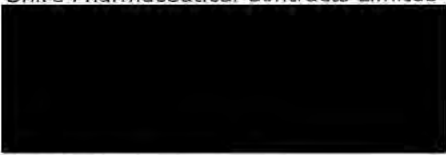


PASS Information

Title	SPD489-825: Cohort Study of the Incidence of Major Cardiovascular Events in New Adult Users of Lisdexamfetamine and Remote Adult Users of Other ADHD Treatments
Protocol version identifier	2.0
Date of last version of protocol	08 March 2016
EU PAS register number	Study not yet registered
Active substance	Lisdexamfetamine dimesylate, ATC code N06BA12
Medicinal product	Elvanse Adult
Product reference	UK: 08081/0059-0061, Sweden: 50796 – 8, Denmark: 53795 – 7
Procedure number	UK/H/5567/01-03 – Post-approval commitment
Marketing authorisation holder(s)	SHIRE Pharmaceutical Contracts Ltd.
Joint PASS	No
Research question and objectives	This study research question of interest is to evaluate the long-term cardiovascular safety of lisdexamfetamine (LDX) in adults. To address this research question, the study will include an evaluation of the occurrence of coronary and cerebrovascular events potentially associated with LDX use.
Country(-ies) of study	United Kingdom, Denmark, and Sweden
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Project Title: SPD489-825: Cohort Study of the Incidence of Major Cardiovascular Events in New Adult Users of Lisdexamfetamine and Remote Adult Users of Other ADHD Treatments

Protocol ID Number: SPD489-825

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Version 2.0

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Authors	Cristina Rebordosa, MD, PhD (RTI Health Solutions)
Version	2.0

Shire Pharmaceuticals

Signature	Date
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Signature _____ Date _____

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2 List of Abbreviations

ADHD	attention deficit hyperactivity disorder
AMI	acute myocardial infarction
ATC	Anatomical Therapeutic Chemical (classification system)
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CPRD	Clinical Practice Research Datalink
CT	computed tomography
DDD	defined daily dose
ECG	electrocardiogram
EEG	electroencephalogram
EMA	European Medicines Agency
EMACE	extended MACE endpoint
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GP	General practitioner
HES	Hospital Episode Statistics
HR	hazard ratio
ICD-10	<i>International Statistical Classification of Diseases and Related Health Problems, 10th Revision</i>
ICD-10-CM	<i>International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification</i>
ICD-8	<i>International Classification of Diseases, 8th Revision</i>
IR	incidence rate
IRR	incidence rate ratio
ISPE	International Society for Pharmacoepidemiology
LDX	lisdexamfetamine dimesylate
MACE	major adverse cardiovascular events
MI	myocardial infarction
MRI	magnetic resonance imaging
NHS	National Health Service
ONS	Office for National Statistics
OXMIS	Oxford Medical Information Systems (coding system)
PASS	postauthorisation safety study
PBRER	periodic benefit-risk evaluation report
PPV	positive predictive value
Q _n	quarter of a calendar year
RTI-HS	RTI Health Solutions
SAP	statistical analysis plan
SCD	sudden cardiac death
SD	standard deviation

STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SVA	serious ventricular arrhythmia
TIA	transient ischaemic attack
UK	United Kingdom
US	United States
VA	ventricular arrhythmia
WHO	World Health Organization

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4 Abstract

Title: SPD489-825: Cohort Study of the Incidence of Major Cardiovascular Events in New Adult Users of Lisdexamfetamine and Remote Users of Other ADHD Treatments

Version 2.0, 08 March 2016

Cristina Rebordosa, MD, PhD, RTI Health Solutions, Epidemiology

Rationale and background: Lisdexamfetamine dimesylate (LDX) has been granted marketing authorisation approval for the treatment of attention deficit hyperactivity disorder (ADHD) in adults in the United Kingdom, Denmark, and Sweden. As part of the marketing authorisation approval, Shire has been asked to examine the long-term safety of LDX in adults using surrogate markers for the potential risks of cerebrovascular disorders and ischaemic cardiac events.

Research question and objectives: This study will address the following research question of interest: what is the long-term cardiovascular safety of LDX in adults? To address this research question, the study will include an evaluation of the occurrence of coronary and cerebrovascular events potentially associated with LDX use.

The primary objective of this study is to estimate, in real-world settings, the incidence rate (IR) and the adjusted incidence rate ratios (IRRs) of the composite major adverse cardiovascular events (MACE) endpoint in a cohort of adult patients who are current new users of LDX (the LDX cohort) compared with a cohort of remote users of other ADHD treatments in three European data sources. Combined IRs and IRRs for all data sources will also be estimated, as appropriate.

The secondary objectives are as follows: (1) to evaluate the potential long-term effects of LDX use by estimating the IR and IRRs of MACE among long-term LDX users (i.e., current LDX users with ≥ 12 months of cumulative duration of current LDX use) compared with long-term remote users of other ADHD treatments without exposure to these treatments for a period of at least 12 months after the start of follow-up; (2) to estimate the IR and IRR of all secondary endpoints—an extended MACE endpoint (EMACE) comprising all MACE components plus hospitalisation for either unstable angina or transient ischaemic attack (TIA), the composite coronary and stroke components of EMACE, and a composite of sudden cardiac death and serious ventricular arrhythmias—comparing current LDX use versus remote use of other ADHD treatments; and (3) to estimate the IR and IRR of MACE by subcategories of concomitant use of other ADHD medications during current LDX use (“current single LDX use” and “current multiple drug use,” i.e., LDX plus one or more other ADHD drugs), compared with remote use of other ADHD treatments.

Additional exploratory analysis will estimate IR and IRR of MACE for LDX users versus remote users of other ADHD treatments, by subcategories of current LDX dose, stratified by sex and age categories and previous history of cardiovascular disease, ADHD, and non-ADHD psychiatric conditions.

Study design: This study will consist of multiple observational (non-interventional) population-based cohort substudies of patients initiating LDX compared with patients with remote use of other ADHD medications, in three data sources. The frequency of MACE and the adjusted IRRs will be calculated.

The study will compare adult patients who are new users of LDX (the LDX cohort) with a cohort of patients with remote use of other ADHD medications, matched on age, sex, region, and index date. The study will estimate the IR and IRRs with the corresponding 95% confidence interval, for the comparison between the LDX cohort and the remote use of other ADHD treatments cohort. The analysis will be conducted separately in each data source, and overall estimates of effect will be obtained using meta-analytic techniques as appropriate.

Population: A non-interventional population-based cohort study will be conducted using selected electronically available health care data sources: the Clinical Practice Research Datalink (CPRD) in the United Kingdom (UK), the Danish national registries, and the Swedish national registers.

To be eligible for inclusion into the study population, individuals must be adults (aged 18 years or older) and have at least 12 months of data available prior to the index date. The LDX cohort will be formed by adult patients who have a first dispensing or prescription for LDX (index date), and no evidence of prior use of LDX in the data source.

The remote use of other ADHD treatments cohort will be generated by selecting adult patients with at least one prescription/dispensing for a medication indicated for ADHD, other than LDX, during the 24 months prior to the index date and with no prescriptions/dispensings of these medications in the 180 days before the index date. The index date of each patient in the remote use of other ADHD treatments cohort will be the index date of the matched LDX new user, which will be at least 181 days after the last ADHD medication prescription/dispensing date. These cohort members will be matched in a ratio of up to 5 to 1 to members of the LDX cohort by age, sex, region, and index date.

Variables: The primary endpoint, MACE, will comprise the first occurrence of any of its individual components during follow-up: hospitalisation for acute myocardial infarction (AMI), fatal or non-fatal; hospitalisation for stroke, fatal or non-fatal; out-of-hospital coronary heart disease death; and out-of-hospital cerebrovascular death. Secondary endpoints are an EMACE endpoint that includes hospitalisation for either unstable angina or TIA, the composite coronary and stroke components of EMACE, and an additional secondary endpoint that will be a composite of sudden cardiac death and serious ventricular arrhythmias.

Current use for LDX new users is defined as the duration of the LDX prescription or dispensing plus 30 days. For the primary analysis, follow-up will end at the earliest of death, first occurrence of an outcome of interest, termination of enrolment in the health plan system, or end of study period. Each patient can have multiple outcomes.

The study will define other variables that will be used to describe the study population and to control for confounding, including history of cardiovascular diseases and hypertension, demographic variables, other medical history, and use of other medications.

Data sources¹: To obtain sufficient study size and person-years of LDX use to address the objective, the study will be implemented in multiple health care data sources in European Union (EU) countries where LDX is expected to be approved for use in adult patients with ADHD. In the UK, the data source will be the CPRD, which contains diagnostic and prescribing information recorded by general practitioners (GPs) as part of their routine clinical practice in the UK. In Denmark, the national registries and databases of interest to this study are the Danish Civil Registration System, Danish National Patient Register, Danish Psychiatric Research Central Register, Danish National Prescription Registry, and the Causes of Death Register. In Sweden, the Swedish national databases of interest to this study are the Swedish National Patient Register, Swedish National Prescribed Drug Register, and Swedish Causes of Death Register.

Study size: An LDX cohort size of 7,800 person-years of time at risk of current LDX use should be sufficient to reach, with 80% probability, an IRR upper bound of the 95% confidence interval (CI) for the composite MACE endpoint in LDX new users cohort versus remote use of other ADHD treatments cohort of less than 3 (null hypothesis), under the alternative hypothesis that the IRR is 1 and the incidence rate in the remote use of other ADHD treatments cohort is 1 per 1,000 person-years.

Data analysis: Each research partner will conduct country-specific analyses within each data source to (1) select the study population; (2) describe the study cohorts, including patterns of demographics, medical history, exposures, and endpoints; (3) within its data, estimate exposure propensity scores that will be used to control for confounding; and (4) create a summary of aggregated data set based on counts of patients, person-years, and outcome events according to the strata of age, sex and propensity scores. No person-level data will be shared with the coordinating centre.

After receiving the site-specific, propensity score-stratified tables with aggregated data from each database research partner, the coordinating centre will conduct an analysis of the data from each individual database and an overall analysis combining the data across all databases, as appropriate. Coordinating centre analysis activities include (1) pooled description of study cohorts, (2) analysis of IR and standardised IRs, and (3) analysis of crude and adjusted IRRs. IRs will be standardised to the distribution of person-time of LDX users by age, sex, quintiles of the propensity score, and data source. Mantel-Haenszel methods will be used to summarise IRRs across strata.

Milestones:

- Start of data collection: Q3-Q4 2019
- End of data collection: Q3 2020

¹ Database custodians and research partners have been contacted and confirmed their interest in and availability to participate in the study.

- Annual study progress reports, initially including monitoring counts of adult LDX users (feasibility assessment)
- Final study report: Q4 2020

5 Amendments and Updates

Updates to protocol version 2.0 were made prior to study initiation to clarify study milestones and the definition of remote users and to address comments following review by MHRA.

6 Milestones and Timeline

Milestone	Anticipated Date
Registration in the EU PAS Register	Q3-Q4 2016
Study progress report(s) ^a	Annually starting in 2016
Start of data collection ^b	Q3-Q4 2019
End of data collection ^c	Q3 2020
Interim report(s)	None planned
Final report of study results	Q4 2020

CPRD = Clinical Practice Research Datalink; EU PAS Register = European Union electronic register of postauthorisation studies; Qn = quarter of a calendar year.

Note: Contracts between the sponsor and research organisation(s) and approvals by data protection, data custodian, ethics, and scientific review bodies are pending. Timelines may be impacted by approvals of these bodies, duration of contract reviews, and availability of data and staff at research institutions once contracts and approvals are finalised.

^a Reports will include information on the study progress, and initially a feasibility assessment that includes findings from monitoring the counts of medication users. During monitoring, patient counts will be obtained from the CPRD Knowledge Centre in the United Kingdom (www.cprd.com/contact/) and from publicly available data sources in Denmark and Sweden, Medstats.dk in Denmark (The Danish Health Data Authority, 2015) and the Swedish drug database (Socialstyrelsen, 2014).

^b Start of data collection is "in the case of secondary use of data, the date from which data extraction starts." (EMA, 2013, Section VIII.B.2).

^c End of data collection is "the date from which the analytical data set is completely available" (EMA, 2013, Section VIII.B.2).

7 Rationale and Background

Elvanse Adult® (lisdexamfetamine dimesylate [LDX]) has been granted marketing authorisation approval through the European Decentralised Procedure for the treatment of attention deficit hyperactivity disorder (ADHD) in adults in three European countries: the United Kingdom (UK), Denmark, and Sweden. As part of the marketing authorisation approval, Shire has been asked to examine the long-term safety of LDX in adults using surrogate markers for the potential risks of cerebrovascular disorders and ischaemic cardiac events.

This document describes the core protocol for conducting a European, multinational cohort study to assess the risk of major cardiovascular events in adult new users of lisdexamfetamine and in the population with prior but not current use of other ADHD medication. The study will evaluate populations covered in three automated health databases, one each in Denmark, Sweden, and the UK.

LDX is a therapeutically inactive amphetamine prodrug. Elvanse Adult® is indicated as part of a comprehensive treatment programme for ADHD in adult patients, including first-line pharmacotherapy treatment with LDX.

There has been a concern that stimulants used to treat ADHD may be associated with adverse cardiovascular outcomes, and this potential association has been investigated in population-based non-interventional studies (Schelleman et al., 2013; Westover and Halm, 2012). Among adults, studies evaluating the effect of ADHD treatments on the risk of cardiovascular outcomes showed mixed findings, and although some of the studies reported an association with one of the adverse cardiovascular outcomes under evaluation, uncontrolled confounding and selection bias were primary concerns in these studies. Holick et al. (2009), in a secondary analysis of the United States (US) Ingenix Research Data Mart (2003-2006), found an increased risk (hazard ratio [HR], 3.44; 95% confidence interval [CI], 1.13-10.60) of transient ischaemic attack (TIA) but not cerebrovascular accident (HR, 0.71; 95% CI, 0.34-1.47) among users of atomoxetine or ADHD stimulant medication compared to the general population. However, in this secondary analyses, the authors used an intention-to-treat approach and did not match the cohorts by propensity score as they did in their primary analysis, where they found no association (Holick et al., 2009). Similarly, although Schelleman et al. (2012), in an analysis of US Medicaid (1999-2003) and Health Core Integrated Research Database (2001-2006) reported an increased risk of sudden death or ventricular arrhythmia (HR, 2.74; 95% CI, 2.02-3.71) among users of methylphenidate compared with the general population, the association was attenuated once propensity scores were used to control for confounding (HR, 1.84; 95% CI, 1.33-2.55). In addition, there were inverse associations between high doses of methylphenidate and several outcomes, which according to the authors did not support a causal relationship and were potentially due to lower dosages being prescribed to the patients at higher risk of death (Schelleman et al., 2012). In the same setting and time period, Schelleman et al. (2013) repeated the previous study but with amphetamines and atomoxetine as the exposures of interest and did not find an association with elevated risk of cardiovascular events (Schelleman et al., 2013). Finally, Habel et al. (2011), in a study of more than 440,000 adults from four US study populations (1986-2005), did not find an increased risk of cardiovascular events among individuals exposed to ADHD medications compared to the general population. On the contrary, results suggested that longer exposure duration was protective, although this was reported as "biologically implausible." An alternative hypothesis is that susceptible patients are more likely to experience an event early after starting a causative agent (Habel et al., 2011).

8 Research Question and Objectives

This study will address the following research question:

- What is the long-term cardiovascular safety of LDX in adults?

To address this research question, the study will include an evaluation of the occurrence of coronary and cerebrovascular events potentially associated with LDX use, and with long-term LDX use. The study will also include an evaluation of the occurrence of coronary and cerebrovascular events potentially associated with concomitant use of other ADHD medication, and an extended definition of the endpoints of interest.

8.1 Primary Objective

The primary objective of this study is to estimate, in real-world settings, the incidence rate (IR) and the adjusted incidence rate ratios (IRRs) of the composite major adverse cardiovascular events (MACE) endpoint in a cohort of adult patients who are current new users of LDX (the LDX cohort) as compared with a cohort of remote users of other ADHD treatments in three European data sources. Combined IRs and IRRs for all data sources will also be estimated, as appropriate.

8.2 Secondary Objectives

- To evaluate the potential long-term effects of LDX use by estimating the IR and the IRRs of MACE among long-term LDX users (i.e., current LDX users with ≥ 12 months of cumulative exposure to LDX, that is those with ≥ 12 months duration of current LDX use) compared with long-term remote users of other ADHD treatments without exposure to these treatments for a period of at least 12 months after the start of follow-up.
- To estimate the IR and IRRs of all secondary endpoints—(1) an extended MACE (EMACE) endpoint comprising all MACE components plus hospitalisation for either unstable angina or TIA, (2) the composite coronary components of EMACE, (3) the composite stroke components of EMACE, and (4) a composite endpoint of sudden cardiac death (SCD) and serious ventricular arrhythmia (SVA)—comparing current LDX use versus remote use of other ADHD treatments, in each data source, and estimating a combined IRR for all data sources, as appropriate.
- To estimate the IR and IRR of MACE by subcategories of concomitant use of other ADHD medications during current LDX use (“current single LDX use” and “current multiple drug use,” i.e., LDX plus one or more other ADHD drugs), compared with remote use of other ADHD treatments.

8.3 Specific Aims

This study aims to include sufficient person-time of LDX time at risk to have the upper bound of the 95% CI of the IRR for the composite MACE endpoint in LDX new users cohort versus remote use of other ADHD treatments cohort be less than 3.0 if the true

IRR is 1.0. This approach is consistent with the aim to conduct surveillance for a large excess in the rate of specific rare or very rare events with a very low background incidence rate for which there has been no signal from clinical development.

9 Research Methods

9.1 Study Design

9.1.1 Study Tasks

The study will be conducted as a collaborative study involving three research centres: RTI Health Solutions (RTI-HS), which will serve as the coordinating centre and will lead the analysis using data from the Clinical Practice Research Datalink (CPRD) in the UK, and two additional database research partners—Aarhus University in Denmark and Karolinska Institutet in Sweden, which will lead the analyses in their respective country databases. Study conduct and coordination will be performed independently from the study sponsor, although responsibility for scientific integrity is shared by the collaborating institutions, including the study sponsor. Each participating database research partner will adapt this core protocol to the specific attributes of the local database.

Responsibilities

The coordinating centre will have the following primary roles and responsibilities:

- Coordinate study activities
- Lead preparation of the final version of this core study protocol with input from all research partners
- Guide database-specific adaptation of the protocol, with a focus on consistency with the core protocol of variable definitions and other methodological aspects across adapted protocols
- Prepare the data on annual monitoring of adult LDX users to be reported by Shire in the periodic benefit-risk evaluation report (PBRER) after being reviewed by research partners
- Provide scientific support to the study implementation phase, including apply for ethics committee approvals, generate a common statistical analysis plan and support adapted versions of the statistical analysis plan (SAP) for each data source, and develop case validation efforts when needed
- Support integration of study results by analysing stratified aggregated data from each database research partner to estimate overall measures of effect
- Facilitate research network communications, study reporting, and dissemination of study results

The database research partners will have the following primary roles and responsibilities:

- Provide input into the final version of this core protocol
- Develop the protocol adaptation to each database
- Review data on annual monitoring of adult LDX users to be reported by Shire in the PBRER
- Implement the study in the respective database, including applying for ethics committee approvals, implementing the SAP
- Liaise with the coordinating centre during study implementation as needed
- Contribute to the preparation of study reports and dissemination of results

Shire will have the following primary roles and responsibilities:

- Serve as the study sponsor
- Provide input into the final version of this core protocol
- Review and provide input during the study implementation phase

Sequence of Study Tasks

Because of uncertainties surrounding availability of sufficient numbers of LDX new users to conduct the study, the study will be conducted in phases, initially monitoring annually the number of adult LDX users, and generating a final study report:

- Study progress reports will be produced annually starting in 2016. These study progress reports will include information on the study progress, such as ongoing activities; next steps; and status of the contracts with research partners, adapted protocol, SAP and adapted SAPs, data analyses, and the study results report. At least initially, progress reports will also include results of monitoring counts of LDX users (i.e., during the feasibility phase) until the target sample size is reached.
 - Monitoring the number of adult LDX new users: The accumulating number of LDX new adult users in the data sources will be monitored annually, starting with the number of LDX new adult users during 2016. Data on patient counts will be retrieved from the CPRD Knowledge Centre in the UK (www.cprd.com/contact/) and from publicly available data sources in Denmark and Sweden, Medstats.dk in Denmark (The Danish Health Data Authority, 2015) and the Swedish drug database (Socialstyrelsen, 2014). The number of adult LDX users will be reported to Shire for inclusion in the PBRER after being reviewed by and in agreement with the study investigators.
- Final study report: This report will include the evaluation of long-term cardiovascular safety of LDX in adults. Collaborating research centres will conduct data source-specific analyses, and the coordinating centre will coordinate and pool the number of events and person-time and conduct the combined analysis, as appropriate.

9.1.2 Research Design

A non-interventional population-based cohort study will be conducted using selected electronic health care data sources; the CPRD in the UK, the Danish national registries, and the Swedish national registers. The study period in each data source will begin on the date of first recorded prescription/dispensing for LDX among adults in each country (2013), including use before the adult indication was granted, and end with the most recent data available in each data source as of late 2019.

The study will compare adult patients who are new users of LDX ("LDX cohort") with a cohort of patients with remote use of other ADHD medications, matched on age, sex, region (practice in CPRD), and index date. The study will estimate the crude and propensity score-standardised IR and the crude and adjusted IRR (with the corresponding 95% CIs) for the comparison between the LDX cohort and remote use of other ADHD treatments cohort. The analysis will be conducted separately in each data source, and overall estimates of effect will be obtained using meta-analytic techniques as appropriate.

The main composite cardiovascular endpoint of interest, MACE, will comprise the first occurrence of any hospitalisation for fatal or non-fatal acute myocardial infarction (AMI) or for fatal or non-fatal stroke or out-of-hospital coronary or cerebrovascular death. Secondary endpoints will include an extended MACE (EMACE) including additional hospitalisation for either unstable angina or TIA. The composite coronary and stroke components of EMACE will be also evaluated separately, if numbers allow. An additional secondary endpoint will be a composite of SCD and SVA.

This common study protocol will be adapted to the specifications of each of the participating data sources.

9.1.3 Rationale for Choice of Study Design

Population-based health care data sources, which include information from usual health care utilisation, have been used for several decades to evaluate the frequency and risk factors of outcomes among users of medications of interest compared with users of other medications. This population-based approach to evaluating the medication of interest by including diverse countries, practices, and patients is useful for obtaining large numbers of patients, desired precision of outcome frequencies, and broad understanding of the safety profile in diverse types of patients in general health care systems.

A cohort design will allow direct estimation of the absolute incidence rates and IRRs of multiple outcomes of interest among new users of LDX compared with remote users of other ADHD treatments. A cohort study design will also allow accurate chronological confounder assessment and assessment of the outcomes at multiple time points. The covariate information will be assessed during the time preceding treatment initiation and will include all historical information available for each patient. Follow-up will start the day after treatment initiation.

A case-crossover study design (a type of self-controlled design) was considered not appropriate to address the study objectives because the effect of long-term exposure to LDX was of special interest. In addition, the case-crossover design can be implemented successfully only for an appropriate study hypothesis. Specifically, the exposure must vary over time within a substantial proportion of the study subjects. Because of the self-matching feature, all the elementary comparisons are made within a person; if the exposure remains constant within a person, then there is no information from that person about the possible effect of exposure. The exposure must also have a short induction period and a transient effect; otherwise, exposures in the distant past could be the cause of a recent disease onset. The disease must also have an abrupt onset (Rothman, 2012a; Rothman et al., 2008).

Remote users of other ADHD medications will be selected as the comparator cohort to minimise potential confounding due to the healthy user effect among patients with treated ADHD (Habel et al., 2011). The selection of the comparator cohort was based on the need to select an unexposed comparison group, since an association with cardiovascular events has also been suggested for most of the ADHD drugs in some but not all studies (most commonly stimulants: other amphetamines or methylphenidate) (see Section 7). In addition, the suggested mechanism by which these stimulant drugs would increase the risk of cardiovascular events, an increase in the heart rate and blood pressure (Stiefel and Besag, 2010), would be the same for LDX. A comparison group of patients with ADHD was thought to be less prone to selection bias and confounding by indication than the general population. In addition, since we are evaluating adults, it may be that patients with ADHD are diagnosed and treated during childhood, but may not have a recent record of a diagnosis of ADHD during adulthood (Biederman et al., 2010). Thus, by selecting patients with relatively recent use of ADHD drugs (6 to 24 months prior to study entry), we expect to have an adult patient population with ADHD more similar to the LDX cohort than if we selected persons from the general population or untreated patients with an ADHD diagnosis.

Methods to reduce the bias of effect estimates derived from observational studies focus on minimising the differences in the study groups being compared in the absence of randomisation. To control for confounding, exposure propensity scores will be estimated and analyses will be performed by stratifying study patients by ranges of the propensity score. Propensity scores will incorporate measured potential predictors of therapy and outcome as independent variables and exposure group status as the outcome. Because exposure propensity scores focus on the indication for use and non-use of medications, they can be useful to control for confounding by indication. Propensity scores can perform better than conventional regression methods when the number of events relative to the number of potential confounders is small, because rather than having to model the events with many variables, one can instead model the exposure, which may have ample data to accommodate a rich model (Cepeda et al., 2003). This advantage may be important in this study, given the low number of expected events for the study endpoints.

9.2 Setting

9.2.1 Population

The source population will be all individuals aged 18 years or older registered in the study databases from the date LDX will become available for the treatment of ADHD in adults in each country until the end of study period. To be eligible for inclusion into the study population, individuals should have at least 12 months of data available prior to cohort entry. The study will include two cohorts identified from all eligible individuals in the study data sources: the LDX cohort and the remote use of other ADHD treatments cohort.

The LDX cohort will be formed from adults with a dispensing or prescription for LDX, at least 12 months of data in the data source prior to the first dispensing or prescription date (index date), and no evidence of prior use of LDX in the data source. The first prescription of LDX will be the index prescription, prescribed or dispensed on the index date during the study period.

The remote use of other ADHD treatments cohort will be generated by selecting adult patients with at least one prescription/dispensing for a medication indicated for ADHD, other than LDX, during the 24 months prior to the index date and with no prescriptions or dispensings of these medications in at least the last 180 days before index date. The index date of each patient in the remote use of other ADHD treatments cohort will be the index date of the matched LDX new user, which will be at least the 181 days after the last ADHD medication prescription/dispensing date. The members of the remote use of other ADHD treatments cohort will be matched to each LDX new user in a ratio of up to 5 to 1 by age, sex, region (practice in the CPRD), and index date. Patients in the remote use of other ADHD treatments cohort will be suitable to be matched from the time point when there has been no prescription/dispensing in the previous 180 days for any ADHD medication, after their last prescription/dispensing, and their data are of a quality suitable for research (in the CPRD). Patients in the remote users of other ADHD treatments cohort will be matched to LDX new users by applying greedy matching techniques within each category.

The specific inclusion criteria for the LDX cohort are as follows:

- Be aged 18 years or older on the index date
- Have at least 12 months of data available prior to the index date; in the CPRD, must have been continuously registered in an up-to-standard practice for at least 12 months before the index date; in Sweden and Denmark, patients must not have immigrated during the last 12 months
- Have no record of prior prescription or dispensing of LDX at any time before the index date

The specific inclusion criteria for the cohort of patients with remote use of at least one prescription/dispensing for a medication indicated for ADHD, other than LDX, are as follows:

- Be aged 18 years or older on the index date
- Have at least 12 months of data available prior to index date; in the CPRD, must be registered in an up-to-standard practice for at least 12 months before the index date; in Sweden and Denmark, patients must not have immigrated during the last 12 months
- Have no record of prior prescription or dispensing of other ADHD treatments within the last 180 days before index date, but have at least one prescription between 181 days and 24 months prior to the index date.

Patients from the remote use of other ADHD treatments cohort who initiate LDX will be allowed to enter the LDX cohort if they fulfil the inclusion criteria at the index date.

9.2.2 Study Period

All adult use of LDX will be included, including use before the Elvanse Adult® indication was granted. The study period is defined in each data source as the time between the date of first recorded prescription/dispensing for LDX among adults and the latest date of data availability (see Table 1). Data availability in each data source depends on the frequency with which data are updated at each data source and on the approval time necessary for obtaining the data (3 to 12 months for the CPRD, UK; 12 to 24 months in Denmark; and 12 to 24 months in Sweden). However, the Danish Register of Causes of Death and the Swedish Causes of Death Register each have a 2-year lag time for data availability, and the UK Office for National Statistics (ONS) has a 1-year lag time for mortality data availability. Thus, a 1-year lag time in the UK and a 2-year lag time in Denmark and Sweden, between the end of the study observational period (September 2019, for the UK and September 2018 for Denmark and Sweden) and the submission date of the final study report (late 2020) is needed to obtain cause-of-death data in all three countries.

Table 1. Estimated Study Period in Each Study Data Source

Event	CPRD, UK	National Registries, Denmark	National Registers, Sweden
LDX initial launch in country ^a	Mar 2013	Mar 2013	Sep 2013
Elvanse Adult® approval in the UK, Denmark, and Sweden ^a	2015	2015	2015
Study period in each data source (based on first recorded prescription of LDX in each country among adults and data availability in each data source) ^b	Mar 2013 – Sep 2019	Mar 2013 – Sep 2018	Sep 2013 – Sep 2018

^a Provided by Shire.

^b All use of LDX among adults is of interest, including data among adults before Elvanse Adult® authorisation was granted.

9.2.3 Follow-up

Follow-up will start at the index date and end on the earliest of the following possible follow-up termination dates for both exposure groups: (1) first diagnosis of any of the individual cardiovascular events of interest for the composite endpoints (an individual can have more than one endpoint and, depending on which composite endpoint is being considered, follow-up may be censored at the first or at a later event date), (2) end of the study period, (3) termination of enrolment in the health plan or system (or emigration), (4) death, or (5) the date a patient in the remote use of other ADHD treatments cohort is prescribed any other ADHD drug.

If a patient in the remote use of other ADHD treatments cohort is prescribed/dispensed LDX he/she will enter the LDX cohort, if all other inclusion and exclusion criteria are met at that date, and his/her time in the remote use of other ADHD treatments cohort will be censored.

9.3 Variables

9.3.1 Exposure Assessment

The **index medication** in the LDX cohort is the lisdexamfetamine (Anatomical Therapeutic Chemical [ATC] code, N06AB12) exposure that qualifies the patient to enter the study. The index LDX prescription is the first LDX prescription/dispensing in the data source delineating entry into the LDX study cohort and initiation of patient follow-up. The index date for the LDX cohort is the date of the index LDX prescription.

LDX days' supply will be estimated similarly in all data sources and will be based on the prescription or dispensing information as recorded in each database. When days' supply is not directly provided, this information will be estimated from other information, such as the amount prescribed/dispensed and the defined daily dose (DDD) or numeric daily dose (dosing instructions), the number of individual product packs prescribed, and the pack type or size. The World Health Organization (WHO) definition of a DDD is "the assumed average maintenance dose per day for a drug used for its main indication in adults" (WHO Collaborating Centre for Drug Statistics Methodology, 2009). The DDD for lisdexamfetamine is 30 mg (WHO Collaborating Centre for Drug Statistics Methodology, 2013).

Dose (mg/day) of LDX will be the dose at index date. When the dose is missing, an attempt to estimate the dose will be done using the available recorded information (e.g., strength, number of units, amount of drug prescribed/dispensed). Information on the amount dispensed (package size and number) and strength is recorded in the CPRD and in the Nordic prescription registries.

The **number of LDX prescriptions/dispensings** will be the total number of repeated prescriptions/dispensings of LDX over the study period.

The **index medication in the remote use of other ADHD treatments cohort** is the last prescription/dispensing of other ADHD medications in the data source that occurred at least 180 days before index date. As previously described, the index date of each patient in the remote use of other ADHD treatments cohort will be the index date of the matched LDX new user, which will be at least 181 days after the last ADHD medication prescription/dispensing date. The number and proportion of users of “other ADHD treatments” that qualified for remote use cohort entry by each specific drug substance will be described.

The selection of centrally acting sympathomimetics to be included in the remote use of other ADHD treatments cohort is based on the ATC classification system code N06BA. The following specific ADHD medications will be considered as “other ADHD treatments”:

- Amphetamine (ATC: N06BA01)
- Dexamphetamine (ATC: N06BA02)
- Methylphenidate (ATC: N06BA04)
- Atomoxetine (ATC: N06BA09)

Other medications included in the same ATC group (N06BA), such as dexamethylphenidate, pemoline, or modafinil, will not be included in the remote user cohort because their use is very low or absent in the three countries of interest, or the main indication is not ADHD. Amphetamine will be included in the study because it is used in Denmark and Sweden, although it is not approved in the UK.

9.3.1.1 Time at Risk for the LDX Cohort

The time in the denominator of an IR should include every moment during which a person followed is at risk for an event that could get included in the numerator of the rate (Rothman, 2012a). In this study, we are evaluating the IRs and IRRs of cardiovascular events during “current LDX use,” which is defined as exposure to LDX plus 30 days after the end of the last prescription/dispensing. We postulate that the duration of the effect of LDX exposure starts the same date that the treatment is started and may last up to 30 days after last day of treatment, and this is the reason why a 30-day carryover period has been added to the time at risk for current LDX use. To evaluate if LDX may have a delayed effect on the risk of cardiovascular endpoints, we will also evaluate if there is a risk during the time after LDX exposure, which we will call time of “post-LDX use.”

Current LDX use will be the sum of periods of continuous LDX use (with prescription or dispensing gaps of 30 days or less). Periods of continuous use will be defined as the time elapsed between the date of LDX prescription/dispensing start and 30 days after the date of end of days’ supply. A gap will be the period between the date of end of days’ supply and the date of the next LDX prescription or dispensing. After a treatment gap of more than 30 days, follow-up time from the current LDX use category will resume upon LDX re-initiation if a follow-up termination event has not occurred. Exposure time from overlapping prescriptions/dispensings of LDX will be stacked (i.e., the start of the

subsequent overlapping prescription will be reassigned to the day after the end of days' supply for the prior prescription).

Discontinuation of LDX use occurs when there is no repeated prescription within 30 days after the estimated end of the last prescription/dispensing of index medication. Use of another ADHD medication does not affect the estimated time of LDX discontinuation.

Current LDX use will also be classified in subcategories based on duration of current LDX use during follow-up. The patients will accrue person-time in each category in a time-dependent manner: the time at risk in the category of long-term duration will start after 12 months of current LDX use. A cohort member can contribute to person-time in more than one category of duration of current LDX use.

Current LDX use will also be classified in two subcategories based on concomitant ADHD drug use during follow-up:

- "Current single LDX use": time of current use in which the patient is exposed to LDX, and no other ADHD treatments are prescribed/dispensed.
- "Current LDX use, multiple drug use": time of current use in which the patient is exposed to LDX and to at least one other ADHD treatment (i.e., amphetamine, dexamfetamine, methylphenidate, and atomoxetine; see ATC code list in Section 9.3.1).

The primary and secondary analyses will be based on current LDX overall use (i.e., LDX alone or concurrently with another ADHD medication) and duration of LDX use.

Exploratory analyses will estimate the IR and IRRs of MACE by subcategories of LDX dose during current LDX use, compared with remote use of other ADHD treatments.

To account for possible non-adherence, as well as potential persistence of the drug effect after discontinuation, a sensitivity analysis will be performed with an extended carryover period, and the allowed gap between prescriptions/dispensings (30 days in the primary analysis) will be extended to 60 days.

Post-LDX use will be the sum of all periods of time starting after the end of current LDX use and ending at the end of follow-up.

Post-LDX use will be subclassified in two subcategories based on use of "other ADHD treatments" (i.e., amphetamine, dexamfetamine, methylphenidate, and atomoxetine; see ATC code list in Section 9.3.1) during follow-up:

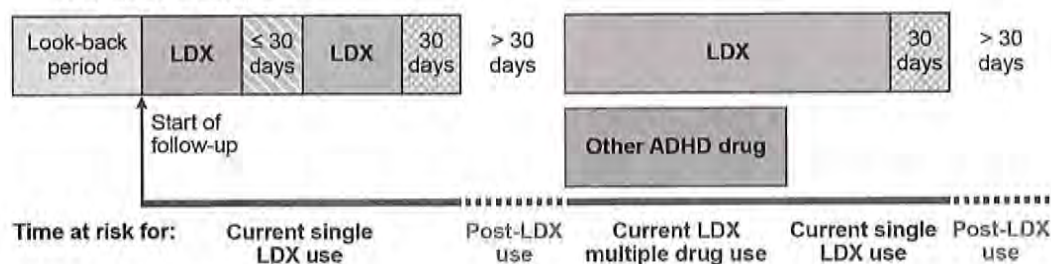
- "Post-LDX use, no ADHD drug use": time of post-LDX use in which the patient is not exposed to any ADHD drug
- "Post-LDX use, with other ADHD drug use": time of post-LDX use in which the patient is exposed to "other ADHD treatment(s)"; exposure to other ADHD treatments during this time may be single drug use or use of multiple drugs at the same time.

During the time of post-LDX use, patients could become current LDX users again if they are prescribed/dispensed LDX. To evaluate whether there is a delayed or long-term

cardiovascular effect of LDX exposure, a sensitivity analysis will be performed comparing post-LDX use versus remote use of other ADHD treatments. To evaluate potential effect of exposure to "other ADHD treatments" in the comparison between post-LDX use versus remote LDX use, an additional secondary analysis will be performed using the time at risk for "post-LDX use, no other ADHD drug use" and "post-LDX use, with other ADHD drug use."

Figure 1 summarizes the time periods of patient observation, including those for calculating time at risk from current LDX use of a study medication.

Figure 1. Summary of the Time Periods of Observation for Each Patient in the LDX Cohort



ADHD = attention deficit hyperactivity disorder; LDX = lisdexamfetamine.

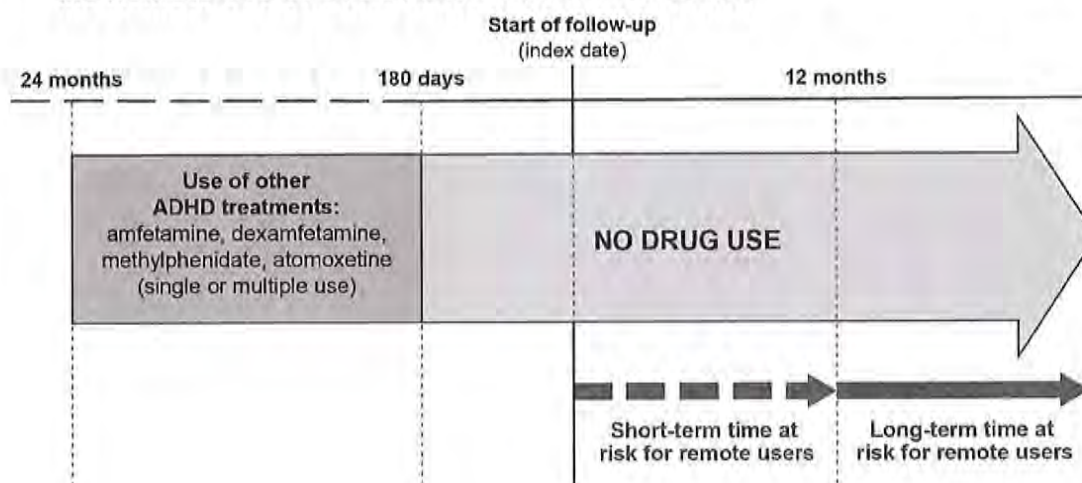
9.3.1.2 Time at Risk for the Remote Use of Other ADHD Treatments Cohort

As previously described, the remote use of other ADHD treatments cohort will be generated by selecting adult patients with at least one prescription/dispensing for amphetamine, dexamphetamine, methylphenidate, or atomoxetine during the 24 months prior to the index date and with no prescription/dispensing of these medications in at least the last 180 days before the index date. Thus, follow-up for the remote use of other ADHD treatments cohort will start at the index date (assigned as the index date of the matched pair or index member of the LDX cohort, which will be at least 181 days after the last ADHD medication prescription/dispensing date) and end at the end of follow-up (see Figure 2).

If individuals in the remote use of other ADHD treatments cohort start treatment with LDX, their time of follow-up in the remote use cohort will end the day before the LDX prescription/dispensing, and they will be allowed to enter the LDX cohort, if all other inclusion criteria for this cohort are fulfilled at that date. If individuals in the remote use of other ADHD treatments cohort start treatment with ADHD drugs other than LDX, their follow-up will end (as described in Section 9.2.3).

Remote users of other ADHD treatments will be classified in subcategories based on duration of follow-up after index date. The patients will accrue person-time in each category in a time-dependent manner: the time at risk in the category of long-term duration of remote use will start after 12 months of follow-up after index date (long-term remote users). A cohort member can contribute to person-time in more than one category of duration of remote use.

Figure 2. Summary of the Time Periods of Observation for Each Patient in the Remote Use of Other ADHD Treatments Cohort



Note: Follow-up for the remote use of other ADHD treatments cohort starts at index date. Once the follow-up starts, patients in the remote use of other ADHD treatments cohort accrue time in the "short-term remote use" category, and on day 366 after index date, the patients in the remote use of other ADHD treatments cohort start accruing time in the "long-term remote use" category.

9.3.2 Study Endpoints

The primary endpoint or main composite cardiovascular endpoint of interest, a MACE type, will include the first occurrence of any of the following individual components during the follow-up:

- Hospitalisation for AMI, fatal or non-fatal
- Hospitalisation for stroke, fatal or non-fatal
- Out-of-hospital coronary heart disease death, including SCD
- Out-of-hospital cerebrovascular death

The secondary endpoints of interest are as follows:

1. An expanded composite cardiovascular endpoint, "EMACE," that includes the first occurrence of any of the following individual components during the follow-up:
 - a. Hospitalisation for AMI, fatal or non-fatal
 - b. Hospitalisation for unstable angina, fatal or non-fatal
 - c. Out-of-hospital coronary heart disease death (including SCD)
 - d. Hospitalisation for stroke, fatal or non-fatal
 - e. Hospitalisation for TIA, fatal or non-fatal
 - f. Out-of-hospital cerebrovascular death
2. A composite "coronary heart disease" endpoint that includes the first occurrence of either a, b, or c, listed in item 1

3. A composite “cerebrovascular” endpoint that includes the first occurrence of either d, e, or f, listed in item 1
4. A composite endpoint that includes SCD and SVA, including ventricular tachycardia, ventricular flutter, and ventricular fibrillation.

Clinical Definitions

The American Heart Association and the World Heart Federation define an AMI by the evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia, including ST elevation myocardial infarction and non-ST elevation myocardial infarction (Thygesen et al., 2012).

Central nervous system infarction is defined as brain, spinal cord, or retinal cell death attributable to ischaemia, based on neuropathological, neuroimaging, and/or clinical evidence of permanent injury. Central nervous system infarction occurs over a clinical spectrum; ischaemic stroke specifically refers to central nervous system infarction accompanied by overt symptoms, while silent infarction by definition causes no known symptoms. Stroke also broadly includes intracerebral haemorrhage and subarachnoid haemorrhage (Sacco et al., 2013).

Unstable angina is defined as new cardiac symptoms or a changing symptom pattern with positive electrocardiogram (ECG) findings, a positive stress test, or a relevant ischaemic substrate on coronary angiography, with or without subsequent percutaneous coronary intervention (Luepker et al., 2003).

Transient ischaemic attack is defined by the American Stroke Association as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischaemia, without acute infarction (Easton et al., 2009).

Serious ventricular arrhythmias will include torsade de pointes, ventricular flutter, and ventricular fibrillation. Torsade de pointes is characterised by ventricular tachycardia associated with a long QT or QTc interval, and electrocardiographically characterised by twisting of the peaks of the QRS complexes around isoelectric line during the arrhythmia (Zipes et al., 2006).

Sudden cardiac death is defined as a sudden pulseless condition (arrest) that was immediately fatal (or rarely resuscitated with death in 48 hours) and was consistent with a ventricular tachyarrhythmia occurring in the absence of a known non-cardiac condition as the proximate cause of the death (Chung et al., 2010).

Operationally, out-of-hospital coronary heart disease, including SCD, or cerebrovascular death include those who died from a cardiovascular or cerebrovascular cause before reaching the hospital and those who die within 30 days after a hospitalisation for a cardiovascular or cerebrovascular cause.

For assessment of the composite endpoints, only the first of any of the individual components occurring during follow-up will be included. For the assessment of each individual endpoint, only the first event of that specific endpoint occurring during follow-

up will be included and the occurrence of one event will not preclude the assessment of a different event type that may happen later. Patients with a prior history of the events of interest will not be excluded at cohort entry, and the presence of prior history of cardiovascular or cerebrovascular events will be taken into account when adjusting the analysis.

9.3.2.1 Endpoint Identification

Events will be identified through (1) hospital discharge diagnoses in Denmark and Sweden, and in CPRD data linkable to Hospital Episode Statistics (HES), (2) electronic algorithms applied to primary care data in CPRD data not linkable to HES, and (3) cause-of-death records from the cause-of-death registries in Denmark and Sweden, and in CPRD data linkable to ONS mortality data. To identify events of interest during follow-up, each data source will be searched for electronic codes that indicate potential occurrences of endpoints. A case-finding algorithm in which cases are identified based on a combination of relevant codes for diagnoses, procedures, and pharmaceutical treatments will be customised and implemented in each data source. These algorithms are based on information from prior published and validated case ascertainment algorithms to maximise case ascertainment sensitivity while retaining those with a high positive predictive value.

The table below presents descriptions of the algorithms for case finding of each endpoint and includes the ICD-10 (*International Statistical Classification of Diseases and Related Health Problems, 10th Revision*) codes for identification of each outcome. Additional details on the validity of the identification algorithms can be found in Annex 3.

Case Identification in Denmark, Sweden, and CPRD Data Linkable to HES/ONS

- **Hospitalisation for AMI, stroke, unstable angina and TIA** events will be identified based on the presence of a hospitalisation with a primary or secondary hospital discharge code (ICD-10) for AMI, stroke, unstable angina or TIA (see Table 2). These events will be considered fatal if the patient died within 30 days after the admission or event date, irrespective of the cause and place of death.
- **Out-of-hospital coronary heart disease death (including SCD) and out-of-hospital cerebrovascular death** events include death events from a cardiovascular or cerebrovascular cause before reaching the hospital. These events will be identified through any out-of-hospital death record with an underlying cause of death recorded in the death certificate being any of the ICD-10 codes listed in Table 2, in the absence of a code for a terminal illness or end-of-life care. The out-of-hospital death endpoint will also include death events that occur outside of a hospital but within 30 days after a hospitalisation for a cardiovascular or cerebrovascular and that will be identified through a record of out-of-hospital death occurring outside of a hospital within 30 days after a hospitalisation (admission or event date) for AMI or unstable angina/stroke or TIA, irrespective of the cause of death.
- **SCD/SVA** events will be identified based on the presence of a hospitalisation with a primary or secondary discharge code for SCD or SVA (see Table 2), with SVA either associated or not associated with death at discharge. SCD/SVA events will

also include any out-of-hospital death with an underlying cause of death in the death register with any of the listed codes for SCD, SVA, or included in the identification of the out-of-hospital coronary heart disease death and in absence of a terminal illness or end-of-life care. These codes have proved to have high positive predictive value (PPV) when evaluating SCD and SVA (De Bruin et al., 2005; Johannes et al., 2010; Varas-Lorenzo et al., 2009).

Case Identification in CPRD Data Not Linkable to HES/ONS

- **Hospitalisation for AMI:** events will be identified through an algorithm based on Read code for AMI, hospitalisation, and other covariables of interest such as coronary revascularisation procedures, coronary angiography, or other imaging procedures, ECGs, positive cardiac enzymes, or thrombolytic therapy.
- **Hospitalisation for stroke:** events will be identified through an algorithm based on Read code for stroke, hospitalisation and other covariables of interest such as records of computed tomography (CT) scans, magnetic resonance imaging (MRI), or electroencephalogram (EEG), referrals to neurologist, stroke-related surgery/procedures, thrombolytic therapy, aspirin, evidence of residual damage (paresis, numbness, speech, vision, swallowing problems), or rehabilitation/physiotherapy.
- **Hospitalisation for unstable angina:** events will be identified through an algorithm based on Read codes for unstable angina, hospitalisation and other covariables of interest that may include chest pain, shortness of breath, left bundle branch block, ECG, coronary revascularisation procedure, stress testing, cardiac enzymes, or coronary angiography results.
- **Hospitalisation for TIA:** events will be identified through an algorithm based on Read code for TIA, hospitalisation and other covariables of interest that may include no evidence of residual damage, rehabilitation or physiotherapy, records of CT scans, MRI, EEG, or symptoms of carotid or vertebrobasilar or uncertain territory, or carotid endarterectomy.
- **Out-of-hospital coronary heart disease death (including SCD) and out-of-hospital cerebrovascular death:** events will be identified through any death out-of-hospital record with an underlying cause of death recorded in the electronic medical record CPRD GOLD database being the translation to Read codes of any of the corresponding ICD-10 codes in Table 2, in absence of a terminal illness or end-of-life care. A record of out-of-hospital death within 30 days after a hospitalisation (admission or event date) for AMI or unstable angina/stroke or TIA irrespective of the cause of death.
- **SCD+SVA (fatal and non-fatal):** events will be identified through an algorithm based on Read codes for SCD, SVA, hospitalisation and other covariables of interest that may include ECG results.

Details on the algorithms and operational definitions will be provided in the SAP.

Table 2. Case Finding of Each Endpoint

Case finding: ICD-10 hospital discharge codes in CPRD data linkable to HES/ONS data and in Denmark and Sweden	
Hospitalisation for AMI	Hospitalisation for Stroke
Joensen et al. (2009); Pajunen et al. (2005)	Andrade et al. (2012); Flynn et al. (2010); Kirkman et al. (2009); Kokotailo and Hill (2005); Krarup et al. (2007); Roumie et al. (2008)
I21, Acute myocardial infarction	- I60, Subarachnoid haemorrhage - I61, Intracerebral haemorrhage - I63, Cerebral infarction - I64, Stroke, not specified as haemorrhage or infarction
Hospitalisation for unstable angina	Hospitalisation for TIA
Joensen et al. (2009)	Johnsen et al. (2002)
I20.0, Unstable angina	G45, Transient cerebral ischaemic attacks and related syndromes
Hospitalisation for SVA/SCD	
De Bruin et al. (2005); Johannes et al. (2010); Varas-Lorenzo et al. (2009); Chung et al. (2010)	
- I47.0, I47.2, I49.0 - I46.0, I46.1, I46.9 - R96.1, R98	
Coronary and cerebrovascular deaths out-of-hospital	
AMI/coronary heart disease death, including SCD	Stroke/cerebrovascular deaths
Chung et al. (2010)	Muller-Nordhorn et al. (2008)
I10, I11.9, I20-I25, I42.8-I42.9, I46, I47.0-I47.2, I49.0, I49.8-I49.9, I51.6, I51.9, I70.9, R96.1, R98	I60-I69, G45, R96.0, R96.1, R98

AMI = acute myocardial infarction; CPRD = Clinical Practice Research Datalink; HES = Hospital Episode Statistics; ICD-10 = *International Classification of Diseases and Related Health Problems, 10th Revision*; ONS = Office for National Statistics (United Kingdom); SCD = sudden cardiac death; SVA = serious ventricular arrhythmia; TIA = transient ischaemic attack.

Note: When a fourth digit is not specified for an ICD-10 code, all subcategories of that code are included. See the complete list of ICD-10 codes and terms for study endpoints in Annex 4.

9.3.2.2 Case Ascertainment

Each data source will be searched for electronic codes that indicate the possibility of an endpoint of interest using electronic case-finding algorithms.

Case Ascertainment in the Danish and Swedish Data Sources and in the CPRD Whose Data Are Linkable to HES or ONS

- Hospitalised cases will be ascertained through primary and secondary hospital discharge diagnoses and considered confirmed if the primary hospital discharge

diagnosis code is consistent with one of the codes listed in Table 2 for the corresponding event of interest. Hospitalised cases ascertained through secondary discharge diagnosis codes will not be considered confirmed unless they have gone through a validation process.

- In CPRD, any potential cases identified by discharge codes in non-primary positions will be further reviewed. In each data source, the best code reflecting a cardiovascular reason for admission will be identified and used to further evaluate the events.
- All deaths occurring during the study will be identified. Death certificate information available from ONS or the national death registries includes the date and causes of death coded according to ICD-10. This data will be linked to the hospitalisation data to classify deaths as occurring inside versus outside the hospital. All patients in Denmark and Sweden will have information on in-hospital and out-of-hospital cause of death available for the entire covered population. In CPRD, in-hospital and out-of-hospital fact and cause of death are available for the approximately 65% of patients whose data are also linkable to HES and or ONS data.
- Out-of-hospital coronary heart disease and cerebrovascular deaths will be considered confirmed if the underlying cause-of-death codes from the national death register are consistent with the codes in Table 2.
- Patients in the CPRD who are linkable to HES or ONS but who do not have event codes ascertained through hospital discharge diagnoses recorded in HES or cause-of-death codes recorded in ONS will also be electronically screened for potential events of interest recorded in the electronic medical record CPRD GOLD database, that might qualify the patient as a case; therefore, the same electronic algorithm based on Read codes used for non-linked patients will be applied.

Case Ascertainment for Patients in CPRD Whose Data Are Not Linkable to HES or ONS

Case finding algorithms will be applied to electronically screen for potential events of interest recorded in the electronic medical record CPRD GOLD database and further information will be obtained for case validation. Manual review of the historical chronological information surrounding the recorded date of death can provide useful information on the cause.

9.3.2.3 Endpoint Validation

Cases identified through electronic algorithm that are not considered confirmed at the identification step, will undergo further validation. The following sections describe the processes for obtaining additional information on the endpoints of interest, for endpoint validation, by data source.

Endpoint Validation in the CPRD

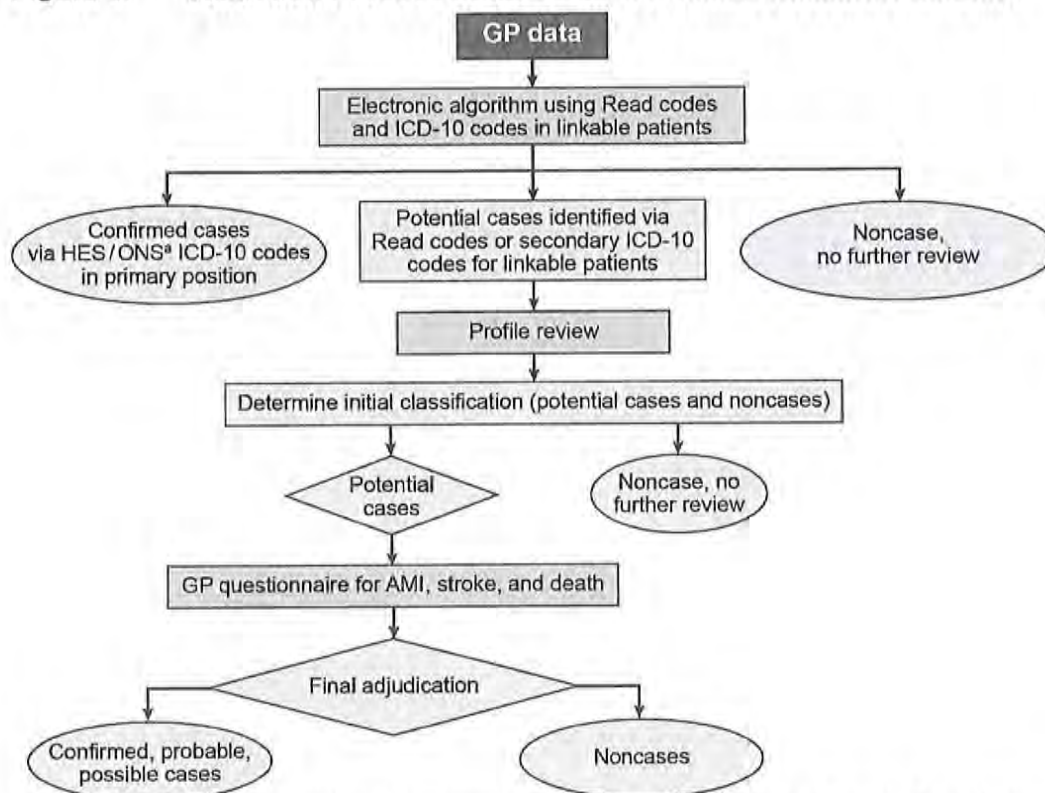
In the UK (CPRD), the general practitioners (GPs) work within the National Health Service (NHS) and are the first point of contact for the patients enrolled into their practices. Therefore, the GP is informed of all visits to the hospital, including emergency

department visits and visits to specialists. As with emergency department visits, it is expected that information from patients who attend chest pain units would be reported to the GP and entered into the patient GP record, which constitutes the data for CPRD. Validation will start after cases have been identified through the electronic algorithm and will end before the final analyses have been completed.

Additional information on the endpoints of interest, for endpoint validation, will be obtained by the following process, which is summarised in Figure 3 on page 34:

1. Patient profile review: the purpose of profile review in the CPRD is to screen out non-cases and make an initial assignment of case status. Patient profiles are chronological listings of the diagnoses, clinical tests, procedures, and medications recorded in the electronic database. A clinician investigator blinded to the exposures of interest will review and screen all the patient profiles and classify each patient as either a potential case, according to level of certainty, or a non-case. For unclear cases and all non-cases, double review by the profile review team lead will take place, and consensus will be reached. A quality review of a sample of 20 cases will be performed.
2. Request additional information: for potential cases identified in the CPRD for which the event was determined using the electronic medical record in the GOLD database (i.e., using the Read code algorithm) and that did not have a confirmed event or that have not been screen out at the patient profile review phase, additional clinical and other information for case validation will be obtained via questionnaires sent to the GP, including a request for copies of selected test results and clinical information from the medical record regarding the event, as available. Previous pharmacoepidemiologic studies of AMI and stroke in the CPRD have conducted partial or overall validation of these endpoints through questionnaires sent to the corresponding GPs for access to information related to the event of interest, including hospital discharge letters (Arana et al., 2006; Garcia Rodriguez et al., 2004; Varas-Lorenzo et al., 2000). Death certificates can be obtained by special request for those fatal cases with recorded unavailable/unknown cause of death; these usually require 4 to 8 weeks for retrieval, with a response rate of approximately 80%.
3. Review and adjudicate cases: clinician reviewers blinded to study exposure will review all available information—including patient profiles, completed GP questionnaires, and electronic copies of other information from the medical record—for each potential event and classify the event as a confirmed, probable, or possible case or a non-case.

Figure 3. Validation Process in the Clinical Practice Research Datalink



AMI = acute myocardial infarction; GP = general practitioner; HES = Hospital Episode Statistics; ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*; ONS = Office for National Statistics.

^a Approximately 50% of patients are linkable to HES and ONS.

Endpoint Validation in Danish National Registries

No validation will be performed in Denmark.

Endpoint Validation in Swedish National Registries

No validation will be performed in Sweden.

9.3.3 Other Variables

The study will define other variables that will be used to describe the study population and to control for confounding (using propensity scores). The availability of data on each variable will vary by data source (e.g., no or limited laboratory data are available in Sweden and Denmark). Outpatient diagnoses will be available for the CPRD before the index date. In Denmark and Sweden, outpatient diagnoses from hospital-based specialist outpatient clinics are available from the national patient registries. In general, in database analyses, the absence of information, such as an outpatient diagnosis, is classified as the absence of the condition. All patients without a dispensing for a

medication are considered unexposed, and all patients without a diagnosis are considered as not having the condition.

Demographics

Data on the following demographic variables will be collected:

- Age
- Sex
- Calendar year of the index date
- Primary care health practice/geographic region
- Duration of available history in the database up to the index date
- Duration of follow-up

Medical History

Medical history (yes/no) ascertained by outpatient (GP, specialist, hospital outpatient) and/or hospital discharge diagnosis codes and/or prior medication prescriptions/dispensings recorded at any time before the index date:

- ADHD-related history:
 - Time since first ADHD diagnosis
 - Number of medical visits with ADHD listed as a diagnosis in the previous year
 - Number of previous ADHD regimens (treatments with different drug substances)
 - Duration of continued use of prior ADHD drugs
 - Use of multiple concurrent ADHD medications
- Cardiovascular disease: assessment of prior occurrence of study endpoints and broader subtype categories such as ischaemic heart disease, heart failure, and cerebrovascular disease
- Other diseases: hypertension (determined by the closest blood pressure measurements to the index date, when available), hyperlipidaemia, diabetes, renal disease, cancer
- Psychiatric comorbidities: mood disorders, anxiety disorders, eating disorders, or alcohol or substance abuse disorders
- Obesity
- Smoking (in the CPRD) and smoking-related disease (e.g., chronic obstructive pulmonary disease)

Use of Other Medications

Prior to index date:

- Use of "other ADHD medications" ever before, among both cohorts, and irrespective of being the prescriptions that qualified for entry into the remote use of other ADHD treatments cohort
- Use of cardiovascular or antihypertensive medications within 6 months before the index date

9.4 Data Sources

To obtain sufficient study size and person-years of LDX use to address the objective, the study will be implemented in multiple health care data sources in European Union (EU) countries where LDX is expected to be approved for use in adult patients with ADHD. Individual studies will be conducted in each EU country according to a common core protocol. Data sources in the countries where the adult indication has been approved include the UK, where the GPs' electronic medical records routinely include hospitalisations and cause of death, and Denmark and Sweden, where outpatient prescriptions, hospital diagnoses, and cause of death are available from national patient registries. No other EU countries have had the adult indication approved; therefore, data on adult use of LDX in other countries are not relevant in the current study. The data sources discussed in the following sections will be used to identify the cohort, exposures, outcomes, and risk factors of interest. Data available in each data source are summarised in Table 3 on page 40.

9.4.1 United Kingdom

In the UK, nearly all residents are registered in a general medical practice that uses electronic medical records. Those records are available for research purposes in the CPRD (<http://www.cprd.com/>). The CPRD contains diagnostic and prescribing information recorded by GPs as part of their routine clinical practice in the UK (<http://www.cprd.com/intro.asp>) and has information on 5.4 million individuals (active contributors), which represent approximately 8.4% of the UK population. Patients registered are representative of the whole UK population in terms of age and sex. The GOLD online database contains the data collected in primary care practices that participate in the CPRD. These data are linkable, at least partially, with other health care data sets (e.g., hospitalisation and national mortality data). Updated, valid, linked data are available through the CPRD Division of the UK Medicines and Healthcare Products Regulatory Agency.

Approximately 65% of the English practices have consented to have their patient information linked to other health care data sets, such as HES and the national death register at the ONS, via the patient's NHS number, sex, date of birth, and postal code. English practices represent approximately 75% of all practices contributing to the CPRD; therefore, approximately half of the total CPRD practices have this link. Linkage to HES enables access to the hospitalisation data, that is, admission date, discharge diagnoses,

and procedure codes. Linkage to the national death register at ONS can be used to ascertain death and causes of death and to validate the mentions of death in the GP records. Death rates by age group and various causes of death, including ischaemic heart disease, are comparable between linked CPRD data and official rates for England and Wales, and the subset of linked CPRD practices seems to be a representative sample of the general population (Setakis et al., 2010). In the CPRD, participating GPs are required by the NHS to record in the database the date of death. The fact of death is well captured in the database, and date of death has been reported to be accurately recorded for most of the recorded deaths (Shah and Martinez, 2004). However, cause of death is recorded with a variable degree of completeness. Data in HES and ONS are updated every 6 months, but the lag time can be more than 1 year.

Detailed information on prescriptions written by GPs, including prescribed dose and duration, is routinely recorded in the data source. Read codes are used for diagnoses, and Multilex codes are used for medications. Additional diagnostic and treatment information can be found in free-text fields, letters from specialists and hospitals, and other sources. Because GPs serve as the gatekeeper for all medical services, any visit to a specialist or hospital requires communication back to the GP, who enters that information into the medical record. The validity of the former General Practice Research Database, upon which the CPRD was founded, as a reliable data source for drug safety studies in numerous therapeutic areas is well established (Jick et al., 1991; Jick et al., 2003).

Research at the CPRD requires approval from the CPRD Independent Scientific Advisory Committee.

9.4.2 Denmark

The Danish national databases of interest to this study are the Danish Civil Registration System, Danish National Patient Register, Danish Psychiatric Central Research Register, Danish National Prescription Register, and Danish Register of Causes of Death.

The Danish Civil Registration System, an administrative database that was established in 1968 (Schmidt et al., 2014), contains individual-level information on all persons residing in Denmark. By January 2014, it had cumulatively registered 9.5 million individuals. A unique 10-digit Civil Personal Register number is assigned to all persons and allows for the individual-level linkage of records in Danish registers. Information on migration and vital status, which is updated daily, allows for nationwide cohort studies with virtually complete long-term follow-up on emigration and death. These data have high accuracy and completeness and can be retrieved for research purposes.

The Danish health care system provides universal coverage to all Danish residents—5.6 million inhabitants (Eurostat, 2014). Health care coverage includes visits to GPs and specialists, hospital admissions, and outpatient visits. The costs of medicines are partially covered by the Danish health service. The Danish Civil Registration System allows for personal identification of each person in the entire Danish population and for the possibility of linkage to all Danish registries containing civil registration numbers,

such as the Danish National Patient Register, Danish National Prescription Registry, and the Danish Register of Causes of Death. Data collected in these registries are available for research purposes. The process requires collaboration with a local university or investigator affiliated with a research institute to access the data and ethics committee notification or approval to handle data (Danish Data Protection Agency, 2011; Danish Health and Medicines Authority, 2014). All applications have to be submitted in Danish.

Denmark's primary health care sector, which includes GPs, specialists, and dentists, generates about 96% of the prescription sales, most of which are reimbursable and are dispensed by community pharmacies. Each dispensing record contains information on the patient, drug, and prescriber. Dispensing records retain the patient's universal personal identifier, allowing for individual-level linkage to all Danish registries and medical databases.

The Psychiatric Central Research Register, established in 1970, provides data on treatments, diagnoses, and referrals for patients treated at psychiatric departments in Denmark (Mors et al., 2011). The ICD-8¹ system was used until 1994, and ICD-10 thereafter. Quality assessment information concerning treatment of several mental disorders are made public every year. The nationwide registration of severe mental disorders is almost complete. However, most cases with mild to moderate mental disorders are managed by GPs or specialists in psychiatry working in private practice and are thus not registered in this database. Since 1995, data for this register have been collected by the Danish National Patient Register.

The Danish National Patient Register includes data on all hospital admissions since 1 January 1977 and on outpatient clinic and emergency department visits since 1995 (Lynge et al., 2011). Hospital discharge diagnoses and information on surgical procedures, in-hospital deaths, and some selected drugs are recorded. After 1993, hospital discharge diagnoses are coded using *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10) codes.

The Danish National Prescription Registry provides patient-level data on drug prescriptions dispensed by pharmacies since 1994 (Kildemoes et al., 2011). The National Prescription Registry collects data on reimbursed and unreimbursed drugs. This registry is administered by Statistics Denmark.

In Denmark, while the data on all-cause mortality comes from the Civil Registration System, the Danish Register of Causes of Death provides data on cause(s) of death for all deaths among citizens who died in Denmark since 1875, and since 1970 has computerised individual records. Classification of cause(s) of deaths is done in accordance to the World Health Organization guidelines; since 1994, cause of death is recorded by ICD-10 codes. The quality of the register on causes of death relies mainly upon the correctness of the physicians' notification and the coding in the National Board of Health (Helweg-Larsen, 2011).

¹ ICD-8 = *International Classification of Diseases, 8th Revision*.

9.4.3 Sweden

The Swedish national databases of interest to this study are the Swedish National Patient Register, the Prescribed Drug Register, and the Causes of Death Register.

In Sweden, the national health care system provides universal coverage to all residents—9.6 million inhabitants (Eurostat, 2014). Health care coverage includes visits to GPs and specialists, hospital admissions, and hospital outpatient visits; drug costs are either partially or completely covered. A centralised Civil Registration System has been in place for many years, enabling personal identification of each person in the entire population and linkage to all national registers containing civil registration numbers (e.g., Swedish National Patient Register, cancer register, Prescribed Drug Register, Causes of Death Register and population registers) (Furu et al., 2010).

The Swedish National Patient Register covers all inpatient care in Sweden since 1964, with national coverage since 1987. The register includes information on diagnoses, surgical procedures, and in-hospital deaths. Since 2001, it also includes outpatient hospital care data. The register includes about 1.5 million discharges annually. Whereas coverage of the inpatient register is currently almost 100%, coverage of hospital-based outpatient care is not complete (about 80%) (Ludvigsson et al., 2011). Visits to GPs outside the hospitals are not included in the registers.

The Prescribed Drug Register provides patient-level data on all dispensed and prescribed drugs (reimbursed and unreimbursed) in ambulatory care to the whole population of Sweden since July 2005. The information on drugs includes drug substance, brand name, formulation and package, dispensed amount, dosage, expenditure and reimbursement, date of prescribing and dispensing, place of residence of the patient, practice issuing the prescription, and prescriber's specialty (Wettermark et al., 2007).

The Causes of Death Register records mortality data starting in 1961. It shows the underlying cause of death coded according to ICD-10 since 1997. The register includes all those who died during a given calendar year and were registered in Sweden at the time of death, regardless of whether the death occurred within the country (Socialstyrelsen, 2016).

Data requests for research purposes require collaboration with university or affiliated researchers and ethics committee approval.

Table 3. Main Features of Selected European Databases

Feature	United Kingdom, CPRD (N = 64,308,261) ^a	Danish Patient and Prescription National Databases (N = 5,627,235) ^a	Swedish Patient and Prescription National Databases (N = 9,644,864) ^a
Database type	Primary health care electronic medical record database plus partial linkage to HES and other data	National health record databases capable of linkage with other databases through a unique personal identification number	National health record databases capable of linkage through the unique civil personal registration number
Database population	5.4 million	5.6 million (Eurostat, 2014)	9.6 million (Eurostat, 2014)
Proportion of the country's population covered by the database	8.4% of UK population: 64.3 million (Eurostat, 2014)	100%	100%
Representativeness of patients	Representative of sex and age of UK population	Total population covered	Total population covered
Data on medications	Any prescribed by GP, prescription date and substance for outpatient prescription medications prescribed by the GP	Pharmacy-dispensed prescriptions, reimbursed and unreimbursed since 1994	Pharmacy-dispensed prescriptions, reimbursed and unreimbursed; Since 2005
Dose	Prescribed dose	Formulation strength	Formulation strength
Duration	Indicated in the written prescription	Based on prescriptions	Based on prescriptions
Drug dictionary codes/therapeutic classification	Multilex/British National Formulary	ATC	ATC
Clinical indication	Diagnosis associated with new courses of medications, but completeness is variable Computerised free-text information is available for review	Not recorded; can be based on proxies	Not recorded; can be based on proxies
Outpatient diagnosis	Yes, also date of GP visit	Only outpatient hospital diagnosis in the National Patient Register	Only outpatient hospital diagnosis in the National Patient Register

Feature	United Kingdom, CPRD (N = 64,308,261) ^a	Danish Patient and Prescription National Databases (N = 5,627,235) ^a	Swedish Patient and Prescription National Databases (N = 9,644,864) ^a
Hospital diagnosis	Date of hospitalisation and diagnosis recorded by GPs and partial linkage to HES (admission and discharge)	Yes	Yes
Disease and procedures codes	Read codes ICD-10-CM codes (HES)	ICD-10	ICD-10
Lifestyle risk factors	Yes, but completeness is variable	No	No
Data availability	Since 1987 Current linkage to HES/ONS for ~55% of practices	Prescriptions since 1994; hospitals since 1977; outpatient hospital specialist clinics since 1995	Prescriptions since July 2005; Hospital, since 1987; outpatient clinics, since 2001
Approximate time lag (updates)	6-12 weeks HES/ONS data: 1+ year	6-18 months, but usually available at midyear	Usually available in quarter 3-4 of the following year
Approval process for database research	Independent Scientific Advisory Committee approval of protocol is required	Approval by Danish Data Protection Agency, Danish Health and Medicines Authority, and Statistics Denmark, depending on level and type of data	Data application and ethics committee approval required

ATC = Anatomical Therapeutic Chemical; CPRD = Clinical Practice Research Datalink; GP = general practitioner; HES = Hospital Episode Statistics (database); ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*; ICD-10-CM = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification*; UK = United Kingdom.

^a Population data from Eurostat (2014).

9.5 Study Size

The study size will be driven by the person-time at risk of current LDX use that will be available in the selected data sources during a defined study period. No prescription of LDX prior to 2013 is recorded in these databases. Given the recent approval of Elvanse Adult®, it is not yet known how much time will be necessary in these countries to provide sufficient size for the study.

Table 4 shows the data on LDX utilisation among adults in Europe from a drug utilisation study conducted by IMS Health (2015) prior to approval of Elvanse Adult®.

- Data from the UK CPRD showed that, during 2014, a total of 281 patients of all ages (14 aged 19-25 years and 17 aged > 25 years), received 1,538 prescriptions for Elvanse. Cumulative data from the UK CPRD showed that, from March 2013 through December 2014, a total of 306 patients of all ages (16 aged 19-25 years and 20 aged > 25 years), received 1,921 prescriptions for Elvanse. The mean duration of exposure was 263 days among patients aged 19-25 years and 186 days among patients aged > 25 years; thus, the estimated total person-time of exposure among patients aged > 19 years in the UK between 2013 and 2014 is 21.7 person-years (11.5 from those aged 19-25 years and 10.2 from those aged > 25 years).
- Data from the Danish National Prescription Registry and the Danish National Hospital Registry showed that between March and December 2013, a total of 1,040 patients of all ages (138 aged 19-25 years and 329 aged > 25 years), received 3,111 prescriptions for Elvanse. The average duration of exposure ranged between 73.8 and 76 days. The estimated total person-time of exposure among patients aged > 19 years in Denmark in 2013 and 2014 is 96.4 person-years (27.9 from those aged 19-25 years and 68.5 from those aged > 25 years).
- Data from the Swedish National Prescription Register showed that, from March 2013 through December 2014, a total of 8,703 patients received 29,380 prescriptions of Elvanse; 5,195 of these patients (60%) were aged > 19 years. The mean duration of exposure among patients of all ages was 144.6 days. In Sweden in 2013 and 2014, the total person-time of exposure among patients aged > 19 years (estimated using the mean duration of exposure for all ages) was 2,058.1 person-years.

Table 4. Number of Adult Patients and Annual Duration of Use of Lisdexamfetamine, by Data Source

Data Source, Year	Age (Years)	Number of Patients	Duration of Exposure (in Days) Mean (SD) Median (min; max)	Calculated Average Daily Dose of Elvanse (mg) Mean (SD) Median (min; max)	Cumulative Person-years ^a
CPRD, 2014	19-25	14	242.0 (104.0) 258 (80; 365)	54.0 (18.3) 70 (30; 70) ^b	9.3
	> 25	17	187.0 (131.1) 204 (14; 365)	46.0 (14.2) 50 (30; 70) ^b	8.7
CPRD, ^c Mar 2013 - Dec 2014	19-25	16	263.0 (124.7) 284 (30; 415)	54.0 (17.5) 50 (30; 70) ^b	11.5
	> 25	20	186.0 (161.7) 149 (14; 460)	45.0 (13.8) 50 (30; 70) ^b	10.2
Denmark, 2013 ^d	19-25	138	73.8 (62.1) 62.7 (12.9; 286.3)	43.8 (14.3) 45.5 (7.1; 69.2) ^e	27.9
	> 25	329	76.0 (68.3) 54.6 (12.9; 412.1)	45.0 (15.1) 42.9 (13.6; 69.8) ^e	68.5
Sweden 2013	19-25	80	All ages 60.1(34.3)	All ages 42.7 (15.7)	13.2
	> 25	302	50 (12; 122)	30 (30; 70)	49.7
Sweden 2014	19-25	1,167	All ages 141.2 (108.7)	All ages 44.7 (15.5)	451.5
	> 25	3,943	106 (15; 365)	50 (30; 70)	1,525.3
Sweden, ^c 2013-2014	19-25	1,184	All ages 144.6 (115.9)	All ages 44.6 (15.5)	469.1
	> 25	4,011	106 (15; 487)	50 (30; 70)	1,589.0

CPRD = Clinical Practice Research Datalink; SD = standard deviation.

^a Estimated by RTI-HS based on (number of patients * mean duration)/365.^b Based on an unknown number of prescriptions.^c Cumulative data for the stated time period.^d Data from the National Prescription Registry and the National Hospital Registry from March to December 2013.^e Data for all ages, based on 770 of the 3,111 prescriptions.

Source: IMS Health (2015).

Table 5 shows the estimated person-years of LDX current use needed to have an 80% probability that the upper limit of the 95% CI for the IRR for the MACE endpoint in the LDX new users cohort versus the remote use of other ADHD treatments cohort is less than 1.5 to 5 if the true IRR is 1.0, for MACE incidence rates ranging from 1 to 5 events per 1,000 person-years in the remote use of other ADHD treatments cohort. Calculations were made by using Episheet (Rothman, 2012b). For example, if the incidence rate is 1 per 1,000 person-years, the true IRR is 1.0, and the LDX new users meeting study criteria have a total of 7,800 person-years of exposure, there is a probability of 80% that an IRR of 3.0 can be excluded.

Table 5. Estimated Number of Person-years Exposed to LDX Needed to Have an 80% Probability That the Upper Limit for the 95% Confidence Interval of the Incidence Rate Ratio is Below 1.5, 2, 3, 4, or 5

Incidence per 1,000 Person- years	Upper Limit for the 95% Confidence Interval of the Rate Ratio is ...				
	1.5	2	3	4	5
1	57,240	19,590	7,800	4,900	3,640
2	28,590	9,790	3,900	2,450	1,820
3	19,040	6,520	2,600	1,630	1,210
4	14,270	4,890	1,950	1,230	910
5	11,410	3,910	1,560	980	730

LDX = lisdexamfetamine.

Note: The probability that the upper bound of the 95% confidence limit of the incidence rate ratio is 1.5, 2, 3, 4, or 5 assumes that the true incidence rate ratio is 1.0. Assumes a ratio of 5:1 comparator to lisdexamfetamine-exposed person-years.

Table 6 shows the estimated number of people exposed to LDX needed to have an 80% probability that the upper limit for the 95% CI of the IRR is below 1.5, 2, 3, 4, or 5 for average durations of LDX use of 75, 100, 200, and 300 days. For example, if the incidence rate is 1 per 1,000 person-years and the true IRR is 1.0, we would need 37,986 patients with an average duration of LDX use of 75 days, 28,490 patients with an average duration of LDX use of 100 days, 14,245 patients with an average duration of LDX use of 200 days, or 9,497 patients with an average duration of LDX use of 300 days to have an 80% probability that an IRR of 3.0 can be excluded.

Table 6. Estimated Number of People Exposed to LDX Needed to Have an 80% Probability That the Upper Limit for the 95% Confidence Interval of the Rate Ratio is Below 1.5, 2, 3, 4, or 5, by Average Duration of LDX Use

Average Duration of LDX Use	Incidence per 1,000 Person- years	Upper Limit for the 95% Confidence Interval of the Rate Ratio is Below:				
		1.5	2	3	4	5
75 days	1	278,759	95,403	37,986	23,863	17,727
	2	139,233	47,677	18,993	11,932	8,863
	3	92,725	31,752	12,662	7,938	5,893
	4	69,495	23,814	9,497	5,990	4,432
	5	55,567	19,042	7,597	4,773	3,555
100 days	1	209,069	71,552	28,490	17,897	13,295
	2	104,425	35,758	14,245	8,949	6,648
	3	69,544	23,814	9,497	5,954	4,420
	4	52,121	17,861	7,122	4,493	3,324
	5	41,675	14,281	5,698	3,579	2,666

Average Duration of LDX Use	Incidence per 1,000 Person- years	Upper Limit for the 95% Confidence Interval of the Rate Ratio is Below:				
		1.5	2	3	4	5
200 days	1	104,535	35,776	14,245	8,949	6,648
	2	52,212	17,879	7,122	4,474	3,324
	3	34,772	11,907	4,748	2,977	2,210
	4	26,061	8,930	3,561	2,246	1,662
	5	20,838	7,141	2,849	1,790	1,333
300 days	1	69,690	23,851	9,497	5,966	4,432
	2	34,808	11,919	4,748	2,983	2,216
	3	23,181	7,938	3,166	1,985	1,473
	4	17,374	5,954	2,374	1,498	1,108
	5	13,892	4,760	1,899	1,193	889

LDX = lisdexamfetamine.

Note: The probability that the upper bound of the 95% confidence limit of the incidence rate ratio is 1.5, 2, 3, 4, or 5 assumes that the true incidence rate ratio is 1.0. Assumes a ratio of 5:1 comparator to lisdexamfetamine-exposed person-years.

During 2013 and 2014, LDX was not approved for adults, and after regulatory approval of LDX for adults, the actual use is expected to be greater than the projections listed here. The observed use of LDX in 2013 and 2014 suggests that after the adult indication is approved, it is not unreasonable to expect 1,500 person-years of LDX use across all the data sources per year. Thus, a study starting in late 2019 would have accumulated at least 2,176.2 person-years of LDX use from the years 2013 and 2014 (21.7 person-years in the UK, 96.4 in Denmark during 2013, and at least 2,058.1 in Sweden), and would probably have more than 7,800 person-years of LDX use, assuming 1,500 additional person-years per year of LDX current use and accounting for time lag of available data in each country. This would be in line with the 7,800 person-years needed to exclude an IRR above 3 with an 80% probability, if the incidence rate in the remote use of other ADHD treatments cohort is 1 per 1,000 person-years (shown in Table 5).

9.6 Data Collection and Management

Routine procedures will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality-control checks of all programs. Each database custodian will maintain any patient-identifying information securely on site according to internal standard operating procedures.

Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except select study staff.

Appropriate data storage and archiving procedures will be followed (i.e., storage on CD-ROM or DVD), with periodic backup of files. Standard procedures will be in place at each research centre to restore files in the event of a hardware or software failure.

9.7 Data Analysis

Database-specific analyses implemented by collaborating research centres will be conducted using SAS software version 9.2 or higher (SAS Institute, Inc., Cary, North Carolina) for the analysis of the Danish and Swedish data. All analyses implemented by the coordinating centre will use SAS version 9.3 or higher.

This analysis section provides an overview of the analyses that will be conducted for this study. Data analyses will occur in three stages:

1. A feasibility assessment that involves monitoring counts of adult LDX users in each data source will be performed annually; patient counts will be obtained from the CPRD Knowledge Centre in the UK (www.cprd.com/contact/) and from publicly available data sources in Denmark and Sweden, Medstats.dk in Denmark (The Danish Health Data Authority, 2015) and the Swedish drug database (Socialstyrelsen, 2014). These data will be reviewed by the research partners before submission to Shire for inclusion in the PBRERs.
2. A country-specific analysis performed by each of the database research partners that will create stratified tables with cross-classifications of patient and person-time counts by exposure category, endpoint, and quintiles of propensity scores.
3. A pooled analysis conducted at the coordinating centre, where summary data from the collaborating database research partners will be combined, as appropriate, to estimate overall measures of effect.

The database research partners have organisation-specific restrictions on the level and type of information that can be shared externally, and thus patient-level data cannot be combined across all data sources. This two-stage analysis is designed to comply with those restrictions while accomplishing the goal of assimilating the data from the collaborating database research partners into one summary analysis.

A core SAP will be developed separately and will describe methods for the creation of the study cohorts, the descriptive analyses, variable creation including propensity scores, and the IR and IRR analyses. The SAP will also detail the required input data from the individual database research partners that will be used to perform the pooled analysis. Calculation of person-years, IR and IRR, and CIs will be documented. A description of the planned pooled analyses and table shells will be included. Specification of the exact output tables to be provided by the coordinating centre will be included in the SAP. Appendices to the analysis plan will document all diagnosis, procedure, and medication codes to be used in defining the outcomes, exposures, and covariates. The core SAP will be adapted to the specifications of each database.

9.7.1 Country-Specific Analysis

Each database research partner will conduct country-specific analyses within each data source to (1) select the study population; (2) describe the study cohorts including patterns of LDX use among patients with cardiovascular diseases and hypertension, demographics, medical history, exposures, and endpoints; (3) estimate exposure propensity scores within its data; and (4) create a summary data set based on counts of patients, person-years, and outcome events according to the strata of propensity scores.

9.7.1.1 Select Study Population

Each database research partner will first apply the study inclusion/exclusion criteria to select the study population. During this process, each database research partner will create a table showing the impact that each step of applying the study criteria has on the study size, including the number of excluded LDX users and reasons for exclusion. Once the study population has been identified, members of each study cohort will be described as of the index date.

9.7.1.2 Descriptive Analysis of Study Cohorts

For each exposure cohort (LDX cohort and remote use of other ADHD treatments cohort), and within each data source, characteristics of all variables of interest (see also Section 9.3) will be described for each cohort: mean (standard deviation [SD]), median (25th percentile, 75th percentile), and frequency distribution for continuous variables and number and percentage for categorical variables.

Use of LDX and Other Medications

Prior to the index date

1. "Other ADHD treatments" that qualified for remote use cohort entry; number and proportion of patients in each ADHD drug subtype.
2. Use of "other ADHD medications" ever before, among both cohorts, and irrespective of being or not the prescriptions that qualified for remote use cohort entry; number and proportion of patients in each ADHD drug subtype; and total number of prescriptions ever before by categories.

During follow-up

Patterns of LDX and other drug use during follow-up will be described, including description of days' supply; dose; number of LDX prescriptions/dispensings; and duration of use of LDX, when possible (see also Section 9.3.1, Exposure Assessment). Differences in prescribing patterns between countries will be described and taken into account in the analyses, if needed.

Descriptive Analysis of Study Endpoints

For each endpoint, the number of patients identified as individuals falling into each category of the endpoints of interest will be summarised. Categories of interest are the final case classification and sources of information utilised to reach the classification

(e.g., HES linkage, ONS linkage, patient profiles only, or original GP or hospital records). Additional categories will include subcategories of current LDX use and post-LDX use; sex and age categories; and previous history of cardiovascular disease, ADHD, and non-ADHD psychiatric conditions.

9.7.1.3 Estimation of Propensity Scores

Within each data source, person-time and endpoint counts for each cohort will be stratified into quintiles of propensity scores. Stratifying on the quintiles of the propensity score eliminates approximately 90% of the bias due to measured confounders when estimating a linear treatment effect (Austin, 2011). Increasing the number of strata used should improve bias reduction, although a point is reached at which the marginal reduction in bias decreases as the number of strata increases (Austin, 2008). The propensity score will serve as a within-data source variable that summarises the confounding from a large set of variables. The covariates of interest that will be evaluated for potential inclusion in the propensity score estimation will be those in Section 9.3.3. Data aggregated by strata of propensity scores estimated in each data source will be used to estimate overall effects across all of the data sources in the pooled analysis (See Section 9.7.2).

Within each data source, propensity scores will be estimated using unconditional logistic regression. Propensity scores will estimate the probability that a given patient will receive LDX, as opposed to being in the remote use of other ADHD treatments cohort, conditional on measured covariates and can serve as a summary confounder variable. Quintiles of propensity scores will be defined by the distribution of propensity scores for the LDX cohort. Details of the propensity score procedures will be provided in the SAP.

9.7.1.4 Create a Summary Data Set

Each collaborating centre will create summary tables based on counts of patients, person-years, and outcome events according to the strata of age categories (18-34, 35-44, 45-64, 65+ years), sex, propensity score quintiles, and other variables of interest such as those specified in the secondary sensitivity analyses (LDX duration, concomitant use of other ADHD medications) and exploratory analyses (e.g., dose of LDX, previous history of cardiovascular disease, ADHD, and non-ADHD psychiatric conditions). Strata may need to be collapsed depending on the number of events. Specific table shells will be included in the SAP.

9.7.2 Pooled Analysis

After receiving the site-specific, propensity score-stratified tables with aggregated data from each database research partner, the coordinating centre will conduct an analysis of the data from each individual data source and an overall analysis combining the data across all data sources, if appropriate. Pooled analysis activities include (1) pooled description of study cohorts, (2) analysis of IR and standardised IRs, and (3) analysis of crude and adjusted IRRs.

9.7.2.1 Pooled Description of Study Cohorts

After receiving the site-specific description of study cohorts, the coordinating centre will pool the data from all data sources, when possible (i.e., rates and effect estimates are reasonable and consistent between databases), and describe for each exposure cohort (i.e., the LDX cohort and remote use of other ADHD treatments cohort) the characteristics of all variables of interest: mean (SD), median (25th percentile, 75th percentile [or range]) and frequency distribution for continuous variables, and number and percentage for categorical variables.

9.7.2.2 Analysis of the Crude and Standardised Incidence Rates

Crude and standardised (by age categories, sex, and propensity score quintiles) IRs will be estimated within each data source and overall across data source (Rothman et al., 2008), using the event counts and person-time provided by each of the collaborating centres. Crude IRs will be calculated as the number of outcome events divided by the person-time at risk in each cohort. The Poisson distribution will be used to calculate exact 95% CIs for the IRs.

Standardised IRs will be calculated in each data source using the event counts and the person-time distribution across age categories, sex, and centre-specific quintiles of propensity scores using the LDX cohort as the standard population. Additionally, standardised IR and 95% CI over all data sources will be estimated. Methods described in Dobson et al. (1991) will be used to calculate the 95% CI of the standardised IR.

The analysis of crude IRs and IRs standardised by age, sex, and propensity score will include the following:

- Crude IR and IR standardised by age, sex, and propensity score for all primary and secondary endpoints during current LDX use and during follow-up of the remote use of other ADHD treatments cohort, in each data source and combined for all data sources.
- Crude IR and IR standardised by age, sex, and propensity score for MACE by subcategories of LDX duration and dose; by subcategories of concomitant use of other ADHD medications during current LDX use ("current single LDX use" and "current LDX multiple drug use"); and stratified by sex, age categories (stratification by sex and age for the crude IRs only), and previous history of cardiovascular disease, ADHD, and non-ADHD psychiatric conditions.
- Crude IR and IR standardised by age, sex, and propensity score for MACE using other definitions of LDX time at risk (e.g., post-LDX time at risk or extended current use carryover period), as described in the sensitivity analysis section (Section 9.7.3).

9.7.2.3 Analysis of Incidence Rate Ratios

Crude IRRs will be calculated as the crude pooled IR in the LDX cohort divided by the crude pooled IR in the remote use of other ADHD treatments cohort. Mantel-Haenszel methods will be used to estimate the adjusted IRR and 95% CIs, as shown in equation 15-17 in Rothman et al. (2008), by age categories, sex, and quintiles of the propensity

score. Additionally, data source will be retained as a stratification variable, and the effect within each data source will be estimated. This approach will be used to simultaneously adjust for the multiple variables that were used to estimate the propensity scores. This approach is particularly useful when the number of events is small relative to the number of covariates (Rothman et al., 2008).

In each data source and when calculating a combined IRR for all data sources, estimation of IRRs will include the following components:

- IRRs of all endpoints comparing current LDX use with remote use of other ADHD treatments.
- IRR of MACE among long-term LDX users (current LDX users with ≥ 12 months cumulative exposure to LDX, that is, those with ≥ 12 months duration of current LDX use) compared with remote users of other ADHD treatments without exposure to these treatments for a period of at least 12 months after the index date (long-term remote users).
- IRRs of MACE by subcategories of LDX use by subcategories of concomitant use of other ADHD medications during current LDX use ("current single LDX use" and "current LDX multiple drug use").
- Exploratory analyses of endpoints: IRRs of MACE comparing current LDX use with remote use of other ADHD treatments stratified by LDX dose, sex, age categories, and previous history of cardiovascular disease, ADHD, and non-ADHD psychiatric conditions.
- As described in the sensitivity analyses (Section 9.7.3): IRRs of MACE comparing LDX use using other definitions of LDX time at risk (e.g., post-LDX use risk, extended current use lag time and carryover period) and outcome categories (e.g., including secondary discharge diagnosis), versus remote use of other ADHD treatments.

9.7.3 Sensitivity Analyses

Impact of Exposure Time

Sensitivity analyses including estimation of IR and IRRs of MACE comparing current LDX use versus remote use of other ADHD treatments will be conducted by extending the current use carryover period and the allowed gaps between prescriptions/dispensings from 30 days to 60 days, thus lengthening the definition of current exposure to end 60 days after the estimated end of the last dispensing or prescription for LDX. Accordingly, discontinuation will be redefined by assuming that each dispensing lasts until the specified extended duration (60 days) after each dispensings' days' supply.

To evaluate whether there is a delayed cardiovascular effect of LDX exposure, a sensitivity analysis will be performed using the time of post-LDX use versus the remote use of other ADHD treatments cohort. To evaluate the potential effect of exposure to "other ADHD treatments" in the comparison between post-LDX use versus remote use of other ADHD treatments, an additional secondary analysis will be performed using the

time of “post-LDX use, no drug use” and time of “post-LDX use, with other ADHD drug use” as time at risk, respectively.

Finally, a sensitivity analysis will include time at risk from post-LDX use and from current LDX use in an intention-to-treat analysis.

Impact of Outcome Categories

Due to the similarity in case ascertainment, a sensitivity analysis based on results from Denmark and Sweden and only those cases in the CPRD that can be linked to HES/ONS data will be conducted.

An additional subgroup analysis including both primary and secondary discharge diagnoses for the MACE endpoint of interest in Denmark and Sweden, and only those patients in the CPRD for whom data can be linked to HES/ONS data, will be conducted. In Sweden and Denmark, this analysis will include all cases identified by primary and secondary discharge codes; in the CPRD, this analysis will include only those cases considered definite after validation in data linkable to HES/ONS data.

A sensitivity analysis that expands the MACE endpoint to include probable cases, in addition to confirmed cases, will be conducted.

Unmeasured Confounding

It is possible that final relative risk estimates in any study could be confounded by variables that could not be measured or could not be measured accurately in one or more cohorts. This is often a concern in studies based on secondary data. To assess the potential impact of unmeasured confounding on the results in this study, a bias analysis will be implemented (Savitz and Barón, 1989). In this analysis, a range of plausible hypothetical values for the prevalence of the unknown confounder among the exposed and among the unexposed and for the IRR of the unknown confounder and the outcome of interest (e.g., 2 to 3) is applied to assess the hypothetical potential impact of an unknown confounder on the overall IRR. Such analyses show the magnitude of the difference in the prevalence of a confounder between exposed and unexposed groups and the strength of relationship between the confounder and the outcome that is needed to substantially influence the study result.

9.7.4 Methods for Handling Missing Data

In this study, as in most of the studies performed in automated health databases, all patients without a prescription/dispensing for a medication will be considered unexposed, and all patients without a diagnosis will be considered as not having the condition.

When presenting results stratified on a single variable, patients missing the variable value will be reported as a separate category. For modelling (i.e., when computing exposure propensity scores), variables with a significant amount of missing data (e.g., > 10%) may be imputed. The frequency of missing information will be shown in the descriptive analysis. For the unconditional logistic regression used to estimate the

propensity scores (Section 9.7.1.3), confounders with a significant amount of missing data may be imputed, and the method of imputation will be described in the SAP.

9.7.5 Content of Reports

Information regarding the annual monitoring of adult LDX users will be included in the PBRER. The annual counts will be used to determine the timing of analyses and the full study report.

The full study report will describe the cohorts and the results of all analysis. All pooled IRRs will be standardised for propensity score category and data source. All sensitivity analyses will be included.

9.8 Quality Control

Standard operating procedures at each research centre will be used to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

At a minimum, all programming written by one study analyst will be reviewed independently by a different analyst, with oversight by a senior statistician. Appropriate data storage and archiving procedures will be followed (e.g., storage on CD-ROM and DVD), with periodic backup of files. Standard procedures will be in place to restore files in the event of a hardware or software failure at each research centre.

All key study documents, such as the analysis plan and study reports, will undergo quality-control review, senior scientific review, and editorial review.

Procedures will be consistent with the International Society for Pharmacoepidemiology (ISPE) *Guidelines for Good Pharmacoepidemiology Practices* (GPP) (ISPE, 2015).

A quality-assurance audit of this study may be conducted by the sponsor or the sponsor's designees.

9.9 Limitations of the Research Methods

The relevant parameters to consider for the interpretation of the results focus on the point estimate, the upper limit of the 95% CI, and the absolute excess risk. A limitation of the study is the potential low precision of the estimated relative risks for the study endpoints. We estimate that for MACE in the whole population there is an 80% probability that the upper limit of the 95% CI of the observed rate ratio is below 3 if the incidence rate is 3 per 1,000 person-years, the true IRR is 1.0, and the LDX new users meeting study criteria have 7,800 person-years of exposure. However, 19,590 person-years of exposure will be needed to estimate with an 80% probability that the upper limit of the 95% CI of the observed rate ratio is below 2. In terms of absolute risk, a

95% CI upper limit of 3 translates to an increase of about two additional cases per 1,000 person-years of treatment. Although precision may be low, with findings that are compatible with high multiples of risk, the risk is very low for this outcome, and even a multiple of 3 in the rate would correspond to a small absolute increase in risk for MACE. The rate of MACE in the population treated for ADHD (predominantly young adults) is expected to be low. By using multiple data sources, we intend to accrue patient experience more quickly than would be possible using a single data source. There will be some heterogeneity across data sources, which may impact the precision of estimates. The study population size may also limit the ability to evaluate differences in risk across patient subgroups. As with any database study, the actual study size will be determined by the utilisation of the drug of interest and the inclusion/exclusion criteria. Additional rounds of analyses can be implemented as the available number of patients increases, and we will continue to evaluate the feasibility of extending the study to other data sources.

The study will combine results from different data sources with heterogeneity between data sources regarding exposure information (prescribed vs. dispensed medications) and ascertainment of risk factors and confounders. The Danish National Patient Register and the Swedish National Patient Register are based on diagnoses when patients are discharged from the hospital or in connection with a hospital outpatient clinic visit, whereas the CPRD is based on information from primary care GPs. Ascertainment of covariates using hospital discharge diagnoses might result in the identification of individuals with more severe comorbidity. In addition, there may be differences in the prescription patterns between countries due to different treatment guidelines, country-specific recommendations, or public health systems. These different prescribing patterns may lead to different mean doses and durations of use in each country. The effect of different doses and durations of use on the risk of the outcomes of interest will be evaluated as one of the secondary objectives. The effect of the potential differences in exposure information and ascertainment of risk factors and confounders in each data source will be adjusted for in the overall stratified analysis.

Because of the serious nature and clinical guidelines for the management of the acute cardiovascular events of interest, hospitalisation is expected for most of the non-fatal events under study. The selected data sources for this study have been shown to reliably capture and classify hospitalisations for cardiovascular conditions. All data sources will be able to capture conditions and deaths that occur in a hospital, except for some cases in the CPRD that are not linkable to HES or ONS data and that may also not have the death recorded in the GP database. It has been shown that, in general, misclassification of outcomes that do not differ by exposure will underestimate the incidence ratio. However, the impact is expected to be small because validation studies of these outcomes have shown that identification of the cardiovascular outcomes of interest is quite reliable in the planned data sources.

Information on other covariables, including cardiovascular risk factors, is limited to information recorded in the electronic medical record. For many patients, that information will be comprehensive, including factors such as smoking. For other patients, less information will be available, owing to the nature of the data source or the total time

a patient's information is in the data source. Use of over-the-counter medications will not be captured. There is no reason to believe that completeness of historical information would differ between the two study exposure cohorts; therefore, any misclassification would not be differential.

We assumed that LDX and other ADHD medications are prescribed only for ADHD and that members of these cohorts are not required to have a recorded diagnosis of ADHD. However, some patients may have been prescribed these medications for other conditions, such as narcolepsy. Depending on the number of patients that may be prescribed these medications for other diseases, we will minimise the inclusion of these patients by excluding them from the patient population, when possible. Bias from misclassification of ADHD among these patients could be present if the risk of MACE associated with other indications or reasons for prescription of stimulants differs from the risk associated with ADHD. The magnitude of the bias is expected to be low given the low expected proportion of patients prescribed LDX and other ADHD drugs for diseases other than ADHD. In addition, patients taking LDX could be more severely affected than those in the remote use of other ADHD treatments cohort. Determination of severity or duration of ADHD will be a challenge. Clinical data on ADHD are frequently not available in hospital-based data sources, and many adult patients may not be treated unless their disease is severe. There is little evidence that ADHD or that ADHD severity is independently associated with an increased risk for MACE. The matching and propensity score approaches will limit the effect of any confounding. In addition, in Denmark, amphetamine and dexamphetamine are available only via magistral prescriptions (produced by a specialized pharmacy) and are not routinely recorded, leading to misclassification of exposure among remote users of other ADHD treatments; however, utilization of these drugs to treat ADHD is expected to be low (Pottegård et al., 2012).

Determining exposure duration in an accurate manner can be a challenge with secondary health care data. In UK data sources, where the research data are captured through GP prescribing, any prescribing by a specialist is not captured. Thus, if an individual receives a prescription through a specialist, that exposure would not be captured in this study. However, it is common for specialists to write the first prescription and GPs to write follow-up prescriptions. Once a prescription or dispensing appears in the data, we assume that the patient takes the product as prescribed. However, we have no direct measure of patient adherence. It is possible that patients in either cohort will stop medication prematurely and/or reserve medication to take at a later time, resulting in misclassification of exposure. Therefore, we will extend the time at risk to 30 days following the end of the prescription period to account for possible variation in adherence and will evaluate in sensitivity analyses a longer period (60 days after the end of the prescription period).

10 Protection of Human Subjects

This is a non-interventional, population-based study of secondary data and does not pose any risks for patients. All data collected in the study will be de-identified with no

breach of confidentiality with regard to personal identifiers or health information. Each research partner, including RTI-HS for the CPRD study, will apply for an independent ethics committee review according to local regulations; in addition, RTI Health Solutions as the coordinating centre will obtain approval from the RTI International institutional review board.

Country-specific data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants.

11 Management and Reporting of Adverse Events/Adverse Reactions

11.1 Studies Using Secondary Data

Based on current guidelines from the International Society for Pharmacoepidemiology (ISPE, 2015) and the European Medicines Agency (EMA) *Guideline on Good Pharmacovigilance Practices (GVP)* (EMA, 2014), non-interventional studies such as the one described in this protocol, conducted using medical chart reviews or electronic claims and health care records, do not require expedited reporting of adverse events/reactions (EMA, 2014; ISPE, 2015).

12 Plans for Disseminating and Communicating Study Results

The study protocol, study progress reports, and final study report will be included in regulatory communications in line with the risk management plan, PBRER, and other regulatory milestones and requirements. Study reports will be prepared using a template following the *Guideline on Good Pharmacovigilance Practices (GVP)* Module VIII Section B.6.3 (EMA, 2013).

In its *Guidelines for Good Pharmacoepidemiology Practices (GPP)*, the International Society for Pharmacoepidemiology contends that "there is an ethical obligation to disseminate findings of potential scientific or public health importance" (ISPE, 2015); for example, results pertaining to the safety of a marketed medication. Study results will be published following guidelines, including those for authorship, established by the International Committee of Medical Journal Editors (ICMJE, 2015). When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist will be followed (von Elm et al., 2008). The Consolidated Standards of Reporting Trials (CONSORT) statement (Schulz et al., 2010) refers to randomised studies, but provides useful guidance applicable to non-randomised studies as well.

Communication via appropriate scientific venues (e.g., International Society for Pharmacoepidemiology) will be considered.

The marketing authorisation holder and the investigators will agree upon a publication policy: the principal and coinvestigators will coauthor scientific manuscript(s) of the results to be published, irrespective of data ownership. Each research partner has the right to publish country-specific results. The marketing authorisation holder will be entitled to view the results and interpretations included in the manuscript(s) and provide comments prior to submission of the manuscript(s) for publication (EMA, 2013).

13 Other Good Research Practice

This study adheres to the *Guidelines for Good Pharmacoepidemiology Practices (GPP)* (ISPE, 2015) and has been designed in line with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology* (ENCePP, 2015). The *ENCePP Checklist for Study Protocols* (ENCePP, 2013) has been completed (see Annex 2).

The study is a postauthorisation safety study (PASS) and will comply with the definition of the non-interventional (observational) study referred to in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use tripartite guideline *Pharmacovigilance Planning E2E* (ICH, 2004) and provided in the EMA *Guideline on Good Pharmacovigilance Practices (GVP) Module VIII: Post-Authorisation Safety Studies* (EMA, 2013), and with the 2012 European Union pharmacovigilance legislation, adopted June 19, 2012 (European Commission, 2012). The study will comply with the study reporting requirements specified in Module VIII Section VIII.B.6.3.1. "Progress Reports" and VIII.B.6.3.2. "Final Study Report" of the *Guideline of Good Pharmacovigilance Practices* (EMA, 2013).

The study will be registered in the ENCePP EU PAS Register (ENCePP, 2014b) before the study implementation commences. The research team and study sponsor will adhere to the general principles of transparency and independence in the ENCePP Code of Conduct (ENCePP, 2014a).

14 References

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Annex 1.

List of Stand-Alone Documents

None.

Annex 2.

ENCePP Checklist for Study Protocols



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH



European Network of Centres for
Pharmacoepidemiology and
Pharmacovigilance

Doc.Ref. EMEA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional postauthorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

SPD489-825: Cohort Study of the Incidence of Major Cardiovascular Events in New Adult Users of Lisdexamfetamine and Remote Adult Users of Other ADHD Treatments

Study reference number:

[add reference number here]

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 ¹	☒	☐	☐	15
1.1.2 End of data collection ²	☒	☐	☐	15
1.1.3 Study progress report(s)	☐	☒	☐	
1.1.4 Interim progress report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS Register	☒	☐	☐	15
1.1.6 Final report of study results	☒	☐	☐	15

Comments:

Monitoring of adult LDX users will be done annually starting in 2016.

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 management plan, an emerging safety issue)	☒	☐	☐	16-17
2.1.2 The objectives of the study?	☒	☐	☐	17-18
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	20
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no <i>a priori</i> hypothesis?	☐	☐	☒	

Comments:

2.1.4 and 2.1.5 Rather than formal hypothesis testing we will describe the effect measure and confidence interval, adjusting for potential confounders.

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)	☒	☐	☐	18-21
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	17-18 objectives, 28-35 endpoints
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)	☒	☐	☐	47-52

Comments:

Section 4: Source and study populations	Yes	No	N/A	Page Number(s)
4.1 Is the source population described?	☒	☐	☐	37-40

¹ Date from which information on the first study is first recorded in the study data set or, in the case of secondary use of data, the date from which data extraction starts.

² Date from which the analytical data set is completely available.

Section 4: Source and study populations	Yes	No	N/A	Page Number(s)
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	23-24
4.2.2 Age and sex?	☒	☐	☐	22-23
4.2.3 Country of origin?	☒	☐	☐	37-42
4.2.4 Disease/indication?	☒	☐	☐	22-23
4.2.5 Comorbidity?	☒	☐	☐	35-36
4.2.6 Seasonality?	☐	☒	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	22-23

Comments:

4.2.6 There are not concerns about seasonality with this exposure-outcome relationship

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)	☒	☐	☐	24-28
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)	☒	☐	☐	53-55
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	24-28
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	24-28

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?	☒	☐	☐	28-35, and Annex 4
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)	☒	☐	☐	28-35, and Annex 3

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)	☒	☐	☐	35-37

Section 7: Confounders and effect modifiers	Yes	No	N/A	Page Number(s)
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☒	☐	

Comments:

7.2 No effect modifiers have been identified a priori.

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:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	37-42
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.)	☒	☐	☐	37-42
8.1.3 Covariates?	☒	☐	☐	37-42
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)	☒	☐	☐	37-42
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	28-35, 37-42
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, comorbidity, co-medications, life style, etc.)	☒	☐	☐	35-37, 37-42
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	32, and Annex 4
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	32, and Annex 4
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	23 -24
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	37-42

Comments:

Section 9: Study size and power	Yes	No	N/A	Page Number(s)
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	43-46

Comments:

Section 10: Analysis plan	Yes	No	N/A	Page Number(s)
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	47-52
10.2 Is the choice of statistical techniques described?	☒	☐	☐	47-52
10.3 Are descriptive analyses included?	☒	☐	☐	47-52
10.4 Are stratified analyses included?	☒	☐	☐	47-52

Section 10: Analysis plan	Yes	No	N/A	Page Number(s)
10.5 Does the plan describe the methods for adjusting for confounding?	☒	☐	☐	47-52
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

10.6. No effect modifiers have been identified a priori. Before combining the risk estimates, data on the number of events and person-years will be reviewed stratified by relevant covariables such as age, gender and propensity scores.

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?	☒	☐	☐	52-53
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	46-47
11.3 Are methods of quality assurance described?	☒	☐	☐	53
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	53
11.5 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

11.5 Study investigators will review results, as will regulatory agencies. In addition, a manuscript describing the study results will be submitted to a peer-reviewed medical journal.

Section 12: Limitations	Yes	No	N/A	Page Number(s)
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	53-54
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	53-54
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	19, 43-46
12.3 Does the protocol address other limitations?	☒	☐	☐	43-46

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?	☒	☐	☐	55-56
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	55-56

Comments:

13.2 The ethics committee submission has not yet been made.

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?	☒	☐	☐	14

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)?	☒	☐	☐	56-57
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	56-57

Comments:

Name of the main author of the protocol: Cristina Rebordosa

Date:

Signature

Annex 3.

Validity of Endpoint Definitions

Hospitalisations for Acute Myocardial Infarction

Acute myocardial infarction (AMI) will be identified by hospital discharge diagnosis codes. For patient data in the Clinical Practice Research Datalink (CPRD) without direct linkage to hospitalisation discharge diagnoses (i.e., not linked to Hospital Episode Statistics [HES]), algorithms based on available information recorded by the general practitioner (GP) will be used to identify patients who have been diagnosed with an AMI and were hospitalised. Data from the mortality registers will be used to classify deaths as occurring inside versus outside the hospital. Previously published, validated algorithms can be used. The positive predictive value (PPV) of the Read/OXMIS¹ codes used historically by CPRD for AMI has been reported to be approximately 93% (95% confidence interval [CI], 90%-96%) (Hammad et al., 2008).

Hospitalisations for Stroke

Stroke acute events, either of ischaemic or haemorrhagic vascular aetiology, will be identified by hospital discharge diagnosis codes.

For CPRD patients without direct linkage to hospitalisation diagnoses, algorithms based on available information recorded by the GP will be used to identify patients who have been hospitalised and diagnosed with a stroke (see Table 2). Data from the mortality registers will be used to classify deaths as occurring inside versus outside the hospital. Prior validated algorithms to identify ischaemic strokes and cerebrovascular events can be used (Andersohn et al., 2006; Arana et al., 2006; Ray et al., 2009; Rounie et al., 2008). For ischaemic stroke, the PPV has been reported to be approximately 86% (95% CI, 79%-91%) in The Health Improvement Network (Ruigomez et al., 2010).

Hospitalisation for Unstable Angina

Prior studies have investigated the validity of algorithms to identify unstable angina. Joensen et al. (2009) researchers identified patients participating in the "Diet, Cancer, Health" cohort study who had a first-time primary or secondary hospital discharge diagnosis of unstable angina (ICD-10² code: I20.0) in the Danish National Patient Registry between 1993 and 1997 (Joensen et al., 2009). During validation, events were classified in accordance to American Heart Association and European Society of Cardiology criteria (Luepker et al., 2003). Verified events were classified as definite myocardial infarction (MI) (fatal and non-fatal events), probable MI, possible MI, unstable angina pectoris, and medical procedure-related event. The PPV for unstable

¹ OXMIS = Oxford Medical Information Systems.

² ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*.

angina was 27.5%; PPVs were higher for MI (81.9%). The PPVs were also higher among patients diagnosed in a ward than in those diagnosed in the emergency department or at the outpatient clinic (for unstable angina discharged from ward, the PPV was 42%). The PPV for acute coronary syndrome among men was 72.6% (vs. 50.1% among women). The PPV for acute coronary syndrome identified through primary discharge diagnosis was 67.1% (vs. 47.0% for secondary discharge diagnosis). In Sweden, as part of broader study to evaluate the reliability of the Swedish inpatient registry, primary diagnoses of angina pectoris were ascertained, and 18 of the 19 cases (PPV = 95%) identified were confirmed through review of medical charts (Ludvigsson et al., 2011). A cohort study performed in the Canada Saskatchewan Health beneficiaries' database identified all patients aged 40 to 84 years with a hospital primary discharge ICD-9 code 410 (n = 2,260) or code 411 (n = 799), between 1999 and 2001 (Varas-Lorenzo et al., 2008). The Braunwald criteria (Braunwald, 1989) were used to classify unstable angina according to angina class severity and clinical circumstances. Among the 763 validated cases with a discharge code of 411, 561 (73%) were classified as unstable angina/intermediate coronary syndrome, leading to a PPV for 411 to identify unstable angina of 73% (95% CI, 70%-77%) (Varas-Lorenzo et al., 2008).

Hospitalisation for Transient Ischaemic Attack

Two studies have evaluated the validity of the transient ischaemic attack (TIA) diagnosis in the Danish National Patient Register. TIA was defined as first-time primary or secondary hospital discharge diagnosis of TIA (ICD-10 code: G45). Both studies included a small number of TIA events. Validation consisted of medical chart review. Johnsen et al. (2002) considered TIA as confirmed based on the Kraaijeveld criteria which include assessment of the time course of TIA, symptoms of carotid TIA (hemiparesis, aphasia, and amaurosis fugax), symptoms of vertebrobasilar TIA (such as bilateral, basculating, or alternating weakness or sensory symptoms, transient global amnesia) or symptoms of uncertain territory TIA (hemianopia and dysarthria), and symptoms explicitly not acceptable as TIA (Kraaijeveld et al., 1984). Krarup et al. (2007) considered TIA confirmed with the following definition: temporary and focal cerebral dysfunction of presumed vascular origin which lasted no more than 24 hours and left no sequelae (NINDS, 1975). The PPV values for the studies performed in the Danish National Patient Registry ranged from 57.9% to 68.4% (Krarup et al., 2007). In the study by Johnsen et al. (2002), the proportion of verified diagnoses (PPV) by type of department for TIA was 46.7% in the emergency department, 67.4% in the non-specialty departments, and 62.2% in the specialty departments; for ischaemic stroke, 40% in the ER, 87% in the non-specialty departments, and 90.6% in the specialty departments. There was high availability of data on complementary tests, such that the basis for a verified diagnosis of TIA came from computed tomography/MRI scans, 81.4%; ultrasonography, 73.7%; angiography, 5.1%; and echocardiography, 29.7%. Autopsy was conducted in only 5 of 21 fatal cases (23.8%) (Johnsen et al., 2002). One study evaluated the validity of an inpatient diagnosis of TIA recorded in the Swedish inpatient registry, and although the ICD-8 and ICD-9 codes used to define TIA and the definition used to consider TIA confirmed were not provided, the authors reported that after medical record review, 74.2% of the cases of TIA were confirmed (Lindblad et al., 1993). Three studies have been identified that evaluated the validity of TIA diagnosis in the United Kingdom (UK). A

recent study by Wright et al. (2012) included only women and looked into primary or secondary hospitalisation code for TIA (ICD-10 code: G45) in the HES database. After validation based on the review of outpatient data and GP questionnaires, 80% of the TIAs were confirmed (Wright et al., 2012). The study by Arana et al. (2006), performed in the UK CPRD, also included only women. Cases were identified through outpatient records (Read codes not provided), and TIA did not require hospitalisation to be considered confirmed. A random sample of cases were validated; of those, TIA was confirmed in 87% of the cases (Arana et al., 2006). The study by Gibbs et al. (2001) looked into patients with a diagnosis of TIA in the CPRD using OXMIS codes and a referral to specialist. Review of the specialist documentation confirmed 48.15% of the TIAs (Gibbs et al., 2001). A recent systematic review of validated methods for identifying cerebrovascular accident and TIA using administrative data from the US and Canada found seven manuscripts that evaluated ICD-9 or ICD-10 codes, most frequently ICD-9 code 435 and ICD-10 code G45 (Andrade et al., 2012). Most studies were limited to inpatient data. Validation was performed most frequently by review of medical charts, and the confirmation criteria varied. In three of the seven studies evaluating ICD-9 code 435, the PPVs were 70% or higher. Three studies evaluating ICD-9 435 code reported PPVs of 28% to 33%. In the only study that evaluated ICD-10 codes, the PPV of ICD-10 codes G45.x (97%) was found to be higher than the PPV of ICD-9 codes 435.x (70%). Limited data suggest that the PPV may be higher for algorithms using a primary discharge diagnosis only and when using inpatient rather than outpatient diagnoses.

Serious Ventricular Arrhythmia and Sudden Cardiac Death

Hospitalisations for ventricular cardiac arrhythmias and cardiac arrest have a high PPV and are useful for selecting events in epidemiological studies on drug-induced arrhythmias (De Bruin et al., 2005; Johannes et al., 2010; Roumie et al., 2008)). Hennessy et al. (2008) evaluated the validity of OXMIS/Read diagnoses of hospitalisation for sudden cardiac death and ventricular arrhythmia in the General Practice Research Database (forerunner of the CPRD). The study identified occurrences of hospitalisation for sudden cardiac death/ventricular arrhythmia (SCD/VA) in patients receiving outpatient prescriptions for cisapride, domperidone, or metoclopramide. Putative outcomes of SCD/VA were identified by the presence of specific OXMIS/Read codes. Outcome validation consisted in GP questionnaires and review of relevant hospital consultant letters and any electrocardiography. PPVs were calculated as the proportion of individuals with a physician-confirmed outcome. The study cohort consisted of 350,573 users of prokinetic agents of interest in whom the study identified 84 putative SCD/VA outcomes, of which only 30 could be evaluated for validation. Of the 30 evaluable responses, SCD/VA was not confirmed by the GP in 2 responses. Therefore, the PPV for the occurrence of SCD/VA was 93% (95% CI, 78%- 99%). Thirteen (46%) of those 28 outcomes originated in the hospital, the GP did not know the setting in eight (29%), and seven (25%) originated in the outpatient setting. Thus, of the 30 responses evaluated, seven outpatient events led to a PPV of 23% (95% CI, 10%-42%) (Hennessy et al., 2008).

In an observational cohort study by Chung et al. (2010), sudden cardiac death was defined as a sudden pulseless condition (arrest) that was immediately fatal (or rarely

resuscitated with death in 48 hours) and was consistent with a ventricular tachyarrhythmia occurring in the absence of a known non-cardiac condition as the proximate cause of the death. The PPV of the entire study sample identified through the codes listed in Table 2 of the current protocol, was 76.2%, but when additional restriction criteria were used the PPV increased to 79.6% if no evidence of a terminal institutional stay, 85.1% if underlying cause of death code consistent with sudden cardiac death, and 86.0% if no terminal procedures inconsistent with un-resuscitated cardiac arrest (Chung et al., 2010).

Out-of-Hospital Coronary and Cerebrovascular Deaths

All deaths occurring during the study will be identified. Mortality data will be linked to the hospitalisation files to classify deaths as occurring inside versus outside the hospital. The underlying cause of death coded in the national death register file takes into account additional information provided by medical practitioners or coroners after the death has been registered. The classification and inclusion of events based only on hospitalisations will be most homogeneous across the included data sources in this study; however, a consequence will be the incomplete ascertainment of these events as approximately one-third of patients with an AMI die suddenly before arriving at the hospital (Rothwell et al., 2005). Historically, deaths occurring outside of a hospital setting frequently have not been ascertainable in database studies and therefore have not been included in such studies' primary endpoints. We will identify out-of-hospital deaths where information on out-of-hospital deaths is available through recorded causes from death certificates or direct linkage to the national mortality registry.

Out-of-Hospital Coronary Heart Disease Death

Out-of-hospital deaths from coronary heart disease are defined as sudden cardiac death (SCD) or deaths due to AMI in persons dying outside of a hospital setting. These will be ascertained through diagnoses recorded on autopsy reports and death certificates, as available, using a published validated computerised definition (Chung et al., 2010).

Events identified as out-of-hospital deaths must meet the following criteria:

- Have on the death certificate an underlying cause of death that is compatible with SCD or fatal AMI (Chung et al., 2010; Ray et al., 2009); the codes provided in Table 2 have been reported with a high PPV for SCD and AMI
- Have no terminal hospitalisation
- Have a place of death that is not a hospital institution

Out-of-Hospital Death from Cerebrovascular Diseases

A similar approach will be used to identify out-of-hospital cerebrovascular deaths based on available information. Previously validated algorithms to identify strokes (including cerebrovascular death) will be used (see Table 2).

Annex 4.

ICD-10 Codes and ICD-10 Terms for Study Endpoints

ICD-10

Code^a ICD-10 Term

Hospitalisation for AMI

I21 Acute myocardial infarction

Hospitalisation for AMI, fatal^b

I21 Acute myocardial infarction

I22 Subsequent myocardial infarction

I23 Certain current complications following acute myocardial infarction

I24.1 Dressler's syndrome

I51.1 Rupture of chordae tendineae, not elsewhere classified

I51.2 Rupture of papillary muscle, not elsewhere classified

I51.3 Intracardiac thrombosis, not elsewhere classified

Hospitalisation for unstable angina

I20.0 Unstable angina

Hospitalisation for stroke

I60 Subarachnoid haemorrhage

I61 Intracerebral haemorrhage

I63 Cerebral infarction

I64 Stroke, not specified as haemorrhage or infarction

Hospitalisation for stroke, fatal^c

I60 Subarachnoid haemorrhage

I61 Intracerebral haemorrhage

I63 Cerebral infarction

I64 Stroke, not specified as haemorrhage or infarction

I69 Sequelae of cerebrovascular disease

G45 Transient cerebral ischaemic attacks and related syndromes

Hospitalisation for transient cerebral ischaemic attack (TIA)

G45 Transient cerebral ischaemic attacks and related syndromes

Hospitalisation for SVA/SCD

I46.0 Cardiac arrest with successful resuscitation

I46.1 Sudden cardiac death, so described

ICD-10

Code^a ICD-10 Term

I46.9	Cardiac arrest, unspecified
I47.0	Re-entry ventricular arrhythmia
I47.2	Ventricular tachycardia
I49.0	Ventricular fibrillation and flutter
R96.1	Death occurring less than 24 hours from onset of symptoms, not otherwise explained
R98	Unattended death

Coronary and cerebrovascular deaths out-of-hospital

AMI/coronary heart disease death, including SCD

I10	Essential (primary) hypertension
I11.9	Hypertensive heart disease without (congestive) heart failure
I20	Angina pectoris
I21	Acute myocardial infarction
I22	Subsequent myocardial infarction
I23	Certain current complications of acute myocardial infarction
I24	Other acute ischemic heart diseases
I25	Chronic ischemic heart disease
I42.8	Other cardiomyopathies
I42.9	Cardiomyopathy, unspecified
I46.0	Cardiac arrest with successful resuscitation
I46.1	Sudden cardiac death, so described
I46.9	Cardiac arrest, unspecified
I47.0	Re-entry ventricular arrhythmia
I47.2	Ventricular tachycardia
I49.0	Ventricular fibrillation and flutter
I49.8	Other specified cardiac arrhythmias
I49.9	Cardiac arrhythmia, unspecified
I51.6	Cardiovascular disease, unspecified
I51.9	Heart disease, unspecified
I70.9	Generalised and unspecified atherosclerosis
R96.1	Death occurring less than 24 hours from onset of symptoms, not otherwise explained
R98	Unattended death

Coronary and cerebrovascular deaths out-of-hospital

Stroke/cerebrovascular deaths

I60	Subarachnoid haemorrhage
I61	Intracerebral 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

ICD-10

Code^a	ICD-10 Term
I67	Other cerebrovascular diseases
I68	Cerebrovascular disorders in diseases classified elsewhere
I69	Sequelae of cerebrovascular disease
G45	Transient cerebral ischaemic attacks and related syndromes
R96.0	Instantaneous death
R96.1	Death occurring less than 24 hours from onset of symptoms, not otherwise explained
R98	Unattended death

AMI = acute myocardial infarction; ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*; SCD = sudden cardiac death; SVA = serious ventricular arrhythmia; TIA = transient ischaemic attack.

^a This code list will be adapted to each data source.

^b To identify potential events of fatal AMI, the list of codes will also include codes for subsequent myocardial infarction and complications of myocardial infarction that are followed by death within 30 days.

^c To identify cases of fatal stroke, the list of codes will also include codes for stroke sequelae and TIA that are followed by death within 30 days.