PASS Information

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
Version identifier	001
Date of last version	N/A
EU PAS Register No:	Insert registration number in the EU PAS register,
Active substance	Atomoxetine hydrochloride
Medicinal product(s):	10 mg, Netherlands, PRD418134 Spain, PRD408755 Sweden, PRD345584 United Kingdom PRD306571 18 mg Netherlands, PRD418175 Spain, PRD408770 Sweden, PRD345705 United Kingdom PRD306549 25 mg Netherlands, PRD418182 Spain, PRD408796 Sweden, PRD345719 United Kingdom PRD306553 40mg Netherlands, PRD418333 Spain, PRD408828 Sweden, PRD345776 United Kingdom PRD306576 60 mg Netherlands, PRD418363 Spain, PRD408869 Sweden, PRD345784 United Kingdom PRD306577 80 mg Netherlands, PRD418264 Spain, PRD418114 Sweden, PRD345889 United Kingdom PRD306554 100 mg Netherlands, PRD418444 Spain, PRD408882 Sweden, PRD345902 United Kingdom PRD305653
Product reference:	UK/H/0686/002-008

Procedure number:	[If applicable, provide procedure number:] EMA/<X>/<X>/<XXX>. This would be provided from the Pharmacovigilance Risk Assessment Committee (PRAC) review.
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) utilization 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
MAH contact person	Sophie Laribiere Eli Lilly and Company Erl Wood Manor Windlesham, Surrey, GU20 6PH United Kingdom

3. Table of Contents

4. List of Abbreviations

Term	Definition
ADHD	attention-deficit/hyperactivity disorder
ADR	adverse drug reaction
AE	adverse event
AR	adverse reaction
CPRD	Clinical Practice Research Datalink, formerly the General Practice Research Database
CRF	case report form
DA	Disease Analyser
EU	European Union
ERB	Ethical Review Board
GPRD	General Practice Research Database
ICD	International Classification of Diseases
LOT	length of therapy
MAT	moving annual total
MDD	mean daily dose
MPR	medication possession ratio
SAE	serious adverse event
SAR	serious adverse reaction

5. Responsible Parties

The principal investigator

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IMS Health

6. Abstract

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

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 EU (May 2013). The use of ADHD medications, including nonstimulant atomoxetine has been increasing over-time among children, adolescents and among adults (Zoega 2011, Habel 2011, Castle 2007). There has also been a change in the duration of use in more recent years (Habel 2011, Castle 2007).

The main objective of this retrospective database study is to describe atomoxetine (Strattera) utilization patterns for patients treated in the UK, Germany, the Netherlands and Sweden. This protocol describes the updated drug utilisation study for the study previously conducted in Europe (B4Z-MC-B019, submitted November 2011). 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. Strattera utilization trends will be described and other descriptive statistics such as age, gender, common comorbidities and concomitant medications will be included.

7. Amendments and updates

Not applicable.

8. Milestones

Milestone	Planned date
Start of data collection	01 January 2014 01 January 2016 01 January 2018
End of data collection	31 January 2014 31 January 2016 31 January 2018
Registration in the EU PAS register	Estimated 1November 2013
Final report of study results	31 March 2014 31 March 2016 31 March 2018

9. Rationale and background

In 2003, Lilly launched Strattera (atomoxetine), which was the first attention-deficit/hyperactivity disorder (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 (Zoega 2011, Habel 2011, Castle 2007). There has also been a change in the duration of use in more recent years (Habel 2011, Castle 2007).

IMS Healthcare will execute the analysis of data assessing the utilization of Strattera in a multi-country study, in the UK, Germany, the Netherlands and Sweden as requested by the MHRA. 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. The analysis will include and assessment of adherence patterns among users of atomoxetine and will obtain more information on atomoxetine use patterns in the European Union (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 drug utilisation study for the study previously conducted in Europe (B4Z-MC-B019, submitted November 2011), as requested by EU regulatory bodies. Additional drug utilisation data will be provided at the end of Q1 2014 with data coverage through 2013 where available. Two additional drug utilisation studies are planned to be performed biannually, and study reports will be provided in early 2016 and early 2018.

10. Research question and objectives

The objective of this study is to describe atomoxetine (Strattera) utilization 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) 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.
- 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 those patients who stopped taking Strattera.
- Describing the population being treated with atomoxetine in terms of common comorbidities, and concomitant medications.

11. Research methods

11.1. Study design

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

11.2. Setting

This study will include all patients with filled prescriptions of Strattera for the longest available duration in each selected database. In order to be eligible for inclusion patients will need at least two consecutive filled prescriptions.

Patient discontinuation and adherence for a 24 month period (beginning at mid-year, July 1 – June 30) will be estimated for each country. 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 utilization 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.

For Sweden, patients with filled Strattera prescriptions and with at least 24 months of follow up will be followed from their first recorded prescription dispatch date, up to the full extent of the database.

11.3. Variables

Variable	Definition
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)
Daily average consumption/ dose	total treatment dose/treatment duration
Comorbid diagnoses	all ICD-10 diagnoses, at the three-digit level, which have been recorded in the database during follow-up
Length of therapy	time between episodes of treatment and restart of treatment
Mean daily dose	Mean daily dose

Abbreviation: ICD: International Classification of Diseases

11.4. Data sources

Data:

IMS maintains different sets of longitudinal patient data in 11 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 anonymized encrypted patient IDs that enable tracking of the patient over time. The LRx panel in Germany represents 95% of all retail scripts dispensed in the country. The LRx panel in the Netherlands represents 72% of all retail scripts dispensed in the country.

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.

3. The CEBRxA Database in Sweden
   - There is limited information on adherence, average dose, and duration of exposure for ADHD treatment in Sweden. This database contains health records for inhabitants in the greater Gothenburg area, in the South-West region of Sweden where health care resource use (i.e. visits to health care professionals) in outpatient and inpatient care as well as primary care have been collected for all inhabitants in the greater Gothenburg area. This database has been linked with the national medication registry, on an individual level (läkemedelsregistret) since 2005, and thus allows research specifically addressing relationship between diagnosis, resource utilization, and medication over time.

11.5. Study size

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

11.6. Data management

Data acquisition and analysis will be performed by IMS. Datasets and analytic programs will be stored according to the vendor's procedures. IMS 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.

11.7. Data analysis

Patient counts:

For each country, patient counts will be provided for the most recent 5 full calendar years, and the moving annual total (MAT) will be provided for midyear of the most recent year of available data, when appropriate. If actual data are unavailable, the number of unique Strattera patients will be projected for each year and in each country.

Patient exposures:

- Treatment duration, duration of exposure, daily average dose, and frequent comorbid diagnoses will be presented (where available).
- For Sweden, duration of exposure will be presented as a persistence decay curve plotting the percentage of patients remaining on therapy at monthly intervals.

Patient Discontinuation and Adherence:

The following data points will be produced:

- 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 (MDD). 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 observation period.
- 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.

Descriptive analysis

- Descriptive statistics including frequencies and proportions of patient count and demographics, such as age and gender will be provided for each 24 month period and for the total sample.
- Frequencies and proportions will also be provided for population characteristics such as common comorbidities and concomitant medication

11.8. 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 IMS and IMS 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.

11.9. Limitations of the research methods

Limitations to retrospective database studies assessing drug utilization 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.

11.10. Other aspects

Not applicable

12. 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 one 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.

13. Management and reporting of adverse events/adverse reactions

Adverse Event Collection for Prospective Observational Studies-

Not applicable

Adverse Event Reporting Timing for Prospective Observational Studies

Not applicable

Adverse Event Collection for Retrospective Observational Studies-

This retrospective observational database study will collect descriptive data on utilization, demographics, and comorbid conditions. It is not likely that adverse events will be discovered during the analysis. In the event that adverse events are discovered, researchers will report any of the following suspected adverse reactions with attribution explicitly stated in the individual patient records to the appropriate party (for example, regulators or marketing authorisation holder) as they would in normal practice as required by applicable laws, regulations, and practices:

- suspected adverse reactions (AR)s not specific to risk(s) under study with Lilly drug(s)
- suspected non-serious ARs specific to risk(s) under study with Lilly drug(s)
- suspected ARs occurring in temporal relationship with non-Lilly drug(s).

Serious Adverse Events

Study site personnel will notify Lilly or its designee of any **serious** adverse event (SAE) or serious adverse reaction (SAR) with attribution explicitly stated in the individual patient records and arising in temporal association with the Lilly drug(s) within 24 hours of investigator awareness of the event via a sponsor-approved method. Alerts issued via telephone are to be immediately followed with official notification on study-specific SAE forms. An SAE/SAR is any AE/AR from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalisation
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- or is considered significant by the investigator for any other reason.

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered serious adverse drug reactions (ADRs) when, based upon appropriate medical judgment, they may jeopardise the patient.

14. 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 (PSUR) 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.

15. 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 stand-alone documents

Not applicable.

Annex 2. ENCePP Checklist for study protocols

Not applicable.

Doc.Ref. EMA/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 post-authorisation 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: Strattera – Patient exposures and adherence in the United Kingdom, Germany, the Netherlands, and Sweden

Study reference number:

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 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	☐	☐	☒	

[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)**
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?	☒	☐	☐	

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
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?	☐	☒	☐	
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?				

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
	☐	☐	☒	
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?	☒	☐	☐	
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?	☐	☐	☒	
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: Nicole Kellier

Date: / /

Signature: Signature on file