DRAFT STUDY PROTOCOLS

Estimating the association between exposure to antiepileptic medicines in-utero and neurodevelopmental disorders in the offspring

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Contents

Background

Recent reviews have identified an increased risk of neurodevelopmental disorders in children exposed to sodium valproate in-utero. There is concern that this risk may also be present for other antiepileptic medicines.

Aims

This protocol outlines three different methods of estimating the association between exposure to antiepileptic medicines in-utero and neurodevelopmental disorders in the offspring.

Objectives

1. To estimate the association between exposure to antiepileptic medicines in-utero and neurodevelopmental disorders in the offspring, where neurodevelopmental follow-up is done by de novo data collection using available validated questionnaires filled in by parents or by professionals or where standardised assessments of children by psychologists are conducted.
2. To estimate the association between exposure to antiepileptic medicines in-utero and neurodevelopmental disorders in the offspring using data linkage of available electronic healthcare databases.
3. To estimate the association between exposure to antiepileptic medicines in-utero and neurodevelopmental disorders in the offspring using social media

Protocol 1: Neurodevelopmental follow-up obtained by de novo data collection

This protocol firstly describes potential sources from which children with in-utero AED exposure could be recruited. The protocol then details the study once the mothers and children have been identified/recruited. There will be slight differences in how the study can be conducted if different data sources are used (for example if specific cohorts are used the cohorts may have different requirements about contacting women), but the main methods detailed below are applicable to all data sources. Strengths and weaknesses of the different data sources will be discussed at the end of section 1.

1.1 Recruitment of children with in-utero AED exposure

1.1.1 Cohorts of births in which in utero AED exposure could be identified and de-novo data collection could be instigated

EUROmediSAFE identified 55 cohorts of children in the 28 EU member states. Of these 35 had more than 2,500 children, 12 had more than 10,000 children and only one had over 100,000. In order to determine if exposure to AEDs in-utero is associated with neurodevelopmental disorders, a sufficient number of children with AED exposure in-utero need to be identified. From a recent study the prevalence of in-utero AED exposure from 2004-2010 in Europe was 5.1 per 1,000 pregnancies; being lowest in the Netherlands 4.3 per 1,000 and highest in Wales 6.0 per 1,000(Charlton et al. 2015). The EUROmediSAFE report found similar prevalence rates from 2007-2016 during the first trimester of pregnancy; 2.5 per1,000 in Emilia Romagna, 5.1 per 1,000 in Tuscany, 5.3 per 1,000 in France and 7.2 per 1,000 in the UK. The prevalence of a specific AED exposure is likely to be considerably lower – for example for sodium valproate one of the most commonly used AEDs the prevalence varied from < 0.5 per 1,000 up to 2 per 1,000 in the paper by Charlton et al and the EUROmediSAFE report. Therefore, in order for a cohort to have five children with in-utero AED exposure, the cohort needs to contain at least 10,000 children if the prevalence was 0.5 per 1,000 or 2,500 children for a prevalence of 2 per 1,000. In order for de-novo data collection to be considered there needs to be some children still under 18 years of age. Table 1.1 gives all the cohorts identified that have at least 2,500 children with known in-utero medication exposures and in whom participants could be contacted to collect additional neurodevelopmental outcomes. If there were sufficient funds and manpower available smaller cohorts could be included.

In addition, the Norwegian Mother and Baby Cohort (MoBa) includes 113,564 children born 1999-2000, but it is not included in the Inventory as Norway is not in the EU. However, MoBa has participated in many collaborations so it is likely that they could be approached. MoBa contains detailed information on prenatal exposures obtained around gestational week 17 and 30 by self-administered questionnaires in MoBa.

Table 1.1: Cohorts containing children currently under 18 year of age recruited in utero with known in-utero medication exposures and in whom participants could be contacted to collect additional neurodevelopmental outcomes

Cohort	Recruitment years	Size	Information available on neuro-developmental outcomes (and age in years)
Danish National Birth Cohort (DK)	1996 – 2003	96,836	School performance – at age 11 Language – at ages 1, 6, 11 Mental health – at ages <1-7, 11, 18
Etude Longitudinale Francaise depuis l'Enfance (ELFE) (FR)	2011	20,000	Language – at ages 1-3 Mental health – at ages 1-3
Born in Bradford (BIB) (UK)	2007 – 2010	13,776	Cognitive function – all at age 8 years School performance Language ADHD Autism Mental health
Generation XXI (G21) (PT)	2005 – 2006	8,645	None
PrescriptiOn Médicaments Mères Enfants (POMME) (FR)	2010 – 2011 2015 – 2016	8,372	Mental and motor development at 9 months and 24 months
Nascita e INFanzia: gli Effetti dell'Ambiente (NINFEA) (IT)	2005 – 2016	6,832	School performance – at ages 7, 10 ADHD – at ages 4, 10
Amsterdam Born Children and their Development (ABCD) (NL)	2003 – 2004	6,161	Cognitive function – at ages 5, 11 School performance – at ages 5, 11 Language – at age 5 ADHD – at age 5, 11 Mental health – at ages <1, 5, 11
LucKi (NL)	2006 – Ongoing	5,000 (planned)	Language development – at ages 1-4, 4-12 Learning disabilities – at ages 4-12, 12-19 Behavioural problem – at ages 1-4, 4-12, 12-19 School absence – at ages 12-19
Kuopio Birth Cohort (KuBiCo) (FI)	2012 – Ongoing	4,700 (10,000 planned)	None
Kaunas cohort (KANC) (LT)	2007 – 2009	4,405	Mental health – at age 5
Endocrine disruptors:	2002 – 2005	4,000	Cognitive function – at age 6

Longitudinal study on pregnancy abnormalities, infertility, and childhood (PÉLAGIE) (FR)			
Pollution and Asthma Risk: an Infant Study (PARIS) (FR)	2003 – 2006	3,840	None
INMA-Environment and Childhood Project (INMA Project) (ES)	1997 – 2008	3,768	Cognitive function – at ages 1, 4, 11 Language – at ages 1, 4, 11
LIFE Child (DE)	2011 – Ongoing	3,700 (5,000 planned)	Cognitive function – at ages <1-5 School performance – at ages 8-18 Language – at ages 1-5 Mental health – at ages <1-18
Piccolipiù (IT)	2011 – 2015	3,338	Cognitive function – all at age 4 ADHD Autism
PRegnancy and Infant DEvelopment Study (PRIDE Study) (NL)	2011 – 2019	3,200	Cognitive function – at ages <1-6 ADHD – at ages 1-6 Autism – at ages 1-6 Mental health – at ages <1-6
Southampton Women's Survey (SWS) (UK)	1998 – 2002	3,158	Cognitive function – at ages 4, 6, 12 Mental health - at ages 3, 12
GECKO Drenthe cohort (GECKO Drenthe) (NL)	2006 - 2007	2,997	Cognitive function – at ages 5, 10
KOALA Birth Cohort Study (KOALA) (NL)	2000 – 2002	2,843	ADHD – at ages 7-11 Mental health – at ages 1, 2
Odense Child Cohort (DK)	2010 - 2012	2,553	Cognitive function – at age 7 School performance – at age 7 Language – at age 2, 3 ADHD – at age 5 Autism – at age 5 Mental health – at ages 3, 5, 7

1.1.2 Cohorts of births exposed to AEDs in whom de-novo data collection could be instigated

Women With Epilepsy (WWE) cohort

In the UK the Women With Epilepsy (WWE) cohort recruited 277 women with epilepsy and 315 controls from antenatal clinics at 11 National Health Service (NHS) hospitals within Merseyside and Greater Manchester between 2000 and 2006. (Mawer et al. 2010, Bromley et al. 2010, Bromley et al. 2013, Bromley et al. 2008). Of those followed up for six years, 64 children were exposed to sodium valproate, 44 to lamotrigine, 76 to carbamazepine, 14 to other monotherapy treatments and 51 to polytherapy. The study has reported on neurodevelopmental disorders in the children up to the age of six years. Due to the sample sizes only sodium valproate, lamotrigine and carbamazepine could be studied in detail. Therefore, if there was interest in these AEDs it could be investigated if de-novo data collection could be instigated.

Epilepsy Pregnancy Registries and EURAP

EURAP (an international registry of antiepileptic drugs and pregnancy) was launched in Europe in 1999 with the aim to collect and share data on the risk of antiepileptic drugs during pregnancy. At present, physicians from 42 countries including the following 20 European countries are actively collaborating: .

Austria	Belgium	Croatia
Czech Republic	Denmark	Finland
France	Germany	Hungary
Italy	Lithuania	Luxembourg
Netherlands	Poland	Portugal
Slovakia	Slovenia	Spain
Sweden	United Kingdom and Ireland	

Many of these countries also have their own epilepsy pregnancy registry (for example the UK and Ireland Epilepsy and Pregnancy Register).

All women taking antiepileptic drugs at conception are eligible for inclusion whether the indication for treatment is epilepsy or other disorders. To avoid selection bias, only pregnancies enrolled before foetal outcome is known and within week 16 of gestation contribute to their prospective studies.

A recent study published by EURAP (Tomson et al. 2018) compared the risk of major congenital malformations associated with eight different antiepileptic drugs and provided the following table of cases with at least one year's complete follow-up (Figure 1).

Figure 1: Number of exposed pregnancies according to antiepileptic monotherapy in recent EURAP study (Tomson et al. 2018).

	Dose range (mg/day)	Number of pregnancies exposed	Number of major congenital malformation events	Prevalence of major congenital malformation events (95% CI)
Lamotrigine	25–1300	2514	74	2·9% (2·3–3·7)
Carbamazepine	50–2400	1957	107	5·5% (4·5–6·6)
Valproate	100–3000	1381	142	10·3% (8·8–12·0)
Levetiracetam	250–4000	599	17	2·8% (1·7–4·5)
Oxcarbazepine	75–4500	333	10	3·0% (1·4–5·4)
Phenobarbital	15–300	294	19	6·5% (4·2–9·9)
Topiramate	25–500	152	6	3·9% (1·5–8·4)
Phenytoin	30–730	125	8	6·4% (2·8–12·2)

Table 2: **Prevalence of major congenital malformations in offspring exposed prenatally to one of eight different antiepileptic monotherapies**

As given in Table 1.3 (below): to investigate any individual drug around 64 exposed children would be required. Therefore the EURAP registry is likely to have sufficient numbers of such children.
In 2012 EURAP produced a protocol for an international, multicentre, semi/prospective evaluation of children exposed to carbamazepine, lamotrigine or valproate monotherapy during the prenatal period (http://www.eurapinternational.org/pdf/private/NCEP_protocol_revised2011.pdf). This protocol can be adapted to evaluate any other AED.

1.1.3 Creating a new cohort

Retrospective recruitment of women with epilepsy during pregnancy

Women with epilepsy during pregnancy can be identified retrospectively from outpatient epilepsy clinics or antenatal clinics using hospital obstetric records, particularly in referral hospitals for women with medical complications of pregnancy. This has been done in several studies (Dean et al. 2002, Adab et al. 2004, Mawer et al. 2002) and the children identified have subsequently been examined. At least three groups of children should be identified: those exposed to AEDs in-utero, those whose mothers have epilepsy, but they were not exposed to AEDs in utero and those whose mothers did not have epilepsy and they were not exposed to AEDs in utero. In addition, information should be collected about siblings if they were unexposed to any AED during pregnancy. It is important that all information on medications taken are obtained from medical notes before the outcome of the pregnancy.

Prospective recruitment of women with epilepsy during pregnancy

A new cohort of children with in utero AED exposure could be recruited by midwives in antenatal clinics or epilepsy outpatient clinics across Europe. An example of this is the WWE cohort in England (see 1.1.2 above). The methodology for this prospective study differs from all of the above in that the children need to be followed up prospectively. As above four groups of children should be

recruited with, if possible, a set of fathers with epilepsy who take AEDs during the mother's pregnancy (who will also be present in epilepsy outpatient clinics).

1.2 Study methods

1.2.1 Study type

Nested case-control sets of children identified with in utero AED exposure and unexposed controls within pre-existing birth cohorts or in new cohorts will be contacted for de-novo data collection on neurodevelopmental outcomes.

1.2.2 Study period

The study period will be determined by the availability of the data.

1.2.3 Study population

The study population will consist of children with evidence of exposure to specific named AEDs during pregnancy with an indication of the timing of the exposure (in gestational weeks) either actively recruited whilst pregnant or else retrospectively recruited from antenatal clinic records and obstetric notes. Similarly, unexposed controls will be included.
The information about AED exposure must have been collected/recorded before the outcome of the pregnancy was known. All children satisfying the above criteria in a data source should be included in the study – the reasons for not including eligible children should be given as this may be a source of bias. For pre-existing cohorts must have obtained informed consent to re-contact the parents from the mother and/or father according to national legal requirements. For new cohorts informed consent must be obtained.

1.2.4 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 many European countries. In countries where products are not coded using ATC codes (for example the UK where products are given prodcodeida) the product codes associated with each of the ATC codes of interest will be identified and confirmed with a clinical expert in the relevant country.

1.2.5 AED Exposure

AED exposure will be considered valid if it has been recorded by the clinician responsible for the woman's care during pregnancy, has been detailed in the obstetric notes or has been obtained from a questionnaire completed by the mother (prior to the pregnancy outcome). Any female who has received only one AED prescription during the entire study period will be assumed to **not** have been **exposed** to an AED. Paternal exposure to an AED will be recorded if has been obtained from a questionnaire completed by the father (prior to the pregnancy outcome) or was present in hospital records.

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. 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. A sensitivity analysis could be performed by excluding all the prescriptions for whom the duration cannot be calculated.

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 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. If the gap is between 30 days and 90 days the women will be classified as continuing the same product, but no exposure to the product will be assumed. A sensitivity analysis could be performed by comparing the results with an assumption of continuous exposure if the gap is < 90 days.

1.2.6 AED Exposure during pregnancy

Any exposure to any specific drug during the three trimesters of pregnancy, the three months before pregnancy and the twelve months after pregnancy will be recorded. Recording exposure in the twelve months after pregnancy enables comparisons between mothers with exposure during pregnancy with those only with exposure after pregnancy. Comparing these two groups enables some degree of adjustment for the disease, as both groups of mothers are taking the same medication In addition, whether the drug was used as monotherapy or as part of AED polytherapy will be recorded. If possible the dose of drugs will also be taken into account.

1.2.7 Neurodevelopmental outcomes

Neurodevelopment covers a range of different domains and one specific medication may impair one domain (such as language development), but not influence others (such as psychomotor development). It is therefore important when investigating a specific medication to identify if there are specific domains that are likely to be affected from previous studies including any data from animal models if it exists. Table 1.2 provides a list of neurodevelopmental tests that have been used in peer reviewed studies to investigate neurodevelopmental delay in children. However, it is important to involve a psychologist in the study design and for the psychologist to identify the specific domains in which to collect information by assessing the children themselves.

The study should be designed on the assumption that the results from one test will be sufficient to determine any association with neuro-development. This does not mean that subsequent follow-up visits cannot occur, but when planning a study, the sample size should be sufficient to analyse with one test. There is a trade-off of testing children earlier and hence having a quicker result and testing children later and being able to identify neuro-developmental delays with greater sensitivity.

Table 1.2: Validated tests used to measure neurodevelopmental outcomes

Test	Description	Age at testing
Griffiths mental development scales	Griffiths III administered by clinical professional provides an overall measure of a child's development, as well as an individual profile of strengths and needs across five areas: Foundations of Learning Language and Communication Eye and Hand Coordination Personal–Social–Emotional Gross Motor	Birth – 6 years
Bayley Scales of Infant and Toddler Development	Core battery of five scales. Three scales administered with child interaction – cognitive, motor, language. Two scales conducted with parent questionnaires – social-emotional, adaptive behavior.	1-42 months
Ages and Stages Questionnaire (ASQ-3)	Questionnaires completed by parents Areas screened: Communication, gross motor, fine motor, problem solving, and personal-social	1 month to 5.5 years
Wechsler Preschool and Primary Scale of Intelligence (WPPSI)	Clinicians administer questionnaire. Verbal and Performance IQ scores as well as a Full Scale IQ score	2 years 6 months to 7 years 3 months
Schedule of Growing Skills II (SGSII).	Health care professionals or educational staff can administer assessment. Developmental screening tool for children	Birth to 5 years
Childhood Autism Rating Scale (CARS).	A behaviour observation scale in which a trained observer rates the child's behaviour on each of 15 dimensions or symptoms. The total score is a continuous measure of the severity of autism	2 years and above
Modified Checklist for Autism in Toddlers (M-CHAT).	2-stage parent-report screening tool to assess risk for Autism Spectrum Disorder (ASD). It is designed to identify children who should receive a more thorough assessment for possible early signs of autism spectrum disorder (ASD) or developmental delay.	16-30 months

NEPSY Developmental Neuropsychological Assessment-II	Clinicians or researchers can administer. Six functional domains designed to assess cognitive abilities related to disorders that are typically diagnosed in childhood: Executive Functions Language Sensorimotor Visuospatial Learning and Memory Social Perception	Two forms: Ages 3-4 years and 5 to 16 years
Denver Developmental Screening Tool (DDST)	Trained examiners or parents can administer. The tests address four domains: personal-social, fine motor and adaptive, language and gross motor.	Birth to 6 years
Strengths and Difficulties Questionnaire (SDQ)	Can be administered by parents and teachers up to age 11 and then self-administered. The tests identify emotional symptoms, conduct problems, hyperactivity/ inattention, peer relationship problems and prosocial behaviour.	3 – 16 years

Major congenital anomalies.
These will be classified using the EUROCAT congenital anomaly subgroups and the EUROCAT exclusion criteria for minor anomalies.

1.2.8 Potential confounders

Data on potential confounders will be collected from the clinician caring for the mother/father, medical notes or from questionnaires filled in by the mother and/or father.
a. Indication for prescribing/maternal illness particularly whether it was for epilepsy or psychiatric disorders (bipolar disorder/manic depression) with, if possible, additional categories including migraine and neuropathic pain.
b. Severity of epilepsy in particular whether 5 or more generalised tonic-clonic seizures occurred during the pregnancy.
c. Maternal and/or paternal IQ tested using the Wechsler Adult Intelligence Scale
d. Maternal social class and/or education level
e. Maternal smoking during pregnancy
f, Maternal alcohol consumption during pregnancy
g. Comedications taking during pregnancy
h. Relevant comorbidity

1.3 Statistical analysis

1.3.1 Non-attendance / loss to follow up

The potential for any bias to occur due to children not being assessed because of loss to follow-up or non-attendance will be evaluated using the available baseline information collected on the child and mother during pregnancy. In addition censoring weights can be created and used to account for loss to follow-up.

1.3.2 Definition of exposure groups

The AED exposure will be analysed separately for:

1. 3 months before pregnancy
2. 1st trimester
3. 2nd trimester
4. 3rd trimester
5. Up to 1 year after the pregnancy

If possible the dose of drugs will also be taken into account.

1.3.3 Definition of Non Exposure Groups

The control children will be categorised into the following non-exposure groups in order to attempt to examine the effect of maternal morbidity as well as medication exposure:

1. Children whose mothers had no evidence of epilepsy and were not on any AED in whole previous year and 12 months after delivery (Controls)
2. Children whose mothers took an AED sometime during the year before LMP but paused AEDs at least 3 months before LMP (Pausers) and did not take during pregnancy
3. Children whose mothers had no evidence of epilepsy and were not on any AED in whole previous year, but whose fathers had taken an AED sometime during the pregnancy (Paternal controls)
4. Siblings who had not been exposed to an AED in utero (Sibling controls).

1.3.4 Risk of neurodevelopmental disorders in the offspring

All the neurodevelopmental tests result in scores that can be treated as continuous outcomes and hence analysed using standard linear regression models. If data from several different cohorts is being used then, multi-level regression models will be used to adjust for cohort differences. All exposure groups will initially be analysed in separate models comparing the exposed children to children from one of the listed comparison groups. If children are compared to their siblings, then the multilevel models must be nested within families to adjust for family environment. Potential confounders will then be included in the linear regression models.

1.3.5 Propensity Score Methods

In addition to analysing the risks of an adverse outcome adjusted for covariates, the propensity score methods will be employed. For each offspring a propensity score of being exposed to the specific AED will be estimated using logistic regression with the outcome exposure to the AED and the independent variables being the confounders and covariates. Then the overall risk of an adverse outcome will be analysed either by using propensity score stratification or propensity score matching. With stratification a multilevel model is fitted with levels/strata defined by propensity score values. With matching a set of exposed and unexposed children are selected such that each pair has a similar propensity score. This may result in a large loss of data. Covariates such as gender, gestational age and weight will be included in the propensity scores.

1.3.6 Multiple Imputation Methods vs Adjusting Crude Odds Ratios

In all of the above analysis patterns of missingness in the data will be investigated and multiple imputation methods may be employed if considered necessary.

1.4 Sample size

The size of the study will be determined by the size of the neurodevelopmental deficit that is expected to be detected. The number of exposed children needed can be reduced by having a greater proportion of unexposed children. However, when de novo data collection is involved it is unlikely that more than 2 unexposed children per 1 exposed child will be recruited due to the costs of recruitment. The tables below give examples comparing IQ scores, but the same results apply for any score when expressed in terms of sd units (for example 10 pts IQ = 10/15 = 0.66 sds)

Table 1.3: Sample sizes required to achieve a power of 90% at a statistical significance level of 5% when analysing IQ scores with a mean of 100 and sd of 15 in an unexposed population

Expected deficit in IQ score	Ratio of exposed to control children	Number children exposed to AEDs in utero	Number children not exposed to AEDs in utero
10 pts	1:1	48	48
5 pts	1:1	190	190
1 pt	1:1	4729	4729
10 pts	1:2	36	72
5 pts	1:2	142	285
1 pt	1:2	3547	7094
10 pts	1:5	29	143
5 pts	1:5	114	569
1 pt	1:5	2837	14200

Table 1.4: Number of sibling pairs required to achieve a power of 90% at a statistical significance level of 5% when analysing IQ scores with a mean of 100 and sd of 15 in an unexposed population. Note that all these comparisons assume that the mother was taking different medications for the two pregnancies (which may not be the case).

Correlation of IQ scores in siblings in unexposed population	Expected deficit in IQ score	Number of sibling pairs discordant for medication usage
0.5	10 pts	26
0.5	5 pts	97
0.5	1 pt	2367
0.3	10 pts	36
0.3	5 pts	135
0.3	1 pt	3312

1.5 Strengths and limitations

1.5.1 Strengths

AED Exposure

If contact is made with the parents before the outcome of pregnancy, then complete unbiased information on medication exposure can be obtained. If contact is made after the birth of the child there is still the opportunity to potentially clarify any uncertainties about AED exposure during pregnancy. In particular, to determine if prescribed medications were actually taken rather than just dispensed.

Indication for AED prescription

This can be fully explored by obtaining information from the mother if the medical notes are insufficient.

Neurodevelopmental Outcomes

De novo data collection allows the researchers to ensure that the exposed and unexposed children are all tested in the same way, for example within a cohort the same psychologist tests each child. It also enables researchers to ensure that even if the children are from different cohorts they all take the same test. In addition, tests can be used rather than just relying on a binary variable indicating a neurodevelopmental problem. For example, rather than relying on a diagnosis of Autism, the Childhood Autism Rating Scale (CARS) or the Modified Checklist for Autism in Toddlers (M-CHAT) can be used.

Sample Size

As mentioned above tests can be used and analysed as continuous measures rather than binary outcomes. This means that the sample size can be smaller than when relying on binary variables such as a diagnosis of ADHD.

1.5.2 Limitations

Time Scale

It can be very time consuming to contact, recruit individual parents and then examine their children. If recruitment is done before pregnancy neurodevelopmental outcomes cannot be measured for several years.

Costs

The costs for examining each individual child are high. Therefore, usually only one or two unexposed children are recruited for each exposed child, which will mean that more exposed children will be required in order to have a reasonable power in the study. This may be difficult for rare medications.

Recruitment of children

Bias may arise in the recruitment of women to the study, in that there may be an association between the willingness to take part and the health of the child. In addition, it is often difficult to recruit sufficient women who do not have epilepsy.

Assessment of Neurodevelopmental Outcomes

The accurate assessment of neurodevelopmental relies on the validity and reliability of the outcome measures used. A specific medication may affect only specific neurodevelopmental domains (such as language development) and subtle effects may only become apparent in later childhoood. Therefore, a potential limitation of the study is that non-specific assessments or unreliable assessments have been completed at too early a stage of development in the children.

1.6 Ethical and data access approvals

Informed consent will be obtained from every study subject; mother and/or father according to national laws and regulations. Parent/s will sign the consent form on behalf of their children. The data stored in the research database will be anonymous with unique patient identifiers. A separate list with no clinical information will link the identifiers to the patient identifiable information necessary to contact them.

1.7 Quality control

All work should 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. The study protocol will only be amended based on reasonable scientific explanations or feasibility issues and all changes will be documented.

1.8 Timescale and resources (costs)

It is anticipated that the following person-time will be required for the study in which 190 children with exposure in utero to a specific AED are recruited with 190 control children.

Table 1.5: Estimated timescale and resources to perform study with 190 children with in-utero exposure and 190 without the exposure

	Time to Complete	**Funded Time**
Protocol development / Study sponsorship	1- 3 months	1 month
Identifying how to contact children – *A or B* *C*	 1 month or 1 year & several years follow-up	 1 month 1 year & 0.05 per week for follow-up
Designing Parents/Child questionnaire & CRFs	1 month	1 month
Applying for ethics permission to contact parents & children	6 months	1 month
Contacting parents and arranging examinations by professionals	1 year	1 year
Setting up database and analysing results	1 month	1 month
Writing paper for peer review journal	3 months	3 months
Total Time	2-3 years plus years follow-up if needed	20 person months or @ 36 months if (C)

Identifying children: (A) If a pre-existing cohort is to be used collaborations must be instigated with the researchers looking after that cohort, (B) if a retrospective cohort is to be formed then antenatal records will need to be reviewed or (C) if a prospective cohort is to be formed then midwives need to recruit women as they attend ante-natal or epilepsy clinics.

Costs

1. Person time of 20 person months
2. Costs of identifying children
3. Costs of following up children for several years if necessary
4. Costs of interviewing 380 parents and children including travel costs and expenses

Protocol 2: Neurodevelopmental follow-up obtained from secondary data with or without data linkage

This protocol differs from protocol 1 in that there is no de novo collection of neurodevelopmental data, only existing data or data obtained by linkage is available. This means that the precise neurodevelopmental outcome to be collected cannot be specified – only those measures already collected or available, though linkage can be obtained.

2.1 Data Sources

2.1.1 Cohorts with in-utero exposure and neurodevelopmental measures

As was discussed in section 1.1.1 in order for a cohort to have five children with in-utero AED exposure, the cohort in expectation needs to contain at least 10,000 children if the prevalence of a specific AED during pregnancy was 0.5 per 1,000 or 2,500 children for a prevalence of 2 per 1,000. Table 2.1 gives information on 23 pre-existing cohorts that have both in-utero medication exposures and neurodevelopmental measures and more than 2,500 children.

Table 2.1: Cohorts with information on in-utero medication exposure and neurodevelopmental outcomes

Cohort	**Recruitment years**	**Size**	**Information on neuro-developmental outcomes**		
			Outcome	**Age at measurement**	**Tests Applied**
Evaluation chez la Femme Enceinte des MEdicaments et de leurs RISques (EFEMERIS) (FR)(Hurault-Delarue et al. 2016)	2004-2016	128,053	Mental and Motor development	9 months and 24 months	14 questions included in French Health Certificate examinations Completed by GP or paediatrician
Danish National Birth Cohort (DK)(Lemcke 2016, Holst , Larsen et al. 2014)	1996 – 2003	96,836	Neurodevelopment	6 months and 18 months	Telephone interviews with mother on early development
			ADHD	Considered reliable any age from 3 years	Children with ADHD diagnosis are registered in Danish National Patient Register or Danish Psychiatric Central Register. Children that have been medically treated for ADHD (methylphenidate or atomoxetine) are in National Prescription Registry
			Motor development (Developmental Coordination Disorder)	7 years	Parent administered Developmental Coordination Disorder Questionnaire 2007
			Impaired neurodevelopment	7 years	Diagnoses from Danish National Patient Register and Danish Psychiatric Central Register ICD10 codes: seizure disorders/epilepsy (G40-G41), retarded psychomotor development (R62.0), mental

Cohort	Recruitment years	Size	Information on neuro-developmental outcomes		
			Outcome	**Age at measurement**	**Tests Applied**
					retardation (F70–F79), autism spectrum disorder (F84.0, F84.1, F84.5, F84.8, F84.9), developmental disorder of motor function (F82) and attention deficit/hyperactivity disorder (F90.0, F90.1, F90.8, F90.9).
PLASTICITY - life long follow-up of cognitive ability after birth risks (Plasticity) (FI)(Michelsson 1978)	1971 – 1974	22,359	Birth cohort.net states cognitive function measured at 5,9 and 16 years but no further publications identified		
Etude Longitudinale Francaise depuis l'Enfance (ELFE) (FR)(Vandentorren et al. 2009)	2011	20,000	Psychomotor development	3 years	Face to Face interview using psychomotor tests
Millennium Cohort Study (UK)(Barbuscia and Mills 2017)	2000 - 2001	19,519	Cognitive ability Verbal cognitive abilities Expressive verbal ability	3 and 5 years 7 years 11 years	British Ability Scales (BAS II): twelve core sub-tests of cognitive ability and educational achievement At age 3 and 5 years: naming vocabulary component At age 7 years: word reading test At age 11years: Verbal similarity test

Cohort	Recruitment years	Size	Information on neuro-developmental outcomes		
			Outcome	**Age at measurement**	**Tests Applied**
All Babies in Southeast Sweden (ABIS) (SE)	1997 – 1999	17,000	School performance	8 and 11 years	Records from schools
Avon Longitudinal Study of Parents & Children (ALSPAC) (UK)(Freitas-Vilela et al. 2018, Hibbeln et al. 2007)	1990 – 1992	14,000	Gross motor, fine motor, social skills and communication	6,18,30, 42 months	Denver Developmental Screening Test completed by parents
			ADHD	81 months	Strengths and Difficulties Questionnaire completed by mothers
			Mental development	4 and 8 years	Trained psychologists measured IQ using at 4 years: Wechsler Pre-school and Primary Scale of Intelligence – Revised UK edition (WPPSI) and at 8 years: an adapted form of the Wechsler Intelligence Scale for Children-III
			ADHD	8 years	Test of Everyday Attention for Children (TEACh)
			School Performance	4-5 years 7-8 years 10-11 years	Entry assessments to school Standard Assessment Test scores (SATs) for key stage 1 (7-8) and key stage 2 (10-11)
Born in Bradford (BIB) (UK)	2007 – 2010	13,776	Cognitive function	8 years	Planned measures but details not available: School performance, Language, ADHD,Autism

Cohort	Recruitment years	Size	Information on neuro-developmental outcomes		
			Outcome	**Age at measurement**	**Tests Applied**
Healthy Habits for two (HHf2) or referred to as Aalborg-Odense Birth Cohort (DK)(Zhu et al. 2011)	1984 – 1987	11,144	Emotional symptoms, conduct problems, hyperactivity, peer relationship problems, prosocial behaviour	2 years 18-21 years	Strengths and difficulties questionnaire (SDQ) completed by mothers and children
PrescriptiOn Médicaments Mères Enfants (POMME) (FR)(Benevent et al. 2018)	2010 – 2011 2015 – 2016	8,372	Mental and Motor development	9 months 24 months	14 questions included in French Health Certificate examinations Completed by GP or paediatrician
Nascita e INFanzia: gli Effetti dell'Ambiente (NINFEA) (IT)(Vizzini 2018)	2005 – 2016	6,832	ADHD Academic achievement	4 years 7 years	DSM IV questionnaire completed by mother Mother asked child's scores in mathematics and reading/writing (on national tests)
Amsterdam Born Children and their Development (ABCD) (NL)(van Eijsden et al. 2011)	2003 – 2004	6,161	Emotional symptoms, conduct problems, hyperactivity, peer relationship problems, prosocial behaviour	5 years	Strengths and difficulties questionnaire (SDQ): Mothers completes 1 questionnaire, teacher 1 questionnaire & health check at school
LucKi (NL)(de Korte-de Boer et al. 2015)	2006 – Ongoing	5,000 (planned)	Details not published, but birth cohorts.net gives planned tests		Planned: Language development – at ages 1-4, 4-12 Learning disabilities – at ages 4-12, 12-19 Behavioural problem – at ages 1-4, 4-12, 12-19 School absence – at ages 12-19

Cohort	Recruitment years	Size	Information on neuro-developmental outcomes		
			Outcome	**Age at measurement**	**Tests Applied**
Endocrine disruptors: Longitudinal study on pregnancy abnormalities, infertility, and childhood (PÉLAGIE) (FR)(Viel et al. 2017, Béranger et al. 2017)	2002 – 2005	3,421	Emotional symptoms, conduct problems, hyperactivity, peer relationship problems, prosocial behaviour	6 years old	Strengths and Difficulties Questionnaire completed by mothers
			Neurocognitive abilities	6 years old	Psychologisits administered Wechsler Intelligence Scale for Children, 4th edition (WISC-IV).
INMA-Environment and Childhood Project (INMA Project) (ES)(Ferrer et al. 2018)	1997 – 2008	3,768	Cognitive and psychomotor development	5 years old	Tests administered by psychologists McCarthy Scales of Children's Abilities (MCSA)
			Social Competence		Teachers rated California Preschool Social Competence Scale (CPSCS)
			Autism spectrum symptoms		Parents completed childhood autism spectrum test (CAST)
			ADHD		Teachers rated ADHD-DSM-IV
			Attention function, reaction time, accuracy and impulse control		Conner's kiddie continuous performance test (K-CPT) computerised test

Cohort	Recruitment years	Size	Information on neuro-developmental outcomes		
			Outcome	**Age at measurement**	**Tests Applied**
LIFE Child (DE)(Poulain et al. , Poulain et al. 2017)	2011 – Ongoing	3,700 (5,000 planned)	Cognitive development Emotional symptoms, conduct problems, hyperactivity, peer relationship problems, prosocial behaviour	3mths – 3.5 years 10-18 years	Bayley Scales of Infant and Toddler Development, third edition Strengths and Difficulties Questionnaire (SDQ)
Piccolipiù (IT)(Farchi 2014)	2011 – 2015	3,338	Details not published, but birth cohorts.net gives planned tests		Planned cognitive function at age 4 to include ADHD and Autism measures
PRegnancy and Infant DEvelopment Study (PRIDE Study) (NL)(van Gelder 2013)	2011 – 2019	3,200	Details not published, but birth cohorts.net gives planned tests		Planned at ages 1-6 to include ADHD and Autism measures
Southampton Women's Survey (SWS) (UK) (Crozier et al. 2018)	1998 – 2002	3,158	IQ IQ	4years 6-7 years	Wechsler Preschool and Primary Scale of Intelligence (WPPSI) Cambridge Neuropsychological Test Automated Battery (CANTAB®)
GECKO Drenthe cohort (GECKO Drenthe) (NL)	2006 - 2007	2,997	Details not published, but birth cohorts.net gives planned tests		Planned cognitive function ages 5 and 10

Cohort	Recruitment years	Size	Information on neuro-developmental outcomes		
			Outcome	**Age at measurement**	**Tests Applied**
KOALA Birth Cohort Study (KOALA) (NL)	2000 – 2002	2,843	Details not published, but birth cohorts.net gives planned tests		Planned cognitive function age 7
Odense Child Cohort (DK)	2010 – 2012	2,553	ADHD	5 years	Child Behaviour Checklist, ADHD Rating Scale IV Preschool Version (ADHD-RS)

2.1.2 Databases which could be linked to create cohorts with in-utero exposure and neurodevelopmental measures

Table 2.2 gives information on databases that could potentially be used to contribute to the study in 16 of the European countries: Belgium, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Malta, Netherlands, Slovenia, Spain, Sweden and the UK (England, Wales, Scotland, Northern Ireland).

For each country a set of potential databases have been identified that contain information on the following:

1. Pregnancy in the mother
2. Medication usage during pregnancy in the mother
3. Outcome of the pregnancy – termination/still birth/live birth plus gestational age and birthweight
4. Identification of any congenital anomalies in the offspring
5. Identification of the offspring in health care databases - it is assumed that if there are population databases containing information on births with identifiers that mother and baby pairs can be identified – possibly through probabilistic linkage
6. Any diagnoses made or medications prescribed to the offspring
7. Education/any neurodevelopmental outcomes of the offspring
8. The approximate number of births per year that could be linked to obtain information on in-utero medication exposure and any long-term developmental outcomes. If there are several databases containing the same information (for example there are several primary care databases in the UK it is assumed all will be used)
9. The date of availability of the first year of data is given as the earliest date at which all the relevant registers have been collecting data
10. Socio-economic status of the mother
11. Gestational age/ birthweight of the offspring
12. Maternal education
13. Information on breastfeeding

Appendix 1 provides the details for the acronyms and abbreviations in table 2.2 and additional information on each register can be found in the EUROmediSAFE Inventory. The data sources have been identified as containing some relevant variables in addition to personal identifiers. However, as not all registers have been involved in previous linkage studies, personal contact must be made with individuals working with these data sets to determine their suitability for this analysis. Relevant individuals with experience of analysing the data from the databases will need to be identified in order to involve them in the research as it is essential that knowledge about the individual databases is available.

For each country an indication of the number of births occurring in the databases per year that are likely to be able to be linked is given. In several countries primary care databases, which identify women with epilepsy, only cover a proportion of the whole population. The number of births expected in these registries is estimated and it is assumed that all these births would be able to be linked to the national population registries for the longer-term outcomes.

Table 2.2 Databases that have the potential to be linked according to country (Appendix 1 gives list of abbreviations in table. Information on registers is available in EUROmediSAFE inventory)

	Belgium	**Denmark**	**Finland**
Pregnancy Identification	EURAP Belgium - SGP - Intego- MHD-MZG-RHM	Aarhus University Hospital Database - NCBI/MFR - DNBC - FOETO - National Fetal Medicine Database - SSR - LPR - EURAP Denmark	Care Register for Health Care - The Finnish Drugs and Pregnancy Database - EURAP Finland
Medicine Use during Pregnancy	EURAP Belgium - Farmanet - LRx-Belgium - Intego - MPD-MPG-RPM- MHD-MZG-RHM	Aarhus University Hospital Database - FOETO - DUSAS - SSR - LPR - OPED - Register of Medicinal Product Statistics - EURAP Denmark	The Finnish Drugs and Pregnancy Database - Register on Reimbursed Medication and Rights on Special Reimbursement - EURAP Finland
Outcome of Pregnancy	HBD-SHA-AZV	LPR - ABR	Births - Register of Induced Abortions
Congenital Anomalies	Antwerp CA Registry - Hainaut-Namur CA Registry	Odense CA Registry - FOETO	Register of Congenital Malformations
Identification of Child	Flemish Birth Registry-MHD-MZG-RHM	Aarhus University Hospital Database - CPR - DNBC - National Fetal Medicine Database - SSR - BDB	Care Register for Health Care - The Finnish Drugs and Pregnancy Database - Medical Birth Register - AVOHILMO
Child's Diagnoses and Prescriptions	SGP - Farmanet - HBD-SHA-AZV - LRx-Belgium - Intego - MPD-MPG-RPM - MHD-MZG-RHM	Aarhus University Hospital Database - ADHD database - DUSAS - CPOP - SSR - LPR - OPED - Register of Medicinal Product Statistics	Care Register for Health Care - The Finnish Drugs and Pregnancy Database - AVOHILMO - Register on Reimbursed Medication and Rights on Special Reimbursement
Child's Neurodev-elopment /Education		ADHD database - CPOP - SSR - STATISTICS DENMARK	Education - STATISTICS FINLAND
Births per year	2,400	60,000	50,000
First year of data	1994 (2008 IMS)	2010	2008
Gestational age	Yes	Yes	Yes
Socio-economic status (SES)	Yes	Yes	Yes
Maternal education	Yes	Yes	Yes
Breastfeeding Information	Unknown	Yes (BDB)	Unknown

Table 2.2 Databases that have the potential to be linked according to country (cont)

	France	Germany	Hungary
Pregnancy Identification	EFEMERIS - BNPV - PMSI MCO - SNIIRAM and EGB (SNDS) EURAP France – POMME-CRAT - Terappel	EURAP Germany - GePaRD	EURAP Hungary - NEAK
Medicine Use during Pregnancy	EFEMERIS - EPICARD - BNPV - UHDDS - LRx-France - PMSI MCO - SNIIRAM and EGB (SNDS)-POMME - EURAP France- CRAT - Terappel	AOK - TK - EURAP Germany - GePaRD - Aggregated health care data from the statutory health insurance funds - DAPI	EURAP Hungary - NEAK
Outcome of Pregnancy	BNPV - PMI - SNIIRAM and EGB (SNDS) - UHDDS - CRAT - Terappel	AOK - TK - GePaRD - Aggregated health care data from the statutory health insurance funds	Fetal Losses - NIC - Live Birth
Congenital Anomalies	CA Registers: Brittany; REMERA; Auvergne; remaPAR – EPICARD- EFEMERIS - Terappel – POMME - BNPV	Saxony-Anhalt CA Registry; Mainz Model	HCAR
Identification of Child	RHE31 - Civil Register - EFEMERIS - RHEOP - SNIIRAM and EGB (SNDS) - POMME	BELLA	NEAK
Child's Diagnoses and Prescriptions	RHE31 - UHDDS - RHEOP - LRx-France - PMSI MCO - SNIIRAM and EGB (SNDS) - POMME	BELLA - AOK - TK - GePaRD - Aggregated health care data from the statutory health insurance funds - DAPI	NEAK - NIC
Child's Neurodev-elopment /Education	RHE31 - EFEMERIS – RHEOP-POMME		
Number of births per year	10000	150000	130000
First year of data	2004 (EFEMERIS) 2010 (POMME) 2005 (EGB)	2004	2009
Gestational age	Yes	Yes	Yes
Socio-economic status (SES)	Yes	Yes	Yes
Maternal education	Yes	Yes	Yes
Breastfeeding Information	Yes	Unknown	Unknown

Table 2.2 Databases that have the potential to be linked according to country (cont)

	Ireland	Italy	Latvia
Pregnancy Identification	NPRS - NPEC Online Database - HIPE - UK and Ireland Epilepsy and Pregnancy Register	Caserta GP/claims database - ARS - Hospital Discharges Registry (Tuscany, Emilia Romagna) - TPD - PHARM - - ERPD - IQVIA HEALTH LPD - EURAP Italy	Health care payment settlement system
Medicine Use during Pregnancy	PCRS - NPRS - HIPE - UK and Ireland Epilepsy and Pregnancy Register	Caserta GP/claims database - ARS - Hospital Discharges Registry (Tuscany, Emilia Romagna) - TPD - HEIS - HIS - PHARM - ERPD - Health Search - IQVIA HEALTH LPD - EURAP Italy	Health care payment settlement system - Register of Patients with Mental and Behavioural Disorders
Outcome of Pregnancy	NPEC Online Database - NPRS – HIPE	CEDAP - Hospital Discharges Registry (Tuscany, Emilia Romagna) - HEIS - HIS	Newborn Register
Congenital Anomalies	Congenital Anomaly Registers: Cork & Kerry, South East Ireland , Dublin	IMER - R.T.D.C - Lombardy Register - B.D.RE.CAM - I.S.MA.C	Register of Patients with Hereditary Anomalies
Identification of Child	NPEC Online Database	CEDAP	Health care payment settlement system
Child's Diagnoses and Prescriptions	PICANet - PCRN-PCRS - NPRS - HIPE - Growing Up in Ireland	Caserta GP/claims database - ARS - - TPD - HEIS - HIS - PHARM - Hospital Discharges Registry (Tuscany, Emilia Romagna)- ERPD - IQVIA HEALTH LPD	Health care payment settlement system - Register of Patients with Mental and Behavioural Disorders
Child's Neurodev-elopment /Education	NIID - POD - NPSDD		
Number of births per year	70000	500000	20000
First year of data	2006	2005	2005
Gestational age	Yes	Yes	Yes
Socio-economic status (SES)	Yes	Yes	Yes
Maternal education	Yes	Yes	Yes
Breastfeeding Information	Unknown	Unknown	Unknown

Table 2.2 Databases that have the potential to be linked according to country (cont)

	Lithuania	Malta	Netherlands
Pregnancy Identification	The Institute of Hygiene database - EURAP Lithuania	NOIS	PHARMO - LINH - General Practitioner (GP) Database - LifeLines - Hospitalisation Database - PRN - AHD - IPCI - IADB - EURAP Netherlands
Medicine Use during Pregnancy	Register of Medicinal Products - The Institute of Hygiene database - SveiDra - EURAP Lithuania	POYC	PHARMO - LINH - NIVEL - General Practitioner (GP) Database - LifeLines - PRN - Out-patient Pharmacy Database - In-patient Pharmacy Database - AHD - IPCI - IADB - EURAP Netherlands
Outcome of Pregnancy		NOIS	PRN
Congenital Anomalies	LIRECA	Malta Congenital Anomalies Register	NNL - KinCor
Identification of Child	The Institute of Hygiene database	NHIS - NOIS	PHARMO - LifeLines - PRN
Child's Diagnoses and Prescriptions	Register of Medicinal Products - The Institute of Hygiene database - SveiDra	POYC - NHIS - Malta Cerebral Palsy Register	PHARMO - LINH - NIVEL - General Practitioner (GP) Database - LifeLines - Hospitalisation Database - PRN - Out-patient Pharmacy Database - In-patient Pharmacy Database - AHD - IPCI - IADB
Child's Neurodev-elopment/Education			
Number of births per year	Unknown	4000	180000
First year of data	1996	2005	1999
Gestational age	Unknown	Yes	Yes
Socio-economic status (SES)	Yes	Yes	Yes
Maternal education	Yes	Yes	Yes
Breastfeeding Information	Unknown	Unknown	Unknown

Table 2.2 Databases that have the potential to be linked according to country (cont)

	Slovenia	Spain	Sweden
Pregnancy Identification	PIS RS - Out-Patient Healthcare Activity - EURAP Slovenia	SIDIAP - EURAP Spain	SIR - IPR - Medical Brths - Pregnancy Register - Prescribed Drug Register - EURAP Sweden
Medicine Use during Pregnancy	Records of Consumption of Prescription Drugs - Out-Patient Healthcare Activity - EURAP Slovenia	BIFAP - Real Life Data: Big-Pac - LRx_Spain EpiChron - EURAP Spain	SIR - IPR - Prescribed Drug Register - EURAP Sweden
Outcome of Pregnancy	PIS RS - ISSFS	SIDIAP	IPR - SNQ - Medical Birth Registry - Pregnancy Register
Congenital Anomalies		ECEMC - Registry of Congenital Anomalies: Valencia Region & Basque country	Sweden Congenital Anomalies Registry - SWEDCON - Register of Birth Defects and Chromosomal Abnormalities
Identification of Child	Out-Patient Healthcare Activity	SIDIAP	HabQ - CPUP - CLP/LKG - SIR - BEPQ - BHVQ - IPR - Q-bup - BUSA - SNQ - Medical Birth Registry - Pregnancy Register - Prescribed Drug Register - Register of Birth Defects and Chromosomal Abnormalities
Child's Diagnoses and Prescriptions	Records of Consumption of Prescription Drugs - Out-Patient Healthcare Activity	SIDIAP - BIFAP - LRx-Spain - Real Life Data: Big-Pac - EpiChron	HabQ - CPUP - CLP/LKG - SIR - BEPQ - BHVQ - IPR - Q-bup - BUSA - SNQ - Prescribed Drug Register
Child's Neurodev-elopment			HabQ - BUSA
Number of births per year	N/A	40000 (BIFAP)	110000
First year of data	1986	2003	1995
Gestational age	Yes	Yes	Yes
Socio-economic status (SES)	Yes	Yes	Yes
Maternal education	Unknown	Yes	Yes
Breastfeeding Information	Unknown	Unknown	Yes (BHVQ)

Table 2.2 Databases that have the potential to be linked according to country (cont)

	UK: England	UK: Northern Ireland	UK: Scotland	UK: Wales
Pregnancy Identification	CPRD - ChiMat - HES - QRESEARCH - THIN - OPCRD - ONS - RCGP - UK and Ireland Epilepsy and Pregnancy Register - IMS	NIMATS - HIS	eDRIS - SHIP - EURAP Scotland – HIC	SAIL - Patient Episode Database for Wales
Medicine Use during Pregnancy	CPRD - QRESEARCH - THIN - OPCRD - RCGP - UK and Ireland Epilepsy and Pregnancy Register	EDP - OpenDataNI	eDRIS - SHIP - EURAP Scotland – PIS	SAIL - ISD
Outcome of Pregnancy	ChiMat - HES - MBRRACE - IMS	NIMATS - HIS	eDRIs – SHIP - HIC	SAIL - Patient Episode Database for Wales
Congenital Anomalies	NCARDRS - BINOCARD - CRANE			CARIS
Identification of Child	ChiMat - CYPHS/CSDS - HES - IMS	HIS	HIC	
Child's Diagnoses and Prescriptions	CPRD - CYPHS/CSDS - HES - QRESEARCH - THIN - OPCRD - ONS - RCGP - IMS	EDP - OpenDataNI - HIS	eDRIS – SHIP – PIS - HIC	SAIL - Patient Episode Database for Wales - ISD
Child's Neurodev-elopment	CYPHS/CSDS - NPD			SAIL
Number of births per year	190000	24000	50000	20000
First year of data	1989	2010	2009	2000
Gestational age	Yes	Yes	Yes	Yes
Socio-economic status (SES)	Yes	Yes	Yes	Yes
Maternal education	Yes	Yes	Yes	Yes
Breastfeeding Information	Yes (CYPHS/CSDS)	Yes	Unknown	Yes

Methods for linking data sources

In some countries (for example Denmark) every person has a unique id number and all the databases are routinely merged using deterministic linkage by the data providers (for example Statistics Denmark) on receiving requests for data. In some countries the use of unique identifiers is not routine. For example, in England people have a unique NHS number and a different HES number for hospital episodes. Data can be linked by the data providers using deterministic and probabilistic

methods. In addition, data can be linked by individual researchers accessing the databases from "safe haven sites". Some countries also require that "Trusted third parties" are involved in the linkage procedures.
It is assumed that if there are population databases containing information on births with identifiers that mother and baby pairs can be identified. Again, some countries will use deterministic linkage through pairs of identifiers and other countries may use probabilistic linkage with identifiers such as mothers and child's dates of birth and postcodes. In addition, birth weight and gender are often included in such linkages. Linkage has already been done for some databases such as EFEMERIS and POMME in France

2.2 Study Methods

2.2.1 Study Type

Cohort study using linked data from health care databases and national registries stored in local sites, analysed locally using a common data model with results combined centrally using meta-analytic methods. This local analysis is necessary as many countries (for example Denmark) will not transfer data on individuals outside the country, only aggregate data can be transferred.

2.2.2 Study Period

The study period will be determined by the availability of the linked data.

2.2.3 Study Population: Offspring from Pregnancies

The study population will consist of all offspring of pregnancies occurring to females during the study period in each of the databases. 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 a set of prespecified shell tables.

Identifying Pregnancies
Many algorithms have been developed to identify pregnancies within databases and provide best estimates for the start and end dates of a pregnancy. Existing algorithms will be used in the databases they have been developed for and will also be used to develop new algorithms in the databases that do not have existing algorithms.

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. For women with multiple pregnancies during the study period, all pregnancies will be included in the analysis.

Determination of gestational age or pregnancy start and end dates will vary according to the information available in the different databases. All pregnancy related codes in the mother's electronic medical record, with any dates from ultrasound estimates will be used first. Then gestational age data provided in the database will be used.

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.

Identifying Pregnancy Outcomes
If possible the outcomes of all eligible pregnancies will be identified (i.e. live birth, stillbirth, induced abortion (including those induced for non-medical reasons) and spontaneous abortion). In some countries it is not possible to identify pregnancies ending in an induced or spontaneous abortion. In these cases, pregnancy data will be limited to those pregnancies ending in a live or stillbirth.

Identifying Offspring
All live births arising from eligible pregnancies will be included.

2.2.4 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 many European countries. In countries where products are not coded using ATC codes (for example the UK where products are given prodcodeida) the product codes associated with each of the ATC codes of interest will be identified and confirmed with a clinical expert in the relevant country. AED exposure will be determined from the issue of a prescription in primary care databases (for example in the UK) and/or the dispensing of a prescription in the prescription databases.

2.2.5 AED Exposure

All AED prescriptions defined in 2.2.4 that are issued/dispensed to any female during her time in the study cohort will be identified. Any female who has received more than one AED prescription will be considered exposed, any female who has never received an AED prescription or has received only one AED prescription during the entire study period will be considered unexposed.

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. A sensitivity analysis could be performed by excluding all the prescriptions for whom the duration cannot be calculated.

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 two 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 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. If the gap is between 30 days and 90 days the women will be classified as continuing the same product, but no exposure to the product will be assumed. A sensitivity analysis could be performed by comparing the results with an assumption of continuous exposure if the gap is < 90 days.

2.2.6 Exposure During Pregnancy

Any exposure to any specific drug during the three trimesters of pregnancy, three months before pregnancy and the twelve months after pregnancy will be recorded if it is available in the databases. Recording exposure in the twelve months after pregnancy enables comparisons between mothers with exposure during pregnancy with those only with exposure after pregnancy. Comparing these two groups enables some degree of adjustment for the disease, as both groups of mothers are taking the same medication In addition, whether the drug was used as monotherapy or as part of AED polytherapy will be recorded.

2.2.7 Neurodevelopmental Outcomes

Major Congenital anomalies
These will be identified, where possible, using linkage with EUROCAT registries. The EUORCAT CA subgroups and exclusion criteria for minor anomalies will be used for analysis purposes. Congenital anomalies are a risk factor for neuro-developmental outcomes.

Diagnoses of Attention Deficit Hyperactivity Disorder (ADHD), Autism (ASD), Dyspraxia
These will be searched for in primary health care databases and hospital discharge databases. ICD10 codes F70-F79 (Mental retardation) F80-F89 (Disorders of psychological development and F90-F98 (Behavioural and emotional disorders with onset usually occurring in childhood and adolescence) will be searched for, in particular F84.0 (Childhood autism) F90.9 (Disturbance of activity and attention) and F82 (Developmental coordination disorder). These diagnoses will also be searched for in databases using read codes or alternative coding systems (such as ICD9) and potential codes will be confirmed with a clinical expert in the relevant country.

Prescriptions for ADHD
Prescriptions for methylphenidate or atomoxetine will be searched for in prescription and primary health care databases.

Visits to a specialist pertaining to a developmental difficulty or neurodevelopmental disorder
These will be searched for in primary care databases, hospital discharge databases or out-patient databases if present.

Developmental Quotient (DQ)
The DQ can be determined using the Griffith Mental Development Scale, the Bayley Scales of Infant and Toddler Development or the Ages and Stages Questionnaire (ASQ-3) used in the UK and the Boel test used in Denmark (psychomotor development test based on 14 items including screening tests for hearing, sight, and motor attention). These will be searched for in databases. Results will need to be interpreted with the help of an expert in this field.

Intelligence Quotient (IQ)
Any IQ test scores will be searched for in databases.

Data from Schools
The individual grades will be searched for, but also some countries record only whether the child did not attend the exam (i.e. was not in main stream school), failed, passed or passed with distinction. Other countries will record only whether the child had any special needs or not and the number of years for which they attended main stream schools. This may not be available in some countries as to identify children with special needs the name of the child and permission from the parents for the linkage would need to be obtained.

Items related to psychomotor development in mandatory health certificates (such as in France)
In France the certificates that are completed at 9 and 24 months by a general practitioner or a paediatrician include 14 items related to psychomotor development. Each item is represented by a binary variable (Yes/No). They are designed to detect children at risk of psychomotor development abnormalities. Some of these elements are relevant to motor development, whereas others are relevant to mental development. The 14 items are the following:

- At 9 months: unable to play 'peek-a-boo', absence of symmetric movement of the 4 limbs, unable to finger point, unable to react to his/her name, unable to take an object using the thumb, unable to move around, unable to repeat syllables, and, unable to sit up
- At 24 months: unable to understand a simple order, unable to give a name to one picture at least, unable to overlay objects, unable to combine two words, absence of symmetric movement of the 4 limbs, unable to walk, and, age (months) of walking acquisition

Neurodevelopmental deficiency justifying inclusion in the "Registre des handicaps de l'enfant de Haute-Garonne (RHE31)"

- Motor impairment: ICD-10 code, etiology (ICD code), severity assessed by walking ability
- Severe visual impairment, severe hearing loss
- Pervasive developmental disorder (ICD code)

- Severe mental retardation (corresponding to a level of IQ <50) if it is the only deficiency justifying inclusion in the register (ICD code corresponding to the degree of severity) Mental retardation regardless of the degree of severity if it is associated with another neuro-developmental deficiency (ICD code corresponding to the degree of severity)
- Epilepsy associated with neurodevelopmental impairment (yes / no), current treatment of epilepsy

2.2.8 Potential Confounders and Mediators

Indication for prescribing

The primary aim will be to distinguish between AED prescribing for epilepsy and prescribing for psychiatric disorders (bipolar disorder/manic depression) as maternal illnesses are potentially important confounders. If feasible from the data available, in addition to epilepsy, bipolar disorder/manic depression, additional categories will include migraine and neuropathic pain. 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 databases. In some databases 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. In some 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 (Naldi et al. 2016). This algorithm could be adapted for use in other databases. This algorithm excludes 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 some databases an algorithm will be created to determine the indication for prescribing using 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.

Severity of epilepsy

The seizure frequency in pregnancy (≥5 generalised tonic-clonic seizures) is potentially an important confounder. It will be searched for in any electronic antenatal notes available.

Gender of the offspring

This is expected to be present in all datasets. A difference in neurodevelopmental impact on girls and boys may occur. Analysis stratified by gender are important if there is sufficient power.

Birth weight and Gestation Age
This is expected to be present in all data sets. Prematurity is specifically relevant to neurodevelopmental outcomes in children.

Maternal IQ and/or Paternal IQ
This is an important mediator when analysing the IQ in the offspring. However, it is unlikely to be present in routine administrative health data.

Maternal and Paternal socio-economic status and/or educational attainment
This is an important confounder when analysing neurodevelopmental outcomes. In many countries there are maps of post codes to deprivation indices (for example the Townshend Index of Deprivation). In some countries other measures of SES are recorded in routine administrative data, such as maternal occupation. Other countries, such as Denmark, record the highest level of maternal education attained.

Maternal co-prescribing / Co-morbidity
This is available from the majority of countries with prescription databases. The exception is Denmark, where for data extraction the specific drugs that you wish to analyse have to be pre-specified, precluding you receiving information about co-prescribing unless it is pre-specified.

Folic acid
Where possible information on folic acid prescriptions will be sought. Women taking AEDs are recommended to take a dose of 4mg/day, which is higher than the usual recommended dose of 0.4 mg for all women. The higher dose is usually obtained on prescription and hence is likely to be in the databases. The lower dose is usually available OTC and hence is difficult to obtain data on.

Maternal Smoking
Where possible information on maternal smoking will be sought.

Maternal Alcohol Consumption
Where possible information on maternal alcohol consumption will be sought.

2.3 Statistical Analysis

2.3.1 Creation of the common data model

A common data model will be created, which will contain detailed information on the coding of each variable that will be used for analysis. Relevant elements from existing common data models, such as that developed by EUROlinkCAT, will be used where possible. Each database will be responsible for developing code to create the variables specified in the common data model.
This will enable the analyses below to be carried out separately for each database at their host institution using standardised scripts for the statistical software available at each institution. The code will be reviewed and compared between centres to ensure the analyses are directly comparable. The results from each analysis may be in the form of total numbers of cases – in which case the data can be analysed by aggregating the cases over the different registries (if appropriate) or fitting logistic regression models. In other analysis, the results will be in the form of log odds and their associated standard errors. In these cases, the log odds can be aggregated using random

effects meta-analytic techniques (including meta-regression) to derive summary estimates of the associations being investigated.

2.3.2 Evaluating Quality of linkage

The linkage quality must be evaluated in order to inform the validity of the results from subsequent analysis. It will be dependent on the information provided by the data providers performing the linkage and there may also be several different linkages occurring (for example separately to health and education data). For each linkage occurring the following table should be completed, as the quality of matching may change over time. Years with a high level of incomplete matches should be excluded.

Birth Year	Successful matches rated EXCELLENT/GOOD	Successful matches rated FAIR/POOR	Unsuccessful matches
X			
X+1			
X+2			
X+3			

2.3.3 Prevalence of AED prescribing during pregnancy

In order to provide confidence in the linkage procedures and to inform the interpretation of any associations identified, the prevalence of AED prescribing during pregnancy should be investigated in each trimester of pregnancy.

2.3.4 Definition of Pregnancy Exposure Groups

Offspring will be categorised into the following AED exposure groups (they may be included in more than one exposure group):

1. 3 months before pregnancy
2. 1st trimester
3. 2nd trimester
4. 3rd trimester

2.3.5 Definition of Pregnancy Non Exposure Groups

Offspring will be categorised into the following exposure groups in order to attempt to examine the effect of maternal morbidity as well as medication exposure on the offspring:

1. Offspring to women with no evidence of epilepsy and not on AEDs in whole previous year and 12 months after delivery (CONTROLS)
2. Offspring to women with evidence of epilepsy but not on AEDs in whole previous year and 12 months after delivery (EPILEPSY CONTROLS)
3. Offspring to pausers. That is women who took AEDs sometime during the year before LMP but paused AEDs at least 3 months before LMP and restarted within 12 months of delivery (PAUSERS)
4. Offspring to stoppers. That is women who took AEDs sometime during the year before LMP and who stopped AEDs at least 3 months before LMP and didn't restart within 12 months of delivery (STOPPERS)

The main analyses will be comparing exposed children to controls and also to a combined group of 2,3 and 4 - Epilepsy controls. Further analysis may examine 2,3 and 4 separately.

2.3.6 Risk of adverse pregnancy outcome associated with AED prescribing

It is important to evaluate if exposure to an AED increases the risk of an adverse pregnancy outcome, particularly the chance of an induced or spontaneous abortion. Therefore, the odds of this occurring will be compared in the 1st trimester exposure groups compared with the CONTROLS, EPILEPSY CONTROLS, PAUSERS and STOPPERS specified above. The odds ratios from each database will be combined using standard meta-analysis.

2.3.7 Risk of neurodevelopmental disorders in the offspring

Two types of outcome will be considered: Binary outcomes of the form that neurodevelopmental disorder has occurred or has not occurred and Continuous outcomes (for example a child's IQ). Logistic regression models will be used to analyse binary outcomes and standard linear regression models will be used for continuous outcomes.

2.3.8 Analysis Exposure and Comparison Groups

Each offspring can belong to more than one exposure group. All exposure groups will initially be analysed in separate models comparing the exposed offspring to offspring from one of the listed comparison groups. The models are nested case-control models within the pregnancy cohorts. For each model frequency tables of the numbers of exposed and unexposed offspring and their outcomes will be created and also summary estimates (means, medians, standard deviations and inter quartile ranges) of continuous variables (for example IQ) according to exposure will be created. In addition, logistic regression models will be fitted. All results will be combined across countries using standard meta-analytic techniques.

In order to adjust for potential confounders logistic regression models will be fitted in each country with the binary outcome, the exposure and the selected relevant confounders. The adjusted odds ratios from these models can also be combined across countries. Similarly, linear regression models will be fitted for continuous outcomes. Potential mediators for neuro-development (rather than confounders) such as gender, birthweight and gestational age will be included in the models. If sample sizes are sufficient separate models will be fitted for males and females.

2.3.9 Sibling Comparisons

For databases in which siblings can be identified a comparison group of siblings in whom the pattern of medication differed will be identified. Siblings need not have the same father. For each exposed pregnancy all siblings not exposed at the time point of interest can be included in the analysis. The models fitted will be multilevel models in which children are nested within their families to adjust for family environment. The results of the analysis will either be an estimated odds of neurodevelopmental outcome given AED exposure with its associated standard error or else a mean difference (in IQ say) given AED exposure and its standard error. These can both be combined using random effects meta-analysis models to estimate the overall odds of neurodevelopmental and the overall mean difference in IQ given AED exposure having adjusted for family environment.

2.3.10 Propensity Score Methods

In addition to analysing the risks of an adverse outcome adjusted for covariates, propensity score methods will be employed. For each offspring a propensity score of being exposed to the specific AED will be estimated using logistic regression with the outcome exposure to the AED and the independent variables being the confounders and covariates. Then the overall risk of an adverse outcome will be analysed either by using propensity score stratification or propensity score matching. With stratification a multilevel model is fitted with levels/strata defined by propensity score values. With matching a set of exposed and unexposed children are selected such that each pair has a similar propensity score. This may result in a large loss of data. Covariates such as gender, gestational age and weight will be included in the propensity scores.

2.3.11 Multiple Imputation Methods vs Adjusting Crude Odds Ratios

In all of the above analysis multiple imputation methods may be employed if there is missing data. However, for databases with severe levels of missing data only crude odds ratios will be calculated. The association between crude and adjusted odds ratios in registers with complete data will be evaluated and it will be judged to see if the crude odds ratios from certain registers can be adjusted by similar amounts to obtain estimates of “adjusted odds ratios” if information on confounders had been sufficiently complete to allow adjusted odds ratios to be estimated.

2.3.12 Use of paternal exposure

Examining if paternal exposure increases the risks of an adverse outcome can be a useful way to determine the effects of confounders, as the fathers are negative controls. This can be performed in some of the birth cohorts, such as the Danish and Norwegian birth cohorts. However, in some of the other linkage studies it would be necessary to identify the fathers in a new dataset. This linkage is likely to be problematic, especially if the father’s name is not on the birth certificate. Therefore, for these studies paternal exposure will not be analysed.

2.4 Sample Size

The size of the study will be determined by the prevalence of the AED exposure, the prevalence of the outcome of interest and the increased risk that is expected to be detected.

Table 2.3: Sample sizes required to achieve a power of 90% at a statistical significance level of 5%

Outcome of Interest	Unexposed Prevalence	Odds ratio exposed to unexposed	Number exposed pregnancies†	Number exposed pregnancies using sibling controls; % of siblings with no AED exposure:	
				50%	10%
Any major congenital anomaly	2%	1.5	2822	8517	31647
		4	151	529	1949
Diagnosis of Autism	1%	1.5	5557	16794	62427
		4	292	1029	3798
Diagnosis of ADHD	3%	1.5	1911	5760	31292
		4	105	362	1333
Diagnosis of Dyspraxia	5%	1.5	1184	3557	13202
		4	67	230	843
Visits to a specialist concerning developmental difficulty or neurodevelopmental disorder.	1%	1.5	5557	16794	62427
		4	292	1029	3798
Attendance special school	5%	1.5	1184	3557	13202
		4	67	230	843
Special education needs	15%	1.5	465	1379	5098
		4	31	101	365
For continuous outcomes of interest					
Intelligence Quotient	Mean Unexposed IQ = 100 with sd = 15 For siblings corr = 0.5	Reduction 10 pts	26	52	260
		Reduction 5 pts	104	208	1040
		Reduction 1 pt	2601	5202	26010

† assuming more than 10 unexposed pregnancies for each exposed pregnancy

Table 2.4: Example calculations of the number of pregnancies expected to obtain a specified number of exposures

Prevalence of specific AED exposure in pregnancy (A)	Number of exposed pregnancies from above table (B)	Total number of pregnancies (B/A)
3 per 1,000	5557	1,852,333
1 per 1,000	5557	5,557,000
0.5 per 1,000	5557	11,114,000
0.1 per 1,000	5557	55,570,000
3 per 1,000	2822	940,667
1 per 1,000	2822	2,822,000
0.5 per 1,000	2822	5,644,000
0.1 per 1,000	2822	28,220,000
3 per 1,000	292	97,333
1 per 1,000	292	292,000
0.5 per 1,000	292	584,000
0.1 per 1,000	292	2,920,000
3 per 1,000	105	35,000
1 per 1,000	105	105,000
0.5 per 1,000	105	210,000
0.1 per 1,000	105	1,050,000

Estimating number of pregnancies needed from number of exposed pregnancies

The following factors need to be taken into account when deciding the number of pregnancies to start with

a. Incorrect linkage
b. Loss to Follow-Up
c. Missing data.

2.5 Strengths and Limitations

2.5.1 Strengths

Representativeness of the Cohort

As data from all children in the cohort that can be identified as being exposed will be analysed, no bias will arise due to not wishing to participate in the study, but bias may arise due to missing data.

Size of the cohort

The costs of data collection are often not directly related to the amount of data collected and therefore a large number of unexposed children can be identified and compared to each exposed child.

2.5.2 Limitations

Neurodevelopmental Outcomes

Neurodevelopment covers a range of different domains and one specific medication may impair one domain (such as language development), but not influence others (such as psychomotor development). It is therefore important when investigating a specific medication to identify if there are specific domains that are likely to be affected from previous studies including any data from animal models if it exists. The validity and reliability of the tests/assessments and diagnoses reported in the databases must be carefully evaluated by a psychologist with respect to detecting impairments in the domains of interest. Therefore, a potential limitation of the study is that non-specific assessments or unreliable assessments have been completed at too early a stage of development in the children. In addition if several databases are used the dassessment of neurodevelopmental outcomes may be very heterogeneous.

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 suggest actual use. A further weakness is that many databases do not record the precise dose of the drugs and therefore dose response analysis may not be able to be performed.

Very few databases capture AED prescriptions issued during an in-patient hospital stay. In addition, in some primary care databases, 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. AED prescriptions in prescription databases will also often 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 example for migraine may not be captured. In addition, in some countries, a small number of specific AED products are not reimbursed (for example in Italy 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.

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. Co-prescribing may reflect co-morbidity (for example a psychiatric condition in addition to epilepsy) rather than the management of symptoms of a single condition and attempts will be made to distinguish between these where possible.

Availability of data

Administrative and national databases typically have a time lag of between one and two years, particularly the registration of birth outcomes. As many of the databases identify pregnancies based on a pregnancy outcome and then use that information to work backwards to determine the start date of the pregnancy, it will not be possible to include women with an on-going pregnancy who have not completed their pregnancy by the end of the study period. Some databases do not have all the risk factors mentioned above (for example: IQ)

Quality of Linkage

If the linkage is not perfect, linkage errors and missed links will dilute any associations.

2.6 Ethical and data access approvals

All centres will be responsible for obtaining the necessary ethics and data access approval once the protocol is finalised. 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.

2.7 Quality Control

All work should 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. 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. A neurologist and/or a prescriber relevant to the database in each of the participating countries should be involved to inform the interpretation.

2.8 Timescale and Resources

It is anticipated that the following person-time will be required for the study

Table 2.5: Estimated timescale and resources to perform linkage study

	Time to Complete	**Funded Time**
Co-ordinating Centre		
Protocol development / Study sponsorship	1- 3 months	1 month
Input from clinical expert		
Development common data model	1 month	1 month
Development local analysis programs	1 month	1 month
Distribution local analysis programs and collection of results	3 months	1 week
Meta- analysis of individual study results	1 month	1 month
Writing paper for peer review journal	3 months	3 months
For each database		
Required approvals including ethics if needed	6-12 months	1 month
Linkage	1-3 months	Dependant on who carries it out
Implementation of common data model	1 months	1 week
Completion of analysis	1 year	4 months to 1 year
Input from clinical expert to ensure codes for AEDs and for outcomes are correctly interpreted		1 day
Comments on drafts of paper for peer review journal	1 month	1 week

Costs in addition to person months

Costs of the data will depend on each individual cohort – these have not been specified as most data providers will only provide an estimation of the costs once they have a detailed protocol about the data required.

Protocol 3: Use of social media

3.1 Use of social media for recruitment of study subjects

Globally Facebook is the most popular social media site with over 2.19 billion active users in the first quarter of 2018. Therefore, Facebook can be used to contact large numbers of people and has been shown to be a useful method for recruiting people particularly younger people. A recent review of studies that used Facebook to recruit subjects found that recruitment can cost between $1.36 and $110 per person and that 86% of studies concluded that their samples were representative of samples recruited via traditional methods (Thornton et al. 2016). The review concluded that Facebook was an effective and cost-efficient recruitment method. However a study that recruited pregnant women to participate in the NINFEA birth cohort noted that when compared to pregnancy records, created by midwives at the time of the delivery the associations of educational level with other risk factors (such as alcohol intake, maternal age and previous miscarriages) did differ slightly between the two cohorts (Pizzi et al. 2012).

A further concern with recruiting women over the internet is whether high levels of follow-up can be achieved. A recent study reported that there was an association between the communication strategies used for recruitment and follow-up participation in nine internet-based cohorts (Bajardi et al. 2014). Follow-up participation for between 15 months and seven years varied from 43% to 89%, with participants who became aware of the study through an online communication campaign compared with those through traditional offline media (for example leaflets or posters in antenatal clinics) having a lower follow-up rate. They concluded that high levels of follow-up were possible, but that off-line enrolment campaigns were advisable.

3.2 Studies of internet birth-cohorts

There are two reported studies which have used the internet to recruit pregnant women to birth-cohorts: the NINFEA from Turin, Italy(Richiardi et al. 2007) and the ELF study from Wellington, New Zealand (Firestone et al. 2015). Details of the NINFEA study are given in the EUROmediSAFE Inventory, but the ELF study is not included as it is not European based. However, both will be discussed below. The aim of both cohorts was to investigate the association between prenatal and postnatal exposures and subsequent health outcomes.

3.2.1 Recruitment methods

NINFEA Cohort

The NINFEA cohort started recruitment in July 2005 with the aim of recruiting at least 7,500 participants. 7003 were recruited by March 2015 and recruitment is still continuing (Firestone et al. 2015). Ethics approval was obtained. Members of the cohort are children whose mothers are able to complete an online questionnaire in Italian at some time during their pregnancy. The website is accessible globally, but offline advertisement of the study is local, with posters and leaflets being available in hospitals in Turin and health professionals mentioning the study to pregnant women when they attended hospitals or family clinics. Online recruitment also occurs through social networks and websites. The majority of women were from the Piedmont Region (62%), Tuscany Region (22%), and Lombardy Region (4%) in Italy. All questionnaires are completed online.

ELF Cohort

The ELF cohort recruited 2197 women from September 2008 to September 2012. Ethics approval was obtained. The women were recruited from “parent and child shows” which over 22,000 people visit annually. Parent-child shows are large-scale events, marketed at expecting and experienced parents, where they can purchase standard and newly available products, services (including child-care), education programs, and specialist advice on child care. Parents were also recruited using leaflets and posters in antenatal clinics and some parents enrolled through an Internet search engine. Parents could complete the questionnaires online or offline (`postal’) if they wished. A final total of 2197 women were recruited in the study from September 2008 to September 2012. The majority of women were from Wellington (43.5%), Auckland (37.5%) and Canterbury (11.8%). The majority of respondents (55%) took part via an offline mode, compared to 45% of online participants.

3.2.2 Follow-up methods

NINFEA Cohort

Each questionnaire is available to be completed on the website for several months – women are reminded of the questionnaire via e-mail, telephone calls, texts, and regular mail. Out of all women recruited at baseline, 88% completed the 6-month questionnaire, 83% completed the 18-month questionnaire, and 78% completed the 4-year questionnaire.

ELF Cohort

The same methodology was used as in the NINFEA cohort with questionnaires being available on the website for several months**.** Out of all the pregnant women recruited at baseline only 47% completed the Phase I questionnaire with 45% of online participants compared with 55% of offline participants completing the questionnaire.

3.2.3 Data collected

Both studies have several sets of questionnaires, with the first prenatally for both studies, the second at 3 months for ELF and 6 months for NINFEA, the thirds at 15 an 18 months respectively, fourth at 2 and 4 years and NINFEA at 7 years. The questionnaires cover a wide range of exposures and outcomes including medication during pregnancy and cognitive development in the child. In addition, the NINFEA study at 6 months parents are sent, if they wish, self-collection saliva sample kits and the mother and child is asked to provide saliva samples.

3.2.4 Cohort characteristics

Both cohorts are representative of the populations they represent in terms of maternal age. However, both cohorts are mothers with lower parity and higher education level than their populations. Of importance is the fact that women recruited in the third trimester of pregnancy were most likely to continue to participate after the baseline questionnaire.

3.2.5 Relevant Publications

The NINFEA cohort investigated the risk of wheezing in offspring of mothers who took paracetamol during pregnancy and concluded that the observed increased risk could be explained by confounding(Migliore et al. 2015). The NINFEA cohort also investigated the risk of wheezing in

offspring of mothers who took antibiotics during pregnancy. They concluded that prenatal antibiotic exposure in the first trimester and infant wheezing could be largely explained by confounding factors, in particular respiratory infections during pregnancy. However an excess risk of wheezing after antibiotic exposure during the third trimester of pregnancy remained after adjusting for confounders.(Popovic et al. 2014)

3.2.6 Comments about internet birth cohorts

The NINFEA cohort demonstrates that internet birth cohorts can be a useful tool for addressing the issue of the long term effects of medication exposure in-utero. The four-year completion rate of 78% is very impressive and comparable to many more traditional birth cohorts. The researchers for ELF collaborated with those from NINFEA and attempted to base their cohort on similar methodology. However, their much higher attrition rate demonstrates that extreme care must be taken in engagement of participants. An analysis of retention in internet cohorts did conclude that recruitment methods were a major factor (Bajardi et al. 2014).

3.3 Proposed Methods for recruitment of internet birth cohort

Ethics approval should be obtained before recruitment. Pregnant women could be recruited by health professionals recommending the website / joining the cohort to their patients and providing written information in antenatal clinics. Professional bodies, such as the RCOG in the UK, should be involved in recruitment by encouraging clinicians to recommend joining the cohort to the pregnant women they care for. Information should be available on a website translated into all the European languages to encourage European wide participation. At least three groups of pregnant women should be identified: those taking AEDs, those who have epilepsy, but are not taking AEDs and those who do not have epilepsy and are not taking any AEDs. It is important that all information on medications taken are obtained from the mothers before the outcome of the pregnancy. The women should complete recruitment information by logging on to a website. Informed consent to re-contact the mother and/or father must be obtained according to national legal requirements. Several methods of recontacting should be established (for example email, facebook, phone)

3.3.1 Study Type

Nested within the internet cohort, case-control sets of children identified with in utero AED exposure and unexposed controls will be contacted via facebook or other previously agreed methods for de-novo data collection on neurodevelopmental outcomes.

3.3.2 Study Period

It would be expected that it would take at least 2 to 5 years to recruit sufficient women in the cohort. Once the women have been recruited the follow up time needs to be sufficient (Ie at least two years) in order to start to be able to detect any neurodevelopmental differences in the children. Continued contact should be made with the parents during the whole follow up period in order to try and ensure minimum loss to follow-up.

3.3.3 Antiepileptic Drugs (AEDs)

Mother's will be asked about their use of AED's by showing pictures of all licensed AED medications available in Europe. 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 many European countries. In countries where products are not coded using ATC codes (for example the UK where products are given prodcodeida) the product codes associated with each of the ATC codes of interest will be identified and confirmed with a clinical expert in the relevant country.

3.3.4 AED Exposure

AED exposure will be obtained from on-line questionnaires completed by the mother (prior to the pregnancy outcome). The questionnaires will be sent at recruitment (hopefully within the first trimester), at the end of the second trimester and within 1 month of the birth and 12 months after the birth. The questionnaires will ask for information on duration of medication use as well as dose. Medications taking during the year before pregnancy will also be asked about. Any female who has received only one AED prescription during the entire study period will be assumed to **not** have been **exposed** to an AED.

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. Women who take two products simultaneously whilst undergoing a switch will be categorised as polytherapy during that time.

Discontinuation

Discontinuation 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.

3.3.5 Neurodevelopmental Outcomes

Data on developmental outcomes will be collected by mother's completing a questionnaire concerning the heath of their child. The following questionnaires are designed to be completed by the parents and are therefore potentially suitable for this study. A psychologist would need to be involved to determine the specific questionnaire to be used according to the medication being investigated. Neurodevelopment covers a wide range if different domains and a specific medication might be expected to affect only specific domains. So it must be insured that the assessments used are valid and reliable in measuring deficits in those specific domains.

Table 3.1: Potential Questionnaires for completion by mothers to determine neurodevelopment of their children

Test	Description	Age at testing
Ages and Stages Questionnaire (ASQ-3)	Areas screened: Communication, gross motor, fine motor, problem solving, and personal-social	1 month to 5.5 years
Modified Checklist for Autism in Toddlers (M-CHAT).	2-stage parent-report screening tool to assess risk for Autism Spectrum Disorder (ASD). It is designed to identify children who should receive a more thorough assessment for possible early signs of autism spectrum disorder (ASD) or developmental delay.	16-30 months
Denver Developmental Screening Tool (DDST)	The tests address four domains: personal-social, fine motor and adaptive, language and gross motor.	Birth to 6 years
Strengths and Difficulties Questionnaire (SDQ)	Can be administered by parents and teachers up to age 11 and then self-administered. The tests identify emotional symptoms, conduct problems, hyperactivity/ inattention, peer relationship problems and prosocial behaviour.	3 – 16 years

3.3.6 Potential Confounders and Modifiers

Data on potential confounders will be collected from questionnaires filled in by the mother:
a. Indication for prescribing/maternal illness particularly whether it was for epilepsy or psychiatric disorders (bipolar disorder/manic depression) with, if possible, additional categories including migraine and neuropathic pain.
b. Severity of epilepsy in particular whether 5 or more generalised tonic-clonic seizures occurred during the pregnancy.
c. Gender of the child
d. Birth weight and gestation age at birth of the child
e. Maternal education
f. Maternal smoking during pregnancy
g, Maternal alcohol consumption during pregnancy
h. Maternal co-morbidity
i. Maternal co-medications
j. Parent-child interactions for example frequency of reading stories

3.4 Statistical Analysis

3.4.1 Loss to Follow Up

The potential for any bias to occur due to children not being assessed because of loss to follow-up will be evaluated using the available baseline information collected on the mother during pregnancy and may be adjusted for in the analysis using appropriate weights.

3.4.2 Definition of Exposure Groups

The AED exposure will be analysed separately for:

1. 3 months before pregnancy
2. 1st trimester
3. 2nd trimester
4. 3rd trimester

If possible the dose of drugs will also be taken into account.

3.4.3 Definition of Non Exposure Groups

The control children will be categorised into the following non-exposure groups in order to attempt to examine the effect of maternal morbidity as well as medication exposure:

1. Children whose mothers had no evidence of epilepsy and were not on any AED in whole previous year and 12 months after delivery (Controls)
2. Children whose mothers had evidence of epilepsy but were not on any AED in whole previous year and 12 months after delivery (Epilepsy controls)
3. Children whose mothers took an AED sometime during the year before LMP but paused AEDs at least 3 months before LMP (Pausers) and did not take during pregnancy

3.4.4 Risk of neurodevelopmental disorders in the offspring

All the neurodevelopmental tests result in scores that can be treated as continuous outcomes and hence analysed using standard linear regression models. If data from several different cohorts (for example countries) is being used then, multi-level regression models will be used to adjust for potential cohort (country) differences. All exposure groups will initially be analysed in separate models comparing the exposed children to children from one of the listed comparison groups. Potential confounders will then be included in the linear regression models.

3.4.5 Propensity Score Methods

In addition to analysing the risks of an adverse outcome adjusted for covariates, propensity score methods will be employed. For each offspring a propensity score of being exposed to the specific AED will be estimated using logistic regression with the outcome exposure to the AED and the independent variables being the confounders and covariates. Then the overall risk of an adverse outcome will be analysed either by using propensity score stratification or propensity score matching. With stratification a multilevel model is fitted with levels/strata defined by propensity score values. With matching a set of exposed and unexposed children are selected such that each pair has a similar propensity score. This may result in a large loss of data. Covariates such as gender, gestational age and weight will be included in the propensity scores

3.4.6 Multiple Imputation Methods vs Adjusting Crude Odds Ratios

In all of the above analysis multiple imputation methods may be employed if there is missing data.

3.5 Sample Size

The size of the study will be determined by the same factors considered in section 1.1.1 and Table 1.3 estimates the sample sizes required to achieve a power of 90% at a statistical significance level of 5% when analysing IQ scores with a mean of 100 and sd of 15 in an unexposed population. As was

discussed in section 1.1.1 in order for a cohort to have 29 children with in-utero AED exposure, the cohort in expectation needs to contain at least 58,000 children if the prevalence of a specific AED during pregnancy was 0.5 per 1,000 or 14,500 children for a prevalence of 2 per 1,000. These numbers are considerably greater than the only two other internet cohorts (ELF cohort = 2197; NINFEA Cohort = 7,003). These figures do not include loss to follow-up, which may be large. Therefore, a sample size of at least about 100,000 should be aimed for.

3.6 Strengths and Limitations

3.6.1 Strengths

AED Exposure

As contact will be made before the outcome of pregnancy, then complete unbiased information on medication exposure can be obtained. The use of the internet will hopefully ensure that medications mentioned were actually taken rather than just prescribed.

Indication for AED prescription

This can be fully explored by obtaining information directly from the mother.

Neurodevelopmental Outcomes

The use of the internet allows identical data collection from exposed and unexposed children. In addition, tests can be used rather than just relying on a binary variable indicating a neurodevelopmental problem. For example, rather than relying on a diagnosis of Autism, the Modified Checklist for Autism in Toddlers (M-CHAT) can be used.

Sample Size

As mentioned above tests can be used and analysed as continuous measures rather than binary outcomes. This means that the sample size can be smaller than when relying on binary variables such as a diagnosis of ADHD.

3.6.2 Limitations

Time Scale

To manage to recruit @100,000 women will be very time consuming. In addition, sufficient time will be needed for the children to be old enough to examine as neurodevelopmental outcomes cannot be measured for several years.

Costs

The costs for recruiting 100,000 pregnant women and following up their children with questionnaires will be comparatively low. However, effort must be taken to try and continually engage the women to reduce the loss to follow up. This can be costly in terms of person time.

Recruitment of children

Bias may arise in the recruitment of women to the study, in that there may be an association between the willingness to take part and the health of the mother. It is now considered that requiring access to the internet is not likely to result in a biased sampling procedure.

Assessment of Neurodevelopmental Outcomes

The accurate assessment of neurodevelopmental relies on the validity and reliability of the outcome measures used. A specific medication may affect only specific neurodevelopmental domains (such as language development) and subtle effects may only become apparent in later childhoood. Therefore, a potential limitation of the study is that non-specific assessments or unreliable assessments have been completed at too early a stage of development in the children.

3.7 Ethical and Data Access Approvals

Informed consent will be obtained from every study mother according to national laws and regulations. Parent/s will sign the consent form on behalf of their children. The data stored in the research database will be anonymous with unique patient identifiers. A separate list with no clinical information will link the identifiers to the patient identifiable information necessary to contact them.

3.8 Quality Control

All work should 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. The study protocol will only be amended based on reasonable scientific explanations or feasibility issues and all changes will be documented.

3.9 Timescale and Resources (costs)

It is anticipated that the following person-time will be required for the study in which 29 children with exposure in utero to a specific AED are recruited and a nested case-control study involving an additional 143 children without AED exposure.

Table 1.4: Estimated timescale and resources to perform study with 29 children with in-utero exposure and 143 without the exposure

	Time to Complete	Funded Time
Protocol development / Study sponsorship	1-3 months	1 month
Developing material and distributing it to health care professionals in order to aid recruitment	3 months	3 months
Applying for ethics permission to contact parents	6 months	1 month
Development recruitment website etc	3 months	3 months
Recruiting Mothers	2-5 years	0.1 per week once website all set up
Designing Parents / Child questionnaire & CRFs	3 months	3 months
Setting up database and analysing results	1 month	1 month
Writing paper for peer review journal	3 months	3 months

Total Time	4 – 7 years	22 months

Costs

1. Person time of 22 person months
2. Costs of providing material to health care professionals in order to aid recruitment
3. Costs of following up children for several years
4. Costs of contacting specific 172 parents / ensuring they complete the questionnaires etc

Note

These costs are extremely unrealistic as such a cohort would not be set up to answer just one question on AEDs.

Appendix 1

Table A1: Register abbreviations used in table 2.2

Country	Abbreviation	Register Name in English	Register Name in Native Language	Region
Multiple countries	EURAP	European Registry of Antiepileptic Drugs and Pregnancy		
Belgium	Farmanet	Farmanet OR Pharmanet		National
	HBD-SHA-AZV	Hospital Billing Data	Hospital Billing Data - Séjours Hospitaliers Anonymisés - Anonieme Ziekenhuis Verblijven	National
	LRx-Belgium	IMS LifeLink: Longitudinal Prescription Data		National
	MHD-MZG-RHM	Minimum Hospital Data Set	Minimum Hospital Data - Minimale Ziekenhuisgegevens - Résumé Hospitalier Minimal	National
	MPD-MPG-RPM	Minimal Psychiatric Data	Minimal Psychiatric Data -Minimale Psychiatrische Gegevens - Résumé Psychiatrique Minimum	National
	SGP	Belgian network of Sentinel General Practitioners		Regional
Denmark	ABR	Register of Legally Induced Abortions	Register over legalt provokerede aborter	National
	BDB	The Children's Database	Børnedatabasen	National
	CPOP	Follow-up Program for Cerebral Palsy	Opfølgningsprogram for Cerebral Parese	National
	CPR	Danish Civil and Health Registration System	Det Centrale Personregister	National
	DNBC	Danish National Birth Cohort		National
	FOETO	Danish Pharmaceutical Database	Dansk Føtalmedicinsk Database	National
	LPR	National Patient Register	Landspatientregisteret	National
	NCBI/MFR	Danish Medical Birth Registry	Det Medicinske Fødselsregister (MFR)	National
	OPED	Odense Pharmacoepidemiological Database		Funen and Southern Denmark
	SSR	National Health Insurance Service	Sygesikringsregisteret	National

		Register		
Finland	AVOHILMO	Register of Primary Health Care visits	Perusterveyden-huollon avohoidon hoitoilmoitus	National
France	BNPV	French pharmacovigilance database	Base Nationale de Pharmacovigilance	Regional; National
	CRAT	Teratology Information Service	Centre de Référence sur les Agents Tératogènes	
	EFEMERIS	Evaluation in Pregnant Women of MEdicaments and their RISK	Evaluation chez la Femme Enceinte des MEdicaments et de leurs RISques	Haute-Garonne
	EGB	Frrench Health Insurance System Database	Echantillon Generaliste des Beneficiaires	National
	EPICARD	EPIdemiology of Congenital heARt Diseases	EPIdémiologie des enfants ou fœtus porteurs de CARDiopathies congénitales	Regional
	LRx-France	IMS LifeLink Longitudinal Prescription Data - France OR Longitudinal Prescription Data		National
	PMSI MCO	Medicalization of information systems program in medicine, surgery, obstetrics and odontology	Programme de médicalisation des systèmes d'information en médecine, chirurgie, obstétrique et odontologie	National
	POMME	Prescription medicines for mothers and children	PrescriptiOn Médicaments Mères Enfants	Regional
	remaPAR	Paris Registry of Congenital Malformations	Registre des Malformations congénitales de Paris (remaPAR)	Paris
	REMERA	Rhône-Alpes Malformations Register	Le Registre des Malformations en Rhône-Alpes (REMERA)	Rhône-Alpes
	RHE31	Child Disability Register in Haute-Garonne	Registre des Handicaps de l'Enfant de la Haute-Garonne	Haute-Garonne
	RHEOP	Handicaps of the Child and Perinatal Registry Observatory Isere, Savoie	Registre de l'Enfants et Observatoire Perinatal	Isere, Savoie and Haute-

		and Haute-Savoie		Savoie
	SNDS	National system of health data	Système National des Donnees de Sante	National
	SNIIRAM	National System of Interregional Information of the Health Insurance	Système National d'Information Inter-Régime de l'Assurance Maladie	National
	Terappel	French Pharmacovigilance Centres participating to the Terappel program, a Teratology Information Service		
	UHDDS	French National Uniform Hospital Discharge Data Set Database		National
Germany	AOK	Claims data of statutory health insurance		National
	BELLA	Behviour and wellbeing of children and adolescents in Germany	BEfragung zum seeLischen WohLbefinden und VerhAlten	National
	DAPI	DAPI database	Deutsches Arzneiprüfungsinstitut e.V.	National
	GePaRD	German Pharmacoepidemiological Research Database		National
	TK	Claims data of statutory health insurance	Techniker Krankenkasse	National
Hungary	HCAR	Hungarian Congenital Abnormality Registry		National
	NEAK	National Health Insurance Fund Manager	Nemzeti Egészségbiztosítási Alapkezelő	National
	NIC	Neonatal Intensive Care Database	Magyar Neonatalis Intenzív Centrum Regiszter	National
Ireland	HIPE	Hospital In-Patient Enquiry Scheme		National
	NIID	National Intellectual Disability Database		National
	NPEC Online Database	National Perinatal Epidemiology Centre Online Database		National
	NPRS	National Perinatal Reporting System		National

	NPSDD	National Physical and Sensory Disability Database		National
	PICANet	Paediatric Intensive Care Network database		National
	PCRN	Palliative Care Research Network		National
	PCRS	Primary Care Reimbursement Service		National
	POD	Primary Online Database		National
Italy	ARS	Regional Health Agency of Tuscany	Agenzia Regionale di Sanità della Toscana	Tuscany
	B.D.RE.CAM	Campania Register of Congenital Defects	Registro Campano Difetti Congeniti	Campania
	CEDAP	Certificate of Delivery Assistance database	Certificato di Assistenza Al Parto	National
	ERPD	Emilia Romagna drug prescription in general practice and hospital pharmacy		Emilia Romagna
	HEIS	Healthcare Emergency Information System		Lazio
	HIS	Hospital Information System		Lazio
	IMER	Emilia Romagna Congenital Anomalies Registry	Indagine Malformazioni Congenite Emilia Romagna	Emilia Romagna
	I.S.MA.C	Sicialian congenital malformations Registry	Registro Regionale delle Malformazioni Congenite delle Sicilia	Sicily
	IQVIA HEALTH LPD	Health Search/CSD Longitudinal Patient Database		Firenze, Province of Florence, Toscana
	PHARM	Drug claims information System		Lazio
	RTDC	Tuscany Registry of Congenital Malformations	Registro Toscano Difetti Congeniti	Tuscany
	TPD	Tuscany Prescription Database		Tuscany
Lithuania	SveiDra	Compulsory Health Insurance Information System	Privalomojo sveikatos draudimo informacinės sistemos	National
	LIRECA	Lithuanian Registry of Congenital Anomalies		National
Malta	NHIS	National Hospitals Information System		National

	NOIS	National Obstetrics Information System		National
	POYC	Pharmacy of Your Choice		National
Netherlands	AHD	Achmea Health Database (previously AGIS Health Database)		West, east and central Netherlands
	IADB	IADB Database	IADB	Northern and Eastern Netherlands
	IPCI	Integrated Primary Care Information Database		National
	KinCor	KinCor (congenital heart disease) database	KinCor database	National
	LifeLines	LifeLines cohort study and biobank		Northern Netherlands
	LINH	Netherlands Information Network of General Practice	Landelijk Informatienetwerk Huisartsenzorg	National
	NIVEL	NIVEL Primary Care Database	NIVEL Zorgregistraties eerste lijn	National
	NNL	EUROCAT Northern Netherlands Congenital Malformations Register		Northern Netherlands
	PHARMO	PHARMO Database Network & tailored data collection	PHARMO	National; Regional
	PRN	Netherlands Perinatal Registry	Stichting Perinatale Registratie Nederland	National
Slovenia	ISSFS	Fetal Death Information System	Informacijski Sistem Spremljanja Fetalnih Smrti	National
	PIS RS	Perinatal Information System	Perinatalni Informacijski Sistem	National
Spain	BIFAP	Database for Pharmacoepidemiological Research in Primary Care	BIFAP: Base de Datos para la Investigacion Farmacoepidemiológica en Atención Primaria	National
	CAPV	Basque Country Congenital Malformations Register	Registro Anomalias Congénitas CAPV - Basque Country- Spain	Basque country
	ECEMC	Spanish Collaborative Study of Congenital Malformations		National

	EpiChron	EpiChron Cohort	EpiChron	National
	LRx-Spain	IMS LifeLink: Longitudinal Prescription Data		National
	SIDIAP	Information System for Research in Primary Care	Sistema de informacion para el desarrollo de la investigacion en Atencion Primaria	Catalonia
Sweden	BEPQ	Swedish Children Epilepsy Registry	Svenska Barnepilepsiregistret	National
	BHVQ	Swedish Child Health Registry	Svenska barnhälsovårdsregistret	National
	BUSA	National Quality Registry for ADHD Treatment Follow-up	BUSA Nationellt kvalitetsregister för behandlingsuppföljning av säkerställd ADHD	National
	CLP/LKG	National Quality Registry for Cleft Lip and Palate	LKG-registret (kvalitetsregister för uppföljning av läpp- käk-gomspalt)	National
	CPUP	Cerebral Palsy monitoring program	CPUP (CP-uppföljningsprogrammet i Sverige)	National
	HabQ	National Quality Registry for Child and Adolescent rehabilitation	Nationellt kvalitetsregister för habilitering - HabQ	National
	IPR	Swedish National Inpatient Register OR Hospital Discharge Register	Patientregistret	National
	Q-bup	National Quality Registry for Child and Adolescent Psychiatry	Nationellt kvalitetsregister för barn- och ungdomspsykiatri, Q-bup	National
	SIR	Swedish Intensive Care Register	SIR (Svenska Intensivvårdsregistret)	National
	SNQ	Swedish Neonatal Quality Register	Svenskt Neonatalt Kvalitetsregister (SNQ)	National
	SWEDCON	National Quality Registry for Congenital Heart Disease	SWEDCON (Nationellt register för medfödda hjärtsjukdomar)	National
England, UK	BINOCARD	British and Irish Network of Congenital Anomaly Research Database		Regional
	ChiMat	Child and Maternal Health		National

		Observatory		
	CPRD	Clinical Practice Research Datalink (previously General Practice Research Database (GPRD))		National
	CRANE	Cleft Registry and Audit NEtwork Database		National
	CYPHS/CSDS	Children and Young People's Health Services Data Set OR Community Services Data Set		National
	HES	Hospital Episode Statistics		National
	IMS	Hospital Treatment Insights		National
	MBRRACE	UK data collection for stillbirths, perinatal and neonatal deaths		National
	NCARDRS	National Congenital Anomaly and Rare Disease Registration Service		National
	NPD	National Pupil Database		National
	ONS	Office of National Statistics		National
	OPCRD	Optimum Patient Care Research Database		National
	QRESEARCH	QRESEARCH Database		National
	RCGP	Royal College of General Practitioners Database		National
	THIN	The Health Improvement Network		National
Northern Ireland, UK	EPD	Enhanced Prescribing Database		National
	HIS	Hospital Information System		National
	NIMATS	Northern Ireland Maternity Information System		National
Scotland, UK	eDRIS	The electronic Data Research and Innovation Service		National
	SHIP	Scottish Health Informatics Programme		National
	HIC	IScottish Health Informatics Centre Service		National
	PIS	Prescribing Information System		National
Wales, UK	CARIS	Congenital Anomaly Register and Information Service		National
	ISD	Information Services Division		National
	SAIL	Secure Anonymised Information Linkage Databank		National

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