PASS Information

Title	Strattera patient exposures and adherence in the United Kingdom, Germany, the Netherlands, and Sweden: 2018 Bi-annual assessment report. (B4Z-MC-B026)
Version identifier	001
Date of last version	N/A.
EU PAS Register No:	EUPAS17371
Active substance	Atomoxetine hydrochloride
Medicinal product(s):	10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, 100 mg capsules, and 4 mg/ml oral solution
Product reference:	UK/H/0686/002-009
Procedure number:	Not applicable
Marketing authorisation holder(s)	Eli Lilly and Company
Joint PASS	No
Research question and objectives	The objective of this study is to describe atomoxetine (Strattera) utilisation patterns for patients treated in Germany, United Kingdom (UK), Sweden, and the Netherlands
Country(-ies) of study	The United Kingdom, Germany, the Netherlands, and Sweden
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Marketing Authorisation Holder

Marketing authorisation holder (MAH)	Eli Lilly and Company
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2. List of Abbreviations

Term	Definition
ADHD	attention-deficit/hyperactivity disorder
AR	adverse reaction
ATC	Anatomical Therapeutic Chemical
BNF	British National Formulary
CPRD	Clinical Practice Research Datalink, formerly the General Practice Research Database
DA	Disease Analyser
EphMRA	European Pharmaceutical Market Research Association
ERB	Ethical Review Board
EU	European Union
GPRD	General Practice Research Database
ICD	International Classification of Diseases
LOT	length of therapy
MPR	medication possession ratio
SPDR	Swedish Prescribed Drug Register
UK	United Kingdom

3. Responsible Parties

The principal investigator

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4. Abstract

Title: Strattera® patient exposures and adherence in the United Kingdom, Germany, the Netherlands, and Sweden: Bi-annual assessment reports for years 2014, 2016, and 2018 (2018 report: B4Z-MC-B026).

Version 1.0 **Date**:

Rationale and background: In 2003, Eli Lilly and Company (Lilly) launched Strattera (atomoxetine), which was the first attention-deficit/hyperactivity disorder (ADHD) medication indicated for adult use. The adult indication was recently approved in the European Union (EU) (May 2013). The use of ADHD medications, including nonstimulant atomoxetine has been increasing over-time among children, adolescents and among adults (Castle 2007; Habel 2011; Zoega 2011). There has also been a change in the duration of use in more recent years (Castle 2007; Habel 2011).

Research question and objectives: The main objective of this retrospective database study is to describe atomoxetine (Strattera) utilisation patterns for patients treated in the UK, Germany, the Netherlands, and Sweden, by age group. This includes 1) estimating number of patients exposed to Strattera on years of available data, 2) estimating duration of exposure, medication possession ratio, and dose over the most recent 24 months of data available for capsules and 18 months for the oral solution, 3) for those who stopped taking Strattera, estimating the number that restarted, gap time between, and duration of use in additional exposures over the most recent 24 months for capsules and 18 months for the oral solution, and 4) describing the Strattera population in terms of common comorbidities and concomitant medications. This protocol describes the updated drug utilisation study for the studies previously conducted in Europe (B4Z-MC-B019, submitted November 2011; B4Z-MC-B022, submitted April 2014; B4Z-MC-B025, submitted March 2016). New for the current study (B4Z-MC-B026) is the inclusion of utilisation patterns for patients treated with the atomoxetine oral solution in Germany and Sweden.

Study design: Retrospective cohort study using secondary data.

Population: All patients, including children, adolescents, and adults, with filled prescriptions of Strattera for the longest available duration in each selected database will be eligible and patients will need at least two consecutive filled prescriptions to be included.

Variables: The exposure of interest is atomoxetine use, defined as ≥2 consecutive prescription dispatches (with 90 day allowable gap). The outcomes of interest include exposure counts and drug ulitisation measures including persistence, discontinuation, and re-starting patterns, mean daily dose, medication possession ratios, and length of therapy. The outcomes will be assessed by various patient characteristics including country, age, and gender. Counts will also be provided for ADHD diagnoses, comorbidities (ICD-10 codes), and concomitant medication usage.

Data sources: Data for this study will be drawn from the LRx prescription databases (Germany and the Netherlands), Clinical Practice Research Datalink and Disease Analyzer (UK), and the Swedish National Drug and Patient Register (Sweden).

Study size: This is a descriptive study with no pre-specified sample size for statistical power needs. Study size is driven by utilisation and coverage of databases being accessed.

Data analysis: The number of patients exposed to atomoxetine annually between 2012-2016 will be estimated in each country and stratified by age and formulation. Oral solution counts will only be available for 2015 and 2016, as the oral formulation was not marketed in Germany and Sweden until April and May 2015, respectively. From this count of prevalent users, an incident cohort of capsule atomoxetine users over the most recent 24-month period of data (01 July 2015 through 30 June 2017) will be created. The incident oral solution users will be followed over the most recent 18 month period of data (01 January 2016 through 30 June 2017). Among incident users, duration of exposure, medication possession ratio, and dose over the 24 months will be estimated. Monthly persistence (discontinuation and re-initiation) patterns will be estimated. Attention-deficit/hyperactivity disorder diagnoses, common comorbidities, and concomitant medications will be tabulated.

Milestones: Data collection start 01 April 2017 and end on 31 January 2018; Final study report end of Q1 2018.

5. Amendments and Updates

Not applicable.

6. Milestones

Milestone	Planned date
Start of data collection	01 April 2017
End of data collection	31 January 2018
Registration in the EU PAS register	31 March 2017
Final report of study results	31 March 2018

7. Rationale and Background

In 2003, Lilly launched Strattera (atomoxetine), which was the first ADHD medication indicated for adult use. It belongs to the class of selective norepinephrine reuptake inhibitors. The patterns in ADHD medication use have changed over time and vary by country. The use of ADHD medications, including nonstimulant atomoxetine has been increasing over-time among children, adolescents and among adults (Castle 2007; Habel 2011; Zoega 2011). There has also been a change in the duration of use in more recent years (Castle 2007; Habel 2011). In 2014, the oral solution of atomoxetine was approved and marketing began in 2015 in various EU countries.

QuintilesIMS (formerly IMS Health) will execute the analysis of data assessing the utilisation of Strattera in a multi-country study, in the UK, Germany, the Netherlands, and Sweden as requested by the Medicines and Healthcare products Regulatory Agency. The initial request was to ascertain how atomoxetine is used in everyday clinical practice in the following countries: UK, Germany, Sweden, Norway, Spain, and the Netherlands. During the initial assessment it was found that data were unavailable for Spain and Norway. The current database study will analyse the unique patient exposures to atomoxetine over the history available data in each database. Data specific to the oral solution of atomoxetine is only available within Germany and Sweden. Oral solution is not available in the Netherlands and the feasibility counts in the UK data available to QuintilesIMS were extremely low. The analysis will include an assessment of adherence patterns among users of atomoxetine and will obtain more information on atomoxetine use patterns in the EU, which may have implications for the risk of increased blood pressure and increased heart rate, by virtue of dose/time on treatment and overall exposure/age.

This protocol describes the updated and final drug utilisation study for the studies previously conducted in Europe (B4Z-MC-B019, submitted November 2011; B4Z-MC-B022, submitted April 2014; and B4Z-MC-B025, submitted March 2016), as requested by EU regulatory bodies.

8. Research Question and Objectives

The objective of this study is to describe atomoxetine (Strattera) utilisation patterns for patients treated in the UK, Germany, the Netherlands, and Sweden by:

- Estimating the number of patients exposed to Strattera, stratified by age group (paediatric, adolescent, adult and elderly) and formulation (capsule and oral solution) based on years of available data.
- Estimating the duration of exposure, medication possession ratio, and dose over the most recent 24 months of data available for capsules and 18 months for the oral solution.
- Estimating the number of patients that restarted, the gap time in between, and duration of use in additional exposures over the most recent 24 months for capsules and 18 months for the oral solution, for those patients who stopped taking Strattera.
- Describing the population being treated with atomoxetine in terms of common comorbidities, and concomitant medications.

This is a descriptive study and no formal hypotheses are being tested.

9. Research Methods

9.1. Study design

This is a retrospective cohort database study looking at drug utilisation among users of atomoxetine in the UK, Germany, the Netherlands, and Sweden.

9.2. Setting

This study will include patients with at least two consecutive filled prescriptions of Strattera from January 2012 through December 2016. This is the prevalent user cohort, which is described in detail in Section 9.7.

Patient discontinuation and adherence for incident users of atomoxetine capsules within the most recent 24 month period (01 July 2015 – 30 June 2017) will be estimated for each country. Discontinuation and adherence for incident users of atomoxetine oral solution within the most recent 18 month period (01 January 2016 – 30 June 2017) will be estimated in Germany and Sweden. In order to estimate these measures, a cohort of patients will be identified using a 3 or 6 month window and all patients selected will be time-aligned from the date of inclusion into the cohort. Each patient included in the cohort will be considered persistent until it is estimated that the last days' supply of their last script has been exhausted. The allowable time for utilisation of medication for each script will include a grace period (allowable gap), in order to reduce the probability of misclassification of someone whose 30 day script lasts longer than 30 days. An allowable gap, or grace period of 90 days, due to drug holidays in this therapeutic area will be incorporated. The number of treatment episodes over the 24 (18 for oral solution) month period will be described, as well as the percent reinitiating therapy, mean gap in between episodes, and the duration of use in the episodes (more detail in Section 9.7).

9.3. Variables

Variable	Definition
Exposure	
Atomoxetine use	≥2 consecutive atomoxetine (Strattera) prescription dispatches, with a 90 day allowable gap between.
Outcomes	
Treatment duration	the number of days between the date of the first and the last recorded prescription
Duration of exposure	percentage of patients remaining on therapy over time in monthly intervals
Drug dose	package size multiplied by package dose **Please note, that in the database, package size can be a proportion of the package size. Thus, this proportion will also be used in the calculations
Total treatment dose	sum of the drug doses for all purchases (apart from the last purchase)
Mean daily dose	total treatment dose/treatment duration
Length of therapy	sum of days supplied in treatment episodes, not allowing for treatment gaps.
Other characteristics	
Comorbid diagnoses	ICD-10 diagnoses, at the four-digit level, which have been recorded in the database during follow-up
Concomitant medications	Anatomical Therapeutic Chemical (ATC) or British National Formulary (BNF) codes for medications reported during treatment period

Abbreviation: ICD = International Classification of Diseases

9.4. Data Sources

Data:

QuintilesIMS maintains different sets of longitudinal patient data in over 15 countries around the world. For the purpose of this analysis, the appropriate datasets include:

1. The LRx longitudinal prescription data in Germany and the Netherlands
   - LRx is gathered from pharmacy transactions through coding centers or directly from retail chains. This data source contains anonymised encrypted patient IDs that enable tracking of the patient over time. The LRx panel in Germany represents approximately 60% of all retail scripts dispensed in the country. The LRx panel in the Netherlands represents approximately 75% of all retail scripts dispensed in the country.
   - The LRx data for Germany and Netherlands utilise the European Pharmaceutical Market Research Association (EphMRA) ATC coding scheme for medications.

2. The Disease Analyzer (DA) and the Clinical Practice Research Datalink (CPRD) datasets in the UK.
   - DA is composed of electronic medical records gathered from physician office software and allows the tracking of patients longitudinally.
   - CPRD, formerly the General Practice Research Database (GPRD) data set in the UK, is the new National Health Service observational data and interventional research service that provides large multi-linked observational datasets.
   - Drugs are coded according to the BNF chapter in CPRD and EPhMRA ATC codes in the DA.

3. The Swedish Prescribed Drug Register and Swedish Patient Register
   - The Swedish Prescribed Drug Register (SPDR) covers all drugs dispatched at pharmacies in Sweden dating back to 2005. The SPDR contains information for all prescriptions dispensed to the entire population of Sweden (approximately 9 million inhabitants). For prescribed drugs, the register includes data on dispensed item, substance, brand name, formulation, package size, dispensed package count, strength, date of prescribing and dispensing, as well as prescriber's profession and practice. All drugs are classified according to the ATC.
   - In order to evaluate the indication, the SPDR data will be linked to the Swedish patient register, which includes ICD-10 diagnosis codes associated with all inpatient and outpatient (specialist) health care contacts, also with national coverage.

9.5. Study Size

The study sample will include all identified users of Strattera during the study time period.

9.6. Data Management

Data acquisition and analysis will be performed by QuintilesIMS. Datasets and analytic programs will be stored according to the vendor's procedures. QuintilesIMS will document and retain a quality review of all final deliverables to include the following:

1. Confirm that the source of the data and/or results has been documented and that results and data have been verified against the source.
2. Check the internal consistency of the medical research data presented in the document.

9.7. Data Analysis

Creation of Study Cohorts

Prevalent users will be defined as any patients, within a calendar year, with ≥2 consecutive prescription claims/dispatches of Strattera. Prevalent cohorts will be created for each of the most recent 5 full calendar years of data (January 2012 through December 2016). Prevalent use of oral solution will be available from April 2015 through December 2016. These data will be used to assess patient counts, as well as for assessment of comorbidities and concomitant medication usage.

Incident users will be identified from within the prevalent user cohort. Incident (new) users of Strattera capsules will be defined by a first of two consecutive prescriptions between 01 January 2015 and 30 June 2015. Patients will be excluded if any dispatches of Strattera are identified during the 6-month wash out period (01 July 2014 and 31 December 2014). New capsule users will be followed for a 24 month follow-up period (see Figure 9.1) to assess measures of drug utilisation, as further described below. Incident (new) users of Strattera oral solution will be defined by a first of two consecutive prescriptions between 01 April 2015 and 31 December 2015. Because oral solution was not available prior to 2015, there is no need for a wash-out for oral solution dispensings in the 6-months prior. However, the incident users of oral solution may be previous users of capsules. New oral solution users will be followed for an 18 month follow-up period (see Figure 9.2) to assess measures of drug utilisation.

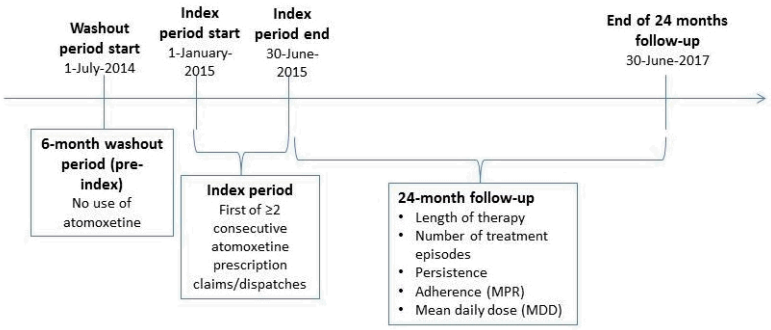

Figure 9.1. **Graphic for identifying incident atomoxetine capsule users for assessing measures of drug utilisation.**

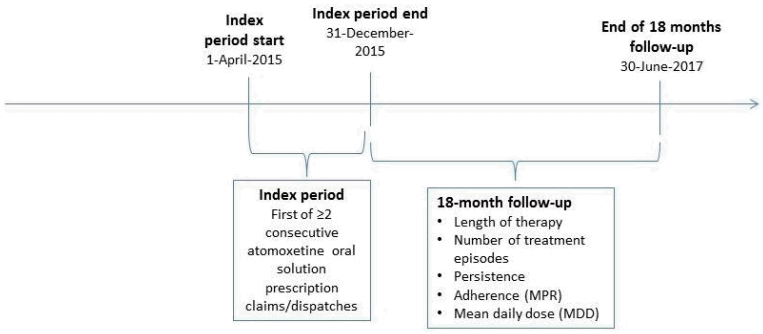

Figure 9.2. **Graphic for identifying incident atomoxetine oral solution users for assessing measures of drug utilisation.**

Patient counts and Descriptive analyses:

For each country, patient counts (and proportions) will be provided for the most recent 5 full calendar years. Counts and proportions will be tabulated by country, year (2012-2016), age group (0-5, 6-9, 10-12, 13-17, 18-34, 35-64, 65+ years), and gender (female/male). These counts will be stratified by formulation (capsules/oral solution). If actual data are unavailable, the number of unique Strattera patients will be projected for each year and in each country. These descriptive statistics will be tabulated in both the prevalent and incident user cohorts.

In addition to Strattera counts, the prevalent user cohort will be used to tabulate frequencies and proportions for ADHD diagnoses, 30 most common comorbidities (defined by 4 digit ICD-10 codes), and concomitant medication usage within a 24-month follow-up period for the capsule users, and up to an 18 month follow-up for the oral solution users.

Patient exposures:

- Treatment duration, duration of exposure, daily average dose, and frequent comorbid diagnoses will be presented (where available), stratified by formulation (capsules/oral solution).

Patient Discontinuation and Adherence:

The following measures of drug utilisation will be estimated based on the cohort of incident users, stratified by formulation:

- The percentage of patients reinitiating therapy and persistence curves showing the percentage of patients remaining on therapy at monthly time intervals.
- A mean and median length of therapy (LOT), including the standard deviation. The mean LOT will be used to calculate patient years (# patients * mean LOT)/365. The method for obtaining the standard deviation will vary for each data source
    - Note that the difference between persistence and LOT is that therapy gaps are counted in persistence and not LOT, where only the actual day's supply prescribed/dispensed are included.
- Mean daily dose. Within the CPRD database the variables numeric daily dose will be used to estimate the mean daily dose. For each of the other databases the mean daily dose is estimated using the following formula (quantity dispensed/day's supply)*strength.
- A distribution of the percentage of patients having undergone one or more treatment episodes over the 24 month (18 month for oral solution) observation period. A single episode is the aggregation of all prescriptions refilled with a 90-day allowable gap after exhausting days supplied in prior prescription.
- The percentage of Strattera patients who stopped taking Strattera and then reinitiated therapy, the gap in between, and the duration of the use in additional exposures.
- The medication possession ratio (MPR), a measure of patient compliance. The MPR will be estimated by dividing the number of day's supply equivalent by the number of days available in a 24 month period.

9.8. Quality Control

The study will adhere strictly to standards consistent with the International Society for Pharmacoepidemiology's Guidelines for Good Pharmacoepidemiology Practices (http://www.pharmacoepi.org). These standards include storage of sensitive data on a server with restricted access. Accuracy and completeness of study data will be assessed by QuintilesIMS and QuintilesIMS will follow its internal policies and procedures to ensure that all data and results have been confirmed against the source and the final deliverables have been quality reviewed by a person external to the report author.

9.9. Limitations of the Research Methods

Limitations to retrospective database studies assessing drug utilisation include:

1. A filled prescription does not guarantee patients are taking the medication or even taking the medication as prescribed. In order to address this, patients will be required to have a minimum of two filled prescriptions.
2. It is difficult to assess the relationship between the treatment of interest and post treatment outcomes.

9.10. Other Aspects

Not applicable.

10. Protection of Human Subjects

Observational studies will be submitted to ethical review boards (ERBs) for approval whenever required by local law. In addition, regardless of local law, all prospective observational studies will be submitted to at least 1 independent body (for example, ERB) per country for review and to confirm that the study is considered noninterventional in that country. Regulatory authorities will be notified and approval sought as required by local laws and regulations. Progress reports will be submitted to ERBs and regulatory authorities as required by local laws and regulations.

This study will be conducted in accordance with applicable laws and regulations of the region, country, or countries where the study is being conducted, as appropriate.

11. Management and Reporting of Adverse Events/Adverse Reactions

During the course of retrospective observational research, information pertaining to adverse reactions (ARs) will not be discovered as the study does not involve identifiable patient data associated with a Lilly drug. The data in this study are only being analysed in aggregate, study data sets do not include safety measures, and there will be no medical chart review or review of free text data fields.

Serious Adverse Events

During the course of secondary use of data in observational research, information pertaining to ARs will not be discovered because the study does not involve identifiable patient data associated with a Lilly product. Data in this study are being analysed in aggregate only, study data sets do not include safety measures, and there will be no medical chart review or review of free text data fields.

12. Plans for Disseminating and Communicating Study Results

Publications may result from this study. A final report will be submitted in a future atomoxetine Periodic Safety Update Report as an EU appendix. As required, study results will be posted to the EU PAS register upon study completion. In the event of an unexpected negative finding, results will be communicated to the appropriate regulatory bodies in the appropriate timeframe.

13. References

Castle L, Aubert R E, Verbrugge RR, Khalid M. Epstein RS. Trends in medication treatment for ADHD. *J Atten Disord*. 2007;10(4):335-342.

Habel LA, Cooper WO. ADHD medications and risk of serious cardiovascular events in young and middle-aged adults.*JAMA*. 2011;306(24):2673-2683.

Zoega H, Furu K. Use of ADHD drugs in the Nordic countries: a population-based comparison study. *Acta Psychiatr Scand.* 2011;123(5):360-367.

Annex 1. List of standalone documents

Not applicable.

Annex 2. ENCePP Checklist for study protocols

Study title: Strattera patient exposures and adherence in the United Kingdom, Germany, the Netherlands, and Sweden: 2018 Bi-annual assessment report (B4Z-MC-B026).

Study reference number: EUPAS17371

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]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Study progress report(s)	☐	☒	☐	
1.1.4 Interim progress report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS register	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an				

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	
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)	☐	☐	☒	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	
4.2.2 Age and sex?	☒	☐	☐	
4.2.3 Country of origin?	☒	☐	☐	
4.2.4 Disease/indication?	☒	☐	☐	
4.2.5 Co-morbidity?	☐	☒	☐	
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)	☒	☐	☐	

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	
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)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

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?	☒	☐	☐	
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)	☐	☒	☐	

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)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	
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.)	☒	☐	☐	
8.1.3 Covariates?	☐	☐	☒	
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)	☒	☐	☐	
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☒	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

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

Comments:

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

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☐	☐	☒	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	
11.3 Are methods of quality assurance described?	☒	☐	☐	

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	
11.5 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☐	☐	☒	
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)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☒	☐	
12.3 Does the protocol address other limitations?	☒	☐	☐	

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?	☒	☐	☐	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.3 Have data protection requirements been described?	☒	☐	☐	

Comments:

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

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

Comments:

Name of the main author of the protocol: Kristin Meyers, PhD MPH

Date: 1/February/2017

Signature: _____

Annex 3. Additional Information

Not applicable.

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