FINAL STUDY PROTOCOL

Utilisation of antiepileptic medicines in girls and women of childbearing potential - a study in three European countries

Prepared for the European Medicines Agency
May 2017

Version 2.0
Approved 15th May 2017

EUROmediSAFE Consortium

TABLE OF CONTENTS

1. BACKGROUND

In October 2013, the Medicines and Healthcare Regulatory Authority issued a referral into the use of sodium valproate in girls and women of childbearing potential, following new evidence in the literature relating to an increased risk of neurodevelopmental disorders in children exposed to sodium valproate in-utero. The review was carried out by the Pharmacovigilance Risk Assessment Committee (PRAC) and in October 2014 the PRAC adopted its recommendation. Following completion of the review, a letter was sent to healthcare professionals in January 2015 informing them of the changes in the recommendations for valproate prescribing. The recommendations resulting from the review included that

- Valproate and related substances should not be used in female children, women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated.
- Valproate and related substances should be contraindicated in prophylaxis of migraine attacks in pregnancy and women of childbearing potential who are not using effective methods of contraception during treatment with valproate.
- Changes should be made to the product information such as warnings and precautions and updated information on the risks related to exposure during pregnancy to better inform healthcare professionals and women.
- There was a need for further risk minimisation measures, such as educational materials, aimed to better inform patients and healthcare professionals on the risks.

The European Medicines Agency now requires a study to characterise the prescription patterns of antiepileptic medicines in women of child bearing potential, giving particular focus to

- Antiepileptic medicines prescribed to first-ever users, by indication and by age
- Time trends in prescribing over a period of at least 8 years, ideally including data for 2015 and 2016
- Switching between antiepileptic drugs, especially in relation to pregnancy

2. AIMS

This study will seek to characterise prescription patterns of antiepileptic drugs (AEDs) in girls and women of childbearing potential between January 2007 and December 2016 using electronic healthcare data from the United Kingdom (UK), France and Italy.

2.1 OBJECTIVES

1. To determine the prevalence of antiepileptic drug prescribing (overall and for specific AEDs) in girls and women of childbearing age, stratified by
    a. Calendar year
    b. Age at prescribing
    c. Indication for prescribing

2. To determine the incidence of antiepileptic drug prescribing (overall and for specific AEDs) in girls and women of childbearing age (first-ever users), stratified by
    a. Calendar year
    b. Age at first prescription
    c. Indication for prescribing

3. To determine the prevalence of antiepileptic drug prescribing (overall and for specific AEDs) during pregnancy and in the 6 months before pregnancy, stratified by pregnancy outcome (live/stillbirths, spontaneous abortions, induced terminations), stratified by
    a. Calendar year
    b. Maternal age at the start of pregnancy
    c. Indication for prescribing

4. To evaluate the extent of switching between antiepileptic drugs, in relation to pregnancy, stratified by
    a. Calendar year
    b. Maternal age at the start of pregnancy
    c. Indication for prescribing
    d. Type of pregnancy outcome

3.0 DATA SOURCES

Four databases will contribute to the study:

- The Clinical Practice Research Datalink (CPRD) in the United Kingdom
- The Echantillon Généraliste des Bénéficiaires (EGB) database in France
- The databases of the Agenzia regionale di sanità della Toscana (ARS), Tuscany, Italy
- The Certificate of Delivery Assistance and prescription databases of Emilia Romagna, Italy

A summary of the databases can be found in Table 1. The databases were selected based on data availability, population coverage, time scales for data approvals, data access and analyst costs.

Table 1. Overview of the databases

Country/Region	United Kingdom	France	Italy - Emilia Romagna	Italy - Tuscany
Population base	5,000,000 (~8% of the UK population)	680,000 (1/97 of French population)	4,200,000	3,700,000
Database for live & stillbirth pregnancy identification	Clinical Practice Research Datalink (CPRD)	French Health insurance system & Hospital Medical Information System databases (PMSI)	Certificate of Delivery Assistance (CeDAP)	Certificate of Delivery Assistance (CeDAP) Hospital Discharges Registry
Database for pregnancy loss identification	CPRD	French Health Insurance System and PMSI	N/A	Discharges for Induced Terminations & Spontaneous Abortions. Hospital Discharges Registry
Database for medicine use data	CPRD	French Health Insurance System Database	Emilia-Romagna Prescription Database (ERPD)	Tuscany Prescription Database (TPD)
Source for medicine use data	GP practice prescribing[1]	Pharmacy Dispensing	Pharmacy dispensing and Healthcare facilities dispensing (except inpatient exposure)[2]	Pharmacy dispensing and Healthcare facilities dispensing (except inpatient exposure)[3]
Start of first data collection	1987	2003	2003	2003
Capture outpatient prescribing	Yes	Yes	Yes[3]	Yes[3]
Capture inpatient prescribing	Some	No	No	No
Involves database record linkage using personal identifiers	No	Yes[3]	Yes	Yes

[1] Including nurse prescribers working within the GP practice
[2] Including only products reimbursed by the Italian National Health Service and excluding those dispensed to outpatients in a hospital pharmacy
[3] Echantillon Généraliste des Bénéficiaires (EGB) database

4.0 METHODS

A common protocol will be used to extract the required data from each of the databases at their host institutions. Code lists and definitions will be agreed by members of the study team and standardised across databases where feasible. Each site will use its own statistical software to extract the data and complete the shell tables in Appendix I.

4.1 STUDY TYPE

Cohort, drug utilisation study

4.2 STUDY PERIOD

The study period will run from 1 January 2007 until 31 December 2016. It is anticipated that data up to the end of 2016 will be available within each of the different centres by the end of June 2017, however it is acknowledged that data towards the end of 2016 may be incomplete in some databases owing to the time and nature of data collection.

4.3 SOURCE POPULATION

The source population will consist of all females aged between 10 and 50 years during the study period in each of the databases. In order to be eligible, females must have contributed a minimum of 365 days to the database. The cohort entry date will be the latest of the date when they joined the database + 365 days, the date of their 10th birthday or 1-Jan-2007. The cohort exit date will be the earliest of the date they left the database, the date of their 51st birthday or 31-Dec-2016.

4.4 ANTIEPILEPTIC DRUGS (AEDs)

AEDs of interest will be those with an anatomical therapeutic chemical (ATC) code starting N03A and also clobazam (ATC N05BA09) which is licensed for epilepsy in the countries under study. In the UK CPRD, products are not coded using ATC codes but are given a distinct prodcodeid, prodcodeids associated with each of the ATC codes of interest will be identified. Table 2 shows which ATC codes have corresponding prescriptions present in any of the four databases and which will be included in the study. AED exposure will be determined from the issue of a prescription in the UK database and the dispensing of a prescription in the French and Italian databases.

Table 2. Antiepileptic drugs to be included in the drug utilisation study

ATC code	Name	Include
N03AA01	Methylphenobarbital	N
N03AA02	Phenobarbital	Y
N03AA03	Primidone	Y
N03AA04	Barbexaclone	Y

N03AA30	Metharbital	N
N03AB01	Ethotoin	N
N03AB02	Phenytoin	Y
N03AB03	Amino (diphenylhydantoin) valeric acid	N
N03AB04	Mephenytoin	N
N03AB05	Fosphenytoin	Y
N03AB52	Phenytoin combinations	Y
N03AB54	Mephenytoin combinations	N
N03AC01	Paramethadione	N
N03AC02	Trimethadione	N
N03AC03	Ethadione	N
N03AD01	Ethosuximide	Y
N03AD02	Phensuximide	N
N03AD03	Mesuximide	Y
N03AD51	Ethosuximide combinations	N
N03AE01	Clonazepam	Y
N03AF01	Carbamazepine	Y
N03AF02	Oxcarbazepine	Y
N03AF03	Rufinamide	Y
N03AF04	Eslicarbazepine	Y
N03AG01	Valproic acid	Y
N03AG02	Valpromide	Y
N03AG03	Aminobutyric acid	Y
N03AG04	Vigabatrin	Y
N03AG05	Progabide	N
N03AG06	Tiagabine	Y
N03AX03	Sultiame	Y
N03AX07	Phenacemide	N
N03AX09	Lamotrigine	Y
N03AX10	Felbamate	Y
N03AX11	Topiramate	Y
N03AX12	Gabapentin	Y
N03AX13	Pheneturide	N
N03AX14	Levetiracetam	Y
N03AX15	Zonisamide	Y
N03AX16	Pregabalin	Y
N03AX17	Stiripentol	Y
N03AX18	Lacosamide	Y
N03AX19	Carisbamate	N
N03AX21	Retigabine	Y
N03AX22	Perampanel	Y
N03AX23	Brivaracetam	Y
N03AX30	Beclamide	N
N05BA09	Clobazam	Y

4.5 AED EXPOSED STUDY POPULATION

All AED prescriptions defined in 4.4 that are issued/dispensed to any female during her time in the study cohort will be identified. Any female who was issued/dispensed ≥1 prescription for an AED during her time in the study cohort will be defined as exposed.

Prescription duration

The duration of each AED prescription will be calculated using the relevant information available within each of the databases (defined daily dose (DDD), quantity dispensed, dosage instruction etc.). The start date will be taken as the date the prescription was issued/dispensed, although an assumption will be made that a new prescription for a particular AED cannot start until the day after the end date of the previous prescription for that same AED. For each product, the median prescription duration will be calculated. Where insufficient information is available to calculate the duration, the duration will be first imputed from any other prescriptions for the same product issued to the same individual. Where this is not possible, the median product-specific duration will be used.

Continuous exposure

A gap in exposure will be taken as >30 days between the end of one prescription and the start date of the next. All gaps of ≤30 days between two prescriptions for the same AED will be filled and taken as continuous exposure.

Monotherapy

Monotherapy exposure will be taken as exposure to a single AED

Polytherapy exposure

AED polytherapy exposure will be taken as exposure to 2 or more AEDs for any length of time. Patients who take two products simultaneously whilst undergoing a switch will be categorised as polytherapy during that time.

Discontinuation

Discontinuation of a particular product will be taken as a gap of at least 90 days between the end of a prescription supply and the next prescription for the same product. Total discontinuation will be taken as a gap of at least 90 days between the end of a prescription supply and the next prescription for any AED.

4.6 COHORT OF FIRST-EVER AED EXPOSED FEMALES

A cohort of first-ever AED users will be identified within the AED exposed cohort. The earliest AED prescription event date will be identified (for any AED) for each female. 'First-ever users' will be those who received an AED prescription during the study period who had been in the database for >365 days prior to the date of their first AED prescription without any other AED prescribing. For women with epilepsy, it is thought that <5% of women would discontinue for more than one year and then restart (personal communication with AED

prescribers in Italy, France and the UK), so 365 days with no prescribing should be sufficient for identifying 'first-ever users'. For the other indications it is possible that there may be a slightly higher number of returning users.

4.7 COHORT OF PREGNANCIES

Each of the contributing institutions already have algorithms in place to identify pregnancies within their databases and provide best estimates for the start and end dates of a pregnancy. All pregnancies will be identified within each of the databases during the study period. Pregnancies will be eligible for inclusion if the woman was in the study cohort for the 6 months before pregnancy and throughout the pregnancy. In the UK, French and Tuscany databases it will be possible to identify pregnancies that end in a live birth, stillbirth, induced termination (including those induced for non-medical reasons) and spontaneous abortion. In Emilia Romagna, the pregnancy data will be limited to those pregnancies ending in a live or stillbirth. In the UK CPRD, an algorithm will be used to determine the start and end dates of the pregnancy which incorporates all pregnancy related codes in the mother's electronic medical record. In the Italian databases, the start of pregnancy will be determined based on gestational age data and in the French database, the start of pregnancy will be determined from information on gestational age or an algorithm incorporating other available pregnancy related data.

Pregnancy trimesters will be defined as

Trimester 1 - First day of last menstrual period to day 90
Trimester 2 - Day 91 to day 188
Trimester 3 - Day 189 to end of pregnancy

4.8 INDICATION FOR PRESCRIBING

When evaluating the indication for prescribing, the main focus will be on distinguishing between AED prescribing for epilepsy and AED prescribing for psychiatric disorders (bipolar disorder/manic depression). If feasible from the data available, in addition to epilepsy, bipolar disorder/manic depression, additional categories will include migraine and neuropathic pain. There will also be an 'other' category. Where the indication for prescribing cannot be determined it will be recorded as 'unknown'. As some patients may have evidence of co-existing conditions, the categories will not be mutually exclusive. The data available on the indication for prescribing and its completeness varies between the participating databases:

In the French database, the indication for prescribing will largely be determined based on information recorded on the specialty of the prescriber (neurologist or psychiatrist) and the product name (which is different depending on the indication). Information on the indication may also be available from the database if the patient has been hospitalised for the indication the AED was prescribed for. Information on co-prescribing of antipsychotics,

lithium and antidepressants may also be used. Migraine is not a licensed indication for valproate in France and when prescribed off label, according to the health insurance code, the drug is not reimbursed to the patient and does not appear in the database.

In the Italian databases, there is no specific information on the indication for prescribing and limited information on the specialty of the prescriber. However, a validated algorithm has been developed using Italian co-prescribing data to distinguish between prescribing for epilepsy and prescribing for psychiatric disorders.[1] A similar algorithm will be used for this study and will determine indication based on the number of AEDs and the number of co-prescribed antipsychotics, lithium (N05A) and antidepressants (N06A), as outlined in the work by Naldi et al. The algorithm by Naldi et al.[1] excluded individuals dispensed only a single AED prescription during the entire observation period, based on the assumption they were either 'pill testers' or there were 'mistakes in the prescribing record', in our study, however, these will be included and sensitivity analyses will be carried out excluding them.

In the UK CPRD, an algorithm will be created to determine the indication for prescribing. This will primarily use diagnoses recorded as Read codes (either restricted to those entered on the date of an AED prescription or those entered at any time depending on the indication; for example, an epilepsy diagnosis code at any time would be used but a code for migraine would only be used if recorded on the same date as an AED prescription where there was a licensed or known off-label indication for that specific AED). For patients who do not have Read code evidence, information on co-prescribing of antipsychotics, lithium and antidepressants will be used, this will be similar to the work carried out in Italy although it is accepted that prescribing practices may differ between the two countries.

4.9 SWITCHING OF AED THERAPY

Identification of switching of AED therapy will be complicated by the common use of these products as polytherapy, the fact that the process of switching can take several months given the need to taper down the current product and continue taking it alongside the new one which is gradually tapered up, and the fact that switching may be initiated by a specialist.

The identification of switching will be an iterative process and will involve the creation of an algorithm that identifies the starting and discontinuation of AED prescriptions. A switch will be identified each time a new product is either issued/dispensed or an existing product is discontinued. The type of switch will then be determined using assumptions similar to those below. Once the algorithm has been implemented, the percentage of patients identified as switching will be discussed with a clinician to determine whether it is in-line with what they

[1] Naldi I, Piccinni C, Mostacci B, Renzini J, Accetta G, Bisulli F*, et al.* Prescription patterns of antiepileptic drugs in young women: development of a tool to distinguish between epilepsy and psychiatric disorders. Pharmacoepidemiology and Drug Safety. 2016;25(7):763-769.

would expect based on their experience in clinical practice in that particular region. Refinements to the algorithm will be made where necessary.

Monotherapy to monotherapy switching

Monotherapy switching between AEDs will be assumed if a new AED is issued/dispensed and there are no further prescriptions for the original product, or the original product is discontinued within 90 days. The timing of the switch will be taken as the date the switch was initiated and the new AED was issued/dispensed. A 90 day overlap has been allowed for because the guidelines in each of the countries recommend that when a new drug is started it should be built up to an adequate maximum tolerated dose before the first drug is tapered off slowly. Discussion with prescribers in each of the countries found that although some women may continue on both products for longer than 3 months this percentage is likely to be small.

Monotherapy to polytherapy switching

Switching from monotherapy to polytherapy AED use will be assumed if a new AED is prescribed and there are further prescriptions for the original product with exposure of both products continuing simultaneously for > 90 days. The timing of the switch will be taken as the date the new AED was issued/dispensed.

Polytherapy to monotherapy switching

Switching from polytherapy to monotherapy AED use will be assumed if one (or more) of the AEDs is discontinued and there are further prescriptions for one of the original products that lasts for >90 days duration. The timing of the switch will be taken as the date the AED was discontinued.

Polytherapy to polytherapy switching

Switching within polytherapy will be assumed when a new AED is prescribed to a patient already on a polytherapy AED regimen. As only a minority of women (<5%) are expected to be co-prescribed more than 2 AEDs, attempts will not be made to determine whether the newly prescribed AED was added to the existing regimen or whether one of the original products was discontinued.

Switch type unknown

Patients who do not have 90 days of follow-up in their medical record after the initiation of a switch will be categorised as switch ‘type unknown’ as there will be insufficient follow-up to determine the type of switch.

5.0 STATISTICAL ANALYSIS

The analyses below will be carried out separately for each database at their host institution. Appendix I contains the shell tables that will be completed for each objective. The statistical analyses will be carried out using the statistical software available at each institution and the code will be reviewed and compared between centres to ensure the analyses are directly comparable.

OBJECTIVE 1. Prevalence of AED prescribing in girls and women of childbearing age

1a) The prevalence of AED prescribing (overall and for specific AEDs) will be calculated per 1,000 female population with 95% confidence intervals (CI_{95}) as

$$\frac{\text{Number of females receiving} \geq 1 \text{ AED prescription}}{\text{All females in the study cohort}}$$

The prevalence of prescribing will be calculated stratified by:

i. calendar year
ii. age at prescription (10-14, 15-19, then 5-year bands until 45-50 years[1])
iii. indication for prescribing
iv. calendar year and indication for prescribing

1b) The prevalence of AED prescribing (overall and for specific AEDs) will be calculated per 1,000 female population with CI_{95} standardised by age. Direct standardisation will be used using the European Standard Population Weights. The Tiwari method of estimating the confidence intervals will be used.

1c) The percentage of all AED exposed females who were prescribed each specific AED will be calculated.

1d) The number of females receiving only a single AED prescription during the entire study period will be reported stratified by AED and also expressed as the proportion of all females exposed to each specific AED.

[1] If sample sizes are small, resulting in unstable estimates and wide confidence intervals, 10-year age categories will be presented

OBJECTIVE 2. Prescribing patterns to first-ever users of AEDs

2a) The incidence of AED prescribing (overall and for specific AEDs) will be calculated per 10,000 person-years with CI_{95} as

$$\frac{\text{Number of first-ever users receiving } \geq 1 \text{ AED prescription}}{\text{Non-exposed person-time at risk}}$$

All females in the study population will be considered 'at risk' up until the time they receive their first AED prescription. Females at risk will not require a diagnosis of a condition that is an indication for AED treatment. For the person-time at risk calculation the denominator will be truncated at the date of their first AED prescription.

The incidence of prescribing will be calculated stratified by:

i. calendar year
ii. age at first prescription (10-14, 15-19, then 5-year bands until 45-50 years)
iii. indication for prescribing
iv. calendar year and age at first prescription
v. calendar year and indication for prescribing

2b) The percentage of all "first-ever" AED exposed females who were prescribed each specific AED will be calculated.

2c) The number of "first-ever" AED exposed females receiving only a single AED prescription during the entire study period will be reported stratified by AED and also expressed as the proportion of all females exposed to each specific AED.

2d) The mean age (with standard deviation) and median age (with interquartile range) at first AED prescription will be calculated for each of the databases, stratified by specific AED and if numbers allow also by calendar year(s).

OBJECTIVE 3. Prevalence of AED prescribing during pregnancy

3a) The prevalence of AED prescribing will be calculated during the 6 months before pregnancy (broken into 3-month time periods) and during each of the pregnancy trimesters. For women with multiple pregnancies during the study period, all pregnancies will be included in the analysis. The prevalence of prescribing will be calculated stratified by

i. pregnancy outcome (livebirth, stillbirth, induced termination , spontaneous abortion, pregnancy loss type unknown)

ii. calendar year at pregnancy start
iii. age at start of pregnancy, (10-14, 15-19, then 5-year bands until 45-50 years)
iv. indication for prescribing
v. calendar year and indication for prescribing

OBJECTIVE 4. Switching of AEDs

4a) The percentage of women prescribed AEDs who initiate a switch in treatment will be calculated (overall and for each specific AED) stratified by:

i. calendar year
ii. age at first switch (10-14, 15-19, then 5-year bands until 45-50 years)
iii. indication for prescribing
iv. calendar year and indication for prescribing

A breakdown of the AEDs that women are switching from and to will be described where possible. The number and proportion of women who initiate multiple switches during the study period will also be described.

4b) The percentage of women who initiate a switch in AED treatment during the 6, 12 and 24 months prior to the start of pregnancy and during each of the pregnancy trimesters will be calculated (overall and for each specific AED) stratified by:

i. calendar year pregnancy started
ii. age at start of pregnancy (10-14, 15-19, then 5-year bands until 45-50 years)
iii. indication for prescribing
iv. type of pregnancy outcome

A breakdown of the AEDs that women are switching from and to will be described where possible.

5.1 SENSITIVITY ANALYSES

1. Single prescriptions - depending on the number of individuals who receive only a single AED prescription during the entire study period, sensitivity analyses will be carried out to look at the impact on the prevalence and incidence estimates overall and for specific AEDs of excluding those who received only a single AED.

2. Polytherapy when switching – sensitivity analyses will be carried out excluding those who take two or more AEDs concomitantly for <90 days whilst in the process of switching from being categorised as polytherapy exposure.

6.0 SAMPLE SIZE

In total, the four contributing databases capture approximately 14 million individuals and around 165,000 pregnancies per year. The analyses will be descriptive and confidence intervals will be provided to enable interpretation of uncertainty of the estimates.

7.0 STRENGTHS AND LIMITATIONS

Selection bias

The population based nature of the four databases and the fact that majority of AED prescribing will be captured, mean this study is unlikely to suffer from selection bias.

Information bias

Exposure to AEDs

As with all studies that use electronic healthcare data, exposure to AEDs will be based on the issue/dispensing of a prescription. This has the benefit of removing any issues relating to recall bias but it means it is not possible to know whether the woman actually took the medicine and whether she took it as and when instructed, although repeat prescribing of these products can be taken to assume suggest actual use.

None of the databases will capture AED prescriptions issued during an in-patient hospital stay. In the UK CPRD, AED prescriptions will not be captured if they are issued by a specialist in secondary care. It is thought, however, that the proportion of prescriptions not captured will be relatively small, as AED prescribing for the majority of patients would be carried out by the patient's GP and even if initiated by a specialist, most subsequent prescribing will be undertaken by the patient's GP. In France, AED prescriptions will not be captured within the database if they are prescribed off label, as they are not reimbursed and therefore do not appear in the database. This is an uncommon situation but does mean that any AEDs prescribed for migraine will not be captured. In Italy, a small number of AED products are not reimbursed by the Italian National Health Service (N03AB52 Phenytoin combinations, N03AG03 Aminobutyric acid and N03AX17 Stiripentol) and therefore will not be captured. In addition, products administered by intravenous injection in a hospital setting will not be captured but the numbers are expected to be low.

Identification of AED treatment switching

Although attempts will be made to programme the identification of switches in as similar way as possible in each of the different databases, country/regional variation in prescribing practices may mean that country specific definitions and assumptions need to be made. Switches that are initiated by a specialist in the UK will not be captured in the CPRD until the GP takes over the continuation of prescribing. For switches that occur close to the end of

the study period or close to a patient exiting the study cohort, there may not be sufficient follow-up in the patient record to determine the type of switch (mono to mono, mono to poly etc.). The numbers are expected to be low and in these cases the switch will be recorded as type unknown.

If for any reason it becomes apparent that it is not feasible to identify switches by mapping prescription durations in one or more of the databases then an alternative method to evaluate switching would likely include a comparison of the actual prescriptions issued for specific products during two or more specific time periods (e.g. before and after the EMA referral). In relation to pregnancy this could involve comparing the specific products individuals were issued in the 7-12 months before pregnancy to those the same individuals were issued in the 6 months before pregnancy and again to those issued during the 1st (and 2nd) trimesters of pregnancy.

Treatment discontinuation

It is possible that in some cases gaps of at least 90 days between prescriptions for the same product may imply non-adherence or re-start rather than true discontinuation. We will investigate the number of times this scenario occurs and in resulting publications this will be discussed as one of the limitations of the study design/data source.

Indication for prescribing

Different methods will be used for each of the databases to determine the indication for prescribing. Although attempts will be made to use all available evidence to determine the indication, it is likely that for some individuals it will not be possible. We are also aware that co-prescribing may reflect co-morbidity or the management of symptoms of a single condition and attempts will be made to distinguish between these where possible.

Length to follow-up

The length of follow-up after the outcome of the PRAC review is limited to a maximum of 2 years as data in the databases are currently only available until the end of 2016. When looking at pregnancies that go to full term, the time period is even shorter as only pregnancies that started before the second quarter of 2016 will be captured. It is therefore not going to be feasible to evaluate the impact of the PRAC referral on valproate prescribing.

8.0 STUDY REPORT AND MANUSCRIPT

The study will be registered in the EU PAS Register prior to its start. A brief summary of study progress will be submitted to the EMA at the end of months 6 and 12. A final study report will be drafted by the project lead and submitted following completion of the study at month 16. All members of the study team and wider EUROmediSAFE consortium will have the opportunity to contribute and comment. The key findings of the research will be written up for submission to a peer-reviewed journal. The Agency will be given the opportunity to comment on the content of the manuscript which will be submitted to them at the end of month 18 but the consortium will have the freedom to publish without restriction.

9.0 COMMUNICATION OF STUDY RESULTS

The study results will be communicated with the European Medicines Agency. They will also be submitted for publication in a peer reviewed journal. All reports and manuscripts will acknowledge the source of funding as outlined in the Collaboration Agreement.

10.0 ETHICAL AND DATA ACCESS APPROVALS

All centres will be responsible for obtaining the necessary ethics and data access approvals. The following ethical and data access approvals will be sought for each of the participating databases, for some this will not be possible until the protocol has been approved by the Agency.

United Kingdom	Protocol approval by the CPRD Independent Scientific Advisory Committee (ISAC).
France	Approval to EGB access through the French National Institute of Health and Medical Research (INSERM).
Tuscany	The advisory board of the Agenzia Regionale di Sanità will be informed of the study.
Emilia Romagna	None required

All data are anonymised and data extraction and analysis will be carried out at each of the database host institutions. Only aggregated data will be reported and leave the host institution. Counts of less than five will be reported as N <5 in all published manuscripts and reports.

11.0 MILESTONES

The Gantt chart below outlines the proposed timeframes for the utilisation study.

	MONTHS from 09 January 2017																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Draft protocol for EMA review																		
Request database approvals																		
Finalise protocol																		
Data extraction from databases																		
Data analysis from databases																		
Compilation of data from databases																		
Write report																		
Incorporate EMA comments																		
Write manuscript																		

12.0 QUALITY CONTROL

The quality assurance procedures used as part of the FP7 funded EUROmediCAT study will be adopted by the EUROmediSafe consortium for this study. All work will be carried out in line with the ENCePP code of conduct. The study will be registered in the ENCePP Register of Studies and the study protocol, together with a signed ENCePP checklist, will be submitted to the ENCePP secretariat by the project group lead. The study protocol will only be amended based on reasonable scientific explanations or feasibility issues and all changes will be documented.

A common protocol will be used for all databases and code for the data extraction and analysis will be compared and reviewed between centres where feasible. Expert clinicians will be involved in the data interpretation to ensure the results can be explained in terms of what they see in clinical practice.

All members of the study team and wider consortium will be given the opportunity to review and interpret the study results to ensure conclusions are informed by those with the required local expertise of the healthcare system. The team will also seek to involve input from a neurologist and/or a prescriber relevant to the database in each of the participating countries to inform the interpretation.

13.0 DATA ACCESS, STORAGE AND SHARING

All data are anonymised and stored and accessed securely as outlined in the table below. Data extraction and analysis will be carried out at each of the database host institutions. None of the centres are able to share raw data and only aggregate data will be made available in reports and publications.

United Kingdom	The University of Bath receives flat-file copies of data from the Clinical Practice Research Datalink at 6 monthly intervals which are stored on a secure server with restricted access. All data are stored in accordance with national data protection legislation.
France	Access to the EGB requires a direct secured connection to a devoted server, with no possibility to import data. Conditions for accessing the EGB are strictly regulated by law. The Health Data Institute [Institut des données de santé (IDS)] ensures the consistency of medical-administrative databases, data quality and availability of databases for research. Any access request to the EGB for a project requires authorization from the IDS.
Tuscany	Agenzia regionale di sanità della Toscana (ARS) has permission to store a full copy of the the administrative data generated by the regional healthcare system in its own premises. data is updated approximately every month.
Emilia Romagna	Data are available on the server of the Emilia Romagna Region Health Authority and can only be accessed by authorized personnel using a password.

14.0 PROTOCOL AUTHORS

Dr Rachel Charlton was the lead author of the protocol and all members of the project team (Dr Rachel Charlton, Professor Joan Morris, Dr Anna Pierini, Dr Rosa Gini, Dr Amanda Neville, Dr Aurora Puccini, Dr Christine-Damase Michael, Dr Caroline Delarue-Hurault and Dr Maria Loane) contributed to the protocol development. The protocol was also reviewed and approved by two members of the The European Medicines Agency, who is the study funder.

15.0 AMENDMENTS AND DEVIATIONS TO THE PROTOCOL

Date	Amendment	Rational

APPENDIX 1

The following shell tables will be populated separately for each database

Objective 1

Shell table 1a (i) Prevalence of AED prescribing per 1,000 females aged 10-50 years **stratified by calendar year**

	2007				2008				……
	AED exposed N	**Population N**	**Prevalence per 1,000**	**CI_{95}**	**AED exposed N**	**Population N**	**Prevalence per 1,000**	**CI_{95}**	……
Any AED									
Monotherapy - any									
- Carbamazepine									
- Lamotrigine									
- Valproate									
…..									
Polytherapy - any									
- inc carbamazepine									
- inc lamotrigine									
- inc valproate									
…..									

Patients prescribed valproate and carbamazepine as polytherapy will be counted in both the Polytherapy valproate and Polytherapy carbamazepine counts.

Shell table 1a (ii) Prevalence of AED prescribing per 1,000 females aged 10-50 years **stratified by age at first prescription during the study period**

	10-14 years				**15-19 years**				**……**
	AED exposed N	**Population N**	**Prevalence per 1,000**	**CI_{95}**	**AED exposed N**	**Population N**	**Prevalence per 1,000**	**CI_{95}**	**……**
Any AED									
Monotherapy - any									
- Carbamazepine									
- Lamotrigine									
- Valproate									
…..									
Polytherapy - any									
- inc carbamazepine									
- inc lamotrigine									
- inc valproate									
…..									

Shell table 1a (iii) Prevalence of AED prescribing per 1,000 females aged 10-50 years **stratified by indication for prescribing**

	Epilepsy				**Mood disorder**				**……**
	AED exposed N	**Population N**	**Prevalence per 1,000**	**CI_{95}**	**AED exposed N**	**Population N**	**Prevalence per 1,000**	**CI_{95}**	**……**
Any AED									
Monotherapy - any									
- Carbamazepine									
- Lamotrigine									
- Valproate									
…..									
Polytherapy - any									
- inc carbamazepine									
…..									

Shell table 1.1a (iv) – Shell table 1.1a (iii) will be repeated further stratified by calendar year

Shell table 1b Prevalence of AED prescribing per 1,000 females aged 10-50 years between 2007 and 2016 **standardised by age**

	AED exposed (N)	**Population (N)**	**Prevalence per 1,000**	**95% CI**
Any AED				
Monotherapy - any				
- Carbamazepine				
- Lamotrigine				
- Valproate				
…..				
Polytherapy - any				
- inc Carbamazepine				
- inc Lamotrigine				
- inc Valproate				
…..				
…..				

Shell table 1c Percentage of all AED exposed females who were exposed to each specific AED

	Specific AED exposed (N)	**All AED exposed (N)**	**Percentage**	**95% CI**
Any AED				
Monotherapy - any				
- Carbamazepine				
- Lamotrigine				
- Valproate				
…..				
Polytherapy - any				
- inc Carbamazepine				
- inc Lamotrigine				
- inc valproate				

Shell table 1d Number and percentage of women who received only a single AED prescription during the entire study period

	Received a single prescription N	**Received ≥1 prescription N**	**Percentage of all women prescribed (%)**	**95% CI**
Any AED				
Monotherapy - any				
- Carbamazepine				
- Lamotrigine				
- Valproate				
…..				
Polytherapy - any				
- inc Carbamazepine				
- inc Lamotrigine				
- inc valproate				
…..				
…..				

Objective 2

Shell table 2a (i) Incidence of AED prescribing in females aged 10-50 years **stratified by calendar year**

	2007				2008				……
	AED exposed N	**Person-years**	**Incidence (per10,000 p/y)**	**CI_{95}**	**AED exposed N**	**Person-years**	**Incidence (per 10,000 p/y)**	**CI_{95}**	……
Any AED									
Monotherapy - any									
- Carbamazepine									
- Lamotrigine									
- Valproate									
…..									
Polytherapy - any									

Shell table 2a (ii) Incidence of AED prescribing in females aged 10-50 years **stratified by age at first AED prescription**

		10-14 years				15-19 years				……
	Mean age Yrs (SD)	**AED exposed N**	**Person-years**	**Incidence (/10,000 py)**	**CI_{95}**	**AED exposed N**	**Person-years**	**Incidence (/10,000 py)**	**CI_{95}**	……
Any AED										
Monotherapy - any										
- Carbamazepine										
- Lamotrigine										
- Valproate										
…..										
Polytherapy - any										
- inc carbamazepine										
…..										

Shell table 2a (iii) Incidence of AED prescribing in females aged 10-50 years **stratified by indication for prescribing**

	Epilepsy				**Mood disorder**				**……**
	AED exposed N	**Person-years**	**Incidence (per 10,000 p/y)**	**CI_{95}**	**AED exposed N**	**Person-years**	**Incidence (per 10,000 p/y)**	**CI_{95}**	**……**
Any AED									
Monotherapy - any									
- Carbamazepine									
- Lamotrigine									
- Valproate									
…..									
Polytherapy - any									
- inc carbamazepine									
…..									

Shell table 2a (iv) – Shell table 2a (i) will be repeated further stratified by age at first prescription
Shell table 2a (v) – Shell table 2a (i) will be repeated further stratified by indication for prescribing

Shell table 2b Percentage of first-ever users who were exposed to each specific AED

	Specific AED exposed (N)	**All first ever users AED exposed (N)**	**Percentage**	**95% CI**
Any AED				
Monotherapy - any				
- Carbamazepine				
- Lamotrigine				
- Valproate				
…..				
Polytherapy - any				
- inc Carbamazepine				

Shell table 2c Number and percentage of first-ever users who received only a single AED prescription during the entire study period

	Received a single prescription N	**Received ≥1 prescription N**	**Percentage of all first-ever users prescribed (%)**	**95% CI**
Any AED				
Monotherapy - any				
- Carbamazepine				
- Lamotrigine				
- Valproate				
…..				
Polytherapy - any				
- inc Carbamazepine				
- inc Lamotrigine				
- inc valproate				
…..				

Shell table 2e Mean age at first-ever prescribing

	Mean age and SD (years)	**Median age and IQR (years)**
Any AED		
Monotherapy - any		
- Carbamazepine		
- Lamotrigine		
- Valproate		
…..		
Polytherapy - any		
- inc Carbamazepine		
- inc Lamotrigine		
- inc valproate		

Objective 3

Shell table 3 Prevalence of prescribing of AEDs in the 6 months before, during and in the 6 months after pregnancy

	Pre2 N (%)	**Pre1** N (%)	**Tri1** N (%)	**Tri2** N (%)	**Tri3** N (%)	**During 6 months before** N (%)	**During Tri1, Tri2 and/or Tri3** **N (%)**	**During any of the time periods** **N (%)**
Any AED								
Monotherapy - any								
- Carbamazepine								
- Lamotrigine								
- Valproate								
…..								
Polytherapy - any								
- inc Carbamazepine								
- inc Lamotrigine								
….								

Shell table 3 (i) Prevalence of prescribing of AEDs in relation to pregnancy **stratified by type of pregnancy outcome**

	Live birth			**Stillbirth**		
	During 6 months before N (%)	**During Tri1** **N (%)**	**Anytime during pregnancy** **N (%)**	**During 6 months before** N (%)	**During Tri1** **N (%)**	**Anytime during pregnancy** **N (%)**
Any AED						
Monotherapy - any						
- Carbamazepine						
- Lamotrigine						
- Valproate						
…..						
Polytherapy - any						
- inc Carbamazepine						
- inc Lamotrigine						
….						

Shell table 3 (ii) Prevalence of prescribing of AEDs during pregnancy **stratified by calendar year**

	2007			**2008**		
	During 6 months before N (%)	**During Tri1** **N (%)**	**Anytime during pregnancy** **N (%)**	**During 6 months before** N (%)	**During Tri1** **N (%)**	**Anytime during pregnancy** **N (%)**
Any AED						
Monotherapy - any						
- Carbamazepine						
- Lamotrigine						
- Valproate						
…..						
Polytherapy - any						
- inc Carbamazepine						

Shell table 3 (iii) Prevalence of prescribing of AEDs during pregnancy **stratified by age at start of pregnancy**

	10-14 years			15-19 years		
	During 6 months before N (%)	**During Tri1** **N (%)**	**Anytime during pregnancy** **N (%)**	**During 6 months before** N (%)	**During Tri1** **N (%)**	**Anytime during pregnancy** **N (%)**
Any AED						
Monotherapy - any						
- Carbamazepine						
- Lamotrigine						
- Valproate						
…..						
Polytherapy - any						
- inc Carbamazepine						

Shell table 3 (iv) Prevalence of prescribing of AEDs during pregnancy **stratified by indication for prescribing**

	Epilepsy			Mood disorder		
	During 6 months before N (%)	**During Tri1** **N (%)**	**Anytime during pregnancy** **N (%)**	**During 6 months before** N (%)	**During Tri1** **N (%)**	**Anytime during pregnancy** **N (%)**
Any AED						
Monotherapy - any						
- Carbamazepine						
- Lamotrigine						
- Valproate						
…..						
Polytherapy - any						
- inc Carbamazepine						

Shell table 3 (v) Shell table iv will be repeated further stratified by calendar year

Objective 4

Shell table 4a (i) Percentage of women who initiate a switch in AED treatment **stratified by calendar year**

	2007				2008				……
	Number initiating a switch (N)	**Number exposed (N)**	**Percentage**	**CI_{95}**	**Number initiating a switch (N)**	**Number exposed (N)**	**Percentage**	**CI_{95}**	……
Any AED									
Monotherapy - any									
- Carbamazepine									
- Lamotrigine									
- Valproate									
…..									
Polytherapy - any									
- inc carbamazepine									
…..									

Shell table 4a (ii) Percentage of women who initiate a switch in AED treatment **stratified by age at first prescription during the study period**

	10-14 years				15-19 years				……
	Number initiating a switch (N)	**Number exposed (N)**	**Percentage**	**CI_{95}**	**Number initiating a switch (N)**	**Number exposed (N)**	**Percentage**	**CI_{95}**	……
Any AED									
Monotherapy - any									
- Carbamazepine									
- Lamotrigine									
- Valproate									
…..									
Polytherapy - any									
- inc carbamazepine									
….									

Shell table 4a (iii) Percentage of women who initiate a switch in AED treatment **stratified by indication for prescribing**

	Epilepsy				**Mood disorder**				**……**
	Number initiating a switch (N)	**Number AED exposed (N)**	**Percentage**	**CI_{95}**	**Number initiating a switch (N)**	**Number AED exposed (N)**	**Percentage**	**CI_{95}**	**……**
Any AED									
Monotherapy - any									
- Carbamazepine									
- Lamotrigine									
- Valproate									
…..									
Polytherapy - any									
- inc carbamazepine									
- inc lamotrigine									
- inc valproate									
…..									

Shell table 4a (iv) - shell table 4a (iii) will be repeated further stratified by calendar year

Shell table 4b Number and percentage of women initiating a switch in AED treatment before and during pregnancy

	Switch in 24m before pregnancy N (%)	**Switch in 12m before pregnancy** N (%)	**Switch in 6m before pregnancy** N (%)	**Switch during Tri1** N (%)	**Switch during Tri2** N (%)	**Switch during Tri3** N (%)	**Switch anytime during pregnancy** N (%)
Any AED							
Monotherapy - any							
- Carbamazepine							
- Lamotrigine							
- Valproate							
…..							
Polytherapy - any							
- inc Carbamazepine							
- inc Lamotrigine							
….							

Shell table 4b (i) – shell table 4b will be replicated stratfied by calendar year

Shell table 4b (ii) – shell table 4b will be replicated stratfied by age at the start of pregnancy

Shell table 4b (iii) – shell table 4b will be replicated stratfied by indication for prescribing

Shell table 4b (iv) – shell table 4b will be replicated stratfied by type of pregnancy outcome