to *Annex 3*).

Data sources
Subjects for inclusion in the study will be selected from three large databases of routine electronic medical records (EMR), namely:

- The Health Improvement Network (THIN) (United Kingdom)
- Disease Analyzer (Germany)
- PharMetrics Plus (USA)

Study size
The three databases populations are expected to yield over a total of about 6,000 ADHD children treated with dexamfetamine over a 5-year period

Data analysis
Incidence proportions and rates for each of the adverse events of interest will be performed. Descriptive analyses will be performed to compare populations who have taken dexamfetamine with those who have taken methylphenidate or lisdexamfetamine. Multivariable analysis will be performed using proportional hazards regression adjusting for a host of potentially confounding factors. Stratification based on sex and dosage will also be conducted where applicable. Patient-level data of the three databases will be pooled to maximize precision of incidence rates of adverse events. A stratified analysis by database will be performed to assess the consistency of the outcomes across countries.

Milestones
After 6 months of start the first interim report is planned. The study progress reports are planned to be annually with the final study report in Q2 2021. For details please see section 5.

4 Amendments and updates

Version 1.0, abbreviated version, was submitted and assessed during the MA application.

Version 2.0 was submitted as condition of the marketing authorisation, including full description of the study design and milestones.

Version 3.0 was submitted in response to comments from the PRAC assessment report (23 April 2015)

Version 4.0 reflects changes made in response to comments from the PRAC assessment report (10 September 2015).

Version 5.0 was submitted after comments from the final PRAC assessment report (11 February 2016) were taken into account.

Version 6.0 was submitted after the question of a Member State how patients who switch between ADHD drugs will be analysed.

5 Milestones

Milestone	Planned date*
Start of data collection	Q2 2016*
End of data collection	Q2 2021*
First report of study results	Q2 2017*
Second report of study results	Q2 2018*
Third report of study results	Q2 2019*
Fourth report of study results	Q2 2020*
Final report of study results	Q2 2021*

*The study time period is to be determined and updated to coincide with the launch of Amfexa in the UK market (with up to 5-year follow-up period).

The progress reports will be submitted as part of the PSURs to the national competent authority in which PASS is conducted according to Module VIII and with any risk management plan updates, where applicable.

6 Rationale and background

Attention-deficit hyperactivity disorder (ADHD) is a common neuro-developmental disorder primarily diagnosed in children who often exhibit signs of inattention, hyperactivity and impulsiveness. Depending on the case definition used and the severity of disease, it is estimated that between 2% to 9% of school-aged children have a diagnosis of ADHD (McCarthy 2009).

Treatment of ADHD is aimed at reducing symptoms and improving functioning. Treatment may include education, psychotherapy and medication. Specific treatment guidelines may vary according to country. In the UK, for instance, ADHD treatment is steered by National Institute of Clinical Excellence's (NICE) guidance. Group-based parent-training education programs are recommended as first-line treatment for pre-

school children (ages 3 to 5 years in the UK) and school-aged children (ages between 5 and 16 years) with moderate impairment. Drug treatment is seen as a second-line treatment option in school-aged children aged 6 years and older only (NICE, 2008). Drug treatment is also recommended for school-aged children as first line if impairment is severe. Where drug treatment is indicated, methylphenidate, atomoxetine and dexamfetamine are considered. Methylphenidate is the first choice of drug treatment in school-aged children and young people up to 17 years old, followed by atomoxetine. Dexamfetamine is considered if ADHD in these age groups is unresponsive to the maximum tolerated dose of methylphenidate or atomoxetine (NICE, 2008).

There has been increasing concern about the adverse events of ADHD drugs. The worst potential adverse events are probably cardiovascular disease, a concern that is not unreasonable given several case reports of cardiovascular disease in children using stimulants and the observation that stimulant use in children relates to small increases in blood pressure and heart rate (Hammermess et al., 2015). Westover & Halm (2012) reviewed 7 epidemiological studies on ADHD drugs in children and cardiovascular disease risk. Six prospective studies reported no increased risk, whereas one case-control study reported that stimulant use was more frequent in a group of youths who had suddenly died from cardiac causes than in the control group of youths who had died as passengers in motor vehicle traffic accidents (Gould et al., 2009). Because of limitations of the latter study, its results need cautious interpretation. A major limitation of all studies is lack of statistical power due to small sample size, which hampers the ability to detect an association between ADHD drugs and cardiovascular disease risk.

As further data about effect of long-term use on psychiatric events is limited, these concerns should be evaluated as well. Amfetamines are known to increase dopamine and norepinephrine in the interneuronal gap. Both of these neurotransmitters have important roles in the aetiology of certain psychiatric symptoms including mood disorders, impulse-control disorders, psychosis, attention disorders, and anxiety disorders. While the specific pathways that are responsible for stimulant-induced psychosis are not mapped out in detail, the pharmacological basis of this adverse drug reaction (ADR) is well accepted. And although preclinical and clinical data did not identify any decreased rate of growth as a risk for amfetamine therapy, a common side effect of amfetamines is loss of appetite resulting in slower weight gain (McDonagh et al, 2011). Therefore, the long-term effect of dexamfetamine use on the growth and sexual maturity should be assessed in real-life data.

Dexamfetamine is an amphetamine derivative. It can improve attention span, concentration, and reduce impulsive behaviour in ADHD by stimulating parts of the brain that control attention and concentration. Dexamfetamine-containing medicines are authorised in most EU Member States for the treatment of narcolepsy as well as for ADHD in children between 6 to 17 years of age who respond insufficiently to methylphenidate. Kohne Pharma GmbH submitted an application for approval of Amfexa (formerly known as Dexamed; dexamfetamine sulphate) 5 mg tablet in a decentralised procedure on the basis of well-established use, i.e. bridging to the literature data of other amphetamine products based on pharmacokinetic (PK) data. In the procedure, UK acted as Reference Member State with eight Concerned Member States: Denmark, Finland, Ireland, Luxembourg, the Netherlands, Norway, Spain, and Sweden.

The DCP started on 29 August 2011.

On Day 210 (10 March 2013) of the DCP, most of the concerned member states (CMS) agreed with the reference member state (RMS) conclusion that the application could be approvable except the Netherlands which raised a potential serious risk to public health (PSRPH) regarding insufficient data to support efficacy in a second line indication and lack of safety regarding abuse potential. A referral was thus triggered at the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMD(h)) and was started on 8 April 2013. In the CMD-referral procedure, a trend-vote revealed a majority (21 vs 5 member states) to endorse the RMS position to consider the application approvable for the second-line indication. NL, BE, FR, HU en SK disagreed. The RMS considered abuse potential to be covered by the Risk Management Plan (RMP) and stressed that national distributing restrictions may be implemented if necessary. The procedure was referred to the Committee for Medicinal Products for Human Use (CHMP) on 10 June 2013.

During the CHMP meeting in June 2013, the Committee appointed Ian Hudson UK as Rapporteur and Barbara van Zwieten-Boot as Co-Rapporteur and adopted a List of Questions and the procedure started on 27 June 2013. The responses to the CHMP LoQ were received from the applicant/MAA on 30 September 2013. The conclusion of the Rapporteur's report was that based on the submitted data provided by the applicant, NL still considers the benefit-risk balance to be negative. According to NL, the applicant has not properly addressed the potential abuse and dependence of this product as well as the clinical evidence that the product is effective as second line treatment in ADHD is not demonstrated. Therefore, the original objections are considered unresolved.

In November 2013, the UK issued an Assessment Report (AR) on the response on the LoQ dated, 6 November 2013: The applicant should demonstrate or justify that the benefit/risk of the product is positive, taking into account:

- Risk for abuse and dependence
- Risk minimization measures taken (i.e., second line, RMP measures)
- Clinical evidence that the product is effective as second line treatment in ADHD

The conclusion of the Rapporteur was that the applicant has adequately addressed the CHMP Rapporteur's opinion that the proposed product is approvable. Based on the assessment of the Co-Rapporteur and the comments of the Member States, a list of outstanding issues (questions in LoOI) dated 21 November 2013 was sent to the applicant:

1. Discuss in detail the proposed strategy for data collection on abuse, misuse, diversion and dependence.

2. Submit synopsis of the protocols of the proposed post authorisation safety study (PASS) and drug utilisation study (DUS).

3. Submit any available data on abuse, misuse, overdose, diversion and dependence of dexamfetamine, particularly in Member States where

dexamfetamine-containing products are currently approved. The risk of abuse, misuse, overdose, diversion and dependence of dexamfetamine with respect to other ADHD treatment options should be discussed by the applicant.

The response to the CHMP LoQ was received from the applicant on 10 February 2014. The conclusion of the Rapporteur was that the presented evidence was sufficient to conclude the safety and efficacy of the product when used as intended. They were also of opinion that the proposed risk minimisation measures including its downgrading to the second line treatment were evidently (according to German and UK experience) sufficient to deal with the perceived risks of misuse of the product. They concluded that the product is approvable. Whereas the Co-Rapporteur considered based on the outline of epidemiological and experimental literature, the abuse-potential of (immediate released-) dexamfetamine to be a serious risk for public health.

On 12 May 2014, SAG Psychiatry meeting took place, and the opinion of the SAG was forwarded to the CHMP. On 20 May 2014, at the CHMP plenary meeting, the applicant summarized their planned actions and the current available data on the abovementioned issues.

On 22 May 2014, the European Medicines Agency (EMA) completed an arbitration procedure following a disagreement among Member States of the European Union (EU) regarding the authorisation of the medicine Amfexa. The CHMP concluded that the benefits of Amfexa outweigh its risks, and the marketing authorisation can be granted in the United Kingdom and in the following countries: Denmark, Finland, Ireland, Luxembourg, the Netherlands, Norway, Spain and Sweden.

Based on evaluation of the currently available data and the scientific discussion within the Committee, the CHMP concluded that the benefits of Amfexa outweigh its risks for second-line treatment of ADHD and recommended that the marketing authorisation be granted in all concerned Member States. The European Commission issued a decision on 06 August 2014, with the obligations to update the RMP section VI.2.5, Annex 2 and 7, and Part III within 3 months of the EU-Commission decision, to provide final protocols for the DUS and PASS, to provide final study results of the PASS by the latest Q2 2020, and that the PASS should run for 5 years instead of 3 years.

In December 2014, the marketing authorisation has undergone a change of ownership to MEDICE, which was completed in January 2015. On 06 May 2015, the name changes in some European Countries were approved (UK/H/5007/001/IB/001). Dexamed is not any longer used and the approved name in UK is Amfexa. In order to fulfil the obligation to conduct a PASS imposed in accordance with Article 107n(3) of Directive 2001/83/EC, The Marketing Authorisation Holder MEDICE Arzneimittel Pütter GmbH & Co. KG. submitted on 12 May 2015 a revised PASS protocol version 3 to the EMA for dexamfetamine.

Medice had subsequently provided a response to the EMA request. However, on 10 September 2015, the Pharmocovigilance Risk Assessment Committee (PRAC) provided additional comments which are recorded in the "PRAC PASS protocol assessment report, Procedure no.: EMEA/H/N/PSP/0018.1." In particular, PRAC had requested that a study with larger sample size covering multiple regions be performed to satisfy the PASS

requirements for Amfexa. This request was met by adding a large US database to the study. On 03 February 2016, PRAC had additional comments on clarification about the sample size calculation between the proposed databases.

IMS Health was asked by Medice to help provide responses to EMA comments, search for and recommend suitable databases, and update the protocol to satisfy PRAC requirements.

7 Research question and objectives

The objectives of this study are to:

1. To assess the incidence proportion and incidence rate for cardiovascular, psychiatric, growth and sexual maturity-related adverse events in children with a diagnosis of ADHD who have been treated with dexamfetamine, methylphenidate or lisdexamfetamine in healthcare databases of three countries

2. To compare the risk of long-term cardiovascular, psychiatric, growth and sexual maturity-related adverse events of dexamfetamine versus methylphenidate or lisdexamfetamine in each database

8 Research methods

8.1 Study design

The study will be carried out using a retrospective cohort design. In addition, the new-user design (Ray, 2003) will be applied in this study in an effort to reduce the likelihood of *prevalent user bias* which could potentially result from comparing patients with different duration of exposure to dexamfetamine. The benefit of the new user design is that it provides a convenient method to restrict the study population to patients without prior exposure to dexamfetamine, which would minimise concerns related to the comparability of exposure times. Specifically, this would reduce two main types of bias: 1) under-ascertainment of events that occur early in therapy and 2) the inability to control for risk factors that may be altered by the study drugs.

Distinct cohorts will be constructed for each of four grouped adverse effects (cardiovascular diseases, psychiatric disorders, growth impairment and problems with sexual maturation). This approach should maximise sample size by only excluding prevalent cases of the outcome of interest in each of the sub-cohorts rather than excluding patients due to prevalence of multiple diseases as is done when using one single cohort. The use of separate cohorts for each outcome also overcomes cessation of follow-up due to occurrence of multiple events. Refer to *Section 8.3.1* for further details on the study cohorts.

8.2 Setting

Subjects for inclusion in the study will be selected from three large databases of routine electronic medical records (EMR), namely:

- The Health Improvement Network (THIN) (United Kingdom)
- Disease Analyzer (Germany)
- PharMetrics Plus (USA)

Subjects will be included in the study if they have a record of ADHD and received their first GP-issued stimulant prescription within the study time period, selected to coincide with the launch of Amfexa in the UK. One exception will be made for the UK database THIN, where about half of the patients with a stimulant prescription do not have a record of ADHD diagnosis. To prevent that half of the exposed children would be excluded from the study, we will relax the inclusion criteria of having a record of an ADHD diagnosis. We will include all patients with stimulant prescriptions by assuming this is because of ADHD. This assumption appears to be valid because we will be excluding patients with a diagnosis of narcolepsy, the only other condition for which stimulants are indicated.

Follow-up in all three databases will be conducted in the longitudinal databases of EMRs.

The study population will consist of children aged 6 to 17 years old with a diagnosis of ADHD recorded with a record of a prescription for a stimulant (i.e. dexamfetamine, methylphenidate or lisdexamfetamine) for the first time during a 5-year study period between 2015 and 2021.

An open cohort design will be used because this would allow for some patients to have a 5-year follow-up period whilst also making full use of data amongst others who enter the study over the course of study follow-up.

NB: The study time period is to be determined to be updated to coincide with the launch of Amfexa *in the UK market (with up to 5-year follow-up period).*

8.3 Participants

8.3.1 Study cohorts

The individual databases will be divided into four distinct cohorts to include ADHD children who are newly exposed to dexamfetamine (or comparison stimulant) according to the study outcome of interest:

	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Outcome	Cardiovascular disease	Psychiatric disorders	Growth impairment	Impairment of sexual maturation
Sample	ADHD children newly exposed to dexamfetamine or another stimulant (applies to all 4 cohorts)			
Exclusion criterion, specific for each cohort	Previous diagnosis of *cardiovascular disease*	Previous diagnosis *psychiatric disorders*	Previous history of *growth impairment*	Previous history of impairment of *sexual maturation*

The case definition in German Disease Analyzer and PharMetrics Plus will be on the basis of having a record of an ADHD diagnosis. In THIN, we will use a modified case definition to overcome excluding half of the children exposed to stimulant drugs because of absence of a record of ADHD diagnosis. Therefore, we will include children with a prescription for stimulant drugs only. This case definition has been used previously by McCarthy et al. (2009) in their CPRD study relating the association of stimulant drugs and mortality.

8.3.2 Inclusion criteria

- Boys and girls 6 to 17 years of age at the time of first stimulant prescription
- At least 1 diagnosis of ADHD based on
    - Read code (THIN) (e.g., E2E0.00 child attention deficit disorder, E2E0100 attention deficit with hyperactivity, etc.)
    - Three character ICD10 code, i.e., F90 (German DA)
    - ICD 9 codes, i.e., 314.01 (PharMetrics Plus)
- At least 1 prescription of a stimulant (dexamfetamine, methylphenidate or lisdexamfetamine) used for the treatment of ADHD (refer to Annex 3 for list of drug codes)
- At least 6 months of enrolment in the database prior to first prescription of stimulant

8.3.3 Exclusion criteria

The following exclusion criteria apply to all three databases:

- Previous diagnosis of cardiovascular disease, psychiatric illness, or impairment in growth or sexual maturation, to be applied for each sub-cohort separately (see table in Section 9.3.1). For example, for cohort 1 that has incident cardiovascular events as outcome of interest, only patients with a history of cardiovascular disease will be excluded.
- History of narcolepsy (all four cohorts)
- Congenital heart disorders (all four cohorts)

8.3.4 Follow-up

Under a new-user design, the start of the at-risk period ("index date") for each patient will begin with the first recorded prescription of dexamfetamine (exposure group) or with the first recorded prescription of methylphenidate or lisdexamfetamine (comparison group). Patients in each of the four cohorts will be followed up until the occurrence of the adverse affect under study, death, loss to follow-up (transfer-out), or end of the 5-year study period, whichever comes first. To take into account that patients may switch pharmacological treatment, a time-varying analysis will be conducted.

Because dexamfetamine is a second-line drug and the comparison drug includes a first-line drug, patients might be different in terms of duration or severity of ADHD. This can introduce confounding by indication, which will be adjusted for using propensity score analysis (refer to *Section 8.8.4 Confounding by Indication*).

8.4 Variables

Variables will be selected using Read codes, ICD 9-CM and ICD-10 for medical events and for test results from clinical visits, and ATC codes used for prescribed drugs. A full list of terms for both exposures and outcomes is available in *Annex 3*.

8.4.1 Exposures

Patients' exposure to stimulants will be ascertained. The main exposure of interest for this study is dexamfetamine. Patients with at least one prescription of dexamfetamine (ATC code N06BA02) will be compared with those prescribed other psycho-stimulants lisdexamfetamine (ATC code N06BA12) and methylphenidate (ATC code N06BA04). We will not include atomoxetine as single drug treatment as comparison drug because this is not classed as a psycho-stimulant. Dosing information will also be captured for each drug exposure of interest if possible.

8.4.2 Outcomes

The four primary outcomes of interest will be examined separately, with outcomes defined by the following grouping of terms using Read codes or ICD 10 codes or ICD 9 codes (see *Annex 3*):

8.4.2.1 Cardiovascular Events

A new record of at least one of the following conditions:

- Hypertension
- Tachycardia
- Arrhythmia
- Myocardial infarction
- Sudden cardiac death
- Cyanosis
- QT prolongation
- Stroke
- Cardiomyopathy

8.4.2.2 Psychiatric disorders

A new record of at least one of the following conditions:

- Depression
- Aggressive or hostile behaviour
- Psychotic reaction (hallucination, mania)

8.4.2.3 Growth effects

For this outcome, we will differentiate between incident growth impairment as captured by Read codes. Growth velocities using actual recorded height and weight measures will be considered only if height and weight data found to be reliably captured in the individual study databases within the study population. We will consider the identification of growth effects through Read codes or ICD 10 or 9 codes as the primary outcome of interest and growth velocities as a secondary outcome.

NB: The analysis of growth effects will only be carried out near to the completion of the 5-year follow-up period (approximately after 4.5 years of follow-up) in order to allow a minimum duration of follow-up for children to experience the adverse event.

In summary:

- Primary outcome of growth effects: a new record of growth impairment or other related conditions identified from Read codes or ICD 10 or 9 codes

- Secondary outcome of growth effects (analysis only to be performed if data are found to be sufficiently reliable):
    - Growth velocities in height and weight will be used to define an impairment of growth if adequate data on height and weight are available in the study databases
    - <2 standard deviations in Z-score for height and weight (Germinario, 2013)

8.4.2.4 Effects on sexual maturity

A new record of problems involving sexual maturation or other related conditions (identified through a corresponding Read or ICD-10 or ICD 9 code)

8.4.3 Potential confounding variables

A broad range of potential confounders (refer to *Annex 3*) will be considered for adjustment in the multivariate analysis which include, and are not limited to, demographic characteristics, duration of ADHD diagnosis, co-morbid conditions, and concomitant medications. Certain covariates will be specific to the adverse event of interest: cardiovascular events (history of cardiac events, BMI, hypertension, diabetes, asthma, use of other sympathomimetic drugs, such as, oral decongestants and inhaled beta/alpha-agonists, antipsychotics, and antidepressants); psychotic events (drug abuse, seasonality, socioeconomic status); growth (eating disorders/malnutrition, smoking status, cancer, socioeconomic status); sexual maturation (family history of

sexual dysfunction, diabetes, cancer).

The final choice of confounders for each exposure-adverse event pair will depend on the availability of data, clinical relevance and overall improvement of fit of the model (refer to the *Data Analysis* section).

8.5 Data sources

In line with the PRAC recommendations data sources will be multi-country and will include databases from the United Kingdom, Germany and the United States.

8.5.1 IMS THIN (The Health Improvement Network) – United Kingdom

THIN is large UK primary care database containing EMR information. As of September 2014, THIN contained pseudonymised primary care medical records from over 13 million patients, of which over 3.5 million are currently active, representing almost 6% of the UK population. The database holds all prescribed medication, signs, diagnoses, lab tests and additional information such as lifestyle factors, BMI and vaccinations. It is possible to obtain additional information from the healthcare team, patients and their carers. THIN data have been shown to be generally representative of the UK in terms of age and gender comparisons, and Quality and Outcomes Framework chronic disease prevalence. In addition, a study has been performed which compares THIN data with data from practices using a different general practice software system (EMIS) and it was shown to match closely with these data, with the main exception that THIN data patients are slightly more highly representative of the more affluent social class. As this socioeconomic information is available in THIN data, researchers are able to adjust for it in analyses.

There is historically recorded data back into the 1990s for many patients, and in most cases there is summarised medical information prior to that. Data files in THIN are arranged in standardised tables. Diagnoses are coded in hierarchical Read codes (described below), which are grouped in themed "chapters" and include terms relating to symptoms, diagnoses, procedures, and laboratory tests. Prescription items are coded using Gemscript codes, based on NHS dictionary of medicines and devices and linked to BNF chapters.

8.5.2 IMS Disease Analyzer – Germany

The German IMS Disease Analyzer is a longitudinal EMR database that has the ability to track patients' diseases and therapies over time, providing valuable insight into what actually happens before, during, and after medical intervention. Longitudinal patient records can be searched for presence or absence of specific events among patients exposed to a specific medication or diagnosed with a condition, and derive appropriate control groups.

Anonymous data are collected continuously through the medical software, allowing longitudinal follow-up of all visits of the same patient consulting the same physician in the panel. The collected data include administrative (e.g., insurance scheme,

socioeconomic status), demographic (e.g., age and sex), clinical (e.g., signs, symptoms and diagnoses according to ICD-10 classification), laboratory (e.g. lab results reported by the physicians) and therapeutic information (e.g., EPHMRA/ATC class, drug name and molecule, dosage and route of administration). Included within the patient records are comprehensive notes of hospital admissions, specialist referrals and laboratory tests. An update of the database is done monthly with a lag time of 6 weeks.

The German DA database is based on patient records continuously collected from 2,500 computerized practices (including specialists) providing information on over 11 million patients with at least one consultation in the last 3 years throughout Germany. Among the unique physicians included, the database covers approximately 2.94% of the approximately 57,100 primary care physicians (PCPs) (n=1,679 physicians at 1,342 practices). Specialist practices include diabetologists, cardiologists, gynecologists, neurologists, orthopedics, pediatricians, psychiatrists and urologists. IMS samples practices with practice management software from MCS, Compugroup or Turbomed.

Patients who change the practice (free doctor choice) cannot be followed any further. The data collected from the electronic systems is used in primary care practices and specialists and enable you to perform analyses about.

The sample is designed to be representative of Germany. Included within the APLD records are comprehensive notes of hospital admission, specialist referral and laboratory test results. The validity and representativeness of IMS Disease Analyzer for use in pharmaco-epidemiological and pharmaco-economic studies has been sufficiently proven and has researched and described in several publications, e.g. in International Journal of Clinical Pharmacology and Therapeutics, Vol. 47, No. 10/2009 (617-626).

8.5.3 IMS PharMetrics Plus – United States

IMS PharMetrics Plus™ database is one of the largest claims database of integrated medical claims in the U.S. The aggregated IMS PharMetrics Plus database is comprised of adjudicated claims for more than 150 million unique enrollees across the U.S. Enrollees with both medical and pharmacy coverage represent 100 million lives. In 2013 approximately 35 million of these patients had active coverage. Data are available from 2006 onwards; with a typical 3-4 month lag due to claims adjudication. PharMetrics Plus data has diverse representation of geography, employers, payers, providers and therapy areas.

Due to the broad reach of the data, patients in the PharMetrics Plus database are similar to the national, commercially insured population in terms of age and sex for individuals aged 65 and under. The data are also longitudinal, with more than 30 million patients who have both medical and pharmacy coverage with 3 or more years of continuous enrollment. Data contributions are subjected to a series of quality checks to ensure a standardized format and to minimize error rates. All data are Health Insurance Portability Accountability Act (HIPAA) compliant to protect patient privacy.

In addition to standard fields such as inpatient and outpatient diagnoses (International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes) and procedures (Current Procedural Terminology, 4th Edition (CPT-4), Healthcare Common

Procedure Coding System (HCPCS), and ICD-9-CM codes), retail and mail order prescription records, PharMetrics Plus has detailed information on the inpatient stay (e.g., admission type and source, discharge status) and provider details (e.g., specialty, provider ID). The majority of 3-digit zip codes in the U.S. are covered and reported. Validated algorithms based on ICD codes are available to enhance case finding within PharMetrics Plus. Other data elements include dates of service, demographic variables (e.g., age, sex, and geographic region), and start and stop dates of health-plan enrolment.

8.6 Study size

Three databases were identified as having the potential to provide sufficient numbers of patients for the study. Feasibility counts were performed for each country (results shown in Annex 5). Based on those feasibility counts the potential study size was estimated.

The available target population for each of the individual databases was estimated and these are shown in the following table. The methodology used to calculate the sample size of patients newly exposed to dexamfetamine was as follows:

1. For PharMetrics Plus and German Disease Analyzer, we estimated the total number of ADHD diagnosed children who were pharmacologically treated with a stimulant. For THIN, we estimated the total number of children with ADHD using the method by McCarthy (2009) who defines ADHD cases to be those who received pharmacological treatment with ADHD medications.
2. For each of the next 5 years a projection of patients using dexamfetamine was calculated as follows:
    i. Starting in 2015 the initial estimates of the target population (from step 1) are used as the base level population
    ii. Incident cases are added to this estimate at the rate of 10 per 100,000 population per year for the estimated pediatric population in each database
    iii. An "at risk" population created by multiplying the ADHD diagnosed population by the proportion assumed to be pharmacologically treated (typically 60% as observed in our databases and by experts in the field (Centers for Disease Control and Prevention, 2005). For THIN, the "at risk" population is composed of children who are pharmacologically treated, assuming all had an ADHD diagnosis
    iv. The number of new dexamfetamine users is determined by multiplying the "at risk" population by the assumed uptake rate of dexamfetamine, which is estimated directly from each database (0.3% in the UK, 0.7% in Germany and 0.6% in the USA)
    v. The target population in the next year is created by removing the new dexamfetamine users from the pool of ADHD diagnosed patients (Disease Analyzer and PharMetrics Plus)or pharmacologically treated patients (THIN) at the end of the previous year
3. This process is repeated each year
4. An individual projection is created for each database

The sample size has been calculated assuming the rate of dexamfetamine use in the current year of each database applies for the next 5 years.

The table below shows the estimated sample size of dexamfetamine patients for each country. Details of the calculations and assumptions used for each database are shown in Annexes 4 and 5.

Country	**Database**	**Historical uptake rate of dexamfetamine***	**No. patients exposed to dexamfetamine**
UK	THIN	0.3%	144
Germany	Disease Analyzer	0.7%	998
USA	PharMetrics	0.6%	5,028
Total			**6,170**

**The figures of 0.3%, 0.7% and 0.6% were obtained from direct examination of the three databases, performed by IMS in February 2016. These figures reflect actual update of dexamfetamine in the most recent data available for each database (see Annex 4).*

For the primary outcome (i.e., proportion of observed adverse outcomes), these sample sizes would allow estimation as follows:

	Observed adverse outcomes (%)		
Sample size	**1.0**	**0.5**	**0.1**
150	0.2,4.2	0.1,3.4	0.0,2.7
500	0.4,2.3	0.2,1.6	0.0,0.6
1,000	0.5,1.8	0.2,1.2	0.0,0.6
1,500	0.6,1.6	0.2,1.0	0.0,0.4
2,000	0.6,1.5	0.2,0.9	0.0,0.3
2,500	0.7,1.4	0.3,0.8	0.0,0.3
5,000	0.7,1.3	0.3,0.7	0.0,0.2
6,000	0.8,1.3	0.4,0.7	0.1,0.2

Table. 95% confidence intervals for observed adverse outcomes for the primary study objective

8.7 Data management

8.7.1 Statistical analysis

All analyses will be performed using SAS analytical software version 9.4.

8.7.2 Database management

8.7.2.1 IMS THIN (UK)

Data selection and retrieval will be performed using database support provided for THIN by *IMS Information Solutions Medical Research Limited*.

8.7.2.2 IMS Disease Analyzer (Germany)

Data selection and retrieval will be performed by using the database support by *IMS Health (Germany)*. All data processing adheres to Health Insurance Portability and Accountability Act (HIPAA) requirements and is augmented by internal IMS Data Governance rules.

8.7.2.3 IMS PharMetrics Plus (US)

Data selection and retrieval will be performed using database support provided for IMS PharMetrics Plus by *IMS Health (US).* All data processing adheres to Health Insurance Portability and Accountability Act (HIPAA) requirements and is augmented by internal IMS Data Governance rules.

8.8 Data analysis

8.8.1 Descriptive analysis

Continuous variables will be evaluated for normality of distribution prior to the statistical analysis, and they will be evaluated for outlying values. Where appropriate, a geometric mean transformation will be applied to handle skewness (back-transformed prior to reporting) or a non-parametric display of information (e.g., medians, IQRs) will be considered. Quantitative variables may be categorised into quartiles as required.

Descriptive analysis will be performed using counts and frequencies for categorical variables, and means and medians for continuous variables. Statistical testing will involve the chi-squared statistic for the comparison of categories and the t-test for continuous variables. Prior to the descriptive analysis, the data will be examined for potential skewness and influential outliers which will be handled appropriately as required (e.g., use of non-parametric methods, dropping of outliers, etc.).

Statistical testing will involve the chi-squared statistic for the comparison of categories and the t-test for continuous variables. Both incidence proportion and incidence rate will be reported for each adverse event of interest.

8.8.2 Long-term safety assessment

With a focus on long-term safety events, the analysis will be performed at 6-month, 1-year, 2-year, 3-year, 4-year and 5-year intervals. Depending on the availability of data, the analysis will be carried out using a composite endpoint (i.e., cardiovascular, psychiatric and growth related events) and/or using separately each component outcome defined in the Outcomes section.

To allow for a sufficient latency period, subjects with at least 6 months of continuous exposure to a stimulant will be included in the analysis on growth trajectories. Growth velocities (height and weight) will be calculated to detect possible differences in growth trajectories between 2 time points (at least 1 year apart). Analysis will be performed using units of Z-scores (Germinario, 2013). Statistical comparisons will be made using ANCOVA to adjust for age and baseline height and weight where appropriate.

8.8.3 Comparing apparent adverse event rates

Multivariate analysis will be performed using regression methods as appropriate: Poisson regression will be applied to provide adjusted rates; linear regression will be applied to outcomes which are continuous (e.g., SBP, height, etc) at appropriate time points (e.g., 6 months, 1 year, 2 years, etc); and proportional hazards regression will be used for time to event analysis of dichotomous outcomes (e.g., hospitalisation for myocardial infarction, sudden death, etc). Regression diagnostics will be performed to evaluate model assumptions. 95% confidence intervals will be reported where possible. Both absolute and relative measures will be considered.

Two approaches will be used to account for patients switching ADHD drugs during their treatment course. First, patients will be censored upon switching to another ADHD drug. This would eliminate any carry-over effect the original ADHD drug may have. Second, a time-varying analysis will be conducted. For example, a time-dependent Cox regression analysis will be carried out, which allows patients to contribute to person-years to both dexamfetamine and comparator drug. When patients switch from dexamfetamine or comparator drug to another ADHD drug not serving as comparator, their follow-up time will be censored.

8.8.4 Confounding by indication

Confounding by indication may be present given that dexamfetamine is indicated as a 2nd line therapy. Thus, patients prescribed dexamfetamine may differ from new users of other stimulants with regard to health status, severity of ADHD or compliance. To reduce the impact of possible bias, the primary analysis will utilise a *propensity score matched analysis* (Brookhart, 2006; Schneeweiss, 2007) which has been recommended in the ENCePP Guide on Methodological Standards (ENCePP, 2010) as a useful approach for reducing the impact of possible confounding by indication. Propensity score analysis will be carried out for each of the four cohorts separately.

Using logistic regression analysis, each patient (including those in the comparison group) will be assigned a propensity score that reflects the likelihood of being prescribed dexamfetamine on the basis of the covariates listed in *Annex 3*. The covariates include,

for example, duration on pharmacotherapy and existing co-morbidities, which could differ between exposure and comparison groups. We will strengthen the matched analysis by matching on important covariates associated with the exposure in addition to the propensity score as originally suggested by Rosenbaum and Rubin (1983) and more recently by Sekhon (2011) as a way of reducing residual confounding. For example, we may match on age, gender, previous co-morbidity history and insist duration of previous medication use be within a specific tolerance for a match, in addition to the propensity score.

We shall assess the effectiveness of the matching by evaluating the balance achieved in the observed covariates listed in Annex 3. Specifically we will use the standardised differences between the matched groups and other diagnostics as suggested by Austin (2009) and Sekhon (2011). Rosenbaum bounds (Rosenbaum, 2009) will be used to quantify the sensitivity of the matched analysis to unobserved confounders. We intend to match each dexamfetamine user to at least one user of either methylphenidate or lisdexamfetamine.

8.8.5 Stratification

In addition to the overall analysis, the analysis will be stratified by gender given that most ADHD occurs in boys. The results will be stratified by age category and daily dosing categories (e.g., <10mg, 10-20mg, >20 mg) assuming adequate data is available in the individual databases. The analysis will be performed using 3 year age bands (6-8 years; 9-11 years; 12-14 years; 15-17 years.

8.8.6 Pooled Analysis

We will present the results of each study database separately. We will also pool the individual-patient data of the three databases to enhance the statistical power of the analysis.

8.8.7 Missing Data

If substantial amounts of missing data exist, multiple imputation will be applied under the missing at random (MAR) assumption to enhance the sample size of the study.

8.9 Ethical Approvals

8.9.1 IMS THIN (UK)

In the UK, all research involving data collected from National Health Service (NHS) patients must be approved by a Research Ethics Committee. The THIN data collection was approved by the NHS South-East Multi-centre Research Ethics Committee (MREC) in 2003. Under the terms of this ethics approval, studies using pre-collected, pseudonymised data must undergo scientific review to help ensure appropriate analysis and interpretation of the data. This approval was recently extended to studies involving

data validation at GP level.

The independent Scientific Review Committee (SRC) was set up in July 2009. IMS Health Real World Evidence administers the SRC application process and can provide support to obtain scientific or ethical approval. Researchers wishing to use only data or data/GP validation (GP questionnaires, hospital discharge notes and death certificates) will need to receive approval from the SRC.

Ethics approval normally takes 3-4 weeks for approval.

8.9.2 IMS Disease Analyzer (Germany)

Since the analysis is a retrospective, fully anonymised data base analysis there is no need of approval by ethical commission. However, given that the results of this study may be published, Medice plans to pursue ethics approval.

8.9.3 IMS PharMetrics Plus (US)

Since the analysis is a retrospective, fully anonymised data base analysis there is no need of approval by ethical commission. However, given that the results of this study may be published, Medice plans to pursue ethics approval.

8.10 Quality control/assurance

At the study level, all aspects of the study from protocol development to the reporting of the results are conducted within the work-frame of IMS Quality Management System (QMS) and in accordance to the following policies and procedures:

- POL_QA_001 "Quality Management System" policy
- POL_QC_001 "Quality Control Strategy" policy
- SOP_QC_002 "Quality Control of Project Deliverables"

According to the policies and procedures above, a Quality Control plan for the study will be developed and executed, which will include quality control on study methodology, statistical analysis plan, programming, data management and analysis, study results, conclusions and study report. Furthermore:

- The study Quality Control plan will establish ownership for the execution of the individual Quality Control steps. The principle of the independence of Quality Control applies
- The Principal in Charge of the study will ensure that individuals responsible for the execution of specific Quality Control steps will have knowledge, capability and experience which are adequate for the task.
- The result of the execution of the individual steps of the Quality Control plan will be documented, and include the required corrective actions, if any.
- The execution of any required corrective action will be documented.
- The executed Quality Control plan will be subjected to a final review and approval for sufficiency and completeness from the Principal in Charge of the study

Also, the principal in charge of the study will verify training compliance of IMS employees contributing to the study, as per IMS procedure SOP_QA_007 "Training of

Quality and Operational Standards".

The principal in charge of the study is a senior epidemiologist with 24 years research experience in population-based research, for which, the last 12 years have been in the field of pharmacoepidemiology. Qualification, role and responsibilities of the principal in charge of the study are described in OST_OT_014 "Senior Principal RWE- Job Description"

8.11 Limitations of the research methods

8.11.1 Database limitations

The individual study databases have limitations typical of other EMR databases:

- Patients and physicians included in the database may not be fully representative of all patients and physicians in their respective countries as data is collected only from physicians who have agreed to participate in the panel
- Inability to see data for patients who seek care outside the panel
- Inability to track actual medication fills, as the prescription information only highlights those prescriptions written by the participating physician
- Depending on the standards of the physician practice, tests/assessments or interventions may be conducted but not recorded
- No information on hospital drug prescribing

8.11.2 Study analysis limitations

A limitation of this study is the potential for confounding by indication: dexamfetamine is a 2nd or 3rd line therapy with all patients being on a comparator drug before dexamfetamine initiation. To limit this effect, we propose to use a propensity score matched analysis to supplement the results of the analysis.

Propensity scores assume that all relevant covariates are included in the model. Given that the individual databases may not contain information on all relevant known and unknown confounding variables, residual confounding may still be present in the study results. For example, with THIN it is not possible to evaluate the extent of maternal smoking, whether a child was breast fed or other environmental conditions which may affect the outcome of growth.

A new user design has been proposed in this study whereby only new, incident users are included in attempt to reduce survivorship bias. However, this approach has the disadvantage of reducing the study sample size which could affect the statistical power of the study. This reduction in statistical power is thought to be acceptable considering the improvement in robustness of the study design, although sample size may be a problem with rarer outcomes, such as delayed sexual maturation.

Missing data may be a limitation in the proposed analysis, particularly concerning the frequency and extent to which height and weight are captured for patients in individual databases with ADHD receiving the treatments of interest. As detailed earlier in the Missing data section, it is proposed to use multiple imputation if substantial data are not

present.

Another limitation regards to sample size is that dexamfetamine will be a newly introduced drug, and therefore the total number of exposed patients early on in the follow-up period could be low. Thus, depending on the level of uptake in the study countries, some patients exposed to dexamfetamine may have short follow up times.

Atomoxtine use is not among the exposure or comparator drugs in the study because it is not a psycho-stimulant. Therefore, results of this study are not generalisable to atomoxetine therapy.

It is assumed in these analyses that all prescribed drugs are filled and then taken by patients in a compliant manner. Non-compliance would result in misclassification of users and could cause an underestimation of the association between exposure and outcome.

8.12 Other aspects

None

9 Protection of human subjects

This study is non-interventional and analysis is based on secondary data use. No identifying data is collected in any of the planned approaches. All databases are set up following local law, including data privacy regulation.

10 Management and reporting of adverse events/adverse reactions

The study being proposed is a non-interventional study design based on retrospective data collection. In accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) guidance which states (Section 8.3):

> *For non-interventional study designs which are based on secondary use of data (such as studies based on electronic healthcare records or meta-analyses), adverse reactions reporting is not required. All adverse events/reactions should be summarised in the study report.*

11 Plans for disseminating and communicating study results

Any amendments to the protocol and plans for communication/publication will be made in accordance of the procedures outlined in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) guidance. This study will be

registered along with study information (protocol, amendments to the protocol, progress reports and final study report) in the register of PASS maintained by the EMA. We will disseminate any findings of potential scientific or public health importance and research sponsors (government agencies, private sector, etc.) will be informed of study results in a manner that complies with local regulatory requirements. Reporting of results will follow the guidance outlined in the STROBE guidance (http://www.strobe-statement.org/).

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13 Amendments and deviations

The following amendments were made for the current version of the protocol:

- The sample size calculations of the expected number of patients to be included in the study have been updated by using the most recent available data;
- To overcome a relatively small sample size of patients in the UK database, a second European database has been added;
- The table in section 8.3.1 (Study cohorts) has been clarified to more accurately reflect that the patients eligible for inclusion are those newly exposed to dexamfetamine or comparison drug;
- Blood pressure and heart rate have been added as baseline measurements;
- The definitions of exposure and comparison drugs and study outcomes in Annex 3 have been updated.

14 Annex 1. List of stand-alone documents

None.

Annex 2. ENCePP Checklist for Study Protocol

Study title: Post-authorisation Safety Study to Evaluate the Long-term Safety of Dexamfetamine (Amfexa)

Study reference number: TBD

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection			X	
1.1.2 End of data collection			X	
1.1.3 Study progress report(s)			TBD	
1.1.4 Interim progress report(s)			TBD	
1.1.5 Registration in the EU PAS register			TBD	
1.1.6 Final report of study results			TBD	11

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk	X			11-12

management plan, an emerging safety issue) 2.1.2 The objective(s) of the study?	X			15
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	X			16
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	X			15
2.1.5 If applicable, that there is no *a priori* hypothesis?			X	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	X			15
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	X			18-19
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	X			24-25

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	X			16, 19-21
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	X			11, 17
4.2.2 Age and sex?	X			16
4.2.3 Country of origin?	X			16-17
4.2.4 Disease/indication?	X			16-17
4.2.5 Co-morbidity?	X			17
4.2.6 Seasonality?	X			19
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	X			16-17

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	X			18
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)			X	

5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)			X	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?			X	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?			X	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	X			18-19
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)			X	

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	X			19
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated			X	

direction of effect)				

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:	X			19-21
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	X			19-21
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	X			19-21
8.1.3 Covariates?	X			19-21
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	X			19-21, Annex 3
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	X			19-21, Annex 3
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	X			19, Annex 3
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	X			18-19
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)		X		
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	X			18
8.4 Is the linkage method between data sources		X		

described? (e.g. based on a unique identifier or other)				

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	X			21-22, Annex 5

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	X			24-25
10.2 Is the choice of statistical techniques described?	X			24-26
10.3 Are descriptive analyses included?	X			24
10.4 Are stratified analyses included?	X			25
10.5 Does the plan describe methods for adjusting for confounding?	X			25
10.6 Does the plan describe methods addressing effect modification?			X	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**

11.1 Is information provided on the management of missing data?	X			26
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	X			23-24
11.3 Are methods of quality assurance described?	X			26-27
11.4 Does the protocol describe possible quality issues related to the data source(s)?	X			27-28
11.5 Is there a system in place for independent review of study results?	X			27

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	X			28
12.1.2 Information biases?	X			28
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)				
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	X			21-23, Annex 5
12.3 Does the protocol address other limitations?	X			28

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	X			26
13.2 Has any outcome of an ethical review procedure been addressed?			X	
13.3 Have data protection requirements been described?			X	

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	X			30-31

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	X			29
15.2 Are plans described for disseminating study results externally, including publication?	X			29

Comments :

Annex 3. Additional information

Definition of ADHD in THIN*

Read code	Term
Eu9y700	[X]Attention deficit disorder
ZS91.12	[X]Attention deficit disorder
Eu90011	[X]Attention deficit hyperactivity disorder
Eu90100	[X]Hyperkinetic conduct disorder
Eu90111	[X]Hyperkinetic disorder associated with conduct disorder
Eu90z00	[X]Hyperkinetic disorder, unspecified
Eu90.00	[X]Hyperkinetic disorders
Eu90z12	[X]Hyperkinetic syndrome NOS
Eu90y00	[X]Other hyperkinetic disorders
ZS91.11	ADD - Attention deficit disorder
ZS91.00	Attention deficit disorder
E2E0100	Attention deficit with hyperactivity
E2E0000	Attention deficit without hyperactivity
E2E0.00	Child attention deficit disorder
E2E0z00	Child attention deficit disorder NOS
E2E..00	Childhood hyperkinetic syndrome
E2E2.00	Hyperkinetic conduct disorder
E2Ez.00	Hyperkinetic syndrome NOS
1BR..00	Reduced concentration
1BR0.11	Short attention span
Z7C5312	Short attention span

* ADHD definition according to Raman et al., 2013.

Definition of ADHD in PharMetrics

ICD-9	Term
314	Hyperkinetic Syndrome of Childhood
314.0	Attention Deficit Disorder of Childhood
314.00	Attention Deficit Disorder of Childhood Without Mention of Hyperactivity
314.01	Attention Deficit Disorder of Childhood With Hyperactivity
314.1	Hyperkinesis of Childhood With Developmental Delay
314.2	Hyperkinetic Conduct Disorder of Childhood
314.8	Other Specified Manifestations of Hyperkinetic Syndrome of Childhood
314.9	Unspecified Hyperkinetic Syndrome of Childhood

Definition of ADHD in Disease Analyzer

ICD-10	Term
F90	Attention-Deficit Hyperactivity Disorders
F90.0	Attention-Deficit Hyperactivity Disorder, Predominantly Inattentive Type
F90.1	Attention-Deficit Hyperactivity Disorder, Predominantly Hyperactive Type
F90.2	Attention-Deficit Hyperactivity Disorder, Combined Type
F90.8	Attention-Deficit Hyperactivity Disorder, Other Type
F90.9	Attention-Deficit Hyperactivity Disorder, Unspecified Type

Definition of exposure drugs in THIN

Drug code	Exposure drugs (all dexamfetamine sulfate)
9738	Dexamfetamine 5mg tablets
14512	Dexedrine 5mg tablets (Auden McKenzie (Pharma Division Ltd)
31623	Dexedrine 15mg Spansules (Imported (United States)
47481	Dexamfetamine 10mg modified-release capsules
47679	Dexamfetamine 15mg modified-release capsules
51453	Dexamfetamine 5mg/5ml oral solution
13238	Dexamfetamine 1mg/ml oral liquid
16185	Dexamfetamine 15mg modified-release capsules
18996	Durophet 20mg Capsule (3M Health Care Ltd)
18998	Durophet 7.5mg Capsule (3M Health Care Ltd)
24116	Durophet 12.5mg Capsule (3M Health Care Ltd)
47099	Dexamfetamine with amfetamine 10mg with 10mg modified-release capsules
47609	Dexamfetamine 5mg modified-release capsules
55495	Dexamfetamine with amfetamine 10mg with 10mg capsules
To be identified	Amfexa

Definition of comparison drugs in THIN

Drug code	Product name	Drug substance
58055	Dexmethylphenidate 10mg modified-release capsules	Dexmethylphenidate hydrochloride
55169	Lisdexamfetamine 50mg capsules	Lisdexamfetamine dimesylate
55747	Elvanse 30mg capsules (Shire Pharmaceuticals Ltd)	Lisdexamfetamine dimesylate
55987	Lisdexamfetamine 30mg capsules	Lisdexamfetamine dimesylate
56336	Elvanse 50mg capsules (Shire Pharmaceuticals Ltd)	Lisdexamfetamine dimesylate
56576	Elvanse 30mg capsules (Shire Pharmaceuticals	Lisdexamfetamine

	Ltd)	dimesylate
56742	Elvanse 70mg capsules (Shire Pharmaceuticals Ltd)	Lisdexamfetamine dimesylate
57786	Lisdexamfetamine 70mg capsules	Lisdexamfetamine dimesylate
576	Methylphenidate 10mg tablets	Methylphenidate hydrochloride
2679	Ritalin 10mg tablets (Novartis Pharmaceuticals UK Ltd)	Methylphenidate hydrochloride
5810	Concerta XL 18mg tablets (Janssen-Cilag Ltd)	Methylphenidate hydrochloride
5811	Concerta XL 36mg tablets (Janssen-Cilag Ltd)	Methylphenidate hydrochloride
6107	Methylphenidate 18mg modified-release tablets	Methylphenidate hydrochloride
6169	Methylphenidate 36mg modified-release tablets	Methylphenidate hydrochloride
6804	Equasym 20mg tablets (Shire Pharmaceuticals Ltd)	Methylphenidate hydrochloride
6868	Equasym XL 20mg capsules (Shire Pharmaceuticals Ltd)	Methylphenidate hydrochloride
7101	Methylphenidate 5mg tablets	Methylphenidate hydrochloride
11536	Methylphenidate 20mg modified-release capsules	Methylphenidate hydrochloride
11733	Methylphenidate 20mg tablets	Methylphenidate hydrochloride
13212	Methylphenidate 10mg modified-release capsules	Methylphenidate hydrochloride
13914	Equasym 5mg tablets (Shire Pharmaceuticals Ltd)	Methylphenidate hydrochloride
13946	Equasym 10mg tablets (Shire Pharmaceuticals Ltd)	Methylphenidate hydrochloride
14331	Equasym XL 30mg capsules (Shire Pharmaceuticals Ltd)	Methylphenidate hydrochloride
14346	Equasym XL 10mg capsules (Shire Pharmaceuticals Ltd)	Methylphenidate hydrochloride
14848	Methylphenidate 30mg modified-release capsules	Methylphenidate hydrochloride
21399	Equasym xl 20mg Capsule (Celltech Pharma Europe Ltd)	Methylphenidate hydrochloride
23161	Tranquilyn 5mg tablets (Genesis Pharmaceuticals Ltd)	Methylphenidate hydrochloride
23173	Tranquilyn 10mg tablets (Genesis Pharmaceuticals Ltd)	Methylphenidate hydrochloride
35159	Concerta XL 27mg tablets (Janssen-Cilag Ltd)	Methylphenidate hydrochloride
35469	Methylphenidate 27mg modified-release tablets	Methylphenidate

		hydrochloride
35515	Methylphenidate 40mg modified-release capsules	Methylphenidate hydrochloride
35658	Medikinet XL 30mg capsules (Flynn Pharma Ltd)	Methylphenidate hydrochloride
35659	Medikinet XL 20mg capsules (Flynn Pharma Ltd)	Methylphenidate hydrochloride
36628	Medikinet XL 10mg capsules (Flynn Pharma Ltd)	Methylphenidate hydrochloride
36910	Medikinet 20mg tablets (Flynn Pharma Ltd)	Methylphenidate hydrochloride
37097	Medikinet 5mg tablets (Flynn Pharma Ltd)	Methylphenidate hydrochloride
37237	Medikinet 10mg tablets (Flynn Pharma Ltd)	Methylphenidate hydrochloride
37658	Medikinet XL 40mg capsules (Flynn Pharma Ltd)	Methylphenidate hydrochloride
46593	Medikinet XL 5mg capsules (Flynn Pharma Ltd)	Methylphenidate hydrochloride
46607	Methylphenidate 5mg modified-release capsules	Methylphenidate Hydrochloride
52233	Methylphenidate 54mg modified-release tablets	Methylphenidate hydrochloride
52461	Equasym XL 10mg capsules (Waymade Healthcare Plc)	Methylphenidate hydrochloride
53527	Equasym XL 30mg capsules (Waymade Healthcare Plc)	Methylphenidate hydrochloride
54504	Methylphenidate 20mg modified-release tablets	Methylphenidate hydrochloride
54804	Equasym XL 10mg capsules (DE Pharmaceuticals)	Methylphenidate hydrochloride
56713	Ritalin-SR 20mg tablets (Imported (United States))	Methylphenidate hydrochloride
57405	Methylphenidate 5mg/5ml oral solution	Methylphenidate hydrochloride
58678	Concerta 54mg modified-release tablets (Imported (Belgium))	Methylphenidate hydrochloride
58691	Methylphenidate 10mg/5ml oral solution	Methylphenidate hydrochloride
60988	Medikinet XL 50mg capsules (Flynn Pharma Ltd)	Methylphenidate hydrochloride
61390	Methylphenidate 50mg modified-release capsules	Methylphenidate hydrochloride
61800	Matoride XL 36mg tablets (Sandoz Ltd)	Methylphenidate hydrochloride

Definition of exposure drugs in German Disease Analyzer

Drug code	Exposure drugs (all dexamfetamine sulfate)	Drug substance
11,077,981	Attentin bet.m	Dexamfetamine sulfate
11,001,886	Attentin bet.m	Dexamfetamine sulfate

Definition of comparison drugs in German Disease Analyzer

Drug code	Product name	Drug substance
14,337,839	Ritalin bet.m	Methylphenidate
14,334,550	Ritalin bet.m	Methylphenidate
14,326,351	Ritalin bet.m	Methylphenidate
14,285,632	Ritalin bet.m	Methylphenidate
14,284,717	Ritalin bet.m	Methylphenidate
14,283,925	Ritalin bet.m	Methylphenidate
14,281,961	Ritalin bet.m	Methylphenidate
14,262,974	Medikine.mde bet.m	Methylphenidate
14,255,442	Medikine.mde bet.m	Methylphenidate
14,231,777	Medikine.mde bet.m	Methylphenidate
14,187,276	Ritalin bet.m	Methylphenidate
13,754,269	Medikine.me0 bet.m	Methylphenidate
13,743,235	Methylph.neu.bet.m	Methylphenidate
13,718,981	Medikine.me0 bet.m	Methylphenidate
13,711,846	Methylph.neu.bet.m	Methylphenidate
13,697,932	Medikine.me0 bet.m	Methylphenidate
13,696,923	Medikine.me0 bet.m	Methylphenidate
13,696,681	Medikine.me0 bet.m	Methylphenidate
13,674,417	Methylph.neu.bet.m	Methylphenidate
13,650,064	Medikine.me0 bet.m	Methylphenidate
13,649,466	Medikine.me0 bet.m	Methylphenidate
13,433,319	Ritalin bet.m	Methylphenidate
13,333,735	Ritalin bet.m	Methylphenidate
13,317,536	Ritalin bet.m	Methylphenidate
13,270,314	Ritalin bet.m	Methylphenidate
13,270,313	Ritalin bet.m	Methylphenidate
13,264,542	Ritalin bet.m	Methylphenidate
13,227,070	Ritalin bet.m	Methylphenidate
13,193,321	Ritalin bet.m	Methylphenidate
12,894,525	Medikine.mde bet.m	Methylphenidate
12,720,819	Medikine.mde bet.m	Methylphenidate
12,695,320	Medikine.mde bet.m	Methylphenidate
12,581,574	Medikine.mde bet.m	Methylphenidate
12,579,453	Medikine.mde bet.m	Methylphenidate
11,669,846	Ritalin bet.m	Methylphenidate
11,655,834	Ritalin bet.m	Methylphenidate
10,568,457	Medikine.me0 bet.m	Methylphenidate

10,551,443	Medikine.me0 bet.m	Methylphenidate
10,543,839	Medikine.me0 bet.m	Methylphenidate
10,542,983	Medikine.me0 bet.m	Methylphenidate
9,972,472	Medikid bet.m	Methylphenidate
9,728,631	Medikid bet.m	Methylphenidate
9,687,173	Medikid bet.m	Methylphenidate
9,659,540	Medikid bet.m	Methylphenidate
9,218,948	Medikid bet.m	Methylphenidate
9,012,921	Medikid bet.m	Methylphenidate
8,967,403	Equasym bet.m(ucb)	Methylphenidate
8,931,394	Medikid bet.m	Methylphenidate
8,855,833	Equasym bet.m(ucb)	Methylphenidate
8,813,647	Equasym bet.m(ucb)	Methylphenidate
8,793,855	Equasym bet.m(ucb)	Methylphenidate
8,788,536	Equasym bet.m(ucb)	Methylphenidate
8,788,192	Equasym bet.m(ucb)	Methylphenidate
8,763,521	Equasym bet.m(ucb)	Methylphenidate
8,757,260	Equasym bet.m(ucb)	Methylphenidate
8,746,696	Equasym bet.m(ucb)	Methylphenidate
8,739,862	Equasym bet.m(ucb)	Methylphenidate
8,735,270	Equasym bet.m(ucb)	Methylphenidate
8,732,941	Equasym bet.m(ucb)	Methylphenidate
8,144,078	Equasym bet.m alt	Methylphenidate
8,049,005	Equasym bet.m alt	Methylphenidate
8,048,798	Equasym bet.m alt	Methylphenidate
8,040,276	Equasym bet.m(ucb)	Methylphenidate
7,975,931	Concerta bet.m	Methylphenidate
7,810,772	Medikine.mde bet.m	Methylphenidate
7,487,454	Equasym bet.m alt	Methylphenidate
7,070,966	Medikine.mde bet.m	Methylphenidate
6,886,968	Equasym bet.m alt	Methylphenidate
6,884,745	Equasym bet.m alt	Methylphenidate
6,882,402	Equasym bet.m alt	Methylphenidate
6,690,217	Ritalin bet.m	Methylphenidate
6,690,181	Ritalin bet.m	Methylphenidate
6,673,403	Ritalin bet.m	Methylphenidate
6,664,117	Ritalin bet.m	Methylphenidate
6,595,305	Ritalin bet.m	Methylphenidate
5,644,863	Equasym bet.m alt	Methylphenidate
5,497,807	Equasym bet.m(ucb)	Methylphenidate
5,131,477	Ritalin bet.m	Methylphenidate
5,130,885	Ritalin bet.m	Methylphenidate
5,129,817	Medikine.me0 bet.m	Methylphenidate
4,883,255	Equasym bet.m alt	Methylphenidate
4,860,933	Equasym bet.m alt	Methylphenidate
4,855,516	Equasym bet.m alt	Methylphenidate

4,726,772	Methylphenidat soh	Methylphenidate
4,567,429	Methylph.1ap bet.m	Methylphenidate
4,505,215	Methylph.1ap bet.m	Methylphenidate
4,490,538	Medikine.mde bet.m	Methylphenidate
4,431,823	Methylph.1ap bet.m	Methylphenidate
4,431,814	Methylphenidat soh	Methylphenidate
4,415,051	Medikine.mde bet.m	Methylphenidate
3,980,635	Methylphenidat soh	Methylphenidate
3,952,321	Methylphenidat soh	Methylphenidate
3,685,446	Methylph.rat.bet.m	Methylphenidate
3,639,900	Methylph.tad bet.m	Methylphenidate
3,594,999	Methylph.tad bet.m	Methylphenidate
3,574,639	Methylph.tad bet.m	Methylphenidate
3,565,956	Methylph.tad bet.m	Methylphenidate
3,558,875	Methylph.tad bet.m	Methylphenidate
3,483,137	Methylphenidat soh	Methylphenidate
2,969,692	Methylph.rat.bet.m	Methylphenidate
2,944,753	Methylphenidat soh	Methylphenidate
2,371,323	Methylphenidat soh	Methylphenidate
2,317,006	Methylph.hex.bet.m	Methylphenidate
1,848,937	Methylphenidat soh	Methylphenidate
1,718,228	Equasym bet.m alt	Methylphenidate
1,698,221	Methylph.hex.bet.m	Methylphenidate
1,474,659	Methylph.hex.bet.m	Methylphenidate
1,403,145	Medikine.mde bet.m	Methylphenidate
1,207,486	Methylphenidat soh	Methylphenidate
720,549	Medikine.mde bet.m	Methylphenidate
266,970	Concerta bet.m	Methylphenidate
221,798	Medikine.mde bet.m	Methylphenidate
211,008	Equasym bet.m alt	Methylphenidate
204,761	Medikine.mde bet.m	Methylphenidate
186,584	Medikine.mde bet.m	Methylphenidate
91,883	Medikine.mde bet.m	Methylphenidate
89,115	Ritalin bet.m	Methylphenidate
87,752	Equasym bet.m alt	Methylphenidate
64,600	Medikine.mde bet.m	Methylphenidate
62,168	Equasym bet.m alt	Methylphenidate
56,116	Equasym bet.m alt	Methylphenidate
55,202	Equasym bet.m alt	Methylphenidate
32,991	Medikine.mde bet.m	Methylphenidate
26,996	Ritalin bet.m	Methylphenidate
25,944	Ritalin bet.m	Methylphenidate
24,082	Concerta bet.m	Methylphenidate
23,839	Medikine.mde bet.m	Methylphenidate
3,933	Concerta bet.m	Methylphenidate
13,165,865	Elvanse	Lisdexamfetamine

13,147,841	Elvanse	Lisdexamfetamine
13,146,265	Elvanse	Lisdexamfetamine

Definition of exposure drugs in PharMetrics Plus

NDC Code	Exposure drugs (all dexamfetamine sulfate)	Drug substance
52054051309	Dexedrine Cap Sr 24hr 10 Mg	Dextroamphetamine Sulfate
54868381100	Dexedrine Cap Sr 24hr 10 Mg	Dextroamphetamine Sulfate
00007351359	Dexedrine Cap Sr 24hr 10 Mg	Dextroamphetamine Sulfate
52054051409	Dexedrine Cap Sr 24hr 15 Mg	Dextroamphetamine Sulfate
54868475800	Dexedrine Cap Sr 24hr 15 Mg	Dextroamphetamine Sulfate
54868475801	Dexedrine Cap Sr 24hr 15 Mg	Dextroamphetamine Sulfate
00007351459	Dexedrine Cap Sr 24hr 15 Mg	Dextroamphetamine Sulfate
52054051209	Dexedrine Cap Sr 24hr 5 Mg	Dextroamphetamine Sulfate
54868340201	Dexedrine Cap Sr 24hr 5 Mg	Dextroamphetamine Sulfate
54868340200	Dexedrine Cap Sr 24hr 5 Mg	Dextroamphetamine Sulfate
00007351259	Dexedrine Cap Sr 24hr 5 Mg	Dextroamphetamine Sulfate
00007351220	Dexedrine Cap Sr 24hr 5 Mg	Dextroamphetamine Sulfate
52054021610	Dexedrine Tab 10 Mg	Dextroamphetamine Sulfate
52054021510	Dexedrine Tab 5 Mg	Dextroamphetamine Sulfate
54868340303	Dexedrine Tab 5 Mg	Dextroamphetamine Sulfate
54868340302	Dexedrine Tab 5 Mg	Dextroamphetamine Sulfate
54868340301	Dexedrine Tab 5 Mg	Dextroamphetamine Sulfate
54868340300	Dexedrine Tab 5 Mg	Dextroamphetamine Sulfate
00007351920	Dexedrine Tab 5 Mg	Dextroamphetamine Sulfate
54868547900	Dextroamphetamine Sulfate Cap Sr 24hr 10 Mg	Dextroamphetamine Sulfate
54868547901	Dextroamphetamine Sulfate Cap Sr 24hr 10 Mg	Dextroamphetamine Sulfate
00555095502	Dextroamphetamine Sulfate Cap Sr 24hr 10 Mg	Dextroamphetamine Sulfate
64720032809	Dextroamphetamine Sulfate Cap Sr 24hr 10 Mg	Dextroamphetamine Sulfate
57866393202	Dextroamphetamine Sulfate Cap Sr 24hr 10 Mg	Dextroamphetamine Sulfate
45963030409	Dextroamphetamine Sulfate Cap Sr 24hr 10 Mg	Dextroamphetamine Sulfate

54505032809	Dextroamphetamine Sulfate Cap Sr 24hr 10 Mg	Dextroamphetamine Sulfate
00406896101	Dextroamphetamine Sulfate Cap Sr 24hr 10 Mg	Dextroamphetamine Sulfate
54868538801	Dextroamphetamine Sulfate Cap Sr 24hr 15 Mg	Dextroamphetamine Sulfate
54868538800	Dextroamphetamine Sulfate Cap Sr 24hr 15 Mg	Dextroamphetamine Sulfate
00555095602	Dextroamphetamine Sulfate Cap Sr 24hr 15 Mg	Dextroamphetamine Sulfate
64720032909	Dextroamphetamine Sulfate Cap Sr 24hr 15 Mg	Dextroamphetamine Sulfate
45963030509	Dextroamphetamine Sulfate Cap Sr 24hr 15 Mg	Dextroamphetamine Sulfate
00406896201	Dextroamphetamine Sulfate Cap Sr 24hr 15 Mg	Dextroamphetamine Sulfate
54505032909	Dextroamphetamine Sulfate Cap Sr 24hr 15 Mg	Dextroamphetamine Sulfate
00555095402	Dextroamphetamine Sulfate Cap Sr 24hr 5 Mg	Dextroamphetamine Sulfate
57866393301	Dextroamphetamine Sulfate Cap Sr 24hr 5 Mg	Dextroamphetamine Sulfate
57866393302	Dextroamphetamine Sulfate Cap Sr 24hr 5 Mg	Dextroamphetamine Sulfate
64720032709	Dextroamphetamine Sulfate Cap Sr 24hr 5 Mg	Dextroamphetamine Sulfate
45963030309	Dextroamphetamine Sulfate Cap Sr 24hr 5 Mg	Dextroamphetamine Sulfate
54505032709	Dextroamphetamine Sulfate Cap Sr 24hr 5 Mg	Dextroamphetamine Sulfate
00406896001	Dextroamphetamine Sulfate Cap Sr 24hr 5 Mg	Dextroamphetamine Sulfate
76181000225	Dextroamphetamine Sulfate Oral Solution 5 Mg/5ml	Dextroamphetamine Sulfate
27808008501	Dextroamphetamine Sulfate Oral Solution 5 Mg/5ml	Dextroamphetamine Sulfate
52536051001	Dextroamphetamine Sulfate Tab 10 Mg	Dextroamphetamine Sulfate
00555095302	Dextroamphetamine Sulfate Tab 10 Mg	Dextroamphetamine Sulfate
64720021610	Dextroamphetamine Sulfate Tab 10 Mg	Dextroamphetamine Sulfate
13107003601	Dextroamphetamine Sulfate Tab 10 Mg	Dextroamphetamine Sulfate
00406895901	Dextroamphetamine Sulfate Tab 10 Mg	Dextroamphetamine Sulfate
58177031204	Dextroamphetamine Sulfate Tab 10 Mg	Dextroamphetamine Sulfate
35356038730	Dextroamphetamine Sulfate Tab 5 Mg	Dextroamphetamine Sulfate
00555095202	Dextroamphetamine Sulfate Tab 5 Mg	Dextroamphetamine Sulfate
52536050001	Dextroamphetamine Sulfate Tab 5 Mg	Dextroamphetamine Sulfate
64720021510	Dextroamphetamine Sulfate Tab 5 Mg	Dextroamphetamine Sulfate

13107003501	Dextroamphetamine Sulfate Tab 5 Mg	Dextroamphetamine Sulfate
00406895801	Dextroamphetamine Sulfate Tab 5 Mg	Dextroamphetamine Sulfate
58177031104	Dextroamphetamine Sulfate Tab 5 Mg	Dextroamphetamine Sulfate
54092045201	Dextrostat Tab 10 Mg	Dextroamphetamine Sulfate
54868454901	Dextrostat Tab 5 Mg	Dextroamphetamine Sulfate
54092044801	Dextrostat Tab 5 Mg	Dextroamphetamine Sulfate
54868454900	Dextrostat Tab 5 Mg	Dextroamphetamine Sulfate
14629011716	Liquadd Oral Solution 5 Mg/5ml	Dextroamphetamine Sulfate
23589003616	Procentra Oral Solution 5 Mg/5ml	Dextroamphetamine Sulfate
13551070105	Procentra Oral Solution 5 Mg/5ml	Dextroamphetamine Sulfate
21724070105	Procentra Oral Solution 5 Mg/5ml	Dextroamphetamine Sulfate
24338085310	Zenzedi Tab 10 Mg	Dextroamphetamine Sulfate
24338085410	Zenzedi Tab 15 Mg	Dextroamphetamine Sulfate
24338085010	Zenzedi Tab 2.5 Mg	Dextroamphetamine Sulfate
24338085510	Zenzedi Tab 20 Mg	Dextroamphetamine Sulfate
24338085610	Zenzedi Tab 30 Mg	Dextroamphetamine Sulfate
24338085110	Zenzedi Tab 5 Mg	Dextroamphetamine Sulfate
24338085210	Zenzedi Tab 7.5 Mg	Dextroamphetamine Sulfate

Definition of comparison drugs in PharMetrics

NDC Code	Comparison Drugs	Drug Substance
65580053101	Methylphenidate Hcl Tab 5 Mg	Methylphenidate Hcl
65580053201	Methylphenidate Hcl Tab 20 Mg	Methylphenidate Hcl
00591588201	Methylphenidate Hcl Tab 5 Mg	Methylphenidate Hcl
00591588401	Methylphenidate Hcl Tab 20 Mg	Methylphenidate Hcl
00591588301	Methylphenidate Hcl Tab 10 Mg	Methylphenidate Hcl
54868073303	Methylphenidate Hcl Tab 10 Mg	Methylphenidate Hcl
49999084330	Methylphenidate Hcl Tab 10 Mg	Methylphenidate Hcl
54868073306	Methylphenidate Hcl Tab 10 Mg	Methylphenidate Hcl
54868073305	Methylphenidate Hcl Tab 10 Mg	Methylphenidate Hcl
54868170404	Methylphenidate Hcl Tab 5 Mg	Methylphenidate Hcl
54868170400	Methylphenidate Hcl Tab 5 Mg	Methylphenidate Hcl
54868170406	Methylphenidate Hcl Tab 5 Mg	Methylphenidate Hcl
54868170403	Methylphenidate Hcl Tab 5 Mg	Methylphenidate Hcl

54868170402	Methylphenidate Hcl Tab 5 Mg	Methylphenidate Hcl
54868170401	Methylphenidate Hcl Tab 5 Mg	Methylphenidate Hcl
54868170405	Methylphenidate Hcl Tab 5 Mg	Methylphenidate Hcl
54868073302	Methylphenidate Hcl Tab 10 Mg	Methylphenidate Hcl
54868073304	Methylphenidate Hcl Tab 10 Mg	Methylphenidate Hcl
54868073301	Methylphenidate Hcl Tab 10 Mg	Methylphenidate Hcl
49999084230	Methylphenidate Hcl Tab 5 Mg	Methylphenidate Hcl
00603457832	Methylphenidate Hcl Tab 20 Mg	Methylphenidate Hcl
00603457821	Methylphenidate Hcl Tab 20 Mg	Methylphenidate Hcl
49999084430	Methylphenidate Hcl Tab 20 Mg	Methylphenidate Hcl
54868073300	Methylphenidate Hcl Tab 10 Mg	Methylphenidate Hcl
43386057101	Methylphenidate Hcl Chew Tab 5 Mg	Methylphenidate Hcl
43386057201	Methylphenidate Hcl Chew Tab 10 Mg	Methylphenidate Hcl
43386057001	Methylphenidate Hcl Chew Tab 2.5 Mg	Methylphenidate Hcl
00406114201	Methylphenidate Hcl Tab 5 Mg	Methylphenidate Hcl
00406114401	Methylphenidate Hcl Tab 10 Mg	Methylphenidate Hcl
64720023810	Methylphenidate Hcl Tab 10 Mg	Methylphenidate Hcl
00406114601	Methylphenidate Hcl Tab 20 Mg	Methylphenidate Hcl
64720023910	Methylphenidate Hcl Tab 20 Mg	Methylphenidate Hcl
64720023710	Methylphenidate Hcl Tab 5 Mg	Methylphenidate Hcl
57664022988	Methylphenidate Hcl Tab 10 Mg	Methylphenidate Hcl
57664022888	Methylphenidate Hcl Tab 5 Mg	Methylphenidate Hcl
63629327901	Methylphenidate Hcl Tab 10 Mg	Methylphenidate Hcl
63629327903	Methylphenidate Hcl Tab 10 Mg	Methylphenidate Hcl
63629327902	Methylphenidate Hcl Tab 10 Mg	Methylphenidate Hcl
57664023088	Methylphenidate Hcl Tab 20 Mg	Methylphenidate Hcl
63629316601	Methylphenidate Hcl Tab 20 Mg	Methylphenidate Hcl
63629316604	Methylphenidate Hcl Tab 20 Mg	Methylphenidate Hcl
63629316603	Methylphenidate Hcl Tab 20 Mg	Methylphenidate Hcl
63629316602	Methylphenidate Hcl Tab 20 Mg	Methylphenidate Hcl
68084082311	Methylphenidate Hcl Tab 10 Mg	Methylphenidate Hcl
68084082321	Methylphenidate Hcl Tab 10 Mg	Methylphenidate Hcl
68084086011	Methylphenidate Hcl Tab 20 Mg	Methylphenidate Hcl
68084086021	Methylphenidate Hcl Tab 20 Mg	Methylphenidate Hcl
68084080521	Methylphenidate Hcl Tab 5 Mg	Methylphenidate Hcl
68084080511	Methylphenidate Hcl Tab 5 Mg	Methylphenidate Hcl
00781574801	Methylphenidate Hcl Tab 5 Mg	Methylphenidate Hcl
00781884010	Methylphenidate Hcl Tab 5 Mg	Methylphenidate Hcl
00781574901	Methylphenidate Hcl Tab 10 Mg	Methylphenidate Hcl
62175015337	Methylphenidate Hcl Cd Cap Cr 30 Mg	Methylphenidate Hcl
62175015637	Methylphenidate Hcl Cd Cap Cr 60 Mg	Methylphenidate Hcl
62175015537	Methylphenidate Hcl Cd Cap Cr 50 Mg	Methylphenidate Hcl
62175015437	Methylphenidate Hcl Cd Cap Cr 40 Mg	Methylphenidate Hcl
62175015137	Methylphenidate Hcl Cd Cap Cr 10 Mg	Methylphenidate Hcl
62175015237	Methylphenidate Hcl Cd Cap Cr 20 Mg	Methylphenidate Hcl
00093529701	Methylphenidate Hcl Cd Cap Cr 30 Mg	Methylphenidate Hcl
00093529301	Methylphenidate Hcl Cd Cap Cr 60 Mg	Methylphenidate Hcl

00093529801	Methylphenidate Hcl Cd Cap Cr 40 Mg	Methylphenidate Hcl
00093529201	Methylphenidate Hcl Cd Cap Cr 50 Mg	Methylphenidate Hcl
00093529501	Methylphenidate Hcl Cd Cap Cr 10 Mg	Methylphenidate Hcl
00093529601	Methylphenidate Hcl Cd Cap Cr 20 Mg	Methylphenidate Hcl
54868345403	Methylphenidate Hcl Er Tab Cr 20 Mg	Methylphenidate Hcl
54868345406	Methylphenidate Hcl Er Tab Cr 20 Mg	Methylphenidate Hcl
54868345400	Methylphenidate Hcl Er Tab Cr 20 Mg	Methylphenidate Hcl
50458058801	Concerta Tab Sa Osm 27 Mg	Methylphenidate Hcl
50458058601	Concerta Tab Sa Osm 36 Mg	Methylphenidate Hcl
50458058501	Concerta Tab Sa Osm 18 Mg	Methylphenidate Hcl
50458058701	Concerta Tab Sa Osm 54 Mg	Methylphenidate Hcl
54868495701	Concerta Tab Sa Osm 27 Mg	Methylphenidate Hcl
54868495700	Concerta Tab Sa Osm 27 Mg	Methylphenidate Hcl
55289097590	Concerta Tab Sa Osm 27 Mg	Methylphenidate Hcl
55289085490	Concerta Tab Sa Osm 54 Mg	Methylphenidate Hcl
55289085430	Concerta Tab Sa Osm 54 Mg	Methylphenidate Hcl
55289085930	Concerta Tab Sa Osm 36 Mg	Methylphenidate Hcl
55289085990	Concerta Tab Sa Osm 36 Mg	Methylphenidate Hcl
55289083530	Concerta Tab Sa Osm 18 Mg	Methylphenidate Hcl
55289083590	Concerta Tab Sa Osm 18 Mg	Methylphenidate Hcl
54868448900	Concerta Tab Sa Osm 18 Mg	Methylphenidate Hcl
54868448901	Concerta Tab Sa Osm 18 Mg	Methylphenidate Hcl
35356015230	Concerta Tab Sa Osm 27 Mg	Methylphenidate Hcl
35356015290	Concerta Tab Sa Osm 27 Mg	Methylphenidate Hcl
35356015190	Concerta Tab Sa Osm 18 Mg	Methylphenidate Hcl
35356015130	Concerta Tab Sa Osm 18 Mg	Methylphenidate Hcl
35356015430	Concerta Tab Sa Osm 54 Mg	Methylphenidate Hcl
35356015490	Concerta Tab Sa Osm 54 Mg	Methylphenidate Hcl
35356015390	Concerta Tab Sa Osm 36 Mg	Methylphenidate Hcl
35356015330	Concerta Tab Sa Osm 36 Mg	Methylphenidate Hcl
54868478900	Concerta Tab Sa Osm 54 Mg	Methylphenidate Hcl
54868478901	Concerta Tab Sa Osm 54 Mg	Methylphenidate Hcl
54868475902	Concerta Tab Sa Osm 36 Mg	Methylphenidate Hcl
54868475901	Concerta Tab Sa Osm 36 Mg	Methylphenidate Hcl
54868475900	Concerta Tab Sa Osm 36 Mg	Methylphenidate Hcl
54868475903	Concerta Tab Sa Osm 36 Mg	Methylphenidate Hcl
54868448903	Concerta Tab Sa Osm 18 Mg	Methylphenidate Hcl
54868448902	Concerta Tab Sa Osm 18 Mg	Methylphenidate Hcl
00078038105	Focalin Tab 5 Mg	Dexmethylphenidate Hcl
00078038005	Focalin Tab 2.5 Mg	Dexmethylphenidate Hcl
00078038205	Focalin Tab 10 Mg	Dexmethylphenidate Hcl
00078049305	Focalin Xr Cap Sr 24 Hr 15 Mg	Dexmethylphenidate Hcl
00078043105	Focalin Xr Cap Sr 24 Hr 10 Mg	Dexmethylphenidate Hcl
00078060905	Focalin Xr Cap Sr 24 Hr 35 Mg	Dexmethylphenidate Hcl
00078043005	Focalin Xr Cap Sr 24 Hr 5 Mg	Dexmethylphenidate Hcl
00078043405	Focalin Xr Cap Sr 24 Hr 40 Mg	Dexmethylphenidate Hcl
54868568401	Focalin Xr Cap Sr 24 Hr 20 Mg	Dexmethylphenidate Hcl

54868568400	Focalin Xr Cap Sr 24 Hr 20 Mg	Dexmethylphenidate Hcl
00078043205	Focalin Xr Cap Sr 24 Hr 20 Mg	Dexmethylphenidate Hcl
00078060805	Focalin Xr Cap Sr 24 Hr 25 Mg	Dexmethylphenidate Hcl
00078043305	Focalin Xr Cap Sr 24 Hr 30 Mg	Dexmethylphenidate Hcl
54868568301	Focalin Xr Cap Sr 24 Hr 15 Mg	Dexmethylphenidate Hcl
54868568300	Focalin Xr Cap Sr 24 Hr 15 Mg	Dexmethylphenidate Hcl
54868568200	Focalin Xr Cap Sr 24 Hr 10 Mg	Dexmethylphenidate Hcl
54868568201	Focalin Xr Cap Sr 24 Hr 10 Mg	Dexmethylphenidate Hcl
54868568100	Focalin Xr Cap Sr 24 Hr 5 Mg	Dexmethylphenidate Hcl
35356016090	Focalin Xr Cap Sr 24 Hr 20 Mg	Dexmethylphenidate Hcl
35356016030	Focalin Xr Cap Sr 24 Hr 20 Mg	Dexmethylphenidate Hcl
35356015830	Focalin Xr Cap Sr 24 Hr 5 Mg	Dexmethylphenidate Hcl
35356015890	Focalin Xr Cap Sr 24 Hr 5 Mg	Dexmethylphenidate Hcl
35356015930	Focalin Xr Cap Sr 24 Hr 10 Mg	Dexmethylphenidate Hcl
35356015990	Focalin Xr Cap Sr 24 Hr 10 Mg	Dexmethylphenidate Hcl
54868568101	Focalin Xr Cap Sr 24 Hr 5 Mg	Dexmethylphenidate Hcl
00078043905	Ritalin Tab 5 Mg	Methylphenidate Hcl
00078044005	Ritalin Tab 10 Mg	Methylphenidate Hcl
54868170606	Ritalin Tab 5 Mg	Methylphenidate Hcl
54868276200	Ritalin Tab 20 Mg	Methylphenidate Hcl
00078044105	Ritalin Tab 20 Mg	Methylphenidate Hcl
00078037005	Ritalin La Cap Sr 24hr 20 Mg	Methylphenidate Hcl
00078037105	Ritalin La Cap Sr 24hr 30 Mg	Methylphenidate Hcl
54868536701	Ritalin La Cap Sr 24hr 10 Mg	Methylphenidate Hcl
54868536700	Ritalin La Cap Sr 24hr 10 Mg	Methylphenidate Hcl
35356016530	Ritalin La Cap Sr 24hr 20 Mg	Methylphenidate Hcl
35356016590	Ritalin La Cap Sr 24hr 20 Mg	Methylphenidate Hcl
00078042405	Ritalin La Cap Sr 24hr 10 Mg	Methylphenidate Hcl
00078037205	Ritalin La Cap Sr 24hr 40 Mg	Methylphenidate Hcl
54868241806	Ritalin Sr Tab Cr 20 Mg	Methylphenidate Hcl
54868471801	Metadate Cd Cap Cr 20 Mg	Methylphenidate Hcl
54868471800	Metadate Cd Cap Cr 20 Mg	Methylphenidate Hcl
54868066801	Metadate Cd Cap Cr 30 Mg	Methylphenidate Hcl
54868066800	Metadate Cd Cap Cr 30 Mg	Methylphenidate Hcl
53014057907	Metadate Cd Cap Cr 10 Mg	Methylphenidate Hcl
53014058307	Metadate Cd Cap Cr 50 Mg	Methylphenidate Hcl
53014058207	Metadate Cd Cap Cr 40 Mg	Methylphenidate Hcl
53014058407	Metadate Cd Cap Cr 60 Mg	Methylphenidate Hcl
53014058107	Metadate Cd Cap Cr 30 Mg	Methylphenidate Hcl
53014058007	Metadate Cd Cap Cr 20 Mg	Methylphenidate Hcl
54868623401	Metadate Cd Cap Cr 50 Mg	Methylphenidate Hcl
54868539700	Metadate Cd Cap Cr 10 Mg	Methylphenidate Hcl
54868539701	Metadate Cd Cap Cr 10 Mg	Methylphenidate Hcl
54868623400	Metadate Cd Cap Cr 50 Mg	Methylphenidate Hcl
65580059401	Metadate Er Tab Cr 20 Mg	Methylphenidate Hcl
59630075550	Methylin Soln 10 Mg/5ml	Methylphenidate Hcl
59630075050	Methylin Soln 5 Mg/5ml	Methylphenidate Hcl

59630076110	Methylin Chew Tab 5 Mg	Methylphenidate Hcl
59630076010	Methylin Chew Tab 2.5 Mg	Methylphenidate Hcl
59630076210	Methylin Chew Tab 10 Mg	Methylphenidate Hcl
24478021030	Quillivant Xr For Er Susp 25 Mg/5ml (5 Mg/Ml)	Methylphenidate Hcl
24478020525	Quillivant Xr For Er Susp 25 Mg/5ml (5 Mg/Ml)	Methylphenidate Hcl
24478019010	Quillivant Xr For Er Susp 25 Mg/5ml (5 Mg/Ml)	Methylphenidate Hcl
24478020020	Quillivant Xr For Er Susp 25 Mg/5ml (5 Mg/Ml)	Methylphenidate Hcl
54868297401	Methylphenidate Hcl Tab 20 Mg	Methylphenidate Hcl
54868297402	Methylphenidate Hcl Tab 20 Mg	Methylphenidate Hcl
54868297400	Methylphenidate Hcl Tab 20 Mg	Methylphenidate Hcl
54868297404	Methylphenidate Hcl Tab 20 Mg	Methylphenidate Hcl
54868297403	Methylphenidate Hcl Tab 20 Mg	Methylphenidate Hcl
55289082990	Methylphenidate Hcl Tab 10 Mg	Methylphenidate Hcl
55289082960	Methylphenidate Hcl Tab 10 Mg	Methylphenidate Hcl
55289082930	Methylphenidate Hcl Tab 10 Mg	Methylphenidate Hcl
55289081990	Methylphenidate Hcl Tab 5 Mg	Methylphenidate Hcl
55289081960	Methylphenidate Hcl Tab 5 Mg	Methylphenidate Hcl
55289081930	Methylphenidate Hcl Tab 5 Mg	Methylphenidate Hcl
00781575301	Methylphenidate Hcl Tab 20 Mg	Methylphenidate Hcl
65580053001	Methylphenidate Hcl Tab 10 Mg	Methylphenidate Hcl
00093527601	Dexmethylphenidate Hcl Cl Tab 5 Mg	Dexmethylphenidate Hcl
00093527701	Dexmethylphenidate Hcl Cl Tab 10 Mg	Dexmethylphenidate Hcl
00093527501	Dexmethylphenidate Hcl Cl Tab 2.5 Mg	Dexmethylphenidate Hcl
00093555001	Dexmethylphenidate Hcl Cl Cap Sr 24 Hr 5 Mg	Dexmethylphenidate Hcl
00093555101	Dexmethylphenidate Hcl Cl Cap Sr 24 Hr 10 Mg	Dexmethylphenidate Hcl
00781268301	Dexmethylphenidate Hcl Cl Cap Sr 24 Hr 10 Mg	Dexmethylphenidate Hcl
00378408401	Dexmethylphenidate Hcl Er Cl Cap Sr 24 Hr 30 Mg	Dexmethylphenidate Hcl
00781268401	Dexmethylphenidate Hcl Er Cl Cap Sr 24 Hr 15 Mg	Dexmethylphenidate Hcl
00781268901	Dexmethylphenidate Hcl Er Cl Cap Sr 24 Hr 40 Mg	Dexmethylphenidate Hcl
00781268201	Dexmethylphenidate Hcl Er Cl Cap Sr 24 Hr 5 Mg	Dexmethylphenidate Hcl
45963080611	Dexmethylphenidate Hcl Er Cl Cap Sr 24 Hr 15 Mg	Dexmethylphenidate Hcl
45963083311	Dexmethylphenidate Hcl Er Cl Cap Sr 24 Hr 30 Mg	Dexmethylphenidate Hcl
00093556201	Dexmethylphenidate Hcl Er Cl Cap Sr 24 Hr 40 Mg	Dexmethylphenidate Hcl
00093555401	Dexmethylphenidate Hcl Er Cl Cap Sr 24 Hr 30 Mg	Dexmethylphenidate Hcl
00093555201	Dexmethylphenidate Hcl Er Cl Cap Sr 24 Hr 15 Mg	Dexmethylphenidate Hcl
49884043001	Dexmethylphenidate Hcl Er Cl Cap Sr 24 Hr	Dexmethylphenidate Hcl

	30 Mg	
49884042801	Dexmethylphenidate Hcl Er Cl Cap Sr 24 Hr 15 Mg	Dexmethylphenidate Hcl
00781268701	Dexmethylphenidate Hcl Er Cl Cap Sr 24 Hr 30 Mg	Dexmethylphenidate Hcl
54868345404	Methylphenidate Hcl Er Tab Cr 20 Mg	Methylphenidate Hcl
54868345405	Methylphenidate Hcl Er Tab Cr 20 Mg	Methylphenidate Hcl
00591271601	Methylphenidate Hcl Er Tab Sa Osm 27 Mg	Methylphenidate Hcl
00591271801	Methylphenidate Hcl Er Tab Sa Osm 54 Mg	Methylphenidate Hcl
00591271501	Methylphenidate Hcl Er Tab Sa Osm 18 Mg	Methylphenidate Hcl
00591271701	Methylphenidate Hcl Er Tab Sa Osm 36 Mg	Methylphenidate Hcl
62175031037	Methylphenidate Hcl Er Tab Sa Osm 18 Mg	Methylphenidate Hcl
62175031237	Methylphenidate Hcl Er Tab Sa Osm 36 Mg	Methylphenidate Hcl
62175031137	Methylphenidate Hcl Er Tab Sa Osm 27 Mg	Methylphenidate Hcl
54868583201	Methylphenidate Hcl Er Tab Cr 10 Mg	Methylphenidate Hcl
62175031337	Methylphenidate Hcl Er Tab Sa Osm 54 Mg	Methylphenidate Hcl
00406013601	Methylphenidate Hcl Er Tab Sa Osm 36 Mg	Methylphenidate Hcl
00406015401	Methylphenidate Hcl Er Tab Sa Osm 54 Mg	Methylphenidate Hcl
00406012701	Methylphenidate Hcl Er Tab Sa Osm 27 Mg	Methylphenidate Hcl
68084083325	Methylphenidate Hcl Er Tab Sa Osm 54 Mg	Methylphenidate Hcl
00406147301	Methylphenidate Hcl Er Tab Cr 20 Mg	Methylphenidate Hcl
00406144501	Methylphenidate Hcl Er Tab Cr 10 Mg	Methylphenidate Hcl
00591271730	Methylphenidate Hcl Er Tab Sa Osm 36 Mg	Methylphenidate Hcl
67767020201	Methylphenidate Hcl Er Cap Sr 24hr 40 Mg	Methylphenidate Hcl
67767020001	Methylphenidate Hcl Er Cap Sr 24hr 20 Mg	Methylphenidate Hcl
63629306501	Methylphenidate Hcl Er Tab Cr 20 Mg	Methylphenidate Hcl
42291060401	Methylphenidate Hcl Er Tab Sa Osm 54 Mg	Methylphenidate Hcl
42291060301	Methylphenidate Hcl Er Tab Sa Osm 36 Mg	Methylphenidate Hcl
42291060201	Methylphenidate Hcl Er Tab Sa Osm 27 Mg	Methylphenidate Hcl
42291060101	Methylphenidate Hcl Er Tab Sa Osm 18 Mg	Methylphenidate Hcl
68084081611	Methylphenidate Hcl Er Tab Sa Osm 27 Mg	Methylphenidate Hcl
68084081621	Methylphenidate Hcl Er Tab Sa Osm 27 Mg	Methylphenidate Hcl
68084083395	Methylphenidate Hcl Er Tab Sa Osm 54 Mg	Methylphenidate Hcl
68084082995	Methylphenidate Hcl Er Tab Sa Osm 36 Mg	Methylphenidate Hcl
68084082925	Methylphenidate Hcl Er Tab Sa Osm 36 Mg	Methylphenidate Hcl
00591271830	Methylphenidate Hcl Er Tab Sa Osm 54 Mg	Methylphenidate Hcl
67767020101	Methylphenidate Hcl Er Cap Sr 24hr 30 Mg	Methylphenidate Hcl
00781575401	Methylphenidate Hcl Sr Tab Cr 20 Mg	Methylphenidate Hcl
00406300550	Methylphenidate Hydrochlo Soln 5 Mg/5ml	Methylphenidate Hcl
00406301050	Methylphenidate Hydrochlo Soln 10 Mg/5ml	Methylphenidate Hcl
51991071350	Methylphenidate Hydrochlo Soln 10 Mg/5ml	Methylphenidate Hcl
51991071250	Methylphenidate Hydrochlo Soln 5 Mg/5ml	Methylphenidate Hcl
57664036935	Methylphenidate Hydrochlo Soln 5 Mg/5ml	Methylphenidate Hcl
57664036835	Methylphenidate Hydrochlo Soln 10 Mg/5ml	Methylphenidate Hcl
59417010310	Vyvanse Cap 30 Mg	Lisdexamfetamine Dimesylate
59417010210	Vyvanse Cap 20 Mg	Lisdexamfetamine Dimesylate

54868600900	Vyvanse Cap 40 Mg	Lisdexamfetamine Dimesylate
59417010710	Vyvanse Cap 70 Mg	Lisdexamfetamine Dimesylate
59417010610	Vyvanse Cap 60 Mg	Lisdexamfetamine Dimesylate
59417010510	Vyvanse Cap 50 Mg	Lisdexamfetamine Dimesylate
59417010410	Vyvanse Cap 40 Mg	Lisdexamfetamine Dimesylate
59417010110	Vyvanse Cap 10 Mg	Lisdexamfetamine Dimesylate
35356013500	Vyvanse Cap 50 Mg	Lisdexamfetamine Dimesylate
35356013400	Vyvanse Cap 30 Mg	Lisdexamfetamine Dimesylate
35356075130	Vyvanse Cap 20 Mg	Lisdexamfetamine Dimesylate
54868582701	Vyvanse Cap 50 Mg	Lisdexamfetamine Dimesylate
54868600901	Vyvanse Cap 40 Mg	Lisdexamfetamine Dimesylate
54868582700	Vyvanse Cap 50 Mg	Lisdexamfetamine Dimesylate
54868365500	Vyvanse Cap 70 Mg	Lisdexamfetamine Dimesylate
54868365501	Vyvanse Cap 70 Mg	Lisdexamfetamine Dimesylate
54868591600	Vyvanse Cap 30 Mg	Lisdexamfetamine Dimesylate
54868591601	Vyvanse Cap 30 Mg	Lisdexamfetamine Dimesylate

List of Read codes and associated text to capture outcomes of interest from THIN

CARDIOVASULAR EVENTS:

HYPERTENSION

Read code	Read term
6627	Good hypertension control
6628	Poor hypertension control
662b.00	Moderate hypertension control
662c.00	Hypertension six month review
662F.00	Hypertension treatm. Started
662O.00	On treatment for hypertension
662P000	Hypertension 9 month review
7Q01.00	High cost hypertension drugs
7Q01000	Primary pulmonary hypertension drugs Band 1
7Q01100	Primary pulmonary hypertension drugs Band 2
7Q01200	Primary pulmonary hypertension drugs Band 3
7Q01300	Primary pulmonary hypertension drugs Band 4
7Q01y00	Other specified high cost hypertension drugs
8CR4.00	Hypertension clinical management plan
9OIA.11	Hypertension monitored
G20..00	Essential hypertension
G20..11	High blood pressure
G20..12	Primary hypertension
G200.00	Malignant essential hypertension
G201.00	Benign essential hypertension
G202.00	Systolic hypertension
G203.00	Diastolic hypertension
G20z.00	Essential hypertension NOS
G20z.11	Hypertension NOS
G22z.11	Renal hypertension
G24..00	Secondary hypertension
G240.00	Secondary malignant hypertension
G240000	Secondary malignant renovascular hypertension
G240z00	Secondary malignant hypertension NOS
G241.00	Secondary benign hypertension
G241000	Secondary benign renovascular hypertension
G241z00	Secondary benign hypertension NOS
G244.00	Hypertension secondary to endocrine disorders
G24z.00	Secondary hypertension NOS
G24z000	Secondary renovascular hypertension NOS
G24z100	Hypertension secondary to drug
G24zz00	Secondary hypertension NOS
G25..00	Stage 1 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)
G25..11	Stage 1 hypertension
G26..00	Severe hypertension (Nat Inst for Health Clinical Ex 2011)
G26..11	Severe hypertension
G27..00	Hypertension resistant to drug therapy
G28..00	Stage 2 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)

G410.00	Primary pulmonary hypertension
G41y000	Secondary pulmonary hypertension
G41y100	Thromboembolic pulmonary hypertension
G8y3.00	Chronic peripheral venous hypertension
Gyu2000	[X]Other secondary hypertension
Gyu2100	[X]Hypertension secondary to other renal disorders
J623.00	Portal hypertension
L127z00	Pre-eclampsia or eclampsia + pre-existing hypertension NOS
R1y2.00	[D]Raised blood pressure reading

TACHYCARDIA

Read code	**Read term**
2426	O/E - pulse rate tachycardia
2426.11	O/E - tachycardia
3282	ECG: ventricular tachycardia
G55A.11	Tachycardia-induced cardiomyopathy
G570.00	Paroxysmal supraventricular tachycardia
G570000	Paroxysmal atrial tachycardia
G570100	Paroxysmal atrioventricular tachycardia
G570200	Paroxysmal junctional tachycardia
G570300	Paroxysmal nodal tachycardia
G570z00	Paroxysmal supraventricular tachycardia NOS
G571.00	Paroxysmal ventricular tachycardia
G571.11	Ventricular tachycardia
G572.00	Paroxysmal tachycardia unspecified
G572000	Essential paroxysmal tachycardia
G572z00	Paroxysmal tachycardia NOS
G57y700	Sinus tachycardia
G57y900	Supraventricular tachycardia NOS
R050.00	[D]Tachycardia, unspecified
R050.12	[D]Postural orthostatic tachycardia syndrome (POTS)

ARRHYTHMIA

Read code	**Read term**
327..00	ECG: supraventricular arrhythmia
328..00	ECG: ventricular arrhythmia
328Z.00	ECG: ventricular arrhythmia NOS
F256000	Hypsarrhythmia
G57..11	Cardiac arrhythmias
G577.00	Sinus arrhythmia
G57yA00	Re-entry ventricular arrhythmia
Gyu5a00	[X]Other specified cardiac arrhythmias

CARDIOMYOPATHY

Read code	**Read term**
G55..00	Cardiomyopathy
12CJ.00	FH: Cardiomyopathy

G551.00	Hypertrophic obstructive cardiomyopathy
G554400	Primary dilated cardiomyopathy
G554300	Hypertrophic non-obstructive cardiomyopathy
G343.00	Ischaemic cardiomyopathy
12CR.00	FH: Hypertrophic obstructive cardiomyopathy
G55z.00	Cardiomyopathy NOS
G554000	Congestive cardiomyopathy
G55y.11	Secondary dilated cardiomyopathy
G55y.00	Secondary cardiomyopathy NOS
G559.00	Arrhythmogenic right ventricular cardiomyopathy
G554z00	Other primary cardiomyopathy NOS
G55y000	Cardiomyopathy due to drugs and other external agents
G554100	Constrictive cardiomyopathy
G554011	Congestive obstructive cardiomyopathy
Gyu5N00	[X]Other restrictive cardiomyopathy
G55A.11	Tachycardia-induced cardiomyopathy

MYOCARDIAL INFARCTION

Read code	**Read term**
2241	O/E - collapse -cardiac arrest
323..00	ECG: myocardial infarction
9hM..00	Exception reporting: myocardial infarction quality indicator
G30..00	Acute myocardial infarction
G30..13	Cardiac rupture following myocardial infarction (MI)
G30..14	Heart attack
G30..15	MI - acute myocardial infarction
G30..17	Silent myocardial infarction
G301.00	Other specified anterior myocardial infarction
G301z00	Anterior myocardial infarction NOS
G304.00	Posterior myocardial infarction NOS
G305.00	Lateral myocardial infarction NOS
G306.00	True posterior myocardial infarction
G307100	Acute non-ST segment elevation myocardial infarction
G308.00	Inferior myocardial infarction NOS
G30B.00	Acute posterolateral myocardial infarction
G30X.00	Acute transmural myocardial infarction of unspecif site
G30X000	Acute ST segment elevation myocardial infarction
G30y.00	Other acute myocardial infarction
G30yz00	Other acute myocardial infarction NOS
G30z.00	Acute myocardial infarction NOS
G310.00	Postmyocardial infarction syndrome
G311000	Myocardial infarction aborted
G311011	MI - myocardial infarction aborted
G312.00	Coronary thrombosis not resulting in myocardial infarction
G32..11	Healed myocardial infarction
G35..00	Subsequent myocardial infarction
G350.00	Subsequent myocardial infarction of anterior wall
G351.00	Subsequent myocardial infarction of inferior wall
G353.00	Subsequent myocardial infarction of other sites
G35X.00	Subsequent myocardial infarction of unspecified site
G38..00	Postoperative myocardial infarction

G380.00	Postoperative transmural myocardial infarction anterior wall
G381.00	Postoperative transmural myocardial infarction inferior wall
G383.00	Postoperative transmural myocardial infarction unspec site
G384.00	Postoperative subendocardial myocardial infarction
G38z.00	Postoperative myocardial infarction, unspecified
G574011	Cardiac arrest-ventricular fibrillation
G575.00	Cardiac arrest
G575000	Cardiac arrest with successful resuscitation
G575z00	Cardiac arrest, unspecified
Gyu3400	[X]Acute transmural myocardial infarction of unspecif site
Gyu3600	[X]Subsequent myocardial infarction of unspecified site

SUDDEN CARDIAC DEATH

Read code	**Read term**
G575100	Sudden cardiac death, so described

STROKE

Read code	**Read term**
G601.00	Subarachnoid haemorrhage from carotid siphon and bifurcation
G602.00	Subarachnoid haemorrhage from middle cerebral artery
G603.00	Subarachnoid haemorrhage from anterior communicating artery
G604.00	Subarachnoid haemorrhage from posterior communicating artery
G605.00	Subarachnoid haemorrhage from basilar artery
G606.00	Subarachnoid haemorrhage from vertebral artery
G60z.00	Subarachnoid haemorrhage NOS
G61..00	Intracerebral haemorrhage
G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage
G61..12	Stroke due to intracerebral haemorrhage
G610.00	Cortical haemorrhage
G611.00	Internal capsule haemorrhage
G612.00	Basal nucleus haemorrhage
G613.00	Cerebellar haemorrhage
G614.00	Pontine haemorrhage
G615.00	Bulbar haemorrhage
G616.00	External capsule haemorrhage
G617.00	Intracerebral haemorrhage, intraventricular
G618.00	Intracerebral haemorrhage, multiple localized
G619.00	Lobar cerebral haemorrhage
G61X.00	Intracerebral haemorrhage in hemisphere, unspecified
G61X000	Left sided intracerebral haemorrhage, unspecified
G61X100	Right sided intracerebral haemorrhage, unspecified
G61z.00	Intracerebral haemorrhage NOS
G62..00	Other and unspecified intracranial haemorrhage
G620.00	Extradural haemorrhage - nontraumatic
G621.00	Subdural haemorrhage - nontraumatic
G623.00	Subdural haemorrhage NOS
G62z.00	Intracranial haemorrhage NOS
G63..00	Precerebral arterial occlusion
G630.00	Basilar artery occlusion

G631.00	Carotid artery occlusion
G632.00	Vertebral artery occlusion
G633.00	Multiple and bilateral precerebral arterial occlusion
G63y.00	Other precerebral artery occlusion
G63z.00	Precerebral artery occlusion NOS
G64..00	Cerebral arterial occlusion
G64..11	CVA - cerebral artery occlusion
G64..13	Stroke due to cerebral arterial occlusion
G66..12	Stroke unspecified
G663.00	Brain stem stroke syndrome
G664.00	Cerebellar stroke syndrome
G677.00	Occlusion/stenosis cerebral arts not result cerebral infarct
G677000	Occlusion and stenosis of middle cerebral artery
G677100	Occlusion and stenosis of anterior cerebral artery
G677200	Occlusion and stenosis of posterior cerebral artery
G677300	Occlusion and stenosis of cerebellar arteries
G677400	Occlusion+stenosis of multiple and bilat cerebral arteries
G680.00	Sequelae of subarachnoid haemorrhage
G681.00	Sequelae of intracerebral haemorrhage
G682.00	Sequelae of other nontraumatic intracranial haemorrhage
G68X.00	Sequelae of stroke,not specfd as h'morrhage or infarction
G74..13	Arterial embolic and thrombotic occlusion
G76z000	Iliac artery occlusion
G76z100	Femoral artery occlusion
G76z200	Popliteal artery occlusion
G77z000	Capillary haemorrhage
G78..00	Occlusion of artery
G8y0.00	Haemorrhage NOS
Gy51.00	Haemorrhage of dialysis arteriovenous fistula
Gyu6100	[X]Other subarachnoid haemorrhage
Gyu6200	[X]Other intracerebral haemorrhage
Gyu6500	[X]Occlusion and stenosis of other precerebral arteries
Gyu6600	[X]Occlusion and stenosis of other cerebral arteries
Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified

CYANOSIS

Read code	**Read term**
1673	Goes blue
2276	O/E - central cyanosis
2277	O/E - peripheral cyanosis
2276000	Blue lips
2277000	Blue fingers
2277100	Blue toes
G73y200	Acrocyanosis
G73y700	Erythrocyanosis
Q31y400	Perinatal acrocyanosis
R025.00	[D]Cyanosis

QT PROLONGATION

Read code	Read term
32K2.00	ECG: Q-T interval abnormal
32K3.00	ECG: Q-T interval prolonged
G56y500	Long Q-T syndrome

PSYCHOTIC EVENTS:

DEPRESSION

Read code	Read term
2257	O/E - depressed
1B17.00	Depressed
1B17.11	C/O - feeling depressed
1B1U.00	Symptoms of depression
1BT..00	Depressed mood
1BT..11	Low mood
1BT..12	Sad mood
1JJ..00	Suspected depression
388b.00	Depression anxiety stress scales anxiety score
388Z.00	Depression anxiety stress scales depression score
8CAa.00	Patient given advice about management of depression
9HA0.00	On depression register
9k4..00	Depression - enhanced services administration
9kQ..00	On full dose long term treatment depression - enh serv admin
E112.11	Agitated depression
E112.12	Endogenous depression first episode
E112.13	Endogenous depression first episode
E112.14	Endogenous depression
E113.11	Endogenous depression - recurrent
E113700	Recurrent depression
E115.00	Bipolar affective disorder, currently depressed
E115.11	Manic-depressive - now depressed
E115000	Bipolar affective disorder, currently depressed, unspecified
E115100	Bipolar affective disorder, currently depressed, mild
E115200	Bipolar affective disorder, currently depressed, moderate
E115300	Bipolar affect disord, now depressed, severe, no psychosis
E115400	Bipolar affect disord, now depressed, severe with psychosis
E115500	Bipolar affect disord, now depressed, part/unspec remission
E115600	Bipolar affective disorder, now depressed, in full remission
E115z00	Bipolar affective disorder, currently depressed, NOS
E11z200	Masked depression
E130.11	Psychotic reactive depression
E135.00	Agitated depression
E200300	Anxiety with depression
E204.00	Neurotic depression reactive type
E2B0.00	Postviral depression
E2B1.00	Chronic depression
Eu20400	[X]Post-schizophrenic depression

Eu32.12	[X]Single episode of psychogenic depression
Eu32.13	[X]Single episode of reactive depression
Eu32212	[X]Single episode major depression w'out psychotic symptoms
Eu32400	[X]Mild depression
Eu32500	[X]Major depression, mild
Eu32600	[X]Major depression, moderately severe
Eu32700	[X]Major depression, severe without psychotic symptoms
Eu32800	[X]Major depression, severe with psychotic symptoms
Eu32y11	[X]Atypical depression
Eu32z11	[X]Depression NOS
Eu32z13	[X]Prolonged single episode of reactive depression
Eu32z14	[X] Reactive depression NOS
Eu33.12	[X]Recurrent episodes of psychogenic depression
Eu33.13	[X]Recurrent episodes of reactive depression
Eu33211	[X]Endogenous depression without psychotic symptoms
Eu33212	[X]Major depression, recurrent without psychotic symptoms
Eu33312	[X]Manic-depress psychosis,depressed type+psychotic symptoms
Eu33313	[X]Recurr severe episodes/major depression+psychotic symptom
Eu33315	[X]Recurrent severe episodes of psychotic depression
Eu34113	[X]Neurotic depression
Eu34114	[X]Persistant anxiety depression
Eu41211	[X]Mild anxiety depression

AGGRESSION

Read code	**Read term**
1B1f.00	Anger
1P5..00	Aggressive behaviour
E213.11	Aggressive personality
E293000	Adjustment reaction with aggression
E2C0.00	Aggressive unsocial conduct disorder
E2C0000	Aggressive outburst
E2C0100	Anger reaction
E2C0z00	Aggressive unsocial conduct disorder NOS
Eu60311	[X]Aggressive personality disorder
Eu91111	[X]Conduct disorder, solitary aggressive type
Eu91112	[X]Unsocialised aggressive disorder
R00z800	[D]Irritability and anger
R00z900	[D]Hostility

PSYCHOTIC REACTION

Read code	**Read term**
1B1b.00	Transient hallucinations
1B1d.00	Hypnagogic hallucination
1B1E.00	Hallucinations
1B1e.00	Hypnopompic hallucination
1S42.00	Manic mood
E00y.11	Presbyophrenic psychosis
E01yz00	Other alcoholic psychosis NOS
E02z.00	Drug psychosis NOS

E040.11	Korsakoff's non-alcoholic psychosis
E04z.00	Chronic organic psychosis NOS
E11..13	Manic psychoses
E110.00	Manic disorder, single episode
E110.11	Hypomanic psychoses
E110000	Single manic episode, unspecified
E110100	Single manic episode, mild
E110200	Single manic episode, moderate
E110300	Single manic episode, severe without mention of psychosis
E110400	Single manic episode, severe, with psychosis
E110600	Single manic episode in full remission
E110z00	Manic disorder, single episode NOS
E111.00	Recurrent manic episodes
E111000	Recurrent manic episodes, unspecified
E111100	Recurrent manic episodes, mild
E111200	Recurrent manic episodes, moderate
E111300	Recurrent manic episodes, severe without mention psychosis
E111400	Recurrent manic episodes, severe, with psychosis
E111500	Recurrent manic episodes, partial or unspecified remission
E111z00	Recurrent manic episode NOS
E112400	Single major depressive episode, severe, with psychosis
E113400	Recurrent major depressive episodes, severe, with psychosis
E114.00	Bipolar affective disorder, currently manic
E114.11	Manic-depressive - now manic
E114000	Bipolar affective disorder, currently manic, unspecified
E114100	Bipolar affective disorder, currently manic, mild
E114200	Bipolar affective disorder, currently manic, moderate
E114300	Bipolar affect disord, currently manic, severe, no psychosis
E114400	Bipolar affect disord, currently manic,severe with psychosis
E114500	Bipolar affect disord,currently manic, part/unspec remission
E114600	Bipolar affective disorder, currently manic, full remission
E114z00	Bipolar affective disorder, currently manic, NOS
E115.11	Manic-depressive - now depressed
E115400	Bipolar affect disord, now depressed, severe with psychosis
E116400	Mixed bipolar affective disorder, severe, with psychosis
E117400	Unspecified bipolar affective disorder,severe with psychosis
E11y.00	Other and unspecified manic-depressive psychoses
E11y000	Unspecified manic-depressive psychoses
E11y100	Atypical manic disorder
E11y300	Other mixed manic-depressive psychoses
E11yz00	Other and unspecified manic-depressive psychoses NOS
E11zz00	Other affective psychosis NOS
E121.00	Chronic paranoid psychosis
E12z.00	Paranoid psychosis NOS
E130.00	Reactive depressive psychosis
E131.00	Acute hysterical psychosis
E134.00	Psychogenic paranoid psychosis
E13y100	Brief reactive psychosis
E13z.00	Nonorganic psychosis NOS
E141.00	Disintegrative psychosis
E14y100	Borderline psychosis of childhood
E14z.00	Child psychosis NOS
E1z..00	Non-organic psychosis NOS

E211100	Hypomanic personality disorder
Eu02z12	[X] Presenile psychosis NOS
Eu03.11	[X]Korsakov's psychosis, nonalcoholic
Eu05212	[X]Schizophrenia-like psychosis in epilepsy
Eu0z.11	[X]Organic psychosis NOS
Eu0z.12	[X]Symptomatic psychosis NOS
Eu22011	[X]Paranoid psychosis
Eu23012	[X]Cycloid psychosis
Eu23112	[X]Cycloid psychosis with symptoms of schizophrenia
Eu23312	[X]Psychogenic paranoid psychosis
Eu23z11	[X]Brief reactive psychosis NOS
Eu23z12	[X]Reactive psychosis
Eu25000	[X]Schizoaffective disorder, manic type
Eu25011	[X]Schizoaffective psychosis, manic type
Eu25012	[X]Schizophreniform psychosis, manic type
Eu25111	[X]Schizoaffective psychosis, depressive type
Eu25112	[X]Schizophreniform psychosis, depressive type
Eu25212	[X]Mixed schizophrenic and affective psychosis
Eu25z11	[X]Schizoaffective psychosis NOS
Eu2y.11	[X]Chronic hallucinatory psychosis
Eu2z.00	[X]Unspecified nonorganic psychosis
Eu2z.11	[X]Psychosis NOS
Eu30.00	[X]Manic episode
Eu30.11	[X]Bipolar disorder, single manic episode
Eu30200	[X]Mania with psychotic symptoms
Eu30212	[X]Mania with mood-incongruent psychotic symptoms
Eu30y00	[X]Other manic episodes
Eu30z00	[X]Manic episode, unspecified
Eu30z11	[X]Mania NOS
Eu31.11	[X]Manic-depressive illness
Eu31.12	[X]Manic-depressive psychosis
Eu31.13	[X]Manic-depressive reaction
Eu31000	[X]Bipolar affective disorder, current episode hypomanic
Eu31100	[X]Bipolar affect disorder cur epi manic wout psychotic symp
Eu31200	[X]Bipolar affect disorder cur epi manic with psychotic symp
Eu31y12	[X]Recurrent manic episodes
Eu32312	[X]Single episode of psychogenic depressive psychosis
Eu32314	[X]Single episode of reactive depressive psychosis
Eu33213	[X]Manic-depress psychosis,depressd,no psychotic symptoms
Eu33312	[X]Manic-depress psychosis,depressed type+psychotic symptoms
Eu33314	[X]Recurr severe episodes/psychogenic depressive psychosis
Eu33316	[X]Recurrent severe episodes/reactive depressive psychosis
Eu3z.11	[X]Affective psychosis NOS
Eu44.14	[X]Hysterical psychosis
Eu84013	[X]Infantile psychosis
Eu84111	[X]Atypical childhood psychosis
Eu84312	[X]Disintegrative psychosis
Eu84314	[X]Symbiotic psychosis
F481K00	Visual hallucinations
R001.00	[D]Hallucinations
R001000	[D]Hallucinations, auditory
R001100	[D]Hallucinations, gustatory
R001200	[D]Hallucinations, olfactory

R001300	[D]Hallucinations, tactile
R001400	[D]Visual hallucinations
R001z00	[D]Hallucinations NOS
Ryu5300	[X]Other hallucinations

GROWTH RELATED DISORDERS:

Read code	Read term
RO34300	[D] Lack of growth
22I5.00	O/E = lack of growth

SEXUAL MATURITY DISORDERS:

Read code	Read term
E227.00	Psychosexual dysfunction
E227z00	Psychosexual dysfunction NOS
Eu66.00	[X]Psychol and behav disorder assoc with sex dev and orienta
Eu66000	[X]Sexual maturation disorder
Eu66200	[X]Sexual relationship disorder
Eu66y00	[X]Other psychosexual development disorders
Eu66z00	[X]Psychosexual development disorder, unspecified
ZV41700	[V]Problem with sexual function

List of ICD9-CM Codes and associated text to capture outcomes of interest from PharMetrics Plus (USA)

CARDIOVASULAR EVENTS:

HYPERTENSION

ICD9 code	ICD 9 term
348.2	Benign intracranial hypertension
365.04	Ocular hypertension
401.0	Malignant essential hypertension
401.1	Benign essential hypertension
401.9	Unspecified essential hypertension
405.01	Malignant renovascular hypertension
405.09	Other malignant secondary hypertension
405.11	Benign renovascular hypertension
405.19	Other benign secondary hypertension
405.91	Unspecified renovascular hypertension
405.99	Other unspecified secondary hypertension
416.0	Primary pulmonary hypertension
459.30	Chronic venous hypertension without complications
459.31	Chronic venous hypertension with ulcer
459.32	Chronic venous hypertension with inflammation
459.33	Chronic venous hypertension with ulcer and inflammation
459.39	Chronic venous hypertension with other complication
572.3	Portal hypertension
796.2	Elevated blood pressure reading without diagnosis of hypertension
997.91	Complications affecting other specified body systems not elsewhere classified hypertension

TACHYCARDIA

ICD9-CM code	ICD 9-CM term
427.0	Paroxysmal supraventricular tachycardia
427.1	Paroxysmal ventricular tachycardia
427.2	Paroxysmal tachycardia unspecified
785.0	Tachycardia unspecified

ARRHYTHMIA

ICD 9 code	ICD 9 term
427.9	Cardiac dysrhythmias, unspecified

CARDIOMYOPATHY

ICD-9-CM Code	ICD-9-CM Code Description
425	Cardiomyopathy

MYOCARDIAL INFARCTION

ICD9 code	ICD 9 term
410	Acute myocardial infarction
412	Old myocardial infarction
429.71	Certain sequelae of myocardial infarction not elsewhere classified acquired cardiac septal defect
429.79	Certain sequelae of myocardial infarction not elsewhere classified other

STROKE

ICD9 code	ICD 9 term
430	Subarachnoid haemorrhage
431	Intracerebral haemorrhage
432	Other and unspecified intracranial hemorrhage
433	Occlusion and stenosis of precerebral arteries
434	Occlusion of cerebral arteries
435	Transient cerebral ischemia
436	Acute, but ill-defined, cerebrovascular disease
437	Other and ill-defined cerebrovascular disease
438	Late effects of cerebrovascular disease

SUDDEN CARDIAC DEATH

ICD 9 code	ICD 9 term
427.5	cardiac arrest

CYANOSIS

ICD 9 code	ICD 9 term
782.5	Cyanosis

QT PROLONGATION

ICD 9 code	ICD 9 term

426.82	Long QT syndrome
426.89	Other specified conduction disorders

PSYCHIATRIC EVENTS:

DEPRESSION

ICD 9 code	ICD 9 term
296.2	Depressive episode
296.3	Recurrent depressive disorder
301.10	Affective personality disorder, unspecified
301.12	Chronic depressive personality disorder
296.99	Other specified episodic mood disorder
311	Depressive disorder, not elsewhere classified

AGGRESSION

ICD 9 code	ICD 9 term
301.3	Personality disorder, aggressive
312.01	Undersocialized conduct disorder, aggressive type, mild

PSYCHOTIC REACTION

ICD9 code	ICD 9 term
310.9	Unspecified nonpsychotic mental disorder following organic brain damage
300.9	Unspecified nonpsychotic mental disorder
259.30	Paranoid type schizophrenia, unspecified
301.22	Schizotypal personality disorder
297.0	Paranoid state, simple
297.1	Delusional disorder
297.2	Paraphrenia
298.3	Acute paranoid reaction
298.8	Other and unspecified reactive psychosis
297.3	Shared psychotic disorder
295.70	Schizoaffective disorder, unspecified
298.9	Unspecified psychosis

SEXUAL MATURITY DISORDERS:

ICD9 code	ICD 9 term
302.89	Other specified psychosexual disorders
259.0	Delay in sexual development and puberty, not elsewhere classified

List of ICD10 Codes and associated text to capture outcomes of interest from Disease Analyzer (Germany)

CARDIOVASULAR EVENTS:

HYPERTENSION

ICD10 code	ICD 10 term
I10	Essential (primary) hypertension
I11	Hypertensive heart disease
I12	Hypertensive renal disease
I13	Hypertensive heart and renal disease
I15	Secondary hypertension

TACHYCARDIA

ICD10 code	ICD 10 term
I47	Paroxysmal tachycardia
R000	Tachycardia, unspecified

ARRHYTHMIA

ICD10 code	ICD 10 term
I49	Other cardiac arrhythmias

CARDIOMYOPATHY

ICD10 code	ICD 10 term
I42	Cardiomyopathy

MYOCARDIAL INFARCTION

ICD10 code	ICD 10 term
I21	Acute myocardial infarction
I22	Subsequent myocardial infarction
I23	Certain current complications following acute myocardial infarction

STROKE

ICD10 code	ICD 10 term
I60	Subarachnoid haemorrhage
I61	Intracerebral haemorrhage

I62	Other nontraumatic intracranial haemorrhage
I63	Cerebral infarction
I64	Stroke, not specified as haemorrhage or infarction
I65	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
I66	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
I67	Other cerebrovascular diseases

SUDDEN CARDIAC DEATH

ICD10 code	**ICD 10 term**
I461	Sudden cardiac death, so described

CYANOSIS

ICD10 code	**ICD 10 term**
R230	Cyanosis

QT PROLONGATION

ICD10 code	**ICD 10 term**
I458	Other specified conduction disorders
R943	Abnormal results of cardiovascular function studies

PSYCHIATRIC EVENTS:

DEPRESSION

ICD10 code	**ICD 10 term**
F204	Post-schizophrenic depression
F32	Depressive episode
F33	Recurrent depressive disorder
F34	Persistent mood [affective] disorders
F38	Other mood [affective] disorders

AGGRESSION

ICD10 code	**ICD 10 term**
F603	Emotionally unstable personality disorder
F29	Unsocialized conduct disorder

PSYCHOTIC REACTION

ICD10 code	ICD 10 term
F09	Unspecified organic or symptomatic mental disorder
F99	Mental disorder, not otherwise specified
F29	Unspecified nonorganic psychosis
F20	Schizophrenia
F21	Schizotypal disorder
F22	Persistent delusional disorders
F23	Acute and transient psychotic disorders
F24	Induced delusional disorder
F25	Schizoaffective disorders
F28	Other nonorganic psychotic disorders

SEXUAL MATURITY DISORDERS:

ICD10 code	ICD 10 term
F66	Psychological and behavioural disorders associated with sexual development and orientation

Baseline characteristics to adjust for by propensity score matching, according to study outcome

Characteristic	Cohort 1: cardiovascular disease [1]	Cohort 2: psychiatric disorders [2]	Cohort 3: growth impairment [3]	Cohort 4: impairment of sexual maturation [4]
Age at index date	X	X	X	X
Sex	X	X	X	X
Database (CPRD vs THIN)	X	X	X	X
Calendar year of index date	X	X	X	X
Duration of pharmacotherapy for ADHD (any drug)	X	X	X	X
Number of GP consultations 6 month prior to index date	X	X	X	X
History of hospital admission (yes/no)	X	X	X	X
History of cardiovascular disease	(exclusion criterion)	X	X	X
History of psychiatric disorders	X	(exclusion criterion)	X	X
History of growth impairment	X	X	(exclusion criterion)	X
History of sexual maturation impairment	X	X	X	(exclusion criterion)
Socioeconomic position [5]	X	X	X	X
Previous use of psychotropic drugs, antipsychotics, anxiolytics, lithium, and antidepressants	X	X	X	X
Height at index date	X	X	X	X
Weight at index date	X	X	X	X
History of diabetes	X			
History of hypertension	X			
Systolic blood pressure (mmHg) [6]	X			
Diastolic blood pressure (mmHg) [6]	X			
History of tachycardia [6]	X			
Heart rate (bpm) [6]	X			
History of cancer			X	X
History of kidney disease			X	X
History of atopic dermatitis			X	X
History of asthma	X	X	X	X
History of asthma drug use	X	X	X	X
History of drug abuse		X		
History of eating disorders/malnutrition			X	
Family history of	X			X

sudden/unexplained death [6]				
Family history of growth impairment [6]		X		
Family history of sexual dysfunction [6]			X	
Family history of bipolar disorder [6]				X

[1] *Covariates selected partially on the basis of Cooper et al. (2011) and Habel et al. (2011)*
[2] *Covariates selected partially on the basis of Gillberg et al. (2004)*
[3] *Covariates selected partially on the basis of Allen et al. (1994) and Wolter & Price (2014)*
[4] *Covariates selected partially on the basis of Allen et al. (1994) and Wolter & Price (2014)*
[5] *For THIN Socioeconomic position will be estimated by using the Index of Multiple Deprivation score for area of residence (e.g., Thomas et al., 2013).*
[6] *Depending on availability in study databases.*

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Annex 4. Details of study database feasibility counts

	Country		
	UK	Germany	USA
Data base	IMS THIN	Disease Analyzer	IMS PharMetrics Plus
Data sources	GP EMR	Primary care EMR	Prescribing and claims data
Population covered	~5.5 million	~11 million	~35 million
Estimated pediatric population (age less than 18)[1]	~1 million	~1.9 million	~8.6 million
Pharmacologically treated pediatric population	9,517[2]	46,528[3]	155,259[4]
Actual reported dexamfetamine usage in most recent year	32 (0.3%)	199 (weighted average across GPs, paediatricians, psychiatrists and neurologists, 0.65%[5])	970 (0.6%)
Estimated dexamfetamine coverage for the study period (assuming observed rates of prescribing)	**144**	**998**	**5,028**

Notes:

1. Population and age structure from CIA World Factbook https*://www.cia.gov/library/publications/the-world-factbook/fields/2010.html*
2. Unique patients treated in the 5 years to February, 2015 with dexamfetamine, methylphenidate and lisdexamfetamine
3. Unique patients treated in the 3 years to January, 2015 with dexamfetamine, methylphenidate and lisdexamfetamine with a record of an ADHD diagnosis
4. Unique patients treated in 2014 with dextroamphetamine, methylphenidate, lisdexamfetamine, amphetamine and atomoxetine with a record of an ADHD diagnosis
5. The weighted average of dexamfetamine uptake

Annex 5. Country-specific sample size calculations

IMS THIN (UK)

Year of Study	Treated Population[1]	Untreated Population[2]	Incident Cases[3]	At Risk[4]	Newly Treated Each Year[5]	Ending Untreated Population[6]	Cumula-tively Treated Each Year
1	9,517	775,483	79	9,596	29	775,533	29
2	9,518	775,533	79	9,596	29	775,582	58
3	9,518	775,582	79	9,597	29	775,632	86
4	9,519	775,632	79	9,597	29	775,682	115
5	9,519	775,682	79	9,598	29	775,732	144

Notes:

1. In year 1 estimated by IMS as unique individuals diagnosed under the age of 18 years with a prescription for dexamfetamine, lisdexamfetamine or methylphenidate.
2. In year 1, the untreated population is calculated as pediatric population in THIN minus the treated population.
3. Assumed rate of 10 per 100,000 (0.01%) applied to the population of children in the database (n=785,000 patients aged <18 y).
4. Number at risk = pharmacologically treated population + new incident cases.
5. Number newly treated = number at risk x dexamfetamine take up rate (0.3%).
6. Ending untreated population = starting untreated population + incident cases – new treated cases. The ending untreated population of year 1 is the starting untreated population of year 2 etc.

IMS Disease Analyzer (Germany)

Year of Study	ADHD Chil-dren[1]	Un-treated Popu-lation	Treated Popu-lation[2]	Incident Cases[3]	At Risk[4]	Newly Treated Each Year[5]	Ending Untreated Popu-lation[6]	Cumula-tively Treated Each Year
1	46,528	16,071	30,457	187	30,579	200	46,515	200
2	46,515	16,073	30,442	187	30,564	200	46,503	399
3	46,503	16,076	30,427	187	30,550	200	46,490	599
4	46,490	16,077	30,413	187	30,535	199	46,478	798
5	46,478	16,080	30,398	187	30,520	199	46,465	998

Notes:

1. In year 1 estimated by IMS as unique individuals diagnosed with ADHD under the age of 18 years.
2. In year 1 estimated by IMS as unique individuals diagnosed with ADHD under the age of 18 years with a prescription for dexamfetamine, lisdexamfetamine or methylphenidate.
3. Assumed rate of 10 per 100,000 (0.01%) applied to the population of children in the database (~1.8M).
4. Number at risk = treated population + new incident cases.
5. Number newly treated = at risk population x dexamfetamine take up rate (0.65%, weighted average of dexamfetamine prescribed by GPs, pediatricians, psychiatrists and neurologists).
6. Number untreated = ADHD children + incident cases – newly treated cases.

IMS PharMetrics (USA)

Year of Study	ADHD Chil-dren[1]	Un-treated Popu-lation	Treated Popu-lation[2]	Incident Cases[3]	At Risk[4]	Newly Treated Each Year[5]	Ending Untreated Popu-lation[6]	Cumula-tively Treated Each Year
1	267,710	107,084	160,626	855	161,139	1007	267,559	1007
2	267,559	107,023	160,535	855	161,048	1006	267,408	2013
3	267,408	106,963	160,445	855	160,958	1006	267,258	3019
4	267,258	106,903	160,355	855	160,868	1005	267,108	4024
5	267,108	106,843	160,265	855	160,778	1004	266,959	5028

Notes:

1. In year 1 estimated by IMS as unique individuals diagnosed with ADHD under the age of 18 years.
2. In year 1 estimated by IMS as unique individuals diagnosed with ADHD under the age of 18 years with a prescription for dexamfetamine, lisdexamfetamine or methylphenidate.
3. Assumed rate of 10 per 100,000 applied to the population of children in the database.
4. Number at risk = treated population + new incident cases.
5. Number newly treated = at risk population x dexamfetamine take up rate (0.6%).
6. Ending untreated population = starting untreated population + incident cases – new treated cases.