

## IMI2 821520 - ConcePTION

### ConcePTION

**WP1 – Moving beyond pregnancy registries to enhance our understanding of disease-related pregnancy outcomes, medication use and safety of use during pregnancy**

# D1.3 Final Study Protocols for WP1 Demonstration Projects as Submitted to EU PAS Register

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## Document History

Version	Date	Description
V1.0	1 Feb 2022	A compilation and summary of the five WP1 demonstration project protocols as uploaded to the EU-PAS Register

## Abstract

There are five demonstration projects (DP) to be performed in WP1 and the five DP protocols have been submitted to the ENCePP Post Authorization Studies (PAS) Register. The protocols each comprise of a methodological component, a drug utilisation study, and a medication safety study. Protocols examine medications taken during pregnancy, including neuropathic pain medication, medication for migraine, medication for depression, medication for multiple sclerosis, and systematic lupus erythematosus, and medication for pregnancy associated breast cancer.

## Methods

Each demonstration project used their own methodology to address their research question.

## Results

All WP1 DP protocols have been uploaded to the EU PAS Register.

## Discussion

N/A

## Conclusion

DP1 (EUPAS43385) is “Methods for controlling by indication for prescriptions: application to medications for neuropathic pain.” In this protocol the authors use data from six European countries to look at methodological issues in confounding by indication for drugs used for neuropathic pain and other indications. The second part of the protocol describes a drug utilization study of drugs used to treat neuropathic pain among women of childbearing age. Finally, there will be a safety study focusing on pregabalin and gabapentin use during pregnancy and associated adverse pregnancy outcomes including major congenital anomalies, stillbirth, preterm birth, low birth weight, small for gestational age, and long-term neurodevelopmental outcomes.

DP2 (EUPAS43416) is “Exposure to SSRI/SNRI and depression in pregnancy and long-term childhood outcomes: the effect of modifying factors.” This protocol the authors will validate algorithms to identify maternal depression, neurodevelopmental outcomes, and breastfeeding in health care data sources. The second part of the protocol addresses the use of SSRI and SNRIs before, during, and after pregnancy. Finally, the drug safety study will assess the risk for neurodevelopmental outcomes to infants exposed *in utero* to SSRI and SNRIs.

DP3 (EUPAS43420) is “Novel statistics to handle rare diseases and small sample sizes using Bayesian techniques: Application to MS and SLE in pregnancy.” This protocol identifies the most appropriate algorithm to identify MS, SLE, and childhood infections in various health care data sources. The second part of the protocol addresses the utilization of medications for MS and SLE among women of childbearing age and in pregnant women. Finally, the safety study will address pregnancy outcomes, and specifically congenital anomalies, for women exposed to medications to treat MS and SLE during pregnancy.

DP4 (EUPAS43409) is “Demonstrating solutions for studying intermittent medication exposures in diseases with episodic manifestations during pregnancy: application to medication for migraine in pregnancy.” This study will first look at the use of medication for migraine and more specifically intermittent use before, during, and after pregnancy. The study will also estimate the underlying prevalence of gestational diabetes and preeclampsia in this population. The safety study will focus on the use of medication for migraine and adverse maternal outcomes of gestational diabetes and preeclampsia as well as congenital anomalies and low birth weight among the infants.

DP5 (EUPAS43393) is “Studying drug exposure when disease is measured through accurate identification of an incident case: application to breast cancer in pregnancy.” This protocol focuses on the incidence of pregnancy associated breast cancer and non-pregnancy associated breast cancer in European countries, the pattern of treatment for breast cancer in these populations, what medications are used and how the treatment patterns change across pregnancy, pregnancy outcomes, and finally the 5-year survival for women in these two groups adjusted for tumor characteristics and time of diagnosis.

## Repository for primary data

ENCePP EU PAS Register

## Study protocol

# Methods for controlling by indication for prescriptions: application to medications for neuropathic pain

This study will be conducted within the ConcePTION project of the Innovative Medicines Initiative under grant agreement No 821520.

<b>Project leaders</b>	Christine Damase-Michel, Jingping Mo
<b>Authors</b>	Anna-Belle Beau, Christine Damase-Michel, Jingping Mo, Xavier Moisset
<b>Protocol version</b>	1.1
<b>Protocol date</b>	23/09/2021



## PASS information

<b>Title</b>	Methods for controlling by indication for prescriptions: application to medications for neuropathic pain
<b>Protocol version identifier</b>	1
<b>Date of last version of protocol</b>	23/09/2021
<b>EU PAS register number</b>	The study will be registered in the EU PAS register
<b>Active substance</b>	<b><u>Primary exposure of interest:</u></b> Gabapentin: ATC code N03AX12 Pregabalin: ATC code N03AX16
<b>Joint PASS</b>	No
<b>Research question and objectives</b>	<p>The project will be divided into three parts: <b>Part 1.</b> Methodological study, <b>Part 2.</b> Drug utilisation study and <b>Part 3.</b> Drug safety study.</p> <p><b><u>Part 1</u></b> aims to develop a general framework to disentangle several indications for a same medication in large administrative healthcare data sources. The framework will be developed for neuropathic pain medications.</p> <p><b><u>Part 2</u></b> aims to characterize the prescription pattern of medications used to treat neuropathic pain, taking into account the reason for prescribing, among women of childbearing age and pregnant women, focusing on those with limited knowledge on the safety profile during pregnancy such as pregabalin and gabapentin.</p> <p><b><u>Part 3</u></b> aims to assess the association between prenatal exposure to medications used to treat neuropathic pain (especially pregabalin and gabapentin) and the occurrence of congenital anomalies, stillbirth, preterm</p>

	birth, low birth weight, small for gestational age, and long-term neurodevelopmental outcomes.
<b>Countries of study</b>	Norway (Nationwide), Finland (Nationwide), France (Haute-Garonne, Nationwide), UK (Wales, Nationwide), Germany (Nationwide), Italy (two regions: Tuscany and Emilia Romagna), multinational (EUROmediCAT)
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## 1. Table of Contents

PASS information .....	2
1. Table of Contents.....	4
2. List of abbreviations .....	6
3. Responsible parties .....	7
4. Abstract.....	9
5. Amendments and updates .....	15
6. Milestones.....	15
7. Rational and background .....	16
8. Research question and objectives .....	18
Part 1. Methodological study .....	18
Part 2. Drug utilisation study.....	19
Part 3. Drug safety study .....	19
9. Research methods .....	20
9.1. Study design .....	20
9.2. Setting .....	20
Study period.....	22
Source population .....	22
9.3. Variables .....	23
Part 1. Methodological study .....	23
Part 2 and Part 3.....	26
Exposures definition .....	26
Other medications definitions.....	30
Outcomes measures .....	31
	4
Study protocol – Methods for controlling by indication for prescriptions: application to medications for neuropathic pain	

Covariates .....	36
9.4. Data sources.....	36
9.5. Study size.....	41
9.6. Data management .....	42
9.7. Data analysis plan.....	43
Part 1. Methodological study.....	44
Part 2. Drug utilisation study.....	45
Part 3. Drug safety study .....	45
9.8. Quality control.....	49
9.9. Limitations of the research methods.....	49
9.10. Other aspects.....	51
10. Protection of human subjects .....	51
11. Management and reporting of adverse events/adverse reactions.....	52
12. Plans for disseminating and communicating study results.....	52
13. References .....	52
Annex 1. List of stand-alone documents.....	58
Annex 2. ENCePP checklist for study protocols .....	59
Annex 3. Additional information.....	66

## 2. List of abbreviations

Abbreviation	Term
<b>ADHD</b>	Attention-Deficit Hyperactivity Disorder
<b>ATC</b>	Anatomical Therapeutic Chemical
<b>BMI</b>	Body Mass Index
<b>CI</b>	Confidence Interval
<b>CPRD</b>	Clinical Practice Research Datalink
<b>DAP</b>	Data Access Provider
<b>DDD</b>	Defined Daily Dose
<b>GDPR</b>	General Data Protection Regulation
<b>GP</b>	General Practitioner
<b>ICD</b>	International Statistical Classification of Diseases and Related Health Problems
<b>LMP</b>	Last Menstrual Period
<b>OR</b>	Odd Ratio
<b>PI</b>	Principal Investigator
<b>PDD</b>	Prescribed Daily Dose
<b>SAP</b>	Statistical Analysis Plan
<b>SGA</b>	Small for Gestational Age
<b>TOPFA</b>	Termination Of Pregnancy for Foetal Anomaly

### 3. Responsible parties

#### Responsible parties

Name	Role	Institution/company
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<b>Xavier Moisset</b>	Clinical expert (neurologist), protocol development	CHU Clermont-Ferrand, France
<b>Rosa Gini</b> <b>Claudia Bartoloni</b> <b>Olga Paoletti</b>	Statisticians, SAP, coding, and analytics	Agenzia regionale di sanità della Toscana, Italy
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#### Collaborating institutions (contact details in Appendix I)

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<b>Sue Jordan</b> <b>Daniel Thayer</b>	DAP for SAIL Databank	University of Swansea, Wales
<b>Rosa Gini</b>	DAP for Tuscany healthcare administrative data (ARS)	Agenzia regionale di sanità della Toscana, Italy

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*Data sources from other countries may be included, pending on results from the Data characterization (WP7)*

## 4. Abstract

<b>Title</b>	Methods for controlling by indication for prescriptions: application to medications for neuropathic pain Protocol V1 (23/09/2021)
<b>Lead authors</b>	Anna-Belle Beau, Christine Damase-Michel University Hospital of Toulouse, France
<b>Rational and background</b>	<p>One of the major issues that arises when using large administrative health care data sources is the absence of indication for medication use, leading to important limitations for the interpretation of pregnancy medication safety studies.</p> <p>The motivating example for this demonstration project is medications used in the treatment of neuropathic pain. A large number of different medications groups are used including tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitor antidepressants (duloxetine and venlafaxine), pregabalin, gabapentin, tramadol, lidocaine patches, high-concentration capsaicin patches, antiepileptics (AEDs) and strong opioids. Besides neuropathic pain, these medications cover a wide range of indications from epilepsy, anxiety, depression, bipolar disorder, pain, etc. As these conditions might carry different risks for the pregnancy, independent of the medications prescribed, it is important to be able to distinguish the reason for prescribing the medications.</p> <p>Moreover, safety of use during pregnancy of some of these medications is less known than others. For example, there are limited data on the safety of use of pregabalin and gabapentin during pregnancy.</p>



<b>Research question and objectives</b>	<p>The project will be divided into three parts: <b>Part 1.</b> Methodological study, <b>Part 2.</b> Drug utilisation study and <b>Part 3.</b> Drug safety study.</p> <p><b><u>Part 1. The methodological study</u></b> aims to develop a general conceptual framework to disentangle the different indications of medications in large healthcare data sources. The methodology will be developed on medications used to treat neuropathic pain.</p> <p><b><u>Part 2. Drug utilisation study</u></b> aims to characterize the prescription pattern of medications used to treat neuropathic pain among women of childbearing age and pregnant women, focusing on those with limited information regarding the safety profile during pregnancy such as pregabalin and gabapentin.</p> <p><b><u>Part 3. Drug safety study</u></b> aims to assess the association between prenatal exposure to medications used to treat neuropathic pain (especially pregabalin and gabapentin) and adverse pregnancy outcomes, including major congenital anomalies, stillbirth, preterm birth, low birth weight, small for gestational age, and long-term neurodevelopmental outcomes.</p>
<b>Study design</b>	<p><b><u>Part 1. Methodological study:</u></b> Conceptual framework</p> <p><b><u>Part 2. Drug utilisation study:</u></b> Cohort</p> <p><b><u>Part 3. Drug safety study:</u></b> Cohort and case-malformed control</p>
<b>Population</b>	<p><b>The study period:</b> from 1 January 2006 to the most recent date of the data source where medications and outcomes data are available.</p> <p><b><u>Part 1. Methodological study:</u></b> application to population data</p> <p><b><u>Part 2. Drug utilisation study:</u></b> all females aged between 15 and 49 years during the study period in each of the databases</p> <p><b><u>Part 3. Drug safety study:</u></b></p> <ul style="list-style-type: none"> <li>- <b>cohort:</b> all women pregnant during the study period</li> </ul>

	<ul style="list-style-type: none"> <li>- <b>case-malformed control:</b> all cases of major congenital anomalies among live births, foetal deaths of more than 20 completed weeks of gestation and termination of pregnancy for foetal anomaly recorded in the EUROmediCAT Central Database</li> </ul>
<b>Variables</b>	<p><b>Exposure:</b> The medications that are used to treat neuropathic pain will be identified by the Anatomical Therapeutic Chemical classification system. The exposure will be determined from the issue, the dispensing or the reimbursement of a prescription, or maternity records depending on the data sources. The <b>primary exposure</b> will be pregabalin and gabapentin.</p> <p><b>Outcomes:</b> major congenital anomalies, stillbirth, preterm birth, low birth weight, small for gestational age, and long-term neurodevelopmental outcomes.</p> <p>The cohort study will investigate all the outcomes, whereas the case-malformed control study will only investigate major congenital anomalies.</p> <p><b>Co-variates:</b> country of residence, calendar year, age, background characteristics and maternal health before and during pregnancy.</p>
<b>Data sources</b>	<p>The study will be based on eleven data sources, covering six European countries:</p> <ul style="list-style-type: none"> <li>- France: EFEMERIS (Region: Haute-Garonne)</li> <li>- France: SNDS (Sample of the national population)</li> <li>- Finland: linkage of several registries (National)</li> <li>- Norway: linkage of several registries (National)</li> <li>- Italy: administrative health care database (Region: Tuscany)</li> <li>- Italy: administrative health care database (Region: Emilia Romagna)</li> </ul>

	<ul style="list-style-type: none"> <li>- UK: SAIL databank (Country: Wales)</li> <li>- UK: CPRD GOLD (Self-selected primary care practices in: England, Scotland and Northern Ireland)</li> <li>- Germany: GePaRD (covering 15-20% of national population)</li> <li>- Multinational: EUROmediCAT Central Database</li> </ul> <p>Not all of the data sources will be involved in the three parts of the project.</p>
<b>Study size</b>	The eleven contributing data sources will capture approx. 17.7 million pregnancies.
<b>Data analysis</b>	<p><b><u>Part 1. Methodological study.</u></b> We will develop a method to identify medication indication in the data sources. In data sources having access to both diagnoses made during GP or specialist visit and prescriptions, variables on diagnoses are expected to be good markers for prescription indications when dates of diagnosis and dates of prescription/dispensing are very close. In other data sources, we will develop a conceptual framework that can be used to infer medication indication based on a large range of data available such as: product name, specialty of the prescriber, special reimbursement status or exemption codes, hospital diagnoses codes, and co-prescribing data. The method will be developed for medications used to treat neuropathic pain. In the Finnish, CPRD, GePaRD data sources and SAIL databank, the indication of medications will be available through diagnoses in the GP and specialist records and the conceptual framework will be applied in EFEMERIS, SNDS, the Norwegian, Emilia Romagna and Tuscany data sources. The validity of the framework will be investigated using the former data sources.</p>

**Part 2. Drug utilisation study.** We will estimate the prevalence of medications of interest prescribed among women of childbearing age and among pregnant women, as well as the prevalence over the course of pregnancy. Prevalence will be stratified by age, calendar year, data sources, and indication for prescribing as estimated in **Part 1**.

**Part 3. Drug safety study.**

- **First**, we will model a **cohort study** comparing “exposed” and “comparison” women. The “exposed” group will be composed of pregnant women receiving pregabalin or gabapentin (during pregnancy or first trimester of pregnancy, depending on the outcome of interest). We will use various comparison groups to mitigate the effect of confounding, such as:
  - women receiving pregabalin or gabapentin for the same indication as the exposed group prior to but not during pregnancy;
  - women receiving pregabalin or gabapentin for the same indication as the exposed group during the second and third trimester, but not during the first, for studying congenital anomalies;
  - women receiving another neuropathic pain medication than pregabalin or gabapentin for the same indication as the exposed group;
  - women receiving pregabalin or gabapentin for a different indication than the exposed group;
  - women not receiving pregabalin or gabapentin (population comparison group);

	<ul style="list-style-type: none"> <li>- <b>Second</b>, we will model a <b>case-malformed control study</b> using data from EUROmediCAT. We will conduct an exploratory analysis in which, for each analysis, we will consider a single EUROCAT subgroup of congenital anomaly to be the “case” group, excluding those with chromosomal conditions. Two malformed control groups will be used. A first group composed of foetus and infant with a diagnosis of major congenital anomaly after exclusion of the specific congenital anomaly being analysed as the case group and of any subgroup at a hierarchical level above, excluding those with chromosomal/ genetic conditions. A second group composed of foetus and infant with chromosomal/ genetic anomalies.</li> </ul>
<b>Milestones</b>	<p>Registration in the EU PAS register: October 2021</p> <p>Final report of study results: March 2024</p>

## 5. Amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason

## 6. Milestones

The following milestones are planned:

	2020	2021	2022	2023
Data sources seek approval	X			
Finalization of study protocol	X	X		
Upload study protocol to the EU PAS Register		October 2021		
Statistical Analysis Plan (SAP)		X	X	
Data sources: Obtain approvals and data access	X	X	X	
Data sources: Data cleaning and run scripts		X	X	
Pooling of data-results			X	X
Report and manuscripts			X	March 2024

## 7. Rational and background

One of the major issues that arises when using large administrative health care data sources is the absence of indication for medication use. This is a crucial problem for medications with several indications, such as antiepileptics (1), when the risk for adverse pregnancy outcomes is different according to the underlying maternal disease. It is very difficult to separate the effect of the medications from the effect of the underlying disease. This uncertainty is an important limitation for the interpretation of pregnancy medication safety studies, as confounding by indication might be present. Confounding by indication can be mitigated by the use of appropriate comparator groups, such as active comparators (i.e. individuals using a different medication but for the same indication) (2). Nevertheless, as indications are missing in most of the data sources, other techniques such as propensity-score based methods can be used to limit the indication bias (3,4).

In administrative health care data sources where the indication for the prescriptions is absent, one could take advantage of data from primary medical records, in- or out-patient diagnoses, prescriber specialty, co-medications to help in determining the reason for prescribing a specific medication (5,6). The motivating example for this demonstration projects is medications used in the treatment of neuropathic pain. Multiple classes of medications, such as gabapentinoids, serotonin-noradrenaline reuptake inhibitors, tricyclic antidepressants, and local anaesthetic, with more than one indication are used to treat neuropathic pain. Previous studies use diagnostic codes (7–11), diagnostic codes in combination with prescription medication codes (12,13), or complex algorithm to identify patients with neuropathic pain in electronic healthcare data sources (6,14). Some of these studies also involved in reviewing medical records (8,12). These studies will form foundations for developing accurate algorithms in the data sources.

Neuropathic pain refers to a pain caused by a lesion or disease affecting the somatosensory nervous system (15). The disease includes a variety of painful, such as burning, painful cold, electric shocks and non-painful symptoms, most notably tingling, pins and needles, numbness or itching. In addition, pain is frequently located in an area where the physical examination may reveal hypesthesia (to touch, temperature or prick), hyperalgesia or allodynia (i.e. pain produced by a normally non-painful stimulation)(16). Many aetiologies can lead to the development of neuropathic pain. Most of them are due to a lesion of the peripheral nervous system (chronic

sciatica, post-traumatic or post-surgery nerve lesion, diabetes, alcohol or chemotherapies) but central nervous system can also be seen (post-stroke pain, spinal cord injury or multiple sclerosis). The diagnosis might be problematic to set due to the difficulty in distinguishing neuropathic pain from other types of pain. To improve its diagnosis, several screening tools have been proposed, such as the DN4 (17) or the LANSS (18). Such screening questionnaires have allowed to perform large studies.

In the general population the prevalence of neuropathic pain is likely to be between 6.9% and 10% (16,17). A large number of different medications groups are used to treat neuropathic pain. (19,20). First-line treatments include the tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitor antidepressants (duloxetine and venlafaxine), pregabalin, gabapentin, and gabapentin enacarbil. Tramadol, lidocaine patches, and high-concentration capsaicin patches are proposed as second-line treatments. Third-line treatments include botulinum toxin A and strong opioids. Besides neuropathic pain, these medications covered a wide range of indications from epilepsy, anxiety, bipolar disorder, pain, etc (**Table 2**). As these conditions might carry different risks for the pregnancy, independent of the medications prescribed, it is important to be able to distinguish the reason for prescribing the medications.

Moreover, safety of use during pregnancy of some of these medications is less known than others. For example, there are limited data on the safety of use of pregabalin and gabapentin during pregnancy and animal studies have shown the medications to be fetotoxic in rodents (21). Therefore, these medications are labelled not to be used during pregnancy because of very limited safety data. Observational studies on the safety of use of gabapentinoids during the first trimester of pregnancy have led to various conclusions (22–26). However, the largest well-conducted study identified a signal of an increased risk of coarctation of aorta (with 1,671 exposed pregnancies to pregabalin compared with pregnancies not exposed to antiepileptics, OR 5.8, 95% CI 1.6-14.9) (27). The **Appendix II** describes prior evidence on association of in-utero exposure to gabapentinoids and risk of congenital anomalies.

The prescription of gabapentinoids in the general population is increasing, partially owing to an increase in off-label prescribing (28–30). A recent European study found that pregabalin and gabapentin prescribing in pregnancy has markedly increased from around 1 per 1,000 in 2012 in United Kingdom (UK) to 2.5-3 per 1,000 in 2016, around one seventh of the prescriptions being



probably dedicated to pain (14). Concerns also arose due to the potential for misuse and addiction and for overdose of these medications that have been highlighted when used in combination with opioids (31–33).

Hence, it is of relevance to conduct studies that will characterize the prescription pattern of medications used to treat neuropathic pain among women of childbearing age, with a focus on medications with very limited safety data during pregnancy such as pregabalin and gabapentin and to estimate the safety of use of these medications in the context of neuropathic pain. The project will pool data from six European countries which will make it possible to identify a large cohort of women of child-bearing age and pregnant women receiving neuropathic pain medications. The results from this study will provide a general framework for identifying medication indication in large administrative health care data sources and valuable information on the management of neuropathic pain during pregnancy and on the safety of use of gabapentinoids in pregnancy.

## 8. Research question and objectives

The project will be organized in three parts:

- **Part 1.** Methodological study
- **Part 2.** Drug utilisation study
- **Part 2.** Drug safety study

### Part 1. Methodological study

#### Research question

Can we develop a general conceptual framework to disentangle the different indications of medications in large healthcare data sources ?

#### Objectives

- To develop a conceptual framework to identify drug indication in large administrative data sources to evaluate the risk of medications prescribed to pregnant women
- The conceptual framework will be developed for medications used to treat neuropathic pain

## Part 2. Drug utilisation study

### Research question

**What are the prescription patterns** of medications used to treat neuropathic pain among women of childbearing age and pregnant women according to the indication estimated through **Part 1**?

**Part 2** will focus in medications with limited knowledge on the safety profile during pregnancy such as pregabalin and gabapentin. Results from **Part 2** will inform the feasibility of **Part 3**.

### Objectives

- To determine the prevalence for the prescription of medications used to treat neuropathic pain, whatever the reason for prescribing, (overall and separately) in women of childbearing age
- To determine the prevalence for the prescription of medications used to treat neuropathic pain, whatever the reason for prescribing, (overall and separately) in pregnant women
- To describe patterns of use of prescriptions among women of childbearing age and pregnant women according to the indication of medications, and to identify predictors of these patterns
- To evaluate the extent of switching of medications used for the neuropathic pain indication, in relation to the pregnancy

## Part 3. Drug safety study

### Research question

Is prenatal exposure to pregabalin and gabapentin associated with increased risks of adverse pregnancy outcomes and long-term neurodevelopmental outcomes?

## Objectives

- To investigate the association between prenatal exposure to pregabalin and gabapentin (overall and stratifying by reason for prescribing) and the occurrence of congenital anomalies, stillbirth, low birth weight, and small for gestational age
- To investigate the association between prenatal exposure to pregabalin and gabapentin (overall and stratifying by reason for prescribing) and the occurrence of long-term neurodevelopmental outcomes

## 9. Research methods

### 9.1. Study design

- Part 1. (**Methodological study**): conceptual framework
- Part 2 (**Drug utilisation study**): descriptive cohort study
- Part 3 (**Drug safety study**): cohort study and case-malformed control study

### 9.2. Setting

**In Part 1: Methodological study**, the general conceptual framework will be tested among the following population data sources: data from Norway, Finland, France, Italy, UK and Germany.

**In Part 2: Drug utilisation study**, data from 6 countries will be pooled: Norway, Finland, France, Italy, UK and Germany. However, the analysis of women in childbearing age will be limited to data from Norway, France, Italy, UK and Germany (**Table 1**).

**In part 3: Drug safety study**, the **cohort study** will pool data from 6 countries (Norway, Finland, France (Haute-Garonne), Italy, Wales and Germany), whereas the **case-malformed control study** will use data from 19 congenital anomaly registries, and 2 health care databases covering 11 countries (**Table 1**).

**Table 1.** Overview of data sources that will contribute to the project.

Country/Region	Name of the data source	Start of first data collection	Last date of data collection	Number of pregnancies (1,000)	Number of pregnancies (1,000) 2006-2018/2019	Women of childbearing age included	Contribution to the project
France/Haute-Garonne	EFEMERIS	2004	2019	158	41	no	MS, DUS, DSS (cohort study)
France/Sample of national population (10%)	SNDS	2017	2019	300	1330	yes	MS, DUS
Finland/National	Linkage of several registries	1996	2018 (follow-up end of 2019)	1,530	860	no	MS, DUS, DSS (cohort study)
Norway/National	Linkage of three national registries: Prescription registry, Birth Registry and Patient registry	2005	2019	830	820	yes	MS, DUS, DSS (cohort study)
UK/Sample of Wales population (70%)	SAIL Databank	1998	2019	945	33	yes	MS, DUS, DSS (cohort study)
UK/ Sample of national population (5 <sup>1</sup> %)	CPRD GOLD	1987	2019	5,800	Estimate: 1300	yes	MS, DUS
Multinational	EUROmediCAT	1995, years vary across individual registries	2019	15,000 (in 20 registries)	10,500 (based on 18 EUROmediCAT registries and Sweden)	no	DSS (case-malformed control study)
Germany/ 15-20% of national population	GePaRD	2006	2019	1,600	1600	yes	MS, DUS, DSS (cohort study)
Italy/Tuscany	ARS	2003	2020	480	400	yes	MS, DUS, DSS (cohort study)
Italy/Emilia Romagna	ER Healthcare administrative data source	2004	2019	525	500	yes	MS, DUS, DSS (cohort study)

**Foot notes:** MS: Methodological study; DUS: Drug utilisation study; DSS: Drug safety study

*Data sources from other countries may be included, pending on results from the Data characterization (WP7)*

<sup>1</sup>Current patients (CPRD GOLD additionally includes historical records of patients that may have transferred practices or are deceased)

The **appendix I** shows the details of the contact person for each database involved in the project.

### Study period

The study period will run from 1 January 2006 to the most recent date of the data source where medication data are available (**Table 1**).

### Source population: inclusion criteria

#### **Part 1. Methodological study**

The application of the methodological study will be executed on the population data comprising all women aged between 15 and 49 during the study period in each of the databases.

#### **Part 2: Drug utilisation study**

The study population will include all women aged between 15 and 49 during the study period in each of the databases.

#### *Cohort of women of childbearing age*

The cohort entry date: the latest of the date when a woman will join the data source, the date of her 15<sup>th</sup> birthday or the first date of data availability in the data source (**Table 1**).

The cohort exit date: the earliest of the date when a woman left the data source, the date of her 49<sup>th</sup> birthday or the last date of data availability in the data source (**Table 1**).

#### *Cohort of pregnant women*

Each of the contributing data sources has algorithms in place to identify pregnancies and will provide the best estimates for the start and end dates of a pregnancy. All pregnancies will be identified within each of the databases during the study period. Pregnancies will be eligible for inclusion if the woman was in the study cohort for the 3 months before pregnancy and throughout the pregnancy. It will be possible to identify pregnancies that end in a live birth, miscarriage, stillbirth, induced termination (including those induced for non-medical reasons), depending on data availability in each data sources (**Table 5**).

The trimesters of pregnancy will be defined as follow (ACOG definition):

- Trimester 1: from the Last Menstrual Period (LMP) to day 97 after LMP;

- Trimester 2: from day 98 after LMP to day 195 after LMP;
- Trimester 3: from day 196 after LMP onwards.

Two perinatal period will also be defined:

- Prior to conception period: at least 3 months before pregnancy
- Post-natal period: during the 3 months after delivery

### Part 3: Drug safety study

- **For the cohort study:** The study population will include all women pregnant during the observation time and their linked outcomes.
- **For the case-malformed control study:** The study population will include all cases of major congenital anomalies among live births, foetal deaths of more than 20 completed weeks of gestation and termination of pregnancy for foetal anomaly recorded in 16 registries participating in EUROMediCAT Central Database.

### 9.3. Variables

Variables will be defined according to recommendations developed in the ConcePTION project (ConcePTION deliverable D1.2), as well as validated algorithms to define maternal, perinatal and childhood outcomes (ConcePTION deliverable D1.4).

#### Part 1. Methodological study

The variables that will be used to determine the reason for prescribing medications in data sources will be the following: diagnoses in the GP / specialist record, product name, prescriber specialty, co-prescriptions, special reimbursement status or exemption code, hospital discharge and outpatient diagnoses (see **Table 2**).

**Table 2.** Variables available to ascertain reason for prescribing medications

Name of the data source	Indication for prescribing
-------------------------	----------------------------

<b>Finnish data sources</b>	<b>Available</b> from <b>primary health care diagnoses</b> since 2011 and more complete 2013 onwards, and might be supplemented by data on in- and out-patient diagnoses, prescriber specialty, co-medications
<b>SAIL Databank</b>	<b>Available</b> from <b>diagnoses recorded in primary care</b> (READ codes), and might be supplemented by data for hospital admissions (ICD-10 codes), outpatient referrals, and co-medications
<b>CPRD</b>	<b>Available</b> from <b>diagnoses recorded in primary care</b> records (READ codes)
<b>GePaRD</b>	<b>Available</b> from <b>GP and specialist diagnoses</b> , and might be supplemented based on hospital diagnoses (ICD-10 codes), prescriber specialty, and co-medications
<b>EFEMERIS</b>	<b>Not available</b> , might be assessed based on hospital diagnoses during pregnancy, prescriber specialty, co-medications
<b>SNDS</b>	<b>Not available</b> , might be assessed based on hospital diagnoses, long-term disease (ICD-10), prescriber specialty, co-medications
<b>Norwegian data sources</b>	<b>Not available</b> , might be assessed based on hospital diagnoses, prescriber specialty, co-medications
<b>ARS Healthcare administrative data source</b>	<b>Not available</b> , might be assessed based on hospital diagnoses, exemptions from co-payment (ICD9-CM), co-medications
<b>ER Healthcare administrative data source</b>	<b>Not available</b> , might be assessed based on hospital diagnoses, exemptions from co-payment (ICD9-CM), co-medications

The **appendix III** presents the diagnostics codes for identifying neuropathic pain that have been used in the literature and that we will investigate in the data sources.

The **Table 3** presents the ICD-10 codes that will help in determining the reason for prescribing the medications of interest.

**Table 3.** ICD-10 codes to use to determine the indication for prescribing.

<b>Disease</b>	<b>ICD-10 code</b>
<b>Epilepsy</b>	G40-41
<b>Bipolar disorders</b>	F30-31

<b>Alcohol withdrawal</b>	F10
<b>Migraine</b>	G43
<b>Anxiety</b>	F40-43
<b>Depression</b>	F32-F33, F53
<b>Pain unspecified</b>	R52
<b>Headache</b>	R51
<b>Fibromyalgia</b>	M79.7
<b>Cluster Headache</b>	G44
<b>Trigeminal Neuralgia</b>	G50
<b>Restless legs syndrom</b>	G25.81

The **Table 4** presents the ICPC2 codes that will help in determining the reason for prescribing the medications of interest.

**Table 4.** ICPC2 codes to use to determine the indication for prescribing.

<b>Disease</b>	<b>ICPC2 code</b>
<b>Headache</b>	N01
<b>Restless legs</b>	N04
<b>Convulsion/seizure</b>	N07
<b>Fear cancer neurological system</b>	N26
<b>Fear of other neurological disease</b>	N27
<b>Epilepsy</b>	N88
<b>Migraine</b>	N89
<b>Cluster headache</b>	N90
<b>Trigeminal neuralgia</b>	N92
<b>Tension headache</b>	N95
<b>Feeling anxious/nervous/tense</b>	P01
<b>Acute stress reaction</b>	P02
<b>Feeling depressed</b>	P03
<b>Feeling/behaving irritable/angry</b>	P04
<b>Senility, feeling/behaving old</b>	P05
<b>Sleep disturbance</b>	P06
<b>Fear of mental disorder</b>	P27



<b>Anxiety disorder/anxiety state</b>	P74
<b>Depressive disorder</b>	P76
<b>Suicide/suicide attempt</b>	P77
<b>Phobia/compulsive disorder</b>	P79
<b>Post-traumatic stress disorder</b>	P82

Part 2 and Part 3.

### Exposures definition

The medications will be classified according to the Anatomical Therapeutic Chemical (ATC) classification system. Medications used to treat neuropathic pain, whatever the reason for prescribing, will be identified in the data sources. The **appendix IV** shows the recommendations for the pharmacological treatment of neuropathic pain.

The **Table 5** provides a list of medications of interest that are used in the treatment of neuropathic pain. The **primary exposure** will be exposure to **pregabalin** (ACT code: N03AX16) and **gabapentin** (ATC code: N03AX12).

The exposure will be determined from the issue, the dispensing or the reimbursement of a prescription, or from maternity records, depending on data sources as specified in **Table 7**.

The speciality of the prescriber will be retrieved when available. The **appendix V** describes the data available in each data sources to characterize exposure to medications.

**Table 5.** Overview of medications of interest used in the treatment of neuropathic pain (19,34).

ATC code	Name	Other indication
<b>Country</b>	<b>France</b>	
<b>First-line treatments</b>		
N03AX12	gabapentin	epilepsy
N06AA09	amitriptyline	depression
N06AA04	clomipramine	depression, obsessive compulsive disorder, panic disorder
N06AA02	imipramine	depression

N06AX16	venlafaxine	anxiety, depression, panic disorder, phobia
N06AX21	duloxetine	depression, anxiety
N01BB02	lidocaine plasters	pain
<b>Second-line treatments</b>		
N02AX02	tramadol	pain
N03AX16	pregabalin	epilepsy, anxiety
N01BX04	capsaicin	pain
<b>Third-line treatments</b>		
N02AA01	morphine	pain
N02AA05	oxycodone	pain
M03AX01	botulinum toxin A	spasticity
N02AX06	tapentadol	pain
N02BG08	ziconotide	pain
<b>Country</b>	<b>Finland</b>	
<b>Antidepressants</b>		
N06AA10	nortriptyline	
N06AA09	amitriptyline	depression
N06AX16	venlafaxine	anxiety, depression, panic disorder, phobia
N06AX21	duloxetine	depression, anxiety
<b>Antiepileptics</b>		
N03AX16	pregabalin	epilepsy, anxiety
N03AX12	gabapentin	epilepsy
<b>Tramadol</b>		
N02AX02	tramadol	pain
<b>Anaesthetics local</b>		
N01BX04	capsaicin	pain
N01BB02	lidocaine plaster	pain
<b>Country</b>	<b>Norway</b>	
<b>First-line treatments</b>		

N03AX12	gabapentin	
N03AX16	pregabalin	
M03AX01, N06AA04 N06AA02	tricyclic antidepressants: amitriptyline, clomipramine, imipramine	
N06AX21	duloxetine	
<b>Second-line treatments</b>		
N02AX02	tramadol	
N01BX04	capsaicin	
N01BB02	lidocaine plaster	
<b>Third-line treatments</b>		
M03AX01	botulinum toxin A	
N02A	strong opioids	
<b>Country</b>	<b>UK</b>	
<b>First-line treatments</b>		
N03AX12	gabapentin	focal seizures, spasticity or oscillopsia in multiple sclerosis (unlicensed), menopausal symptoms (unlicensed)
N03AX16	pregabalin	adjunct for focal seizures, anxiety
N06AA09	amitriptyline	major depression, migraine prophylaxis, headache prophylaxis, abdominal pain, emotional lability in multiple sclerosis
N06AX21	duloxetine	major depression, generalised anxiety, diabetic neuropathy, stress incontinence
<b>Second-line treatments</b> (If the initial treatment is not effective or is not tolerated, one of the remaining 3 drugs is recommended)		

	amitriptyline + pregabalin	
	nortriptyline (unlicensed)	
N03AX12	gabapentin	
N06AX21	duloxetine	
<b>Third-line treatments</b> (consider switching again if the second and third drugs tried are also not effective or not tolerated)		
N06AA10	nortriptyline	depression
N02AX02	opioids ie tramadol	pain
N01BB02, N01BX04	topical local anaesthetic	pain as ointment (shingles, sore nipples, pruritus).
N01BX04	capsaicin cream	osteoarthritis
<b>Country</b>	<b>Italy</b>	
<b>First-line treatments</b>		
N03AX12	gabapentin	
N03AX16	pregabalin	
N06AX21	duloxetine	
N06AX16	venlafaxin	
N06AA09	amitriptyline	
N06AA04	clomipramine	
N06AA02	imipramine	
N06AA10	nortriptylin	
N03AF01	carbamazepine	
<b>Second-line treatments</b>		
N03AX12	gabapentin	
N03AX16	pregabalin	
N02AX02	tramadol	
N01BB02	lidocaine 5% patch	
N01BX04	capsaicin 8% patch	
<b>Third-line treatments</b>		
N02AX06	Tapentadol	
N02AA01	Morphine	

N02AA55	Oxycodone	
N07BC02	Methadone	
M03AX01	botulinum toxin A (spasticity)	
<b>Country</b>	<b>Germany</b>	
<b>First-line treatments</b>		
N03AX12	Gabapentin	
N03AX16	pregabalin	
N06AA09, N06AA02, N06AA04	tricyclic antidepressants : Amitriptiline, Imipramine, Clomipramine	
N06AX21	Duloxetine	
<b>Second-line treatments</b>		
N01BB02	Lidocaine patches	
N01BX04	Capsaicin patches	
<b>Third-line treatments</b>		
N02A	Tramadol and other $\mu$ -opioid-agonists	
M03AX01	Botulinum toxin A	

### Other medications definitions

The study will identify co-medications that will help in ascertaining the indication for prescribing. These medications will be identified by the ATC codes in each data sources (**Table 5**). Note that this list is not finalized yet and will be updated and adapted during the development of the study according to country-specific prescribing practice.

**Table 6.** Co-medications of interest to determine the indication for prescribing.

ATC code	Name
<b>Epilepsy</b>	
N03	<i>antiepileptics</i>
N05BA09	clobazam

<b>Bipolar disorders</b>	
N05B	<i>anxiolytics</i>
N05AH03	olanzapine
N05AX08	risperidone
N05AN	lithium
<b>Alcohol withdrawal</b>	
N07BB04	naltrexone
N07BB03	acamprosate
N07BB01	disulfiram
<b>Migraine</b>	
N02CC	<i>triptans</i>
N02CA	<i>ergot derivatives</i>
N02CX01	pizotifene
N02CX06	oxetorone
N07CA03	flunarizine
C02CA02	indoramine
<b>Anxiety/depression</b>	
N05BA	<i>benzodiazepine derivatives</i>
N06A	<i>antidepressants</i>

## Outcomes measures

### *Length of treatment*

The duration of prescription will be calculated using the relevant information available within each of the data sources (defined daily dose (DDD), cumulative DDD, prescribed daily dose (PDD), quantity dispensed). The start date will be taken as the date the prescription was reimbursed/ issued/dispensed, depending on availability in data sources.

### *Switching of neuropathic pain medication*

A switch will be defined as a prescription of a medication used to treat neuropathic pain (**Table 5**) other than the initial medication. Medication B can be considered a switch to medication A, if the

dispensing of B, which has the same indication as A, occurred during the dispensing length of A, and if A is not renewed.

### *Adverse pregnancy outcomes*

The adverse pregnancy outcomes will be defined using codes and quality indicators developed in the Core evidence elements document (ConcePTION deliverable D1.2) and in the data characterization study (ConcePTION deliverable D1.4 and D7.14). We will use the same event definitions as in the ConcePTION clinical definition of pregnancy outcomes that will be mapped to the ConcePTION common data model. **Table 7** shows the data sources contributing to each of the outcomes.

### *Primary outcomes*

#### **Major congenital anomalies**

All congenital anomalies will be classified and analysed according to the EUROCAT Classification (EUROCAT Subgroups of Congenital Anomalies). This includes diagnosis in the Q chapter of ICD-10 (and equivalent ICD-9 codes), but excludes a recognized list of minor anomalies, if isolated, as specified by EUROCAT (35). Congenital anomalies will be considered in both live and non-live births after 20 weeks of gestation (i.e. terminated pregnancies and fetal deaths), when available in the data source. The major congenital anomalies will be **ascertained up to 2 years of the child age**, depending on the capacity of the data sources (**Table 7**).

Besides studying combined major congenital anomalies, if statistical power permits, congenital anomalies will be studied stratified by organ class. EUROCAT subgroups will be used. We will provide estimates for the main subgroups of congenital anomalies to facilitate meta-analyses and increased study power.

The major congenital anomalies outcomes will be investigated using both the cohort design and the case-malformed control design. The **aetiological window considered will be the first trimester of pregnancy** (from the Last Menstrual Period (LMP) to day 97 after LMP).

### Secondary outcomes

**Immediate outcomes** will include foetal death (early foetal death/miscarriage and late foetal death/stillbirth), preterm birth (extremely preterm/very preterm/moderate to late preterm), low birth weight (< 2500g at birth; LBW), and small for gestational age (birthweight <10th and 3<sup>rd</sup> percentile for a given gestational age based on local or national charts; SGA) (see **Appendix VI** for definitions).

**Long-term outcomes** will include neurodevelopmental outcomes. We will investigate mainly attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder for which diagnostic codes are available (see **Appendix VI** for definitions). Other neurodevelopment outcomes might be investigated depending on the availability of data in each of the data sources (see **Appendix VII** for definitions). The long-term outcomes will be **ascertained up to 10 years of the child age**, depending on the capacity of the data sources (**Table 7**).

The immediate and long-term outcomes will be investigated using the cohort design and the **aetiological window considered will be all the pregnancy**.



**Table 7.** Data sources contributing to the outcomes.

Outcomes	EFEMERIS	Linkage of several Finnish registries	Linkage of three Norwegian registries	SAIL Databank	GeParD	ARS	ER healthcare data source	EUROmediCAT Central Database
<b>congenital anomalies</b>	Among fetal deaths from 22 weeks of gestational age, TOPFA, and live births <b>Follow-up:</b> up to 2 years of age	Among live births, stillbirths from week 22 of gestation, and TOPFA <b>Follow-up:</b> up to 1 year of age	Among fetal deaths from 20 weeks of gestational age, TOPFA, and live births <b>Follow-up:</b> up to 1 year of age	Among fetal deaths, TOPFA, and live births <b>Follow-up:</b> 1 year of age from 1998 to 2013. 18 years of age from 2014	Among fetal deaths from 20 weeks of gestational age, TOPFA, and live births <b>Follow-up:</b> end of study period, end of insurance, end of available data, or death	Using algorithms record: among fetal deaths from 22 weeks of gestational age including induced abortions, and live births <b>Follow-up:</b> until the end of the study or when the person leaves Tuscany	Among fetal deaths from 22 weeks of gestational age, and live births up to 1 year of age	Among fetal deaths from 20 weeks of gestational age, TOPFA and live births <b>Follow-up:</b> up to 1 year of age
<b>miscarriage</b>	yes	uncertain (if identified by patient registry data)	yes (from 12 weeks of gestation)	no	yes (undercoded)	yes (occurring at the hospital)	no	no
<b>stillbirth</b>	yes	yes	yes	yes	yes	yes	yes	no
<b>preterm birth</b>	yes	yes	yes	yes	yes	yes	yes	no

<b>LBW</b>	yes	yes	yes	yes	yes	yes	yes	no
<b>SGA</b>	yes	yes	yes	yes	yes	yes	yes	no
<b>ADHD</b>	no	yes	Among children born from 2008 onwards	yes (using medications data) <b>Follow-up:</b> up to end of 2018	yes <b>Follow-up:</b> up to end of 2019	Among children born from 2010 onwards	Among children born from 2011 onwards <b>Follow-up:</b> until the end of the study or when the person leaves Tuscany	no
<b>Autism spectrum disorder</b>	no	yes	Among children born from 2008 onwards	yes <b>Follow-up:</b> up to end of 2018	yes <b>Follow-up:</b> up to end of 2019	Among children born from 2010 onwards	Among children born from 2011 onwards <b>Follow-up:</b> until the end of the study or when the person leaves Tuscany	no

### Covariates

Variables for women characterization will include country of residence, calendar year, age, socioeconomic status and education, body mass index, parity, smoking / alcohol use during pregnancy, breastfeeding, folic acid use prior and during first trimester of pregnancy, exposure to known teratogens during first trimester, and comorbidity (such as diabetes). Availability and completeness of these variables will vary across data sources and will be described (see **Appendix VIII**).

The confounders will be chosen based on the literature review and evaluated using Directed Acyclic Graphs (36).

## 9.4. Data sources

The project will be based on secondary use of data. Eleven data sources will contribute data (see **Table 8**).

**Table 8.** Data sources that will contribute to the project.

Country/Region	France/Haute-Garonne	France/Sample of the national population	Finland/National	Norway/National
<b>Name of the data source</b>	EFEMERIS	SNDS	Linkage of several registries	Linkage of three national registries: The Prescription Registry (NorPD) The Patient Registry (NPR) The Medical Birth Registry of Norway (MBRN)
<b>Source for medication use data</b>	Prescribed and dispensed medicines in community pharmacies	Prescribed and dispensed medicines in community pharmacies	Dispensed medicines in community pharmacies	Dispensed medicines in community pharmacies
<b>Pregnancies included</b>	Pregnancies resulting in live birth, miscarriage, stillbirth and induced termination (including those induced for non-medical reasons)	Pregnancies that can be identified by hospital diagnosis and outpatient data (through procedures and ICD codes)	Pregnancies resulting in miscarriage identified by patient registry (through procedures codes, ICD-10 and ICPC-2 codes), live births and stillbirths from 22 weeks of gestation or 500g, and induced abortions (including TOPFA)	Pregnancies from 12 weeks of gestation: live birth, miscarriage, elective abortion, stillbirth and TOPFA

**Table 8.** List of the data sources contributing to the study (continued).

Country/Region	UK/Wales	UK/National	Multinational	Germany/National
Name of the data source	SAIL Databank	CPRD GOLD	EUROmediCAT*	GePaRD
<b>Source for medication use data</b>	Prescribed medicines as recorded in primary care	GP prescribing medicines	Prospective maternity records, or prescribed and dispensed medicines in community pharmacies	Outpatient pharmacy dispensing
<b>Pregnancies included</b>	Pregnancies resulting in live births, stillbirths and TOPFA	Pregnancies identified using Read codes for CPRD's proprietary pregnancy algorithm, including live births, stillbirths, and pregnancy losses	Pregnancies resulting in malformed foetus/child	Pregnancies resulting in live births, miscarriages (undercoded), induced abortions, and stillbirths (identified by outcome algorithm based on hospital delivery dates, hospital and outpatient procedures, and hospital and outpatient diagnoses)

**Table 8.** List of the data sources contributing to the study (continued).

Country/Region	Italy/Tuscany	Italy/Emilia Romagna
<b>Name of the data source</b>	ARS	ER Healthcare administrative data source
<b>Source for medication use data</b>	Dispensed medicines in community and hospital pharmacies (for outpatient use)	Dispensed medicines in community and hospital pharmacies (for outpatient use)
<b>Pregnancies included</b>	Pregnancies resulting in live births, miscarriages, stillbirths, and induced abortions	Pregnancies from 22 weeks of gestation: live birth, stillbirth

*Data sources from other countries may be included, pending on results from the Data characterization (WP7)*

\* *Data sources contributing to EUROMediCAT*

Centre	Years	Births covered	Number of CA cases
<b>EUROMediCAT registries</b>			
Belgium, Antwerp	1997-2017	408,928	10,785
Croatia, Zagreb	1995-2017	142,525	2,669
Denmark, Odense	1995-2018	124,430	3,466
France, Brittany	2011-2018	276,715	10,302
France, Paris	2001-2017	445,975	14,351
Germany, Mainz	1996-2015	65,174	3,019
Germany, Saxony-Anhalt	2000-2018	331,942	10,482
Ireland, Cork and Kerry	1996-2018	205,376	5,675
Italy, Emilia Romagna	1995-2018	807,695	18,407
Italy, Tuscany	1995-2018	664,325	14,698
Malta	1996-2017	93,510	2,988

Netherlands, Northern	1995-2018	433,311	12,157
Poland, excluding Wielkopolska	1999-2018	6,144,011	87,631
Poland, Wielkopolska	1999-2018	744,714	18,838
Spain, Valencian Region	2007-2017	501,943	12,866
Switzerland, Vaud	1997-2018	171,812	6,459
UK, Wales	1998-2018	699,612	25,718

## 9.5. Study size

### **Part 1. Methodological study**

The application of the conceptual framework will be tested among women of childbearing age and among approx. 6.8 million pregnant women.

### **Part 2. Drug utilisation study**

The **drug utilisation study** will be performed among women of childbearing age and among approx 6.8 million pregnant women. The **cohort study** will include approx. 4.2 million pregnancies and the **case-malformed control study** will include more than 35,000 malformed cases with recorded medication exposures. The results from **Part 2. Drug utilisation study** will inform us on the feasibility to conduct **Part 3. Drug safety study**.

**Table 9** presents the prevalence in the general population of outcomes that we will be investigated in the project.

**Table 9.** Prevalence of child outcomes in the general population (37–40).

Child	Prevalence (%)
Major congenital anomalies	2 – 4
Stillbirth ( $\geq 24$ weeks of gestation)	0.3
Preterm birth	6 – 10
Low birth weight	5
Small for gestational age	10
Long-term neurodevelopmental outcomes	ADHD: 2 – 7 autism spectrum disorder: 1 – 4

### **Part 3. Drug safety study**

#### **Cohort study**

For example, in a cohort study, to detect a 50% increased risk for major congenital anomalies with 80% power and type I error rate of 0.05, it would require a sample size of around 350,000 pregnant women (see **Table 10**).

**Table 10.** Study sample size when 1% of the study population are treated for neuropathic pain (cohort study sample sizes – 80% study power and type I error rate of 0.05)



Baseline prevalence of Outcome					
		0.1%	1%	5%	10%
<b>Risk</b>	1.1	81,572,607	8,081,460	1,548,911	732,340
<b>Ratio</b>	1.2	20,968,283	2,076,714	397,462	187,553
	1.5	3,617,363	<b>357,910</b>	68,179	31,960
	2	1,005,338	99,283	18,742	8,672
	5	94,426	9,191	1,609	655

### Case-malformed control study

In a case-control study, to detect a 50% increased risk for major congenital anomalies with 80% power and type I error rate of 0.05, it would require a sample size of around 4,000 cases with the specific anomaly (i.e 40 exposed malformed) and 36,000 controls (i.e 360 exposed controls) without the specific anomalies (see **Table 11**).

**Table 11.** Study sample size when 1% of the controls are treated for neuropathic pain (case-control matched 1:9 sample sizes – 80% study power and type I error rate of 0.05)

Expected proportion exposed in the controls						
		0.1%	1%	5%	10%	25%
<b>Odds ratio</b>	1.1	902,291	91,157	19,099	10,146	4,965
	1.2	232,671	23,534	4,956	2,650	1,321
	1.5	40,449	<b>4,105</b>	878	478	251
	2	11,336	1,157	253	142	80
	5	1,068	113	28	18	14

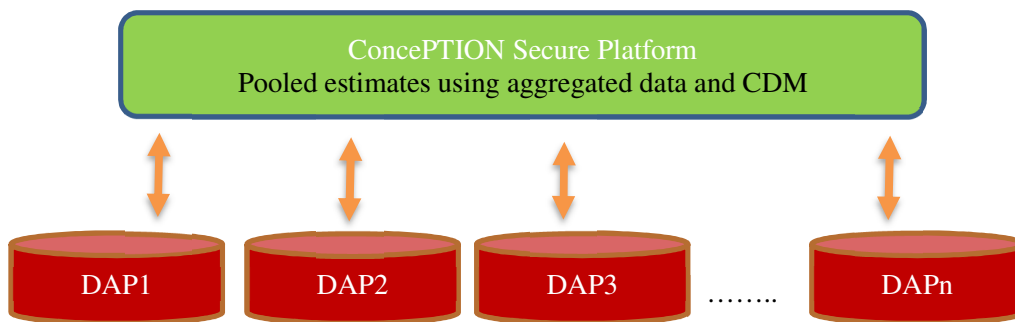
## 9.6. Data management

### Data permit process and data linkage

The study will be based upon the ConcePTION framework working as a distributed network approach with a common data model and common analytics. Data will remain locally at each data source, and only aggregated results and effect estimates will be submitted for pooling to the ConcePTION platform.

Each data source will perform the following tasks:

1. Obtain required ethical and legal permissions to use the data in the study
2. Extract and transform the data locally into the ConcePTION common data model
3. Check and run scripts distributed by the ConcePTION coordinating centre
4. Provide expertise on the data
5. Send aggregated results to the remote ConcePTION Secure Platform for analysis



**Figure 1:** Data flow in ConcePTION. *DAP: Data access provider. CDM: Common data model*

The study team will create the study variables based upon the common data model adopted by all the data sources. Each data sources will run the R scripts and upload the aggregated results into the ConcePTION secure platform. Then, the study team will analysis the data using the platform.

## 9.7. Data analysis plan

Statistical analyses will be carried out through ConcePTION, which will work according to a distributed network approach, with a common data model and common statistical analysis plan.

Meta-analyses will be used to combine aggregate data obtained from each data source.

The planned analyses are briefly presented in this sub-section. A more detailed plan will be prepared in a separate Statistical Analysis Plan (SAP) document.

The study participants will be characterized in terms of background characteristics. Pregnant women will also be described in term of maternal health before and during pregnancy. All continuous variables will be described using the mean and standard deviation. All categorical variables will be summarized with frequencies.

## Part 1. Methodological study

### **Conceptual framework**

We will develop to disentangle the different indications of medications in the data sources as the risk for adverse pregnancy outcomes can be different according to the underlying maternal disease.

Some data sources have access to diagnoses made during GP or specialist visit, these diagnoses are expected to be good markers for prescription indication when dates of diagnosis and dates of prescription/dispensing are very close. Hence, we will divide the data sources into those having access to such data classifying them as having “good markers for medication indication” and those having other types of data available. In the latter group, we will develop a conceptual framework that will be used to infer medication indication based on a large range of data available such as: product name, specialty of the prescriber, special reimbursement status or exemption codes, hospital diagnoses codes, and co-prescribing data. Each type of data (component) can be integrated into the conceptual framework in a hierarchical or overlapping way. We might explore the two possibilities.

**Application:** We will demonstrate the method with medications used to treat neuropathic pain. Examples of algorithms to identify neuropathic pain indication from administrative data sources have been previously described in the literature (13,14,41–46) and will help us to tailored the general conceptual framework to neuropathic pain medications.

In the Finnish, CPRD, GePaRD data sources and SAIL databank, the indication of medications will be available through diagnoses in the GP and specialist records. For example, based on data from the CPRD, a study ascertained the indication for gabapentinoids prescription using READS codes recorded at or around the time of prescription (8).

The conceptual framework will be established in EFEMERIS, SNDS, the Norwegian, Emilia Romagna and Tuscany data sources. French data were previously used to ascertain the indication for prescribing antiepileptic medications in women of childbearing age and pregnant women (6,14). The complex algorithm was based on all available data such as product name, specialty of the prescriber, exemptions from co-payment codes, hospital diagnoses and co-

prescribing medications. Tailored frameworks will be established in close collaboration with each data sources as prescribing practice and the extent of data available varies.

**Validation analyses:** We will try to validate our proposed approach by fitting the conceptual framework in data sources where the reason for prescribing will be ascertain by diagnoses in primary care/specialist visits. We will investigate the concordance/discordance of the results based on diagnoses in primary care/specialist visits alone and on the conceptual framework incorporating other types of data. We will estimate the sensibility and specificity of identifying the reason for prescribing based on results using diagnoses in primary care/specialist visits alone as the reference.

## Part 2. Drug utilisation study

- We will describe the frequency of prescriptions for each medication.
- We will estimate the prevalence of medications of interest prescribed among women of childbearing age and among pregnant women. We will also estimate the prevalence over the course of pregnancy, looking at prevalence during at least 3 months before (broken into 3-month time periods, if available), during each month of pregnancy, during each trimesters of pregnancy, and possibly during the 3 months after delivery, if available.
- The prevalence will be stratified by year, data sources and reason for prescribing.
- Medications exposure will be described using the number of prescriptions issued/dispensed, number of DDDs, cumulative DDDs, PDD and proportion of days covered (number of DDDs divided by the length of pregnancy). If data permit, we will use group-based trajectory modelling to describe the patterns of prescriptions through pregnancy in women treated for neuropathic pain (47,48). This method will allow to summarize complex patterns of exposure through pregnancy.

**Sensitivity analyses:** we will compare the prevalence of women who were using the medications for the neuropathic pain indication between the data sources, and over time.

## Part 3. Drug safety study

This part will include a **cohort study design** and a **case-malformed control design**.

45

Study protocol – Methods for controlling by indication for prescriptions: application to medications for neuropathic pain

### *Cohort study*

**Medications exposed group:** will consist of women receiving pregabalin or gabapentin during pregnancy or during the first trimester, depending on the outcome of interest.

**Comparison group:** The choice of the comparison group will affect the validity of the results. Hence, multiple comparison groups will be used to enhance the confidence in the results. The different comparison groups used will help in mitigate the effect of confounding, especially confounding by indication.

Examples of comparison groups that can be used:

- women receiving pregabalin or gabapentin for the same indication as the exposed group during the second and third trimester, but not during the first, for studying congenital anomalies;
- women receiving pregabalin or gabapentin for the same indication as the exposed group prior to but not during pregnancy;
- women receiving another neuropathic pain medication than pregabalin or gabapentin for the same indication as the exposed group;
- women receiving pregabalin or gabapentin for a different indication than the exposed group;
- women not receiving pregabalin or gabapentin (population comparison group);

It means that in most of comparisons between the groups, the results will be **stratified by indication** of prescription.

Moreover, we will also compare women receiving pregabalin or gabapentin for neuropathic pain indication with women not receiving any neuropathic pain medication, but having a neuropathic pain diagnosis (non-medicated diseased comparison group).

If sample size permits, we will investigate exposure to pregabalin and gabapentin separately.

The analyses will be carried out using multivariate logistic regression, and survival analysis, depending on the outcome of interest to calculate unadjusted and adjusted odds ratios

(ORs) and hazard ratios (HRs), along with 95% confidence intervals (CI). Advanced confounder adjustment methods (such as propensity score methods) might be used when appropriate to further mitigate measured confounding.

### *Case-malformed control design*

A separate protocol will be written focusing on the case-malformed control studies covering three demonstration projects as part of ConcePTION. Briefly, the study population will include all cases of major congenital anomalies among live births, foetal deaths of more than 20 completed weeks of gestation and termination of pregnancy for foetal anomaly recorded in the EUROmediCAT Central Database. Most registries contributed to the EUROmediCAT Central Database include registrations diagnosed up to 1 year after birth.

### *First analysis*

**Cases:** A signal has previously been identified with pregabalin and cardiac anomalies (27,49). Hence, we will define cases as foetus and infant with major cardiac congenital anomalies, excluding those with chromosomal conditions.

**Malformed controls:** Two malformed control groups will be used. A first group composed of foetus and infant with a diagnosis of major congenital anomaly after exclusion of major cardiac congenital anomaly, excluding those with chromosomal/ genetic conditions. A second group composed of foetus and infant with chromosomal/ genetic conditions.

**Exposure:** maternal exposure to pregabalin and gabapentin during the first trimester of pregnancy, recorded mainly from prospective maternity records.

### *Second analysis*

**Cases:** We will conduct an exploratory analysis in which, for each analysis, we considered a single EUROCAT subgroup of congenital anomaly to be the “case” group, excluding those with chromosomal conditions.

**Malformed controls:** Two malformed control groups will be used. A first group composed of foetus and infant with a diagnosis of major congenital anomaly after exclusion of the specific

congenital anomaly being analysed as the case group and of any subgroup at a hierarchical level above, excluding those with chromosomal/ genetic conditions. A second group composed of foetus and infant with chromosomal/ genetic conditions.

**Exposure:** maternal exposure to pregabalin and gabapentin during the first trimester of pregnancy, recorded mainly from prospective maternity records.

Logistic regression will be used to calculate unadjusted and adjusted ORs and 95% CI for the exposure.

### *Additional descriptive analyses*

The Tuscany Registry of Congenital Defects linked to prescription data will be used to further describe in-utero neuropathic pain medications exposure among cases with congenital anomalies in Tuscany region.

### *Pooling of the estimates*

Models will be fitted within each data sources using the available covariates. If appropriate, the results from these multivariable models will be combined in a meta-analysis, which will provide an adjusted estimate of the effect. For the meta-analysis of effects, effect estimates will be pooled using random-effects models. The effects of adjusting for certain covariates in some databases may also be used to predict the effects of such adjustments in other databases, which do not have the covariates accurately recorded. Thus, the meta-analysis on aggregate data will allow for adjustment for country-optimized covariates (**Appendix IX**).

Effect estimates will be presented as relative risk estimates with 95% CI.

### *Handling of missing data*

Patterns of missingness will be explored and handled as the best appropriate manner (50). It is unlikely that multiple imputations by chained equations for missing values in covariates will be supported by ConcePTION tools. Hence, missing data will be handled using a ‘case-complete analysis’.

## **9.8. Quality control**

The project will be conducted in line with the ENCePP Code of Conduct for scientific independence and transparency, and the FAIR (Findable, Accessible, Interoperable, Reusable) principles of the ConcePTION project.

All scripts and code lists will be reviewed by a researcher of the study team.

Data uploaded into the platform will have undergone beforehand several quality checks to ensure quality and completeness (as part of ConcePTION WP 7).

All members of the study team will be given the opportunity to review and interpret the study results to ensure conclusions are informed by those with the required local expertise of the healthcare system.

## **9.9. Limitations of the research methods**

Information bias

*Exposure data*

The issue or dispensing of prescription will be used as a proxy for the exposure to the medications. Even though, it has the strength to remove any issues due to recall bias, the actual intake of the medication is not known.

Moreover, medications delivered at the hospital and over the counter cannot be identified, this could lead to misclassification of the exposure. However, the medications of interest cannot be purchased over the counter and it is likely that a woman receiving neuropathic pain medication during hospitalizations will have the prescription renewed outside the hospital setting. Hence, the likelihood of exposure misclassification in this context is expected to be very limited for neuropathic pain medications.

Additionally, concerns arose due to the potential for misuse of pregabalin and gabapentin (32,33,51,52). Hence, we cannot exclude some exposure misclassification due to women in the “non-exposed” group having purchasing the medications on the illicit market.

In CPRD, prescriptions will not be captured if they are issued by a specialist in secondary care. Even though neuropathic pain prescribing will most likely subsequently be prescribed by the woman’s GP, we cannot rule out exposure misclassification in this context.



In France, we might not capture medications prescribed off-label, as they will not be reimbursed. However, in practice most of the time, the prescriber will not mention that the medication is prescribed off-label to allow the patient to be reimbursed for the expenses. In Norway Finland and Italy, all prescribed medications will be captured as long as they are dispensed and reimbursed. Thus, it is expected to capture all gabapentinoids filled by women outside hospitals.

### *Indication for prescribing*

Data availability varies across data sources, hence the general conceptual framework to identify the reason for prescribing will be tailored to each data sources. The frameworks are likely to differ in their ability to infer accurate indication of the medication in some of the data sources. Hence, when comparing the prevalence of medication prescribed to treat neuropathic pain between data sources, differences might reflect differences in prescribing habits rather than actual differences.

Moreover, validation of our approach in real life setting by looking back at individual medical records is not possible in the ConcePTION project. However, a validation analysis will try to reinforce our proposed approach by fitting the conceptual framework in data sources where the reason for prescribing will be ascertained by diagnoses in primary care/specialist visits. We will investigate the concordance/discordance of the results based on diagnoses in primary care/specialist visits alone and on the conceptual framework incorporating other types of data.

### *Missing data*

Covariates such as SES, smoking during pregnancy and breastfeeding will be affected by missingness. The extent of missing data is likely to vary across data sources and will be described.

### *Identifying pregnancies*

In some data sources, identifying pregnancy start dates can be difficult either due to complex history of multiple pregnancies, conflicting data, or due to a lack of data being reported. However, if the pregnancy duration is incorrectly estimated this has the potential to result in errors in the precise timing of exposure.

## **9.10. Other aspects**

### **Ethical consideration**

This project is based on secondary use of data (i.e. anonymised data), and will follow the ENCePP Code of Conduct, Revision 4. ([www.encepp.eu/code\\_of\\_conduct/](http://www.encepp.eu/code_of_conduct/)) to ensure transparency and high scientific standards. Industry partners, if their company manufactures gabapentinoids, will only be involved up to the protocol development stage i.e. they will not be involved in the analysis/interpretation of results.

The project will follow the EU General Data Protection Regulation (GDPR) as well as all ethical and institutional regulations relevant for each data source in the project. Each data source will ensure that rules and regulations are followed and that required approvals are obtained. Databases may require approval indicating that informed consent is waived and the rationale for this decision will be maintained.

An umbrella protocol has been written that will cover the five population-based demonstration projects involved in ConcePTION. The latter protocol is currently reviewed and approved by the appropriate authority of each data sources (e.g. Research Ethics Board/ Institutional Review Board/Data Protection Officer) before study start. Copies of all approvals will be stored in the ConcePTION secure platform.

### **Confidentiality**

The data sources will ensure that sensitive data is stored and analysed at a local secure platform (GDPR compliant). In some instances, this may include a Data Protection Impact Assessment performed by the appropriate Data Protection Officer.

## **10. Protection of human subjects**

NA

## 11. Management and reporting of adverse events/adverse reactions

NA

## 12. Plans for disseminating and communicating study results

The study will be registered in the EU PAS Register prior to its start. The results of the study will be published as scientific papers in peer-reviewed journals. Preparation of such manuscripts will be prepared independently by the investigators and in accordance with the current guidelines of STrengthening the Reporting of OBservational studies in Epidemiology, the ENCePP standards and EMA guidelines.

The following funding disclosure will be used:

*“The publication is part of the activities within the ConcePTION project. It has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 821520. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.”*

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## Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1	Appendix I	12 April 2021	Data sources and contact person
2	Appendix II	12 April 2021	Available evidence on gabapentin and pregabalin use during pregnancy and major congenital anomaly (CA)
3	Appendix III	12 April 2021	Diagnostics codes for identifying neuropathic pain in health care data sources
4	Appendix IV	12 April 2021	Recommendations for the pharmacological treatment of neuropathic pain
5	Appendix V	12 April 2021	Data on medications available by each data sources
6	Appendix VI	12 April 2021	Definitions of the secondary outcomes
7	Appendix VII	12 April 2021	Measurements of neurodevelopmental outcomes and breastfeeding in the databases
8	Appendix VIII	12 April 2021	Covariate items across Data Sources
9	Appendix IX	12 April 2021	Meta-analytic techniques for use in ConcePTION Demonstration Projects

## Annex 2. ENCePP checklist for study protocols

Doc.Ref. EMA/540136/2009

### ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

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

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

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

**Study title:** Methods for controlling by indication for prescriptions: application to medications for neuropathic pain

**EU PAS Register® number:**  
**Study reference number (if applicable):**

<b><u>Section 1: Milestones</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
1.1 Does the protocol specify timelines for 1.1.1 Start of data collection <sup>1</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2

<sup>1</sup> Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

<b><u>Section 1: Milestones</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
1.1.2 End of data collection <sup>2</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2
1.1.3 Progress report(s)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6
1.1.4 Interim report(s)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
1.1.5 Registration in the EU PAS Register®	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6
1.1.6 Final report of study results.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6

Comments:

<b><u>Section 2: Research question</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
2.1 Does the formulation of the research question and objectives clearly explain:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7
2.1.2 The objective(s) of the study?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8
2.1.5 If applicable, that there is no <i>a priori</i> hypothesis?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

<b><u>Section 3: Study design</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7

<sup>2</sup> Date from which the analytical dataset is completely available.

<b><u>Section 3: Study design</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	11

Comments:

<b><u>Section 4: Source and study populations</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
4.1 Is the source population described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2
4.2.2 Age and sex	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2
4.2.3 Country of origin	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2
4.2.4 Disease/indication	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3
4.2.5 Duration of follow-up	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2

Comments:

<b><u>Section 5: Exposure definition and measurement</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.4
5.3 Is exposure categorised according to time windows?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3

<b><u>Section 5: Exposure definition and measurement</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
5.6 Is (are) (an) appropriate comparator(s) identified?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7

Comments:

<b><u>Section 6: Outcome definition and measurement</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3
6.2 Does the protocol describe how the outcomes are defined and measured?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYs, health care services utilisation, burden of disease or treatment, compliance, disease management)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

Comments:

<b><u>Section 7: Bias</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.9

Comments:

<b><u>Section 8: Effect measure modification</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7

Comments:

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<b><u>Section 9: Data sources</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3
9.1.3 Covariates and other characteristics?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3 Table 7
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Appendix VIII
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3 & Appendix VI and VII
9.3.3 Covariates and other characteristics?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.6

Comments:

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<b><u>Section 10: Analysis plan</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
10.1 Are the statistical methods and the reason for their choice described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7
10.2 Is study size and/or statistical precision estimated?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.5
10.3 Are descriptive analyses included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.5
10.4 Are stratified analyses included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7
10.5 Does the plan describe methods for analytic control of confounding?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7 & Appendix IX
10.6 Does the plan describe methods for analytic control of outcome misclassification?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
10.7 Does the plan describe methods for handling missing data?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7
10.8 Are relevant sensitivity analyses described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7

Comments:

<b><u>Section 11: Data management and quality control</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.6
11.2 Are methods of quality assurance described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.8
11.3 Is there a system in place for independent review of study results?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.8

Comments:

<b><u>Section 12: Limitations</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.9
12.1.2 Information bias?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.9

<b><u>Section 12: Limitations</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.5

Comments:

<b><u>Section 13: Ethical/data protection issues</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.10
13.2 Has any outcome of an ethical review procedure been addressed?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
13.3 Have data protection requirements been described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.10

Comments:

<b><u>Section 14: Amendments and deviations</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
14.1 Does the protocol include a section to document amendments and deviations?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	5

Comments:

<b><u>Section 15: Plans for communication of study results</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	12
15.2 Are plans described for disseminating study results externally, including publication?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	12

Comments:

Name of the main author of the protocol:

\_\_\_\_\_

Date: dd/Month/year



Signature: \_\_\_\_\_

### **Annex 3. Additional information**

*Additional annexes may be included if necessary.*

# Appendix I: Data sources and contact person

Country	Region	Data source	Name of Data source in ConcePTION Name and Email of contact person
France	Haute-Garonne	EFEMERIS database	CHUT: Centre Hospitalier Universitaire de Toulouse Christine Damase-Michel : christine.damase-michel@univ-tlse3.fr
France	Nationwide	SNDS	University of Bordeaux Cécile Droz-Perroteau: cecile.perroteau@u-bordeaux.fr
Finland	Nationwide	Linkage of several national registries	THL: Finnish Institute for Health and Welfare Maarit Leinonen: maarit.leinonen@thl.fi
Norway	Nationwide	Linkage of three national registries	UOSL: University of Oslo Hedvig Nordeng: h.m.e.nordeng@farmasi.uio.no
UK	Wales	SAIL Databank	USWAN: University of Swansea Sue Jordan: s.e.jordan@swansea.ac.uk
UK	Nationwide	CPRD	GSK Keele Wurst: keele.e.wurst@gsk.com Betsy Georgiou: mary.e.jones@gsk.com
Germany	Nationwide	GeParD	Leibniz Institute for Prevention Research and Epidemiology, BIPS Tania Schink: schink@leibniz-bips.de
Italy	Tuscany	Healthcare administrative data source	ARS Agenzia regionale di sanità della Toscana Rosa Gini: rosa.gini@ars.toscana.it
Italy	Tuscany	Tuscany Registry of Congenital Defects	CNR-IFC Anna Pierini : apier@ifc.cnr.it
Italy	Emilia Romagna	Healthcare administrative data source	FERR Università degli Studi di Ferrara – University of Ferrara Amanda Neville : nvm@unife.it
Multinational	Registries: Belgium (Antwerp), Croatia (Zagreb), Denmark (Funen), France (Brittany, Ile de	EUROmediCAT Central Database	Ulster University Maria Loane: ma.loane@ulster.ac.uk

	la Réunion, Paris), Germany (Mainz, Saxony- Anhalt), Ireland (Cork and Kerry), Italy (Emilia Romagna, Tuscany), Malta, Northern Netherlands, Poland <i>(Wielkopolska,  rest of Poland  excluding  Wielkopolska),  Spain (Valencian  Region),  Sweden,  Switzerland  (Vaud), UK  (England, Wales)</i>		
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## Appendix II: Available evidence on gabapentin and pregabalin use during pregnancy and major congenital anomaly (CA)

Table 1. Gabapentin use and risk of congenital anomaly

Study	Region/Country	No. of Women	CA N (%)	OR (95% CI)	Reference Group	Study Period
Cohen JM et al. Comparative safety of antiepileptic drugs and risk of major congenital malformations. Pharmacoepidemiology and Drug Safety. 2019;28 (Supplement 2):13-4.	Denmark, Finland, Iceland & Norway	474	Not reported	1.1 (0.7-1.6)	Lamotrigine monotherapy	1996-2017*
Hernandez-Diaz S et al. Comparative safety of antiepileptic drugs during pregnancy. 2012;1(21):1692-9.	North American AED Pregnancy Registry	145	1 (0.7)	0.6 (0.07–5.2) 0.5 (0.07-4.1)	Unexposed to AEDs Lamotrigine	1997-2011
Molgaard-Nielsen D, Hviid A. Newer-generation antiepileptic drugs and the risk of major birth defects. 2011;1(19):1996-2002.	Denmark	59	1 (1.7)	0.53 (0.07-3.85) <sup>adj</sup>	No prescriptions of newer-generation AEDs during pregnancy	1996-2008
Montouris G. Gabapentin exposure in human pregnancy: results from the Gabapentin Pregnancy Registry. Epilepsy	US	39	2 (4.5)	Not reported	General population	Not reported

Behav. 2003 Jun;4(3):310–7.						
<p>Patorno E et al. Gabapentin in pregnancy and the risk of adverse neonatal and maternal outcomes: A population-based cohort study nested in the US Medicaid Analytic eXtract dataset. PLOS Medicine. 2020 Sep 1;17(9):e1003322.</p>	US	4,642 pregnancies exposed during first trimester	230 (5.0)	1.07 (0.94-1.21)	pregnancies with no gabapentin dispensing from 3 months before the start of pregnancy	2001-2013
<p>Blotière P-O, Raguideau F, Weill A, Elefant E, Perthus I, Goulet V, et al. Risks of 23 specific malformations associated with prenatal exposure to 10 antiepileptic drugs. Neurology. 2019 Jul</p>	France	365	<p>Spina bifida: 1 (2.74) Ventricular septal defect: 1 (2.79) Hypospadias: 1 (7.52)</p>	<p>Spina bifida: 8.4 (0.2–47.1) Ventricular septal defect: 1.1 (0.0–6.3) Hypospadias: 1.6 (0.0–8.9)</p>	women with no reimbursement for AEDs	2011-2015

9;93(2):e167.						
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\*Denmark 1997-2017, Finland 1996-2014, Iceland 2003-2012, and Norway 2004-2017

Table 2. Pregabalin use and risk of congenital anomaly

Study	Region/Country	No. of Women	MCM N (%)	OR (95% CI)	Reference Group	Study Period
Winterfeld U et al. Pregnancy outcome following maternal exposure to pregabalin may call for concern. Neurology. 2016;86(24):2251-7.	TIS in 7 Countries <sup>#</sup>	116	7 (6.0)	3.0 (1.2-7.9)	Unexposed to AEDs	2004-2013
Paterno E et al. Pregabalin use early in pregnancy and the risk of major congenital malformations. Neurology. 2017;88(21):2020-5.	US MAX	477	28 (5.9)	1.16 (0.81–1.67) <sup>adj</sup>	Unexposed to anticonvulsants	2000-2010
	US MarketScan	172	11(6.4)	1.03 (0.56-1.90) <sup>adj</sup>		
Cohen JM et al. Comparative safety of antiepileptic drugs and risk of major congenital malformations.	Denmark, Finland, Iceland & Norway	717		1.2 (0.9-1.7)	Lamotrigine monotherapy	1996-2017*

Pharmacoepidemiology and Drug Safety. 2019;28 (Supplement 2):13-4.						
Fujii H et al. Pregnancy outcomes following gabapentin use: results of a prospective comparative cohort study. Neurology. 2013 Apr 23;80(17):1565–70.	TIS in 5 countries <sup>‡</sup>	223	7 (4.1)	Not reported (p-value= 0.555)	women who contacted the same TIS or pharmacovigilance center with exposure to a nonteratogenic substance	
Blotière P-O, Raguideau F, Weill A, Elefant E, Perthus I, Goulet V, et al. Risks of 23 specific malformations associated with prenatal exposure to 10 antiepileptic drugs. Neurology. 2019 Jul 9;93(2):e167.	France	1,671	Spina bifida: 1 (0.60) Ventricular septal defect: 5 (3.02) Atrial septal defect: 6 (3.63) Hypoplastic left heart syndrome: 1 (0.60) Coarctation of aorta: 4 (2.42) Cleft lip with or without cleft palate: 1 (0.60) Cleft palate: 2 (1.21) Anorectal atresia: 1 (0.60) Hypospadias: 2 (3.40)	Spina bifida: 1.8 (0.0–10.2) Ventricular septal defect: 1.1 (0.5–2.8) Atrial septal defect: 1.9 (0.8–4.1) Hypoplastic left heart syndrome: 5.2 (0.1–29.4) Coarctation of aorta: 5.8 (1.6–14.9) Cleft lip with or without cleft palate: 0.7 (0.0–3.8) Cleft palate: 1.9 (0.2–6.9) Anorectal atresia: 2.1 (0.1–11.6) Hypospadias: 0.7 (0.1–2.6)	women with no reimbursement for AEDs	2011-2015

			Craniosynostosis: 3 (1.81)	Craniosynostosis: 4.4 (0.9–13.0)		
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# France, United Kingdom, Italy, Finland, Switzerland, the Netherlands, and Turkey.

\*Denmark 1997-2017, Finland 1996-2014, Iceland 2003-2012, and Norway 2004-2017

¥ Canada, France, England, Italy, Korea



Appendix III: Diagnostics codes for identifying neuropathic pain in health care data sources

DOI	Region/Country	Data Source(s)	NP Identification																																																						
10.14236/jhi.v19i2.799.	UK (Brent, West London urban area)	100 000 primary care EHR patient from 23 general practices	Patients with READ codes for conditions associated with NP, below list of READ codes from the ANNEX 1 of the paper:																																																						
			<table><tr><th>READ Term</th><th>READ Code</th><th>READ Term</th></tr><tr><td>Acute painful diab neuropathy</td><td>F3720</td><td>Herpes zoster + oth.CNS</td></tr><tr><td>Asymptomatic diab neuropathy</td><td>F3722</td><td>Herpes zoster + other C</td></tr><tr><td>Cerv disc disord + radiculopathy</td><td>N12zH</td><td>Herpes zoster + other s</td></tr><tr><td>Chron painful diab neuropathy</td><td>F3721</td><td>Lu disc prolapse + radi</td></tr><tr><td>Cx disc prolapse + radiculopathy</td><td>N12C0</td><td>Nerve/spinal cord injur</td></tr><tr><td>Disc prolapse + radiculopathy</td><td>N12C.</td><td>Ophthalmic herpes zos</td></tr><tr><td>Geniculate herpes zoster</td><td>A5311</td><td>Polyneuropathy</td></tr><tr><td>Glossopharyngeal neuralgia</td><td>F321.</td><td>Polyneuropathy in diab</td></tr><tr><td>Heredit.periph.neuropathy NOS</td><td>F360z</td><td>Polyneuropathy + herp</td></tr><tr><td>Herpes zost. dermatitis eyelid</td><td>A5320</td><td>Postinfectious polyneur</td></tr><tr><td>Herpes zoster</td><td>A53..</td><td>Postzoster neuralgia</td></tr><tr><td>Herpes zoster + unsp. complic.</td><td>A53y.</td><td>Th disc prolapse + radi</td></tr><tr><td>Herpes zoster NOS</td><td>A53z.</td><td>Trigeminal neuralgia N</td></tr><tr><td>Herpes zoster iridocyclitis</td><td>A5322</td><td>Trigeminal neuralgia O</td></tr><tr><td>Herpes zoster keratoconjunctiv</td><td>A5321</td><td>Zoster encephalitis</td></tr><tr><td>Herpes zoster ophthalmicus</td><td>A5324</td><td>[X]Other chronic pain</td></tr><tr><td>Herpes zoster + ophthalmic comp.</td><td>A532.</td><td></td></tr></table>	READ Term	READ Code	READ Term	Acute painful diab neuropathy	F3720	Herpes zoster + oth.CNS	Asymptomatic diab neuropathy	F3722	Herpes zoster + other C	Cerv disc disord + radiculopathy	N12zH	Herpes zoster + other s	Chron painful diab neuropathy	F3721	Lu disc prolapse + radi	Cx disc prolapse + radiculopathy	N12C0	Nerve/spinal cord injur	Disc prolapse + radiculopathy	N12C.	Ophthalmic herpes zos	Geniculate herpes zoster	A5311	Polyneuropathy	Glossopharyngeal neuralgia	F321.	Polyneuropathy in diab	Heredit.periph.neuropathy NOS	F360z	Polyneuropathy + herp	Herpes zost. dermatitis eyelid	A5320	Postinfectious polyneur	Herpes zoster	A53..	Postzoster neuralgia	Herpes zoster + unsp. complic.	A53y.	Th disc prolapse + radi	Herpes zoster NOS	A53z.	Trigeminal neuralgia N	Herpes zoster iridocyclitis	A5322	Trigeminal neuralgia O	Herpes zoster keratoconjunctiv	A5321	Zoster encephalitis	Herpes zoster ophthalmicus	A5324	[X]Other chronic pain	Herpes zoster + ophthalmic comp.	A532.	
			READ Term	READ Code	READ Term																																																				
			Acute painful diab neuropathy	F3720	Herpes zoster + oth.CNS																																																				
			Asymptomatic diab neuropathy	F3722	Herpes zoster + other C																																																				
			Cerv disc disord + radiculopathy	N12zH	Herpes zoster + other s																																																				
			Chron painful diab neuropathy	F3721	Lu disc prolapse + radi																																																				
			Cx disc prolapse + radiculopathy	N12C0	Nerve/spinal cord injur																																																				
			Disc prolapse + radiculopathy	N12C.	Ophthalmic herpes zos																																																				
			Geniculate herpes zoster	A5311	Polyneuropathy																																																				
			Glossopharyngeal neuralgia	F321.	Polyneuropathy in diab																																																				
			Heredit.periph.neuropathy NOS	F360z	Polyneuropathy + herp																																																				
			Herpes zost. dermatitis eyelid	A5320	Postinfectious polyneur																																																				
			Herpes zoster	A53..	Postzoster neuralgia																																																				
			Herpes zoster + unsp. complic.	A53y.	Th disc prolapse + radi																																																				
			Herpes zoster NOS	A53z.	Trigeminal neuralgia N																																																				
			Herpes zoster iridocyclitis	A5322	Trigeminal neuralgia O																																																				
			Herpes zoster keratoconjunctiv	A5321	Zoster encephalitis																																																				
			Herpes zoster ophthalmicus	A5324	[X]Other chronic pain																																																				
			Herpes zoster + ophthalmic comp.	A532.																																																					

doi:10.1136/ bmjopen-2018-021535	Germany	InGef database	<table><tr><th colspan="2">ICD-10 pain codes “typically neuropathic” (Diagnoses with an improved evidence via controlled randomised studies)</th></tr><tr><td>B02</td><td>herpes zoster</td></tr><tr><td>G500</td><td>trigeminal neuralgia</td></tr><tr><td>G530</td><td>post zoster neuralgia</td></tr><tr><td>G546</td><td>phantom pain</td></tr><tr><td>G9585</td><td>deafferentation pain due to spinal cord impairment</td></tr><tr><td>M797</td><td>fibromyalgia</td></tr><tr><td>T926</td><td>stump pain after traumatically arm amputation</td></tr><tr><td>T936</td><td>stump pain after traumatically leg amputation</td></tr></table> <table><tr><th colspan="2">ICD-10 pain code “possibly neuropathic” (diseases with a potentially neuropathic genesis based upon aetiology/anatomical de independent from the therapeutic benefit of P/G according to the guideline “diagnosis pain” from the German Society of Neurology [1])</th></tr><tr><td>G130</td><td>paraneoplastic neuromyopathy and neuropathy</td></tr><tr><td>G521</td><td>diseases of N. glossopharyngeus and glossopharyngeus neuralgia</td></tr><tr><td>G56</td><td>mono neuropathy of the upper extremity</td></tr><tr><td>G57</td><td>mono neuropathy of the lower extremity</td></tr><tr><td>G58</td><td>other mono neuropathies</td></tr><tr><td>G59</td><td>mono neuropathy parallel to other illness</td></tr><tr><td>G60</td><td>hereditary and idiopathic neuropathy</td></tr><tr><td>G61</td><td>polyneuritis</td></tr><tr><td>G62</td><td>other polyneuropathies</td></tr><tr><td>G63</td><td>polyneuropathy parallel to other illness</td></tr><tr><td>G990</td><td>autonomous neuropathy through endokrinal and metabolic diseases</td></tr><tr><td>M501</td><td>cervical intervertebral disc degeneration with radiculopathy</td></tr><tr><td>M511</td><td>lumbal intervertebral disc degeneration with radiculopathy</td></tr><tr><td>M541</td><td>radiculopathy</td></tr><tr><td>M542</td><td>cervical neuralgia</td></tr><tr><td>M543</td><td>ischialgia</td></tr><tr><td>M544</td><td>lumboischialgia</td></tr></table>	ICD-10 pain codes “typically neuropathic” (Diagnoses with an improved evidence via controlled randomised studies)		B02	herpes zoster	G500	trigeminal neuralgia	G530	post zoster neuralgia	G546	phantom pain	G9585	deafferentation pain due to spinal cord impairment	M797	fibromyalgia	T926	stump pain after traumatically arm amputation	T936	stump pain after traumatically leg amputation	ICD-10 pain code “possibly neuropathic” (diseases with a potentially neuropathic genesis based upon aetiology/anatomical de independent from the therapeutic benefit of P/G according to the guideline “diagnosis pain” from the German Society of Neurology [1])		G130	paraneoplastic neuromyopathy and neuropathy	G521	diseases of N. glossopharyngeus and glossopharyngeus neuralgia	G56	mono neuropathy of the upper extremity	G57	mono neuropathy of the lower extremity	G58	other mono neuropathies	G59	mono neuropathy parallel to other illness	G60	hereditary and idiopathic neuropathy	G61	polyneuritis	G62	other polyneuropathies	G63	polyneuropathy parallel to other illness	G990	autonomous neuropathy through endokrinal and metabolic diseases	M501	cervical intervertebral disc degeneration with radiculopathy	M511	lumbal intervertebral disc degeneration with radiculopathy	M541	radiculopathy	M542	cervical neuralgia	M543	ischialgia	M544	lumboischialgia
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			1 Deutsche Gesellschaft für Neurologie. Diagnostik neuropathischer Schmerzen: S1-Leitlinie 2012.																																																						

<a href="https://doi.org/10.1002/ejp.594">https://doi.org/10.1002/ejp.594</a>	Canada (Southwestern Ontario)	31,300 patients contributed by 23 GPs in 10 primary care practices	<p>The table below reports the definite neuropathic pain etiologies identified using the ICD-9 and ICPC codes or problem list entries. The search was conducted on the codes actually used in the database, which are a natural subset of the total diagnostic codes available in each coding system. Problem list entries were searched for the variations on the descriptions below, which were given to the codes by the providers entering data into the EHRs and do not necessarily reflect the language of the ICD-9 or ICPC code books.</p> <table><tr><th>Code</th><th>Description</th></tr><tr><td>53.200</td><td>POST HERPETIC NEURALGIA</td></tr><tr><td>53.210</td><td>Herpetic neuralgia</td></tr><tr><td>53.220</td><td>NEURALGIA, POST HERPETIC</td></tr><tr><td>337.200</td><td>Reflex Sympathetic Dystrophy</td></tr><tr><td>350.000</td><td>NEURALGIA, TRIGEMINAL</td></tr><tr><td>350.000</td><td>Neuralgia, Trigeminal</td></tr><tr><td>350</td><td>TRIGEMINAL NERVE DISORDERS</td></tr><tr><td>350.001</td><td>N92 TRIGEMINAL NEURALGIA</td></tr><tr><td>350.010</td><td>TRIGEMINAL NEURALGIA</td></tr><tr><td>350.100</td><td>TIC DOULOUREUX</td></tr><tr><td>350.100</td><td>Neuralgia, Trigeminal ( Tic Douleuroux )</td></tr><tr><td>350.200</td><td>MERALGIA PARESTHETICA</td></tr></table>	Code	Description	53.200	POST HERPETIC NEURALGIA	53.210	Herpetic neuralgia	53.220	NEURALGIA, POST HERPETIC	337.200	Reflex Sympathetic Dystrophy	350.000	NEURALGIA, TRIGEMINAL	350.000	Neuralgia, Trigeminal	350	TRIGEMINAL NERVE DISORDERS	350.001	N92 TRIGEMINAL NEURALGIA	350.010	TRIGEMINAL NEURALGIA	350.100	TIC DOULOUREUX	350.100	Neuralgia, Trigeminal ( Tic Douleuroux )	350.200	MERALGIA PARESTHETICA
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			356.000	N94 PERIPHERAL NEUROPATHY
			356	Hereditary and idiopathic peripheral neuropathy
			356.1	PERIPHERAL NEUROPATHY N94
			356.1	CHARCOT-MARIE-TOOTH DISEASE
			351.300	PARASTHESIA
			847.050	CERVICAL ROOT IRRITATION
			53.000	HERPES ZOSTER
			053.000	S70 HERPES ZOSTER, SHINGLES
			053.000	HERPES ZOSTER, SHINGLES
			53.100	SHINGLES
			053.1	HERPES ZOSTER, SHINGLES S70
			053.210	Herpes zoster keratoconjunctivitis
			053.900	Herpes zoster NOS, Shingles
			54.000	HERPES SIMPLEX
			054.000	S71 HERPES SIMPLEX
			054.000	HERPES SIMPLEX, COLD SORE
			054.000	Herpes simplex, cold sore
			54.100	COLD SORE
			054.1	HERPES SIMPLEX S71

			054.200	Herpetetic stomatitis
			340.000	MULTIPLE SCLEROSIS
			340.000	N86 MULTIPLE SCLEROSIS
			340.1	MULTIPLE SCLEROSIS N86
			349.020	TRANSVERSE MYELITIS
			349.2	SENSA.DISTUR/AB INVOL.MOV N06
			349.4	NEURO SYSTEM DSE N99
			350.000	N03 FACE PAIN
			350.1	FACE PAIN N03
			350.201	Pain-Face, Atypical
			351.100	FACIAL NERVE DISORDERS
			356.10	CARPAL TUNNEL SYNDROME
			356.200	POLYNEUROPATHY
			356.300	MONONEURITIS MULTIPLEX
			358.100	MYONEURAL DISORDERS
			372.200	Herpetetic keratitis
			608.1	PAIN IN PENIS Y01
			629.1	FEMALE GENITAL PAIN/OTHER X01
			691.130	NEURODERMATITIS

			709.000	S01 PAIN, TENDERNESS OF SKIN
			722.1	LUMBAR DISC DISORDERS.RADIATION L86
			723.100	Pain-Neck
			729.100	Myofascial Pain Syndrome
			781.120	CHRONIC PAIN
			781.151	CHRONIC PAIN SYNDROME
			784.000	Facial Pain
			847.060	THORACIC PAIN
			847.060	Pain-Thoracic
			847.800	THORACIC OUTLET
			049.000	N29 OTHER SYMPT/COMPLT.NEOUR SYST
			049.1	OTHER SYMPT/COMPLT.NEOUR SYST N29
			52.000	CHICKEN POX
			052.000	A72 CHICKENPOX
			052.1	CHICKENPOX A72
			99.000	HERPES GENITALIS
			099.1	HERPES GENITALIS - MALE Y72
			250.000	DIABETES MELLITUS
			250.001	DIABETES MELLITUS T90

			250.001	T90 DIABETES MELLITUS
			250.010	Diabetes Type 1
			250.020	Diabetes Type 2
			250.100	DIABETES, NIDDM
			250.100	DIABETES - NIDDM
			250.100	Type 2 Diabetes
			250.120	DIABETES - TYPE 2
			250.130	DIABETES - TYPE 1
			266.200	Vitamin B12 Deficiency
			307.430	Restless leg syndrome
			333.940	Restless legs syndrome
			338.400	Chronic Pain Syndrome ( Psychosocial )
			349.003	N99 NEURO SYSTEM DSE
			349.200	MOTOR NEURON DISEASE
			349.210	DISEASE - motor neuron, Huntington's Chorea
			351.000	BELL'S PALSY
<a href="https://dx.doi.org/10.1097/j.pain.0000000000001347">https://dx.doi.org/10.1097/j.pain.0000000000001347</a>	France	EGB: Merged 3 databases:	Chronic pain as a principal or associated diagnosis was identified based on the ICD-10 codes R5210 (chronic neuropathic pain), R5218 (other chronic	



		<ul style="list-style-type: none"> <li>• Drug reimbursement database</li> <li>• National hospital discharge summaries database (PMSI)</li> <li>• Specialized pain centers database</li> </ul>	intractable pain), and R522 (other CP)
10.1016/j.jpain.2003.12.004	US	Protocare Sciences Managed Care Database	ICD-9-CM diagnosis codes (primary or secondary) for any of the following conditions: (1) diabetic neuropathy (ICD-9-CM diagnosis codes 250.6X, 357.2); (2) postherpetic neuralgia (53.1X); (3) back and neck pain with neuropathic involvement (721.1, 721.41, 721.42, 721.91, 722.0, 722.1, 722.10, 722.11, 722.2, 722.7X, 723.0, 723.4, 724.0X, 724.3, 724.4); (4) cancer with neuropathic involvement (malignant neoplasms [excluding squamous or basal cell skin carcinoma] [140.XX-172.XX, 174.XX-208.XX] in conjunction with neuropathy [337.2X, 353.2, 353.3, 353.4, 354.4, 355.7X, 355.9, 729.2, 353.0,

			<p>353.1, 353.8, 353.9, 354.0, 354.1, 354.2, 354.3, 354.5, 354.8, 354.9, 355.0, 355.1, 355.2, 355.3, 355.4, 355.5, 355.6, 355.8, 357.3, 357.8, 357.9]); (5) causalgia, reflex sympathetic dystrophy, and related disorders (337.2X, 353.2, 353.3, 353.4, 354.4, 355.7X, 355.9, 729.2); (6) human immunodeficiency virus/AIDS (HIV/AIDS) with neuropathic involvement (HIV/AIDS in conjunction with neuropathy [337.2X, 353.2, 353.3, 353.4, 354.4, 355.7X, 355.9, 729.2, 353.0, 353.1, 353.8, 353.9, 354.0, 354.1, 354.2, 354.3, 354.5, 354.8, 354.9, 355.0, 355.1, 355.2, 355.3, 355.4, 355.5, 355.6, 355.8, 357.4, 357.8, 357.9]); (7) phantom limb pain (353.6); (8) trigeminal neuralgia (350.1); (9) atypical facial pain (350.2, 352.1); or (10) other disorders of peripheral nervous system associated with neuropathic pain (353.0, 353.1, 353.8, 353.9, 354.0, 354.1, 354.2, 354.3, 354.5, 354.8, 354.9, 355.0, 355.1, 355.2, 355.3, 355.4, 355.5, 355.6, 355.8).</p>
<a href="https://dx.doi.org/10.1111/j.1533-2500.2008.00244.x">https://dx.doi.org/10.1111/j.1533-2500.2008.00244.x</a>	Germany	IMS MediPlus-Disease Analyzer database (IMS Health, Frankfurt, Germany)	

			<table><tr><th>Painful Neuropathic Disorders</th><th>ICD-10 Diagnosis Codes</th></tr><tr><td>Diabetic neuropathy</td><td>E10.4, E11.4, E11.6, E11.7, E11.8, E12.4, E13.4, E13.6, E14.4, E14.6, E14.7, E14.8, G59.0, G63.2</td></tr><tr><td>Post-herpetic neuralgia</td><td>B00.9, B02.2, B02.3, B02.8, B02.9, G53.0</td></tr><tr><td>Back pain with neuropathic involvement</td><td>G54.3, G54.4, G83.4, M47.1, M47.2, M48.0, M51.0, M51.1, M54.1, M54.3, M54.4, M99.5, G99.3</td></tr><tr><td>Neck pain with neuropathic involvement</td><td>M50.0, M50.1, M50.2, M54.2</td></tr><tr><td>Cancer with neuropathic pain</td><td>G63.1</td></tr><tr><td>Causalgia</td><td>G56.4, M89.0</td></tr><tr><td>Phantom limb pain</td><td>G54.6</td></tr><tr><td>Trigeminal neuralgia</td><td>G50.0, G50.8, G50.9</td></tr><tr><td>Atypical facial pain</td><td>G50.1, G52.1</td></tr><tr><td>Other painful neuropathies</td><td></td></tr><tr><td>  Neuropathic pain, unspecified</td><td></td></tr><tr><td>    Other soft tissue disorders, not elsewhere classified: Neuralgia and neuritis, unspecified</td><td>M79.2</td></tr><tr><td>    Inflammatory polyneuropathy: Inflammatory polyneuropathy, unspecified</td><td>G61.9</td></tr><tr><td>    Inflammatory polyneuropathy: Other inflammatory polyneuropathies</td><td>G61.8</td></tr><tr><td>  Impingement syndromes</td><td></td></tr><tr><td>    Mononeuropathies of upper limb: Carpal tunnel syndrome</td><td>G56.0</td></tr><tr><td>    Mononeuropathies of lower limb: Meralgia paraesthetica</td><td>G57.1</td></tr><tr><td>    Mononeuropathies of lower limb: Tarsal tunnel syndrome</td><td>G57.5</td></tr><tr><td>  Other</td><td></td></tr><tr><td>    Other mononeuropathies: Intercostal neuropathy</td><td>G58.0</td></tr><tr><td>    Other polyneuropathies: Polyneuropathy, unspecified</td><td>G62.9</td></tr><tr><td>    Disturbances of skin sensation: Paraesthesia of skin</td><td>R20.2</td></tr><tr><td>    Disturbances of skin sensation: Other and unspecified disturbances of skin sensation</td><td>R20.8</td></tr><tr><td>    Mononeuropathies of upper limb: Lesion of ulnar nerve</td><td>G56.2</td></tr><tr><td>    Other mononeuropathies: Other specified mononeuropathies</td><td>G58.8</td></tr><tr><td>    Other mononeuropathies: Mononeuropathy, unspecified</td><td>G58.9</td></tr><tr><td>    Mononeuropathies of lower limb: Lesion of lateral popliteal nerve</td><td>G57.3</td></tr><tr><td>    Nerve root and plexus disorders: Nerve root and plexus disorder, unspecified</td><td>G54.9</td></tr><tr><td>    Other polyneuropathies: Other specified polyneuropathies</td><td>G62.8</td></tr><tr><td>    Nerve root and plexus disorders: Brachial plexus disorders</td><td>G54.0</td></tr><tr><td>    Nerve root and plexus disorders: Lumbosacral plexus disorders</td><td>G54.1</td></tr><tr><td>    Other polyneuropathies: Alcoholic polyneuropathy</td><td>G62.1</td></tr><tr><td>    Mononeuropathies of upper limb: Lesion of radial nerve</td><td>G56.3</td></tr><tr><td>    Inflammatory polyneuropathy: Guillain-Barré syndrome</td><td>G61.0</td></tr><tr><td>    Nerve root and plexus disorders: Cervical root disorders, not elsewhere classified</td><td>G54.2</td></tr><tr><td>    Benign neoplasm of other and unspecified sites: Peripheral nerves and autonomic nervous system</td><td>D36.1</td></tr><tr><td>    Mononeuropathies of lower limb: Lesion of plantar nerve</td><td>G57.6</td></tr><tr><td>    Personal history of certain other diseases: Personal history of diseases of the nervous system and sense organs</td><td>Z86.6</td></tr><tr><td>    Mononeuropathies of upper limb: Mononeuropathy of upper limb, unspecified</td><td>G56.9</td></tr><tr><td>    Mononeuropathies of lower limb: Lesion of sciatic nerve</td><td>G57.0</td></tr><tr><td>    Other polyneuropathies: Polyneuropathy due to other toxic agents</td><td>G62.2</td></tr><tr><td>    Disturbances of skin sensation: Hyperaesthesia</td><td>R20.3</td></tr><tr><td>    Hereditary and idiopathic neuropathy: Idiopathic progressive neuropathy</td><td>G60.3</td></tr><tr><td>    Mononeuropathies of lower limb: Mononeuropathy of lower limb, unspecified</td><td>G57.9</td></tr><tr><td>    Hereditary and idiopathic neuropathy: Other hereditary and idiopathic neuropathies</td><td>G60.8</td></tr><tr><td>    Other polyneuropathies: Drug-induced polyneuropathy</td><td>G62.0</td></tr><tr><td>    Mononeuropathies of upper limb: Other lesions of median nerve</td><td>G56.1</td></tr><tr><td>    Mononeuropathies of lower limb: Lesion of femoral nerve</td><td>G57.2</td></tr><tr><td>    Hereditary and idiopathic neuropathy: Hereditary and idiopathic neuropathy, unspecified</td><td>G60.9</td></tr><tr><td>    Hereditary and idiopathic neuropathy: Hereditary motor and sensory neuropathy</td><td>G60.0</td></tr><tr><td>    Mononeuropathies of upper limb: Other mononeuropathies of upper limb</td><td>G56.8</td></tr><tr><td>    Nerve root and plexus disorders: Other nerve root and plexus 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M54.4, M99.5, G99.3	Neck pain with neuropathic involvement	M50.0, M50.1, M50.2, M54.2	Cancer with neuropathic pain	G63.1	Causalgia	G56.4, M89.0	Phantom limb pain	G54.6	Trigeminal neuralgia	G50.0, G50.8, G50.9	Atypical facial pain	G50.1, G52.1	Other painful neuropathies		Neuropathic pain, unspecified		Other soft tissue disorders, not elsewhere classified: Neuralgia and neuritis, unspecified	M79.2	Inflammatory polyneuropathy: Inflammatory polyneuropathy, unspecified	G61.9	Inflammatory polyneuropathy: Other inflammatory polyneuropathies	G61.8	Impingement syndromes		Mononeuropathies of upper limb: Carpal tunnel syndrome	G56.0	Mononeuropathies of lower limb: Meralgia paraesthetica	G57.1	Mononeuropathies of lower limb: Tarsal tunnel syndrome	G57.5	Other		Other mononeuropathies: Intercostal neuropathy	G58.0	Other polyneuropathies: Polyneuropathy, unspecified	G62.9	Disturbances of skin sensation: Paraesthesia of skin	R20.2	Disturbances of skin sensation: Other and unspecified disturbances of skin sensation	R20.8	Mononeuropathies of upper limb: Lesion of ulnar nerve	G56.2	Other mononeuropathies: Other specified mononeuropathies	G58.8	Other mononeuropathies: Mononeuropathy, unspecified	G58.9	Mononeuropathies of lower limb: Lesion of lateral popliteal nerve	G57.3	Nerve root and plexus disorders: Nerve root and plexus disorder, unspecified	G54.9	Other polyneuropathies: Other specified polyneuropathies	G62.8	Nerve root and plexus disorders: Brachial plexus disorders	G54.0	Nerve root and plexus disorders: Lumbosacral plexus disorders	G54.1	Other polyneuropathies: Alcoholic polyneuropathy	G62.1	Mononeuropathies of upper limb: Lesion of radial nerve	G56.3	Inflammatory polyneuropathy: Guillain-Barré syndrome	G61.0	Nerve root and plexus disorders: Cervical root disorders, not elsewhere classified	G54.2	Benign neoplasm of other and unspecified sites: Peripheral nerves and autonomic nervous system	D36.1	Mononeuropathies of lower limb: Lesion of plantar nerve	G57.6	Personal history of certain other diseases: Personal history of diseases of the nervous system and sense organs	Z86.6	Mononeuropathies of upper limb: Mononeuropathy of upper limb, unspecified	G56.9	Mononeuropathies of lower limb: Lesion of sciatic nerve	G57.0	Other polyneuropathies: Polyneuropathy due to other toxic agents	G62.2	Disturbances of skin sensation: Hyperaesthesia	R20.3	Hereditary and idiopathic neuropathy: Idiopathic progressive neuropathy	G60.3	Mononeuropathies of lower limb: Mononeuropathy of lower limb, unspecified	G57.9	Hereditary and idiopathic neuropathy: Other hereditary and idiopathic neuropathies	G60.8	Other polyneuropathies: Drug-induced polyneuropathy	G62.0	Mononeuropathies of upper limb: Other lesions of median nerve	G56.1	Mononeuropathies of lower limb: Lesion of femoral nerve	G57.2	Hereditary and idiopathic neuropathy: Hereditary and idiopathic neuropathy, unspecified	G60.9	Hereditary and idiopathic neuropathy: Hereditary motor and sensory neuropathy	G60.0	Mononeuropathies of upper limb: Other mononeuropathies of upper limb	G56.8	Nerve root and plexus disorders: Other nerve root and plexus disorders	G54.8	Mononeuropathies of lower limb: Other mononeuropathies of lower limb	G57.8	Mononeuropathies of lower limb: Lesion of medial popliteal nerve	G57.4	Injury of nerves at forearm level: Injury of ulnar nerve at forearm level	S54.0	Other mononeuropathies: Mononeuritis multiplex	G58.7	Injury of nerves at forearm level: Injury of median nerve at forearm level	S54.1	Injury of nerves at forearm level: Injury of radial nerve at forearm level	S54.2
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<a href="https://dx.doi.org/10.1111/ijcp.12182">https://dx.doi.org/10.1111/ijcp.12182</a>	Stockholm, Sweden	National registers and the regional	Diagnoses related to central or peripheral neuropathic pain (ICD-10 codes G35.9, G50.0, G50.1, G51.0, G53.0, G54.4, G54.6, G55.0, G55.1, G56.0, G56.2, G56.4, G56.9, G57.0, G57.1, G57.8, G57.9, G58.0,																																																																																																																						

		primary care database of Stockholm County	G58.7, G58.8, G62.9, G63.2, G82.1, G95.0, G95.2, G95.8, G97.9, I69.1, I69.3, M48.0, M50.1, M53.0, M53.1, M54.1, M54.3, M54.4, M79.2 and M89.0).
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## Appendix IV: Recommendations for the pharmacological treatment of neuropathic pain

### 1. Evidence-based recommendations for the pharmacological treatment of neuropathic pain from the Special Interest Group on Neuropathic Pain of the International Association for the Study of Pain (1)

The study revised the recommendations for the pharmacotherapy of neuropathic pain based on the results of a systematic review and meta-analysis (1). Briefly, a systematic review and meta-analysis of randomised controlled trials of all drug treatments for neuropathic pain published since 1966 and of unpublished trials with available results were conducted. Using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE), the authors rated the quality of evidence and the strength of recommendations. On the basis of the results of the review and meta-analysis, the recommendations of the Special Interest Group on Neuropathic Pain of the International Association for the Study of Pain for the systemic and topical pharmacological treatment of neuropathic pain were revised (**Table 1**). Non-pharmacological management strategies such as neurostimulation techniques were beyond the scope of the study.

**Table 1. Drugs or drug classes with strong or weak recommendations for use based on the GRADE classification**

	Total daily dose and dose regimen	Recommendations
<b>Strong recommendations for use</b>		
Gapabentin	1200–3600 mg, in three divided doses	First line
Gabapentin extended release or enacarbil	1200–3600 mg, in two divided doses	First line
Pregabalin	300–600 mg, in two divided doses	First line
Serotonin-noradrenaline reuptake inhibitors	60–120 mg, once a day (duloxetine); 150–225 mg, once a day (venlafaxine extended release)	First line
Tricyclic antidepressants	25–150 mg, once a day or in two divided doses	First line†
<b>Weak recommendations for use</b>		
Capsaicin 8% patches	One to four patches to the painful area for 30–60 min every 3 months	Second line ( peripheral neuropathic pain)‡
Lidocaine patches	One to three patches to the region of pain once a day for up to 12 h	Second line ( peripheral neuropathic pain)
Tramadol	200–400 mg, in two (tramadol extended release) or three divided doses	Second line
Botulinum toxin A (subcutaneously)	50–200 units to the painful area every 3 months	Third line; specialist use (peripheral neuropathic pain)
Strong opioids	Individual titration	Third line§

## 2. Norwegian recommendations for the treatment of neuropathic pain (2)

The Norwegian recommendations are following the Evidence-based recommendations for the pharmacological treatment of neuropathic pain from the Special Interest Group on Neuropathic Pain of the International Association for the Study of Pain (1).

### **First-line treatments:**

- gabapentin
- pregabalin
- Tricyclic antidepressants: amitriptyline, clomipramine, imipramine
- duloxetine
- carbamazepine (for trigeminal neuralgia)

### **Second-line treatments:**

- tramadol
- capsaicin
- lidocaine

### **Third-line treatments:**

- botulinum toxin A
- strong opioids

## 3. Finish recommendations for the treatment of neuropathic pain (3)

### **Antidepressants:**

- Tricyclic antidepressants: nortriptyline, amitriptyline
- SNRIs: venlafaxine, duloxetine

### **Antiepileptics:**

- gabapentin
- pregabalin

### **Tramadol**

### **Topical treatments:**

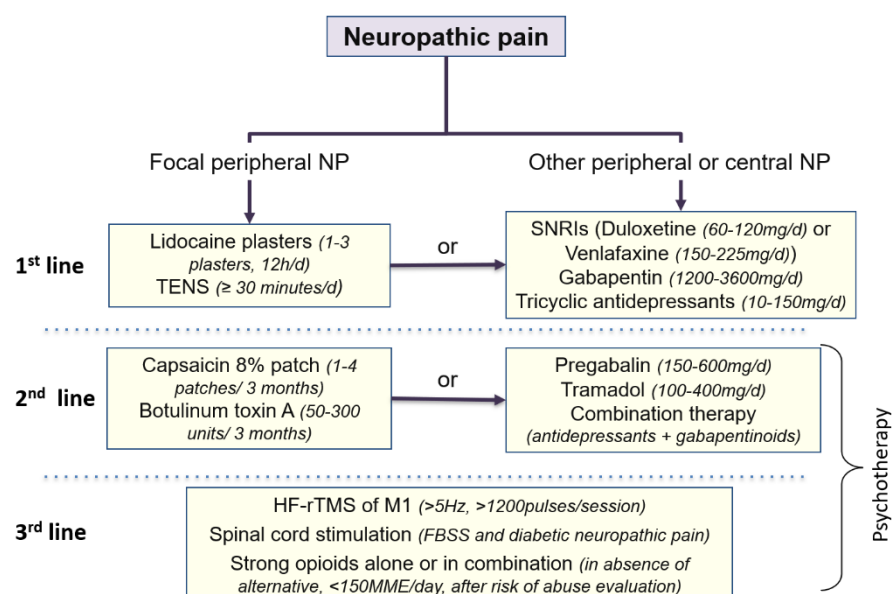
- Capsaicin
- Lidocaine

## 4- French recommendations for the treatment of neuropathic pain

The recently updated French recommendations take also into account the non-pharmacological therapies(4). Comparing these recommendations with those proposed in 2015 by the NeuPSIG, it can

be noted that lidocaine plasters are proposed first line and that pregabalin has been downgraded to the second line due to misuse issues and lower efficacy.

**Figure 1. Proposed therapeutic algorithm for neuropathic pain treatment in adults.**



## References

1. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *The Lancet Neurology*. 2015 Feb 1;14(2):162–73.
2. Nevropatisk smerte [Internet]. NEL - Nevrologiske prosedyrer. [cited 2021 Jan 19]. Available from: <https://nevrologi.legehandboka.no/handboken/sykdommer/nevromuskulare-sykdommer/sykdommer-og-symptomer/nevropatisk-smerte/>
3. Finnish recommendations for treatment of pain [Internet]. [cited 2021 Jan 19]. Available from: <https://www.kaypahoito.fi/hoi50103#s21>
4. Moisset X, Bouhassira D, Avez Couturier J, Alchaar H, Conradi S, Delmotte MH, et al. Pharmacological and non-pharmacological treatments for neuropathic pain: Systematic review and French recommendations. *Rev Neurol (Paris)*. 2020 May;176(5):325–52.
5. Smith LK, Hindori-Mohangoo AD, Delnord M, Durox M, Szamotulska K, Macfarlane A, et al. Quantifying the burden of stillbirths before 28 weeks of completed gestational age in high-income countries: a population-based study of 19 European countries. *The Lancet*. 2018 Nov 3;392(10158):1639–46.

# Appendix V: Data on medications available by each data sources

Name of the data source	EFEMERIS	SNDS	Finland	Norway	SAIL Databank	CPRD	EUROmediCAT	GePaRD	ARS	Tuscany Registry of Congenital Defects	ER Healthcare Administrative data source
brand name	yes	yes	yes	no	yes (from READ codes)	yes	No (sometimes)	yes	Yes	no	yes
ATC codes / DDD	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
date	yes	yes	yes	yes	yes	yes	1 <sup>st</sup> T exposure only	yes	yes	yes	yes
quantity of drug dispensed unit characterizing quantity i.e. 1 package	yes	yes	yes	yes	no	yes	no	yes	yes	yes	yes
strength i.e. 500mg	yes (from product name)	yes	yes (free text, poor quality. accessible through nordic product_code 'vnro')	yes	yes	yes	no	yes	yes	no	yes
dosage amount per day i.e. 450 mg/d	no	no	no	no	no, unless in ATC code	yes	no	no	no	no	DDD



duration of treatment	no	no	no	no	dates for first and last prescriptions	yes	no	no	no	yes	DDD
speciality of prescriber	yes	yes, for medications dispensed at community pharmacies only	yes (vocabulary only in Finnish, data only up to 2014)	yes	only GPs prescriptions	only GPs prescriptions	no	yes	no	no	no
box size unit i.e. 10 tablets	yes (from product name)	yes	yes (free text, poor quality. accessible through nordic product_code 'vnro')	yes	no, standard sizes are in the formulary	yes	no	yes	yes	no	no
drug form i.e. tablet, capsule, oral solution, cream, patch ...	yes (from product name)	yes	yes (from product code)	yes	yes	yes	no	yes	yes	no	yes
route of administration i.e oral, injection ...	yes (from product name)	yes	yes (from product code)	yes	yes (in ATC codes)	yes	no	yes	yes	no	no

## Appendix VI: Definitions of the secondary outcomes

The adverse pregnancy outcomes will be defined using codes and quality indicators developed in the ConcePTION data characterization study (ConcePTION deliverable D1.4 and D7.14).

**Immediate outcomes** will include foetal death (stillbirth/late foetal death and miscarriage/early foetal death, if data available), preterm birth, low birth weight, and small for gestational age.

- A **stillbirth** will be defined as a fetal death at or after 24 completed weeks of gestation (5). A fetal death occurring before this threshold will be named a **miscarriage**
- A **preterm birth** will be classified on the basis of gestational age at delivery in the following subcategories: 22+0 to 27+6 weeks of gestation (extremely preterm), 28+0-31+6 weeks of gestation (very preterm) and 32+0-36+6 weeks of gestation (moderate to late preterm) (World Health Organization, 2018a).
- **Low birth weight** will be defined as a birthweight less than 2500g among a full-term baby (> 37 weeks of gestation).
- **Small for gestational age** will be defined as a birthweight less than the 10<sup>th</sup> percentile for a given gestational age based on local or national charts (Committee on Practice Bulletin, 2015; McCowan, 2018). Sever SGA defined as a birthweight less than the 3<sup>rd</sup> percentile for a given gestational age might be used.

**Long-term outcomes** will include neurodevelopmental outcomes. We will investigate mainly attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder for which diagnostic codes are available.

- **ADHD** is characterized by a persistent pattern (at least 6 months) of inattention and/or hyperactivity-impulsivity, with onset during the developmental period, typically early to mid-childhood (Faraone, 2015). ADHD will be defined using the ICD10 codes F90.
- **Autism spectrum disorder** is characterized by persistent deficits in the ability to initiate and to sustain reciprocal social interaction and social communication, and by a range of restricted, repetitive, and inflexible patterns of behaviour and interests (Masi, 2017; Ousley, 2014). Autism will be defined using the ICD10 codes F84.

ADHD and autism spectrum disorder are mostly diagnosed within the first five-ten years after birth, so a long follow-up in the data source will be needed.

Appendix VII: Measurements of neurodevelopmental outcomes and breastfeeding in the databases

<b>Data sources</b>	<b>ND measurement available</b>	<b>Breastfeeding information</b>
<b>Finnish data source</b>	ICD or ICPC2 codes recorded in outpatient or GP care	None
<b>EFEMERIS database</b>	Certificates completed at 9 and 24 months by a general practitioner or a paediatrician - include 14 items designed to detect children at risk of psychomotor development abnormalities	Health certificates completed during mandatory medical examinations at 8 days, 9 months and 24 months old record breastfeeding (Yes/No), duration of breastfeeding (in weeks) and duration of exclusive breastfeeding (weeks)
<b>POMME database</b>	Certificates completed at 9 and 24 months by a general practitioner or a paediatrician - include 14 items designed to detect children at risk of psychomotor development abnormalities.	Health certificates completed during mandatory medical examinations at 8 days, 9 months and 24 months old record breastfeeding (Yes/No), duration of breastfeeding (in weeks) and duration of exclusive breastfeeding (weeks)
<b>Norwegian data sources</b>	ICD codes (specialist care): -ADHD: F90 -Autism spectrum disorder: F84 ATC codes -ADHD medication use in child	None
<b>SAIL databank</b>	ICD/Read codes, child health developmental examinations and educational attainment	Health visitors record at birth and 6 weeks- 'any' breastfeeding
<b>GePaRD (Claims data)</b>	ICD codes recorded as part of 'early detection examinations'	None

## Appendix VIII: Covariate items across Data Sources

Information item	Norway	EFEMERIS	GePaRD	SNDS	CPRD	Finland	SAIL	ER	ARS	Tuscany Registry of Congenital Defects	EUROmediCAT
<i>Maternal disease/medication indication</i>											
Diagnosis in healthcare database e.g. ICD10	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/> <sup>1</sup>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Diagnosis in disease registry	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Type of ward where the diagnosis was given	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Intervention in healthcare database as surrogate for disease	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/> <sup>2</sup>	<input type="checkbox"/>
Healthcare admission as surrogate for disease/disease severity	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Co-morbid diagnosis/diagnoses	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
<i>Confounders</i>											
Folic acid – prior to/during	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/> <sup>3</sup>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Maternal age at delivery	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Occupation	<input checked="" type="checkbox"/> <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/> <sup>5</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Level of education	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Deprivation score	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Smoking status – prior to/ during pregnancy	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Alcohol consumption – during pregnancy	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Substance misuse - during pregnancy	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Body mass index, obesity, underweight	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/> <sup>6</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/> <sup>7</sup>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Parity	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Plurality	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Breastfeeding	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

### Footnotes:

<sup>1</sup> information from hospital discharge record for which ward type is recorded, admission and dismissal diagnosis in ICD9, and length of stay.

<sup>2</sup> through PROCEDURES

<sup>3</sup> undercoded as mostly OTC

<sup>4</sup> coded 1 = Not employed; 2 = Employed, full-time; 3 = Employed, part-time

<sup>5</sup> socioeconomic status is a combination of occupation and level of education and status at labour market. However, lots of missing data

<sup>6</sup> only if coded as diagnosis, the last digit gives category of BMI

<sup>7</sup> only available 2005 onwards

## Appendix IX: Meta-analytic techniques for use in ConcePTION Demonstration Projects

By Prof. Joan Morris

### 1. Purpose

The purpose of this document is to suggest possible methods for use by the different demonstration projects for pooling analytic results and aggregate data from the different databases in ConcePTION.

All DPs consist of

#### Medication Utilisation and Event/Outcome Definition Study:

The aim of the medical utilisation study is to describe the frequency / quantity of prescriptions of specified medications in the database and in particular in pregnant women within the database. The aim of the event outcome definition study is to define specific algorithms to identify outcomes / events. This is likely to involve analysing prevalence of events/outcomes over time and possibly by pre-specified subgroups of interest, in particular pregnant women. But there may be additional information on, for example, groups defined according to socio-economic status

#### Medication Safety Study:

The aim is to assess the safety of specified medications in pregnancy. Safety will be assessed using a range of outcomes and confounders and mediators are likely to be included in analyses.

It is expected that both study types will use similar meta-analytic techniques to analyse their results when appropriate. However, many of the results from these studies are expected to be database specific and therefore meta-analytic techniques will not be required.

### 2. Use of Controls

When combining results from different data sources (especially if they are from different countries) it is highly recommended that all analyses include controls in order to reduce country specific differences. For example, when analysing birthweight in women taking a specific medication the birthweight of babies not exposed to the medication should be also analysed as it will vary by data source. The ideal measure to summarize across data sources would be the difference in birthweight compared to unexposed babies with a confidence interval for this difference – the difference could be on an arithmetic (the actual difference) or log scale (the proportional difference). Similarly, when analysing the occurrence of SGA, the ideal comparison would be the increased odds of SGA compared to unexposed pregnancies.

### 3. Considerations

Before combining results between countries, it is key that the effect estimates to be combined are logically comparable. The following questions should be considered before conducting any meta-analysis of effect estimates across countries:

- Are the outcome definitions being analysed by each country the same?
- Are the methods used to obtain exposure definitions comparable between countries?
- Do the countries have comparable drug utilisation profiles?
- Do the data sources being compared have any other underlying differences?

When extreme heterogeneity present between countries, it would not be advisable to produce a combined effect estimate as its interpretable value is low and may be misinterpreted by readers.

## Random Effects vs Fixed Effects

When conducting meta-analyses, most methods fall into one of two categories, fixed effect models or random effect models. Fixed effects models assume that the true effect being estimated in each country is the same. However, random effect models assume that the true effect being estimated varies between countries and so the estimates will also vary. The model accounts for this by assuming these estimates will follow a distribution around the true effect (usually a normal distribution). Which models are used should be decided prior to analysing the data.

### 4. Bias

When performing meta-analysis, it is recommended that the STATA programs metabias and metafunnel are run to examine potential bias in estimates. This may not be applicable in this situation when you are analysing data from different data sources rather than from published studies. So it is not essential to run these.

### 5. Effects of Covariates

The biggest challenge in this analysis is that it is not likely to be possible to fit individual models to the data in each data source, to examine the fit of the data and to adapt the models for each data source. As the data will vary between data sources this means that many may not have the same complete set of covariates. It will need to be decided if multivariate models can be fitted or whether adjusting for each covariate separately may provide sufficient information. If you have access to at least one data base the whole range of models can be fitted and then inferences can be made about the model fitting to other data sets.

## 6. Summary of Meta-Analysis Techniques and Procedures in STATA

### 1. **METAN – Meta-analysis of binary or continuous data with fixed or random effects and by subgroups**

metan tdeath tnodeath cdeath cnodeath

metan tsample tmean tsd csample cmean csd,

metan logor selogor

metan mean semean

metan mean lowerci upperci

metan percent lowerci upperci (see metaprop below)

### 2. **METAAN - Similar to metan, but a greater range of estimation methods and different inputs:**

metaan eff SEeff,

metaan eff effvar, varc

### 3. **METAPROP– Meta-analysis of proportions with fixed or random effects and by subgroups[1]**

(ftt Calculate the pooled estimate after Freeman-Tukey Double Arcsine Transformation)

metaprop num denom, ftt

But this has been identified as prone to errors[2] so see also GLMM procedure in STATA

### 4. **METAREG : Meta-analysis of binary or continuous data with fixed or random effects relating value(s) of each study to the observed relative risk or mean**

metareg logrr latitude, wsse(selogrr)

metareg smd abstract duration itt, wsse(sesmd) permute (10000)

**5. MVMETA : Meta-analysis of several variables simultaneously and can include regression[3]**  
mvmeta b V

b : set of variables all starting with b for example if looking at related factors such as diagnosis other maternal diseases : diabetes , epilepsy, other all as binary variables you would code them b1 , b2 and b3 and do a meta-analysis of the 3 beta's simultaneously.

**7. Additional programs in STATA**

**6. XTPOISSON : Analysing counts with random effects / mixed effects models[4]**

a. Can use small time intervals and then model risk (an event occurring within time interval) against potential confounders etc. Gives greater flexibility to use of multilevel models

b. Stsplit in STATA will create a data set of small time intervals

**7. GLST : Generalized Least Squares for trend estimation of summarized dose-response data[5, 6]**

glst depvar dose [indepvars], se(varname) cov(n cases)

Can use to model changes in log(rr) according to dose. So could have potential when looking at SES categories for instance.

**8. MEGLM: Multilevel mixed-effects generalized linear model**

These can be used to overcome the issues in METAPROP for count data and can also be specified using MELOGIT or MEPOISSON

**8. Meta-analysis of survival curves**

The analysis of survival curves is a different situation as there will be estimated probabilities of survival for a set of different time points. These probabilities are all highly correlated and hence should not ideally be analysed without including information about these correlations.

**1. Use of MVMETA**

The survival probabilities can be combined if there are only 2 or 3 time points. You may need to use the Freeman-Tukey double arcsine transformation to stabilize the variances first.

**2. Multivariate meta-analysis on conditional probabilities [7]**

MetaSurv in R does this:

i. Calculate probability survival up to fixed time points conditional on survival up to that time point as the conditioning means that the estimates are not correlated

ii. Combine these probabilities

iii. Multiply these together to get overall estimate

However, MetaSurv includes a continuity correction of 0.5, which creates bias for combining small samples sizes. SGUL are writing a program that will include a smaller continuity correction that will reduce the bias.

**3. Bayesian multivariate meta-analysis on conditional probabilities**

A Bayesian version of the method proposed by Combescure has been developed by SGUL but is currently being assessed in comparison with Frequentist variants.



## 9. Potential Issues: Mainly Small Numbers

### 1. Continuous Measures

Generally, OK particularly if analysing means as you can always estimate a mean and its se if you have at least two data points – the lack of data will usually be reflected in the variance. However, if you only have two data points and they are extremely close then the variance may be very low. You do need to examine all your data carefully.

### 2. Proportions and Odds Ratios

This can be very problematic as you may have no events and hence 0 in specific cells. Many programs either drop all data from that database or else automatically insert a 0.5 and carry on. You need to check what is happening with this. If there are several databases with this issue it may have a large effect on your overall estimates. There is a difference between medication not being prescribed in a country and hence no events with exposure for that medication in the country with no events occurring when the medication is being prescribed. The FTT transformation in METAPROP may introduce bias especially if your databases vary greatly in size.

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concePTION  
SAFETY EVIDENCE ECOSYSTEM

Protocol for DP 1.2

# Exposure to SSRI/SNRI and depression in pregnancy and long-term childhood outcomes: the effect of modifying factors.

This study will be conducted within the ConcePTION project of the Innovative Medicines Initiative under grant agreement No 821520.

<b>Project leaders</b>	Maria Loane, Florence Coste
<b>Authors</b>	Joanne Given, Florence Coste, Maria Loane
<b>Protocol version</b>	1.0
<b>Protocol date</b>	01/10/2021

## Table of contents

<b>1. List of abbreviations .....</b>	<b>6</b>
<b>2. Responsible parties .....</b>	<b>8</b>
<b>3. Abstract.....</b>	<b>9</b>
<b>4. Amendments and updates .....</b>	<b>11</b>
<b>5. Milestones .....</b>	<b>11</b>
<b>6. Rationale and background .....</b>	<b>12</b>
<b>7. Research question and objectives .....</b>	<b>15</b>
<b>Part 1. Develop algorithms to identify exposures and outcomes .....</b>	<b>15</b>
<b>Part 2. Medication utilisation study .....</b>	<b>17</b>
<b>Part 3. Medication safety study .....</b>	<b>18</b>
<b>8. Research methods .....</b>	<b>18</b>
<b>8.1. Study design .....</b>	<b>18</b>
<b>8.2. Setting .....</b>	<b>19</b>
Study period .....	21
Study population .....	22
<b>8.3. Variables .....</b>	<b>25</b>
Exposure definition .....	25
Exposure window .....	28
Outcomes of utilisation study.....	30
Outcomes of the Safety cohort and cross-sectional studies .....	33
<b>Part 2 (Medication utilisation): Co-variables.....</b>	<b>34</b>
<b>Part 3 (Medication safety) Co-variables: confounders, mediators, moderators .....</b>	<b>34</b>
Child factors .....	36
<b>8.4. Data sources .....</b>	<b>36</b>
<b>8.5. Study size .....</b>	<b>41</b>
<b>8.6. Data management.....</b>	<b>41</b>
<b>8.7. Data analysis.....</b>	<b>41</b>
Descriptive analysis .....	45
Primary analysis.....	45
Comparison groups.....	45
Analysis of Time varying confounders .....	46
Sub-analyses .....	47
Missing data .....	48
Sensitivity analyses .....	48
Breastfeeding sub-study.....	50
Valproic acid .....	51
<b>8.8. Quality control .....</b>	<b>52</b>
<b>8.9. Limitations .....</b>	<b>54</b>
Ascertainment of exposure .....	54
Ascertainment of disease and disease severity .....	54

Limited/missing covariate information .....	55
Study power .....	55
<b>9. Other aspects .....</b>	<b>57</b>
Ethical considerations .....	57
<b>10. Protection of human subjects .....</b>	<b>57</b>
<b>11. Management and reporting of adverse events/adverse reactions .....</b>	<b>58</b>
<b>12. Plans for disseminating and communicating study results .....</b>	<b>58</b>
<b>13. References .....</b>	<b>60</b>
Appendix 1 Directed acyclic graphs showing confounding and time varying confounding .....	66
Appendix 2 Identification of maternal depression .....	67
Appendix 3 Attention Deficit Hyperactivity Disorder (ADHD) .....	80
Appendix 4 Autistic Spectrum Disorders .....	82
Appendix 5 Learning disability or disorders of intellectual development .....	87
Appendix 6 EFEMERIS/POMME developmental assessments .....	92
Appendix 7: List of teratogenic medications .....	93
Appendix 8 Information items of interest to this project .....	94
Appendix 9 Subtask 1.3.3 – Neurodevelopment .....	96
Appendix 10 Subtask 1.3.7 - Breastfeeding .....	122
Appendix 11 Medication, ATC code and P-gp or BCRP substrates (S) or inhibitors (I) status .....	140
Appendix 12 Covariates available across data sources .....	144
Appendix 13 Meta Analytic Techniques for use in ConcePTION .....	146
Appendix 14 SSRI/SNRI signal anomalies identified in the literature .....	150
Appendix 15 ENCePP checklist for study protocols .....	156

## PASS information

Title	Exposure to SSRI/SNRI and depression in pregnancy and long-term childhood outcomes: the effect of modifying factors
Protocol version identifier	1.3
Date of last version of protocol	01 October 2021
EU PAS register number	“Study not registered yet”
Active substance	N06AB03, N06AB04, N06AB05, N06AB06, N06AB08, N06AB10, N06AX16, N06AX17, N06AX21, N06AX23.
Medicinal product	(included as main exposure) Fluoxetine, citalopram, Paroxetine, Sertraline, Fluvoxamine, Escitalopram, Venlafaxine, Milnacipran, Duloxetine, and Desvenlafaxine.
Product reference	N/A
Procedure number	N/A
Marketing authorisation holder(s)	N/A
Joint PASS	No
Research question and objectives	<p>This study is based on electronic health care data from health care databases in six European countries and congenital anomaly registry data from 14 countries between 1995 and 2019. The primary objectives are to:</p> <ol style="list-style-type: none"> <li>1) develop algorithms to identify and validate maternal depression, neurodevelopmental outcomes and breastfeeding in healthcare data sources.</li> <li>2) describe patterns of SSRI/ SNRI antidepressant use before, during, and after pregnancy and during lactation. This includes describing co-medication patterns, predictors of discontinuation, switching patterns, and trajectories of use over time.</li> <li>3) assess the association between in utero exposure to SSRI / SNRIs and neurodevelopmental outcomes and major congenital anomalies (CA). It will examine the potential additional impact of maternal depression, breastfeeding and concomitant exposure to P-gp or BCRP transporter substrates/inhibitors on risk of major CAs and neurodevelopmental outcomes in children.</li> </ol>
Country(-ies) of study	Finland (Nationwide), France (Haute-Garonne), Germany (Nationwide sample), Italy (regional: Tuscany and E. Romagna), Norway (Nationwide), UK (Wales), and pan-European (EUROmediCAT) – <i>pending on results from the data characterisation (WP7).</i>

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## **1. List of abbreviations**

AD Antidepressant

ADHD Attention deficit hyperactivity disorder

AED Antiepileptic drug

ASD Autism spectrum disorders

ATC Anatomical Therapeutic Chemical

BCRP Breast Cancer Resistance Protein

BMI Body Mass Index

CA Congenital Anomaly

CDM Common Data Model

DAG Directed Acyclic Graph

DAP Data Access Provider

DDD Defined Daily Dose

DSM-V Diagnostic and Statistical Manual of Mental Disorders 5<sup>th</sup> Edition

EFEMERIS Evaluation chez la Femme Enceinte des MEDicaments et de leurs RISques

ENCePP European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ETL Extract, Transform, and Load

FDA Food and Drug Administration

GDPR General Data Protection Regulation

GePaRD German Pharmacoepidemiological Research Database

HPA Hypothalamic–Pituitary–Adrenal

HV Health Visitor

ICD International Classification of Diseases

ID Intellectual development

IMD Index of Multiple Deprivation

IMI Innovative Medicines Initiative

IPTW Inverse-Probability-of-Treatment Weighting

LMP Last Menstrual Period

MCA Major Congenital Anomalies

MPR Medication Possession Ratio

NCARDS National Congenital Anomaly and Rare Disease Registration Service

OHDSI Observational Health Data Sciences and Informatics

P-gp P-glycoprotein

PDC Percent Days Covered

POMME PrescriptiOn Médicaments Mères Enfants

RWD Real World Data

RWE Real World Evidence

SAP Statistical Analysis Plan

SES Socioeconomic status

SGA Small for Gestational Age

SNRI Serotonin-Norepinephrine Reuptake Inhibitor

SSRI Selective Serotonin Reuptake Inhibitor

TOPFA Terminations of Pregnancy for Fetal Anomaly

WCBA Women of Child-Bearing Age



## **2. Responsible parties**

DP leads: Maria Loane and Florence Coste

Postdoc researcher: Joanne Given

Team: Rebecca Bromley, Sue Jordan, Sandra Lopez-Leon, Heli Malm, Helen Dolk.

Development of algorithms: Elsie Grace, Anasofia Afonso

WP7 representatives: Claudia Bartoloni, Olga Paoletti (SAP review, R coding and SAP analytics)

Statistical expert: Joan Morris

Data Access Providers (DAPs):

- Finland, Finnish Registries: Maarit Leinonen, Visa Martikainen and Mika Gissler
- France, EFEMERIS and POMME: Christine Damase-Michel and Anna-Belle Beau
- Germany, GePaRD, Leibniz Institute for Prevention Research and Epidemiology – BIPS (BIPS): Tania Schink
- Italy, Agenzia Regionale di Sanita, ARS, Tuscany: Rosa Gini\*
- Italy, Emilia Romagna: Amanda Neville and Elisa Ballardini
- Italy, Tuscany CA registry: Anna Pierini and Alessio Coi
- Norway, Norwegian Registries: Hedvig Nordeng and Angela Lupattelli
- Spain, Valencian Region: Clara Caverio
- UK, Wales (SAIL): Sue Jordan, Daniel Thayer
- Europe, EUROmediCAT Central Database: Maria Loane

Data from the following DAPs may be included in this study pending the availability of data:

- UK, Public Health Scotland: Rachel Wood and Marion Bennie

\* Protocol review lacking

Due Date (Month 27)

Version 1.0 (01 October 2021)

### 3. Abstract

Title: Exposure to SSRI/SNRI and depression in pregnancy and long-term childhood outcomes: the effect of modifying factors

Rationale and background:

Approximately, 10-20% of pregnant women suffer from depression and 4-10% use selective serotonin reuptake inhibitor (SSRI) antidepressants during some stage of pregnancy. There is conflicting evidence regarding the risk of congenital anomalies and long-term neurodevelopmental outcomes such as autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) associated with in utero exposure to SSRI and serotonin and norepinephrine reuptake inhibitors (SNRI). Existing studies in the literature often lack the power to assess the effect of time varying confounders such as variation in maternal disease status, breastfeeding, and transient or chronic interactions with other medications on risk of adverse outcomes, and few examine other aspects of neurodevelopment. This study will help create evidence-based clinical guidelines on risks and benefits of antidepressant treatment in pregnancy.

Research question and objectives:

This study has 3 parts. Part 1 will develop algorithms to identify and validate maternal depression, neurodevelopmental outcomes and breastfeeding in healthcare data sources for use in the **medication utilisation study** (Part 2) and in the **medication safety study** (Part 3).

The objective of the **medication utilisation study** (Part 2) is to describe patterns of SSRI/SNRI medication use before, during, and after pregnancy and during lactation. This includes describing co-medication patterns, predictors of discontinuation, switching patterns, and trajectories of use over time.

The objective of the **medication safety study** (Part 3) is to assess the association between in utero exposure to SSRI / SNRIs and neurodevelopmental outcomes. It will examine the potential additional impact of maternal depression, breastfeeding and concomitant exposure to P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) transporter inhibitors/substrates on neurodevelopmental outcomes in children. A second objective is to perform a **EUROmediCAT safety study** to assess the risk of major congenital anomalies associated with exposure to SSRI / SNRIs in the first trimester of pregnancy, and to evaluate the impact of co-medication with P-gp or BCRP transporter substrates on risk.

Study design

**Medication utilisation and safety studies:** These studies are multinational cohort studies using secondary data sources.

**EUROmediCAT safety study:** This is a case-malformed control study.

Population

**Medication utilisation and safety studies:** The study population will be all pregnant women aged between 15 and 49 years during the study period in each European data source contributing to these studies.

Sub-studies will include all women of child-bearing age, aged between 15 and 49 years, during the study period in European data sources with this information.

**EUROmediCAT safety study:** All live births, fetal deaths from 20 weeks gestational age and terminations of pregnancy for fetal anomaly (TOPFA) with a major congenital anomaly recorded in each registry/ health care database contributing to this study.

Variables:

**Disease:** Depression

**Exposure:** SSRI/SNRI antidepressants prescribed or dispensed during the exposure windows of interest.

P-gp and BCRP substrate and inhibitor status of individual SSRI/SNRI antidepressants. Valproic acid (positive control).

All medications will be identified using the Anatomical Therapeutic Chemical classification system (ATC).

**Outcomes:** Neurodevelopmental outcomes (ADHD, ASD, Learning disability/intellectual development disorders and delayed infant language/motor development).

Major congenital anomalies (overall and by organ system).

**Covariates:** Maternal age at birth, calendar year of birth, parity, maternal marital status (if available), socioeconomic status, maternal education, maternal occupation, smoking status at start of pregnancy (if available), breastfeeding (if available), co-medications and co-morbidities.

Data sources:

The **medication utilisation and safety studies** are based on electronic health care data from health care databases in six European countries: Finland (Nationwide), France (Haute-Garonne), Germany (Nationwide sample), Italy (regional: Tuscany and Emilia Romagna), Norway (Nationwide) and UK (Wales).

The **EUROmediCAT safety study** is based on data from 17 registries and 3 healthcare databases in 14 European countries.

Study size:

We estimate that the six data sources contributing to the **medication utilisation study** will include 5.6 million pregnancies with medication exposures in the study period and over 6 million births, between 1996 and 2019.

In the **medication safety study**, power calculations show that if 1% of women use SSRI/SNRIs during pregnancy, we would require a sample size of around 360,000 children to detect a 50% increased risk for ASD/intellectual development disorders; and a sample size of 68,000 children to detect a 50% increased risk for ADHD. If 5% of women use SSRI/SNRIs during pregnancy, we would require a sample size of around 75,000 children to detect a 50% increased risk for ASD/intellectual development disorders, and a sample size of 14,000 children to detect a 50% increased risk for ADHD.

In the **EUROmediCAT safety study**, we estimate that we will have over 300,000 congenital anomaly cases (live births, fetal deaths from 20 weeks gestational age, and TOPFA), between 1995 and 2019.

Data analysis:

**Medication utilisation studies:** We will estimate the prevalence of medications used to treat depression among pregnant women 3 months before, during, and 3 months after pregnancy

and the prevalence in women of childbearing age. We will also provide prevalence estimates of placental transporter substrate and inhibitor co-medications during pregnancy. We will describe breastfeeding in a subset of the study population (defined by data availability) in relation to use of SSRI/SNRIs up to 1 year of age.

**Medication safety studies:** We will estimate the risk of adverse neurodevelopmental outcomes up to a maximum age of 18 following exposure to SSRIs/SNRIs during pregnancy. The women exposed to SSRIs/SNRIs during pregnancy will be compared with 2 main comparator groups:

- women who discontinued antidepressants (+/- a diagnosis of depression) at least three months before pregnancy or who had a depression diagnosis with no exposure to antidepressants before or during pregnancy (unmedicated disease comparator)
- women with no history of depression or mental health medications.

Each DAP will conduct univariate and multivariate logistic, poisson, or linear regression, Kaplan-Meier or Cox proportional hazards regression with robust standard errors as appropriate. Analysis will also include advanced confounder adjustment methods such as marginal structural models. We will use appropriate meta-analytic methods to pool effect estimates using random-effects models. The meta-analyses on aggregate data will allow for adjustment for country-optimized covariates.

**EUROlinkCAT safety study:** A case-malformed control analysis will be performed to estimate the risk (odds ratio) of a specific anomaly associated with first trimester exposure to SSRIs/SNRIs.

#### 4. Amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1	Date	Text	Text	Text
...	Date	Text	Text	Text

#### 5. Milestones

Milestone	Planned date
Registration in the EU PAS register	October 2021
Study progress report 1 (Internal) –Final list of DAPs included in study; Part 1 results	March 2022
Statistical Analysis Plan (SAP)	April 2022
Study progress report 2 (Internal) -Part 2 results; Interim results for Part 3	March 2023
Final report of study results	March 2024

## 6. Rationale and background

The study described in this protocol is performed within the framework of the IMI project ConcePTION (<https://www.imi-conception.eu/>) Work package 1, Task 1.5. The core goal of Work Package 1 is to develop methods for better use of routinely collected healthcare data. The goal of Task 1.5 is to execute five demonstration projects (DP) for established and newly marketed products to tackle methodological or data source issues where progress and innovation are needed. This protocol addresses Demonstration project #1.2.

### Serotonin and brain development

Approximately 10-20% of pregnant women suffer from depression and 1-10% use selective serotonin reuptake inhibitor (SSRIs) or serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants during some stage of pregnancy (Gorman, Kao and Chambers, 2012; Charlton *et al.*, 2015; Zoega *et al.*, 2015; Molenaar *et al.*, 2020). SSRIs/SNRIs pass through the placenta (Hendrick *et al.*, 2003; Rampono *et al.*, 2009; Merwood *et al.*, 2014; Pogliani *et al.*, 2017) and appear in cord blood (Laine *et al.*, 2003; Salisbury *et al.*, 2009) in proportion to the dose administered (Hendrick *et al.*, 2003).

Serotonin plays an important role in neurogenesis (Sodhi and Sanders-Bush, 2004). It has been suggested that prenatal exposure to SSRIs could potentially alter the development of the neuronal architecture, manifesting as poorer neurodevelopmental outcomes including cognitive and behavioural disorders in childhood, adolescence, or adulthood (Migliarini *et al.*, 2013; Sprowles *et al.*, 2016; Gingrich *et al.*, 2017). This may be the mechanism underlying delays in fine motor development at 3 years (Handal *et al.*, 2016) or autistic-like behaviours secondary to increased serotonin post-partum (Gemmell *et al.*, 2018), although research evidence has not been consistent. Prenatal exposure to SSRIs may also affect monoamine metabolism in the foetus, resulting in neonatal problems such as restlessness, tremor and incoordination (Laine *et al.*, 2003; Sprowles *et al.*, 2016). Epigenetic changes, activation of the hypothalamic–pituitary–adrenal (HPA) axis and transfer of cortisol and other mediators to the foetus are associated with both maternal depression and antidepressants (Kendall-Tackett and Hale, 2010; Gentile and Fusco, 2017) and their impacts on neurodevelopment are difficult to disentangle (Gemmell *et al.*, 2018).

Assessments of neurodevelopmental harms associated with exposure to antidepressants during foetal life are largely derived from observational cohort studies which collect primary data and population-based cohort studies using secondary data. Both have inherent methodological limitations. Traditional observational cohort studies recruit pregnant women with depression directly within hospital or community-based health care settings and the participants are followed up using study-specific standardised protocols often utilising sensitive assessments, administered in a blinded fashion (Hanley, Brain and Oberlander, 2015). However, such methodologies often offer low statistical power to detect adverse neurodevelopmental outcomes, and short follow-up periods (typically only up to pre-school age). The latter is a major limitation as brain development continues into adolescence, and some functions cannot be assessed until children have reached an age where more complex tasks are demanded. Cohorts derived from population-based electronic records alternatively, offer large numbers of exposed children often across a broader range of maternal indications and may follow children to adolescence. The use of such data poses a methodological challenge however, due to a reliance on diagnostic codes or service referrals (Mansournia *et al.*, 2017a) and multiple assessors who may not be blinded to the medication exposure history of the child.

A recently published systematic review of the literature on human studies on neurodevelopmental outcomes after prenatal medication exposures found highly

inconsistent results (Hjorth *et al.*, 2019): some link antidepressants to adverse neurodevelopmental outcomes such as attention deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASD) and motor- and cognitive dysfunction. Others do not, and have attributed observed effects to the underlying illness, other residual confounding, differences in study populations, sample heterogeneity or short follow-up time. Specifically, there is conflicting evidence regarding the risk of ASD (Kobayashi *et al.*, 2016; Brown *et al.*, 2017; Mezzacappa *et al.*, 2017; Sujan *et al.*, 2019), ADHD (Morales *et al.*, 2018; Uguz, 2018; Halvorsen *et al.*, 2019) motor and language skills (Rotem-Kohavi and Oberlander, 2017) associated with in utero exposure to SSRIs. Conflicts are likely due to the methodological variation observed across different studies. For example, even in large population-based datasets it is important that children should have been followed up long enough for outcomes to be measured/identified and the average age of diagnosis may vary across countries. The follow-up period should be at least 2 years for infant psychomotor outcomes and at least 7 years, and preferably 12 years, for ADHD (to cover the time period when most children are diagnosed with ADHD). However, the longer the follow up period, the smaller the available study population with the required years of follow up data. Conversely, a shorter follow-up period may lead to bias towards the more severe cases.

### Time varying confounders

The conflicting evidence to date for neurodevelopmental outcomes may in part be explained by time varying confounders such as variation in recording of maternal disease status, breastfeeding, and transient or chronic interactions with other medications. Underlying maternal mental illness in pregnancy and/or the postpartum period has been shown to be associated with suboptimal behavioural, cognitive, and socio-emotional development in the child (Field, 2011; Kingston, Tough and Whitfield, 2012; Kingston and Tough, 2014; Kobayashi *et al.*, 2016; Kaplan *et al.*, 2017; Wood *et al.*, 2018; Halvorsen *et al.*, 2019). Both maternal depression and SSRIs/SNRI use may alter and even resolve over time (Lupattelli *et al.*, 2018), hence maternal depression has the potential to be a time-varying confounder (Mansournia *et al.*, 2017b).

Directed acyclic graphs (DAG) showing confounding and time varying confounding are shown in Appendix 1. There are two distinct types of time-varying confounders: (1) time-varying confounding not affected by prior treatment, and (2) time-varying confounding affected by prior treatment (Burcu and Oehrlein, 2016). Conventional statistical methods can introduce bias in the presence of time varying confounding (Mansournia *et al.*, 2017b) particularly time-varying confounding affected by prior treatment (Burcu and Oehrlein, 2016). This can happen due to over-adjustment bias, which occurs as a result of blocking the effect of past exposure on outcome, mediated through later confounders, leading to a downward bias (underestimation of the effect) and selection (also known as collider stratification) bias, which occurs by inappropriately adjusting for a time varying confounder that may share a common cause with the outcome (Mansournia *et al.*, 2017b).

### Effects of breastfeeding

It has been reported that children who were breastfed, particularly those breastfed for at least 6 months, when compared with children never breastfed, have lower rates of ADHD (Orsolini and Bellantuono, 2015), lower rates of ASD diagnosis (Al-Farsi *et al.*, 2012; Ravi *et al.*, 2016; Cheng *et al.*, 2019; Tseng *et al.*, 2019; Ghozy *et al.*, 2020), better cognitive outcomes (Orsolini and Bellantuono, 2015), higher IQ (Kramer *et al.*, 2008; Horta, de Sousa and de Mola, 2018), higher school achievement, and higher income in adulthood (Horta, de Sousa and de Mola, 2018). This effect persists after controlling for maternal IQ (Horta, Loret De Mola and Victora, 2015). Women with major depressive disorder who take antidepressants during pregnancy are less likely to intend to breastfeed and to initiate

breastfeeding (Gorman, Kao and Chambers, 2012; Lewis *et al.*, 2016; Leggett *et al.*, 2017) which may result in risk of poorer outcomes for their children. Furthermore, for women who continue to take SSRIs/SNRIs while breastfeeding there is the potential for the child to be exposed through breastmilk by an average of 3-5% (with a maximum of 10%) of maternal dose (Merlob and Schaefer, 2015). Unmedicated depression is also associated with increased exclusive formula feeding at 6-8 weeks (Jordan *et al.*, 2019). Breastfeeding therefore has potential to be both a confounding factor and a mediator for neurodevelopment in relation to maternal depression and SSRI/antidepressant use (Jordan *et al.*, 2021).

#### Effect of co-medications

A further factor which may alter levels of SSRI exposure in the womb is commonly used medications which may interact with placental passage of SSRIs. P-glycoprotein (P-gp, encoded by ABCB1 gene) and breast cancer resistance protein (BCRP, encoded by ABCG2 gene) are considered the two most important efflux medication transporters in the human placenta, restricting transfer of medications that are substrates for these transporters from mother to foetus. Their presence in the placenta suggests an important barrier function, preventing medications from entering the fetal circulation and protecting the foetus from exogenous chemicals. The function of these efflux transporters is inhibited by several medications which are commonly used during pregnancy (proton pump inhibitors, several antihistamines and macrolide antibiotics, among others) (Ellfolk *et al.*, 2020). Concomitant use of SSRIs or SNRIs that are transporter substrates with these inhibitors may increase fetal exposure to the antidepressant. As teratogenesis is a dose dependent phenomenon, higher exposure to a potentially harmful agent may result in an increased risk of fetal adverse effects (Jelínek, 2005). While little is known about the clinical significance of placental transporter protein mediated medication interactions, recent research suggests that these interactions may be associated with an increased risk of congenital anomalies (CA) (Ellfolk *et al.*, 2020). The impact of placental transporter protein mediated medication interactions on a range of neurodevelopmental outcomes is not known.

First trimester exposure to SSRIs and SNRIs has been associated with increased risk of major congenital anomaly (MCA), particularly severe cardiac defects (Myles *et al.*, 2013; Bérard *et al.*, 2016; Zhang *et al.*, 2017; Gao *et al.*, 2018). The evidence is conflicting however (Wang *et al.*, 2015) and evidence for an impact of placental transporter mediated proteins would contribute to the evidence base.

#### Determinants of antidepressant use

Age, sex and socioeconomic factors, such as education and income, as well as the interaction between these factors, can influence patient health and well-being and have an impact on access to, and use of, health care services and prescription drugs (Elseviers *et al.*, 2016). A study in Norway reported that apart from education level of parents, all indicators of low socioeconomic status were related to higher rates of antidepressant prescription, which could be due to the association of low socioeconomic status with higher levels of anxiety and depression (von Soest *et al.*, 2012). A study in Finland collected data on living arrangements and concluded that people who live alone were more likely to have material and psychosocial problems, which might have contributed to excess mental health problems in this population group (Pulkki-Råback *et al.*, 2012). Several sociodemographic and lifestyle factors have been associated with antidepressant use in pregnancy. These include age, maternal smoking habits, ethnicity, educational level, marital status, occupation, geographic region of residence, country of residence, parity, body weight and social class (Elseviers *et al.*, 2016); and heavy alcohol use and substance misuse referral (Jordan *et al.*, 2016).

Other determinants relate to the health care systems within countries, disease patterns, types of antidepressants used, prescribing guidelines issued by professional associations, pharmaceutical marketing practices, reimbursement/financing systems and the availability of non-pharmaceutical alternatives.

This Demonstration Project will help create evidence-based clinical guidelines on risks and benefits of antidepressant treatment in pregnancy and to establish appropriate methods for dealing with confounders/moderators in relation to long term neurodevelopmental outcomes.

## **7. Research question and objectives**

The project will be organized in three parts:

- **Part 1.** Develop algorithms to identify exposures and outcomes
- **Part 2.** Medication utilisation study
- **Part 3.** Medication safety study

The results from Part 1 will inform Parts 2 and 3.

### ***Part 1. Develop algorithms to identify exposures and outcomes***

**Part 1** will develop algorithms to identify and validate maternal depression, neurodevelopmental outcomes and breastfeeding in healthcare data sources for use in Parts 2 and 3. As the study uses secondary data it is not possible to use a gold standard when evaluating algorithms. Instead, where available, results will be compared to relevant published prevalence rates.

#### **Maternal depression**

Aims:

1. To compare a range of algorithms to identify depression before, during and after pregnancy.
2. To determine how the prevalence of depression varies in the pre-pregnancy, pregnancy and post-natal periods based on the algorithms used to identify depression.

Maternal depression will be identified based on the following codes (see Appendix 2):

- ICD-9: Major Depressive Disorder, single episode (296.2), Major Depressive Disorder, recurrent episode (296.3), Dysthymic Disorder/neurotic depression (300.4) Depressive Disorder not elsewhere Classified (311), Mental disorders complicating pregnancy childbirth or the puerperium (648.4).
- ICD-10: depressive episode (F32), Recurrent depressive disorder (F33), dysthymia (F34.1), mixed anxiety and depressive disorder (F41.2), postnatal/postpartum depression (F53.0).
- ICPC2: It is not possible to distinguish those who had just depression in ICPC2. Depressive disorder code includes depressive neurosis/psychosis; mixed anxiety and depression; puerperal/postnatal depression; reactive depression) (P76).
- Read codes: depression diagnosis, symptom and review codes.



## Neurodevelopmental outcomes

Aim: Develop algorithms to identify neurodevelopmental outcomes.

The neurodevelopmental outcomes included in this demonstration project are based on work in ConcePTION Task 1.2 (Damase-Michel *et al.*, 2020) and will be finalised following assessment of their validity (**Part 1**) and quality and completeness (WP7 data characterisation). The neurodevelopmental outcomes of interest are:

1. ADHD: characterized by a persistent pattern (at least 6 months) of inattention and/or hyperactivity-impulsivity, with onset during the developmental period, typically early to mid-childhood (World Health Organisation, 2021). This will be based on:
  - ICD-10, ICD-9, ICPC-2 or Read codes (see Appendix 3)
  - Childhood medication use: Stimulant medication use will be used as a surrogate for ADHD diagnosis (Wong *et al.*, 2019): amphetamine/amfetamine (N06BA01), dexamfetamine sulfate (N06BA02), Methylphenidate (N06BA04), atomoxetine (N06BA09), dexamethylphenidate (N06BA11), lisdexamfetamine (N06BA12), guanfacine (C02AC02) and racemic amphetamine sulfate.
2. ASD: characterized by persistent deficits in the ability to initiate and to sustain reciprocal social interaction and social communication, and by a range of restricted, repetitive, and inflexible patterns of behaviour and interests (Ousley and Cermak, 2014; Masi *et al.*, 2017).
  - ICD-10, ICD-9, ICPC-2 or Read codes (see Appendix 4 ).
3. Learning disability or intellectual development (ID) disorders: characterized by significantly below average intellectual functioning and adaptive behaviour that are approximately two or more standard deviations below the mean (approximately less than the 2.3rd percentile), based on appropriately normed, individually administered standardized tests (Centers for Disease Control and Prevention, 2020).
  - ICD-10, ICD-9, ICPC-2 or Read codes (see Appendix 5).
4. Delayed infant development:
  - Motor developmental outcomes assessed at 24 months in France (EFEMERIS/POMME), (see Appendix 6).
  - Locomotion, manipulation, behaviour and speech development assessed by health visitors at 27-30 months - Wales.
  - Gross motor skills, fine motor skills, language, perception/cognition, social/emotional competence or interaction/communication problems if coded, e.g., based on 'early detection examinations', which are recommended and in some federal states mandatory, at 21-24 months using ICD codes – GePaRD.

Objectives:

- a) To identify ADHD, ASD, ID disorders and delayed infant development in data sources
- b) To characterise the outcomes by type of measurement used to assess neurodevelopment.
- c) To calculate annual background prevalence of the ADHD, ASD, ID disorders and delayed infant development in each of the specific datasets.
- d) To calculate the distribution of age of diagnosis or measurement in each of the specific datasets.

## **Breastfeeding**

### **Aims:**

1. Examine the availability, status, provenance and validity of breastfeeding data at any postnatal age in the databanks used in the demonstration projects.
2. Investigate selected factors associated with breastfeeding status including specified prescription medications and diagnoses.

### **Objectives:**

- a) Examine the availability, status, provenance and validity of breastfeeding data at any postnatal age in the DAPs used in this demonstration project
- b) Report on the definitions and terminology used when recording infant feeding in each data source.
- c) Compare breastfeeding rates and other data with external sources.

## ***Part 2. Medication utilisation study***

**Part 2** will describe patterns of SSRI/ SNRI medication use before, during, and after pregnancy and during lactation. This includes describing co-medication patterns, predictors of discontinuation, switching patterns, and trajectories of use over time.

### **Research Questions:**

1. What are the maternal characteristics associated with SSRI/ SNRI antidepressant medication use in pregnancy?
2. What are the predictors of SSRI/ SNRI antidepressant medication discontinuation?
3. What medications are commonly used concomitantly with SSRI/ SNRI antidepressants (co-prescriptions)?
4. How does SSRI/ SNRI antidepressant medication prescribing / dispensing change over the course of pregnancy and lactation?

### **Objectives:**

- a) determine the prevalence of recorded diagnoses of depression in women before, during, and after pregnancy. We expect the time window to be 12 months before and 12 months after pregnancy, but this is dependent on the findings from Part 1.
- b) describe the pattern of SSRI and SNRI use in women 3 months before, during, and 3 months after pregnancy.
- c) describe variation in prevalence of depression and SSRI/SNRI use by DAP, and by maternal characteristics such as age, parity, socioeconomic and/or educational status (where available) and trends over time in pregnant women.
- d) describe patterns of P-gp or BCRP transporter substrates used concomitantly with SSRIs/SNRIs in women 3 months before, during, and 3 months after pregnancy.
- e) identify predictors of SSRI and SNRI medication discontinuation.

In data sources with information on women of childbearing age (WCBA):

- i. describe the incidence of pregnancy among WCBA using the medications of interest.
- ii. describe the pattern of SSRI and SNRI use in WCBA
- iii. describe patterns of breastfeeding in the study population in relation to use of SSRI/SNRIs up to 1 year of age.

### ***Part 3. Medication safety study***

**Part 3** will assess the association between in utero exposure to SSRI / SNRIs and a) neurodevelopmental outcomes and b) major congenital anomalies (MCA). It will examine the potential additional impact of maternal depression, breastfeeding and concomitant exposure to P-gp or BCRP transporter substrates or inhibitors on neurodevelopmental outcomes in children. It will also examine the potential additional impact of P-gp or BCRP transporter substrates/inhibitors on risk of MCA.

#### Research Questions

Is SSRI/SNRI medication exposure during pregnancy associated with increased risk of adverse neurodevelopmental outcomes or MCA in children?

#### Objectives:

- a) Is prenatal exposure to SSRIs / SNRIs 3 months before and during pregnancy associated with an increased risk of ASD, ADHD, ID disorders or delayed infant language or motor development in children, after taking into account maternal depression during and after pregnancy, and breastfeeding status (at 4-8 weeks).
- b) whether comedication with prescribed P-gp or BCRP transporter substrates (S) or inhibitors (I) affects the risk of ASD, ADHD, ID disorders and delayed infant language and motor development.
- c) whether in utero exposure to SSRI and SNRIs in the first trimester of pregnancy is associated with an increased risk of MCA, subgroups of MCA and signal anomalies identified in the literature and if there is additional impact of co-medication with P-gp or BCRP transporter substrates/inhibitors
- d) investigate factors putatively associated with breastfeeding status including specified prescription medications and diagnoses.
- e) whether prenatal exposure to SSRIs and SNRIs is associated with an increased rate of exclusive formula feeding after taking into account maternal depression during and after pregnancy and relevant covariates, using a subsample of data sources.

## **8. Research methods**

### ***8.1. Study design***

**Part 1 Develop algorithms:** Algorithms will be developed to identify and validate data in the data sources contributing to this demonstration project.

**Part 2 Medication utilisation study:** Non-interventional longitudinal cohort study conducted with secondary data obtained from population-based registries, electronic medical records, or administrative healthcare databases in different European countries.

#### **Part 3 Medication safety study:**

**Cohort study:** A multinational European retrospective cohort study using secondary data sources.

**Case-control study, with malformed controls:** A multinational European case-control study, with malformed controls, using the EUROMediCAT central database and three health care databases.

## **8.2. Setting**

**In Part 1: Develop algorithms**, validation of neurodevelopmental outcomes and depression diagnoses will be conducted on data sources from the following six countries: Finland, France, Germany, Italy, Norway, and UK (Wales). Breastfeeding data will be characterised in France (Haute-Garonne), Italy (Tuscany) and the UK (Wales) (**Table 1**).

Results of data validation and data characterisation (WP7) will determine the optimal combination of data years/ data sources to be included in the drug utilisation and safety studies.

**In Part 2: Medication utilisation study**, data from the following six countries will be included: Finland, France, Germany, Italy, Norway, and UK (Wales). The analysis of WCBA will be limited to data from Italy, Germany, Norway, UK, and the analysis of breast-feeding data will be limited to France, Italy (Tuscany) and Wales, UK, **Table 1**.

**In part 3: Medication safety study**, the cohort study on neurodevelopmental outcomes will include data from six countries (Finland, France, Germany, Italy, Norway, and UK), (**Table 1**). The sub-study exploring the impact of breastfeeding as a mediator/confounder will be conducted in three countries with neurodevelopmental and breastfeeding data: France, Italy (Tuscany) and the UK (Wales), **Table 1**. The **case-malformed control study** will use data from 17 EUROMediCAT congenital anomaly registries, and three health care databases (the English National Congenital Anomaly and Rare Disease Registration Service (NCARDRS), Sweden and France (EFEMERIS)) covering 14 countries, see Table 2.

**Table 1** Region, number of pregnancies and availability of data on medication exposures, depression, neurodevelopmental outcomes and breastfeeding (pending data characterisation results)

Region	Pregnancies per year (1,000)	Pregnancies with medication exposure in period covered (1,000)	Medication exposure <sup>1</sup> (Utilisation and safety studies)	Depression diagnosis (Validation, utilisation, safety <sup>2</sup> )	Neurodevelopmental outcomes <sup>2</sup> (Validation, and safety studies)	Breast-feeding data (Validation, utilisation and safety studies)
			Years with available data			
Finland <sup>3</sup>	53	1,575	1996-2019	1996-2019	1996-2019	-
France Haute-Garonne (EFEMERIS) <sup>3</sup>	10	156	2004-2019	2004-2019	2004-2019	2004-2019
France Haute-Garonne (POMME) <sup>3</sup>	10	18	2010-2019 cohort 2015-2019 cohort	July 1 <sup>st</sup> , 2010 - June 30 <sup>th</sup> , 2011 July 1 <sup>st</sup> , 2015 - June 30 <sup>th</sup> 2016	2010-2019 cohort 2015-2019 cohort	2010-2019 cohort 2015-2019 cohort
Germany, GePaRD <sup>4</sup>	135	1,200	2006-2019	2004-2019	2006-2019	-
Italy Emilia Romagna	36	573	2004-2019	2004-2019	2010-2019	-
Italy Tuscany	30	480	2003-2019	2003-2019	2010-2019	2003-2019
Norway	60	890	2004 -2019	2008-2019	2008 -2019	-
Wales	33	726	1998-2020	2000-2020 <sup>5</sup>	2000-2020	2005-2020

<sup>1</sup> Maternal medication or child ADHD medication.

<sup>2</sup> Primary care or hospital in/outpatient database sources. The table shows the **first year data** are available in a data source e.g. in Finland, hospital data starts 1996 and primary care starts in 2013; the table shows 1996 as the first year that information on neurodevelopmental outcomes is available. Please note that this is not the birth year.

<sup>3</sup> Finland and France do not have information on women of childbearing age in this study.

<sup>4</sup> GePaRD covers 20% of national population; n=about 180,000 pregnancies per annum, but successful mother-child link is expected in 135,000.

<sup>5</sup> Primary care data available for 79% of population.

Table 2 Data sources contributing to the **Part 3** Case-control study

Centre	Years	Births covered	Number of MCA cases
<b>EUROmediCAT registries</b>			
Belgium, Antwerp	1997-2017	408,928	10,785
Croatia, Zagreb	1995-2017	142,525	2,669
Denmark, Odense	1995-2018	124,430	3,466
France, Brittany	2011-2018	276,715	10,302
France, Paris	2001-2017	445,975	14,351
Germany, Mainz	1996-2015	65,174	3,019
Germany, Saxony-Anhalt	2000-2018	331,942	10,482
Ireland, Cork and Kerry	1996-2018	205,376	5,675
Italy, Emilia Romagna	1995-2018	807,695	18,407
Italy, Tuscany	1995-2018	664,325	14,698
Malta	1996-2017	93,510	2,988
Netherlands, Northern	1995-2018	433,311	12,157
Poland, excluding Wielkopolska	1999-2018	6,144,011	87,631
Poland, Wielkopolska	1999-2018	744,714	18,838
Spain, Valencian Region	2007-2017	501,943	12,866
Switzerland, Vaud	1997-2018	171,812	6,459
UK, Wales	1998-2018	699,612	25,718
<b>Health care databases contributing aggregate data</b>			
France, EFEMERIS	2005-2019	145,303	3,661
Sweden	2007-2016	1,106,663	30,368
UK, NCARDRS (Northern England)	2021	628,171	13,408
<b>Total</b>	1995-2021	<b>14,142,135</b>	<b>307,948</b>

## Study period

**Part 3 Cohort study:** The study period will include data from 1 January 1996 or the first year pregnancy, medication AND subsequent neurodevelopmental outcomes are available (whichever is latest) and will end at the most recent date of the data source where medication AND subsequent neurodevelopmental outcome data are available. For example, if medication exposure in pregnancy is available from 2000 but infant neurodevelopmental outcome measured at 24 months is not available until 2009 only pregnancies from 2007 will be included in the study.

If data were extracted in December 2021 but the lag time for information about birth outcomes is more than a year, then the study period will end in December 2020.

The study period is the same for Part 2 (medication utilisation study) and Part 3 (medication safety study).

**Part 3 Case-control study:** The study period will include births from 1<sup>st</sup> January 1995 or the first year registries have medication data coded using Anatomical Therapeutic Chemical (ATC) classifications (whichever is latest) and will end in 2019. NCARDRS will contribute data for births born in 2021.

## Study population

### Part 1 (Develop algorithms):

#### Maternal depression

The population will include all WCBA aged between 15 and 49 during the study period and women with a pregnancy in each of the databases. For Finland and EFEMERIS/POMME only those with a pregnancy during the study period will be included. See **Table 1**.

#### Neurodevelopmental outcomes

The study population will consist of all children aged between 6 months and up to 18 years during the study period in each of the databases. Only children who can be linked to maternal exposures will be included.

#### Breastfeeding

All live births during the study period with survival of mother and infant to the time point breastfeeding is recorded.

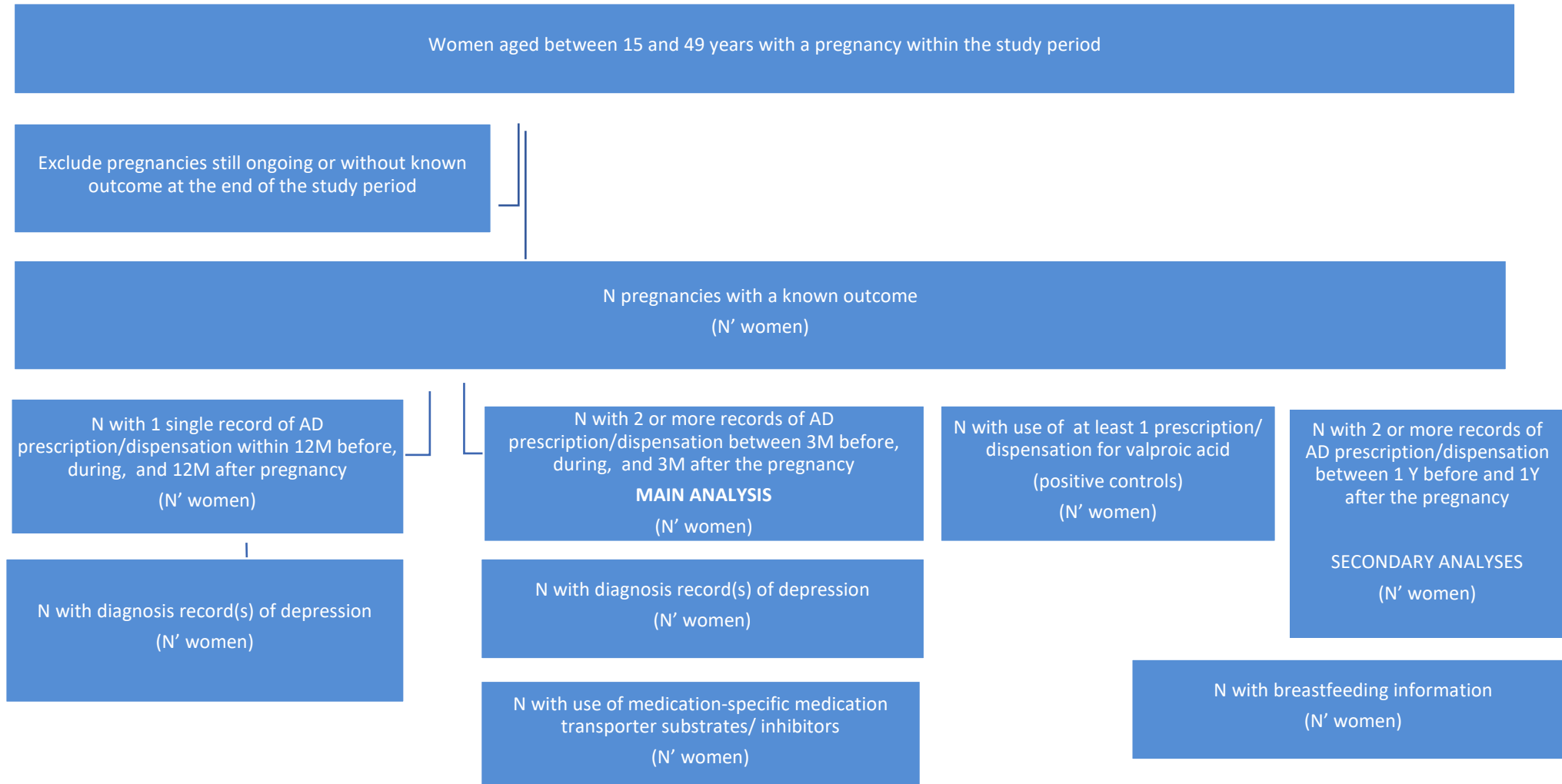
### Part 2 Medication utilisation study

Study population for the main analyses: Establish a cohort of women present in each data source from 12 months before to 12 months after pregnancy with pregnancy outcome(s) identified during the study period. The main analyses will be based on this cohort i.e. pregnant women with at least 2 antidepressant prescriptions or dispensations between 12 months before, during, and 12 months after pregnancy, with or without a diagnosis of depression, see Figure 1. The date of the first record of antidepressant medication prescription or dispensation will define the index date.

Study population for secondary analyses: based on data sources with data on WCBA (15-49 years) (see Figure 1).

The index date for valproic acid derivative exposed pregnancies is the date of the first prescription for valproate recorded between 3 months before to the end of pregnancy. The index date for the population comparison group, i.e. women without any antidepressant prescription records or diagnosis of depression within one year prior or during pregnancy, is one year before pregnancy.

Figure 1 Flow chart of the main / secondary study cohorts



AD=Antidepressant



## Exclusions

### Maternal exclusions

A number of exclusions will be made.

1. Teratogenic medication exposure 3 months before to end of pregnancy or maternal conditions (see list in Appendix 7)

Child exclusions (due to increased risk of ASD and ADHD in these children).

1. Neurological or genetic conditions such as Tuberous Sclerosis

Note: Valproic acid exposures are included as positive controls in this study so they will not be excluded in this DP.

Where exposures associated with adverse outcomes cannot be determined in the data sources, this will be listed in the study limitations e.g. substance misuse & heavy alcohol use referrals.

## Part 3: Medication safety study

**Study population for the cohort study:** The study population will include all women pregnant during the study period linked with a live birth. Where the datasets allow (some only have medication exposure 3 months pre-pregnancy), women must have been in the database for at least 12 months before they became pregnant in order to identify a depression diagnosis. (We expect this to be 12 months before pregnancy, but this is dependent on the findings from Part 1).

The population will be divided into the following:

1. Pregnant women with at least two antidepressant medication prescriptions/dispensations 3 months before pregnancy through to the end of pregnancy with or without a depression diagnosis ("**Exposed population**")
2. Pregnant women with a depression diagnosis or special reimbursement for "depression as a long term disability" before pregnancy with no exposure to antidepressants before or during pregnancy OR pregnant women with or without a diagnosis of depression who discontinued antidepressants at least 3 months before pregnancy and during pregnancy ("**Unmedicated disease population**")
3. Pregnant women with at least one prescription for valproic acid in the three months before pregnancy through to the end of pregnancy ("**Valproic acid positive control group**")
4. Pregnant women with no mental health medication, mental health diagnosis, special reimbursement for "depression as a long term disability" or valproic acid exposure at any time before or during pregnancy ("**Population comparison group**")

## Exclusions

Exclusions will be as per **Part 2**.

**For the case-malformed control study:** The study population will include registries that record, or can link to, medication exposures in pregnancy using ATC classifications.

#### Cases of congenital anomaly (“registrations”):

Cases of major congenital anomaly include livebirths, fetal deaths (stillbirths and spontaneous abortions) from 20 weeks gestational age, and TOPFA (at any gestational age). Henceforth, these will be referred to as “registrants” so that the distinction can be made between cases and controls in the analysis.

Registrations will be classified into EUROCAT subgroups (see EUROCAT Guide 1.4 [https://eu-rd-platform.jrc.ec.europa.eu/eurocat/data-collection/guidelines-for-data-registration\\_en#inline-nav-2](https://eu-rd-platform.jrc.ec.europa.eu/eurocat/data-collection/guidelines-for-data-registration_en#inline-nav-2) (EUROCAT Central Registry, 2013)) for analysis, and genetic syndromes will be analysed separately as controls, see below.

#### Exclusion criteria:

- registrations with a record of exposure to established teratogens: maternal epilepsy or antiepileptic exposure; maternal diabetes or insulin exposure; other established teratogenic exposure as detailed in Appendix 7.
- registration with teratogenic syndromes (congenital infections, valproate and other antiepileptic drug (AED) syndromes, diabetic embryopathies).
- registrations with a record of exposure to the medication(s) of interest but where timing of the exposure in the first trimester is unknown.
- TOPFA in registries where medication exposure is not recorded for TOPFA: Emilia Romagna, Valencian Region, Sweden
- Cases with minor anomalies only according to EUROCAT Guide 1.4.

### **8.3. Variables**

Variables will be defined according to recommendations developed in the ConcePTION project (ConcePTION deliverable D1.2). The information items of interest to this project are shown in Appendix 8.

#### Exposure definition

##### **Part 1 (Develop algorithms):**

##### **Maternal depression**

Maternal depression may be identified based on medication exposure (see below), depression diagnoses (primary care, inpatient or outpatient diagnosis), special reimbursement status for depression as a chronic illness (the method used is dependant on the data source). See Appendix 2 for more detail.

##### **Neurodevelopmental outcomes**

ADHD, ASD and ID disorders will be identified based on primary care or outpatient diagnoses. ADHD may also be identified based on medication use. Infant developmental assessments are recorded as part of child developmental assessments in routine care. See Appendix 9 for more detail.

##### **Breastfeeding**

Many databases do not capture breastfeeding data, and across those which do there is no single standardised recording method. Both breastfeeding pattern and duration are of interest. Ideally the below information would be available (World Health Organization, 2018):

- early initiation of breastfeeding within one hour after birth
- any breastfeeding at 4–6 weeks
- exclusive breastfeeding at 4–6 weeks
- any breastfeeding at 6 months
- exclusive breastfeeding at 6 months
- giving any additional foods or fluids in the first 2 days after birth – as Indication of struggling to breastfeed.
- use of artificial teats and bottles in the first 6 months – to distinguish formula feeding from other feeding e.g. solids

The available breastfeeding data, in data sources contributing to this study, will be characterised in this validation exercise but variables of interest would include child age at breastfeeding assessment, duration of breastfeeding and how infant feeding is recorded (breastfeeding yes/no, exclusive breastfeeding etc.). Since few data sources collect breastfeeding information with optimal detail, some assumptions may need to be made, e.g. that an infant breastfed at 6 months is likely to have been breastfed at earlier ages. Decisions on the categories above will be made when we have access to the WP7 data characterisation results on breastfeeding data, see Appendix 10.

## **Part 2 and Part 3 cohort study**

Medication exposure can be identified by prescription (prescribed, dispensed or reimbursed) records. The timing and dose (where available) of SSRIs and/or SNRIs (individually **and/or** as a class) will be defined by algorithms according to the quantity supplied (e.g. number of tablets), strength of unit dispensed (tablet) and prescription/dispensing dates.

The exposure sub-categories of interest are:

1. Any antidepressant
2. Any SSRI and/or SNRI
3. Any SSRI
4. Any SNRI
5. Individual substance observed among the top 3 (or 5) most frequent within a class
6. Any antidepressant other than SSRI or SNRI.

Medications will be classified according to the ATC classification system and the Defined Daily Dose (DDD). To quantify medication exposure, the quantities of medications prescribed or dispensed will be transformed in the standard units of measurement of the WHO DDD, defined as the average adult dose recommended for the main indication. DDD scores are thus measures of treatment intensity (drug burden). The duration of treatment and the dates of exposure will be estimated based on the frequency, amount and duration of exposure (representing the cumulative exposure). Medications prescribed/dispensed during the three months before the beginning of pregnancy will be included.

The medications investigated are listed in Table 3.

*Table 3 Medications to be examined, ATC codes, name and defined daily dose (DDD)*

	ATC	International non-proprietary name	DDD	DDD unit	Route
Any antidepressant medication	N06A				
SSRI	N06AB03	fluoxetine	20	mg	O
	N06AB04	citalopram	20	mg	O
			20	mg	P
	N06AB05	paroxetine	20	mg	O
	N06AB06	sertraline	50	mg	O
	N06AB08	fluvoxamine	100	mg	O
	N06AB10	escitalopram	10	mg	O
SNRIs	N06AX16	venlafaxine	100	mg	O
	N06AX17	milnacipran	100	mg	O
	N06AX21	duloxetine	60	mg	O
	N06AX23	desvenlafaxine	50	mg	O
Other antidepressant medications	N06 other than SSRI/SNRI listed above				

O=oral, P=parenteral

### Concomitant medication use - P-gp and BCRP substrate and inhibitor status

Co-medication with medication-specific medication transporter substrates/ inhibitors have been identified from the University of Washington Metabolism and Transport Drug Interaction Database (UW Metabolism and Transport Drug Interaction Database, DIDB 2015) and previously published literature based on the DIBD data (Ellfolk *et al.*, 2020). The DIBD database is a manually curated knowledge base containing both in vitro and in vivo medication-medication interaction data developed by University of Washington's Department of Pharmaceutics, School of Pharmacy. In the Ellfolk *et al.* study, approximately 100 most commonly used medications in the pregnant cohort were identified for their P-gp and BCRP substrate/ inhibitor status (Ellfolk *et al.*, 2020). The transporter substrate/ inhibitor status for individual SSRIs and other SNRI antidepressants obtained from the DIDB are presented in Table 4 below.

*Table 4 P-gp and BCRP substrate (S) and inhibitor (I) status of individual SSRIs and SNRI antidepressants included in the study, according to previous research (Ellfolk *et al.*, 2020)*

SSRI	P-gp	BCRP
Citalopram (N06AB04)	(S), (I)	
Fluvoxamine (N06AB08)	(I)	
Sertraline (N06AB06)	(I)	
Paroxetine (N06AB05)		(S; metabolite)

SSRI/SNRIs not listed above were not identified as P-gp or BCRP substrates or inhibitors in the DIBD 2015 database.

A list of medications, with their P-gp and BCRP substrate and inhibitor status, was included in (Ellfolk et al., 2020), see Appendix 11. This list will be updated for the SSRIs and SNRIs to take into account subsequent evidence from the literature.

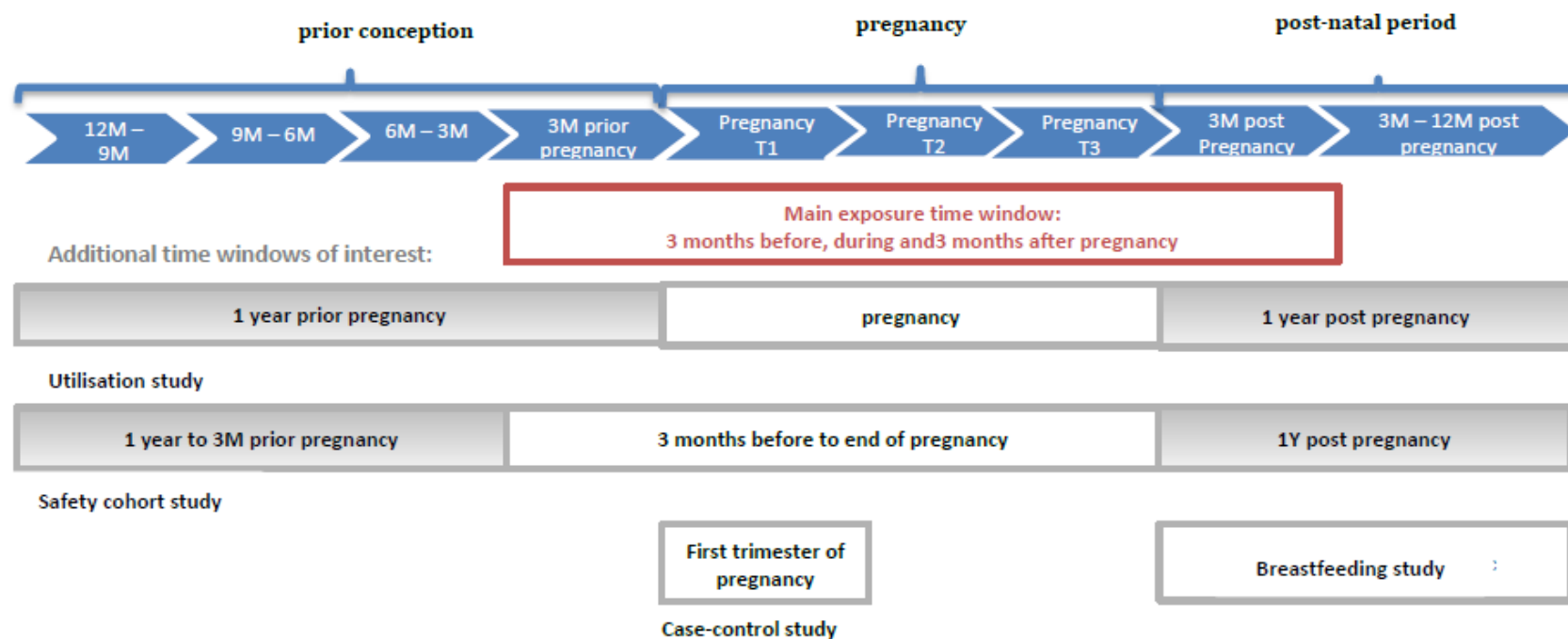
### **Valproic acid exposure**

A single VPA exposure with or without antidepressants or other AEDs in the 3 months before to the end of pregnancy..

### **Exposure window**

Various time windows will be considered for the exposure to medications or presence of depression or breastfeeding information (see Figure 2). The main exposure window in both the utilisation and safety studies is 3 months before pregnancy and during pregnancy. The case-control study will only examine first trimester exposures.

Figure 2 Time periods of interest in Part 2 (medication utilisation) and Part 3 (safety cohort study)



### **Part 3 case-control study**

In EUROMediCAT, first trimester medication exposure is coded to the WHO ATC classification. Medication exposure is usually obtained from medical records created during pregnancy, but some registries use additional sources such as maternal interview, or prescription records (EUROMediCAT Central Database, 2017). Exposure is recorded if there is evidence that the woman took the medication in the first trimester – generally, preconception exposures for a medication with a long half-life are not recorded, although this may be specified in the text information (e.g. for drugs with long half-life like isotretinoin, fluoxetine/ norfluoxetine).

SSRI/SNRI exposures to be investigated are listed in Table 3.

### **Outcomes of utilisation study**

The following estimates will be generated from the overall population of WCBA:

- prevalence of use of antidepressant medication, overall and by calendar year of birth

The following estimates will be generated from the population of women with a pregnancy, overall, by time period of interest (defined below) and by sub-population defined in Figure 1.

- prevalence of SSRI/SNRI use in the 3 months before pregnancy until 3 months after the end of pregnancy, overall and by calendar year.
- prevalence of SSRI/SNRI use and depression diagnosis in the 3 months before pregnancy until 3 months after the end of pregnancy, overall and by calendar year.
- prevalence of antidepressant use within the year following pregnancy, overall and by calendar year
- prevalence of antidepressant use and depression diagnosis within the year following pregnancy, overall and by calendar year

#### **Utilisation patterns of antidepressant medication:**

Patterns of medication use (details to be provided in Statistical Analysis Plan (SAP)) will be evaluated across various time periods. The main time period of interest is 3 months before the estimated pregnancy start until the end of pregnancy (whatever the outcome is), as well as the split between pregnancy exposure trimesters e.g. last menstrual period (LMP) to day 97 (trimester 1); day 98 after LMP to day 195 (trimester 2); day 196+ (trimester 3).

Other time periods of interest will be considered according to data availability, as per below:

- the pre-pregnancy exposure window: within 365 to 90 days before pregnancy estimated start date, and split by 90-day interval (pre1, pre2, etc)
- the post-pregnancy exposure window: within 365 days after estimated pregnancy end (whatever the pregnancy outcome is)
- Combination of the pre-pregnancy exposure window and the main time period OR/AND the main time period and the post-pregnancy exposure window

The issue of overlapping pregnancies (where the post pregnancy period in the first pregnancy overlaps with the pre-pregnancy period in the second pregnancy) will be dealt with in sensitivity analysis i.e. we will restrict analysis to a single pregnancy for women with more than one pregnancy in the study period.

Chronic use: repeated prescription/dispensing records without discontinuation, number of prescriptions fills, and sum of DDDs i.e. each ATC code has a DDD which gives the amount of active ingredients. These can be added up to give the cumulative exposure based on the frequency, amount and duration of exposure. The total medication exposure can subsequently be transformed into number of DDD per month of pregnancy (or per trimester of pregnancy). We will liaise with DAPs to get their definition of repeat prescriptions to identify chronic use. We will calculate:

- percentage of women receiving (prescribed/issued/dispensed) an SSRI or SNRI (= number of deliveries in which the woman received an SSRI prescription during the period of interest / total number of deliveries, overall and by time period of interest.

Discontinuation: the number of days without coverage by prescription/ dispensation is DAP specific. For instance, in Wales or Finland, 3 months (90 days) would be considered appropriate, whereas in Italy, only 2 packets of the same medication can be dispensed in one day. We will liaise with DAPs to get their country definition of discontinuation. We will calculate the:

- percentage of women who discontinued before pregnancy and did not restart i.e. there were no prescription records for SSRIs/ SNRIs during or after pregnancy
- percentage of women who discontinued before pregnancy and a prescription/ dispensation was recorded during trimester 2 or trimester 3
- percentage of women who discontinued before pregnancy and a prescription/ dispensation was recorded after delivery (or pregnancy end), see Figure 1
- percentage of women who discontinued during trimester 1 and did not restart i.e. there were no further prescription/ dispensation records for SSRIs/ SNRIs throughout the rest of the pregnancy or after pregnancy
- percentage of women who discontinued during trimester 1 and a prescription/ dispensation was recorded after delivery (or pregnancy end)
- percentage of women who had no prescription/ dispensation recorded during trimester 2 or trimester 3
- percentage of women with continuous use (i.e. without discontinuation) throughout pregnancy and three months post pregnancy

#### Switching:

A switch in antidepressant medication is defined as a discontinuation of the index (or first-line) medication, a prescription of a new (second-line) medication, and no renewal of the index medication. Patients who have a change in antidepressant medication together with a consecutive repeat prescription of the index one or with an overlap of the two medications for >30 days would be categorised as augmentation rather than a treatment switch (Mars *et al.*, 2017).

The occurrence of switching or augmenting will be expressed as a proportion of the population of pregnant women, overall and by trimester and after birth.

#### Adherence:

Adherence is a broad term defined as the extent to which a person's drug-taking behaviour corresponds with agreed recommendations from a health care provider (Grégoire and Moisan, 2016). For this study, the outcomes of interest to characterize adherence will be:



- Non-renewal: the extent to which a newly prescribed drug treatment is undertaken i.e.: proportion of women with a single record of antidepressant prescription/dispensation within 3 months before and 3 months after pregnancy (sometimes referred to as non-initiation).
- Persistence: the extent to which the treatment is taken for the recommended duration (based on local DAP knowledge). The percent days covered (PDC) and the number of discontinuation or treatment gaps (as defined above) observed during pregnancy are proposed as proxies of persistence.

For this calculation, we assume that all women use the drug in the defined daily dose, as we do not have access to information on what dosage was prescribed. The information available is number of DDDs dispensed and number of days between dispensations. We will allow for DAP-specific number of days of non-overlap (grace period) before we consider a period as uncovered (=discontinuation). A PDC cut-off of 0.8 is suggested to distinguish between treatment adherence and non-adherence.

#### Trajectory methods (modelling to be performed by DAPs using individual case data):

The intensity of drug exposure may be estimated using the longitudinal K means clustering algorithm. For the analysis, clusters of mothers with homogenous trajectories of medication exposure will be identified. The longitudinal K means clustering algorithm will be applied to create K clusters with homogenous trajectories, as empirically driven by the data. No assumption about the number of clusters is made prior to running the algorithm. Mean DDD trajectories will be plotted for each cluster and the shape described. It is anticipated that several clusters will be identified with homogenous trajectories of exposure around the pregnancy time period. Then, descriptive statistics will summarise distribution of exposure to each SSRI/SNRI as a class within each cluster (Hurault-Delarue et al. 2016).

#### Breastfeeding

Outcomes specific to the sub-population with breast-feeding information available:

The following estimates will be generated from the main population with a pregnancy episode:

- prevalence of breast-feeding in women with at least 2 records of antidepressant medication prescription or dispensation, stratified by presence of diagnosis of depression, overall and by calendar year, at the time of birth and during the post-natal period
- prevalence of breast-feeding in women without any antidepressant medication, stratified by presence of diagnosis of depression, at birth and during the post-natal periods, overall and by calendar year
- prevalence of breastfeeding at birth and in the post-natal period according to exposure to potential covariates, as outlined in Appendix 10.

#### **Use of other medications:**

The following estimates will be generated from the main population with a pregnancy episode:

- use of valproic acid (at least 1 prescription/dispensation) in pregnant women (three months before to the end of pregnancy), overall and by calendar year.

Concomitant exposure to SSRI/SNRI and to the following categories of substances will be described:

#### P-gp substrate/ inhibitor

Monotherapy with an SSRI/SNRI which is a P-gp substrate (SSRI/SNRI-P-gp-S) and an SSRI/SNRI-P-gp-S, and another medication which is a P-gp substrate or inhibitor:

- Citalopram monotherapy (allowing other medications prescribed so long as they are not listed as P-gp substrates or inhibitors)
- Citalopram co-prescribed with a medication that is a P-gp substrate or inhibitor (allowing one or more medications that are P-gp substrates or inhibitors)

Monotherapy with an SSRI/SNRI that is a P-gp substrate (SSRI/SNRI-P-gp-S) and an SSRI/SNRI-P-gp-S and another medication that is a P-gp inhibitor:

- Citalopram monotherapy (allowing other medications prescribed so long as they are not listed as P-gp substrates or inhibitors)
- Citalopram co-prescribed with a medication that is a P-gp inhibitor (allowing one or more medications that are P-gp inhibitors)

#### BCRP substrate/ inhibitor

Monotherapy with an SSRI/SNRI that is a BCRP substrate (SSRI/SNRI -BCRP-S) and an SSRI/SNRI-BCRP-S and another medication that is a BCRP substrate or inhibitor:

- Paroxetine monotherapy (allowing other medications prescribed so long as they are not listed as BCRP substrates or inhibitors)
- Paroxetine co-prescribed with a medication that is a BCRP substrate or inhibitor (allowing one or more medications that are BCRP substrates or inhibitors)

Monotherapy with an SSRI/SNRI that is a BCRP substrate (SSRI/SNRI -BCRP-S) and an SSRI/SNRI-BCRP-S and another medication that is a BCRP inhibitor:

- Paroxetine monotherapy (allowing other medications prescribed so long as they are not listed as BCRP substrates or inhibitors)
- Paroxetine co-prescribed with a medication that is a BCRP inhibitor (allowing one or more medications that are BCRP inhibitors)

A list of P-gp substrate/ inhibitors and BCRP substrate/ inhibitors is included in Appendix 11. This list will be updated before the analysis commences and may provide more information on individual SSRI/SNRI substrate/inhibitor status.

### [Outcomes of the Safety cohort and cross-sectional studies](#)

#### **Primary outcomes - Neurodevelopmental outcomes**

The neurodevelopmental outcomes will be based on **Part 1**, see Appendix 9 .

#### **Secondary outcomes**

Major congenital anomalies

EUROmediCAT registries record all MCA in their registry area following EUROCAT definitions. Children with only minor anomalies are excluded (EUROCAT Central Registry, 2013). EFEMERIS, NCARDS and Sweden will contribute aggregate data rather than individual level data. Sweden and NCARDS record MCA using EUROCAT definitions.

EFEMERIS records diagnoses using ICD codes and these will be converted into the corresponding EUROCAT subgroups using a Stata script developed as part of the EUROLINKCAT project (Morris *et al.*, 2021).

## **Part 2 (Medication utilisation): Co-variates**

The following maternal factors will be considered as covariates and included according to availability in each data source (see Appendix 12):

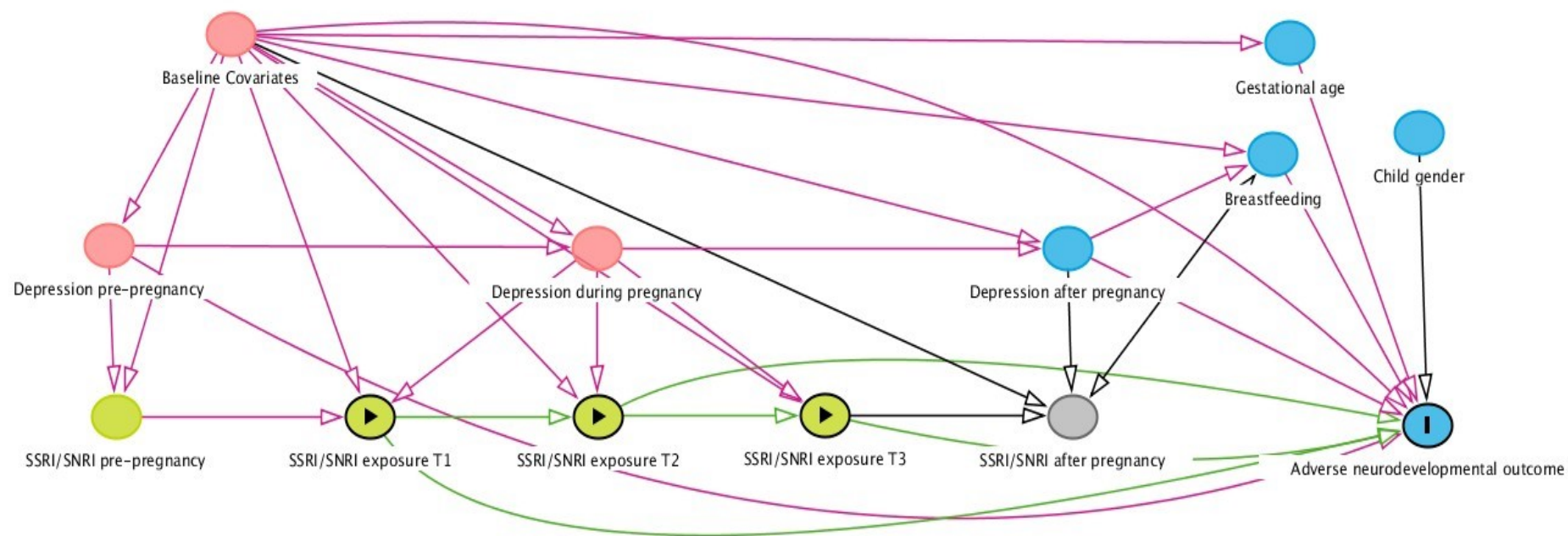
- Country, region and area (where applicable)
- Maternal age at birth in completed years
- Calendar year at index date
- Parity (as primiparous/ multiparous)
- Maternal marital status
- Maternal education
- Maternal occupation
- Socioeconomic status (SES)
- Smoking status – at start of pregnancy
- Multiple birth
- Other pregnancy(ies) in study period

## **Part 3 (Medication safety) Co-variates: confounders, mediators, moderators**

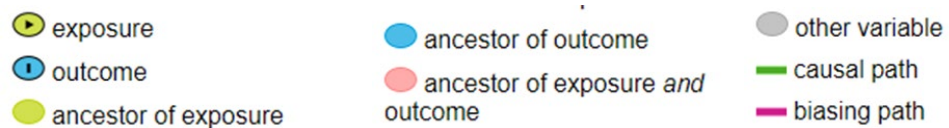
### **Cohort study**

A minimal sufficient adjustment set of covariates will be defined using DAGs (Greenland and Pearl, 2011) informed by literature review, see Figure 3 below for a preliminary example and Appendix 12 for covariates available across data sources.

Figure 3 A preliminary DAG



Baseline covariates would include for example maternal age, socioeconomic status and highest level of education. T1 – trimester 1, T2 – trimester 2, T3 – trimester 3.



## Maternal depression

Maternal depression will be identified based on **Part 1**, see Appendix 2.

## Breastfeeding

Breastfeeding status will be based on the information provided in Part 1, see Appendix 10.

## Child factors

- Year of birth
- Sex
- Gestational age in completed weeks based on the best obstetric estimate. If the estimate is not available, gestational age will be calculated based on birth date and date of LMP
- Birth weight
- Small for Gestational Age (SGA), defined as <10<sup>th</sup> centile. We will use the <3<sup>rd</sup> centile, where available as this is clinically important.
- Neonatal adaptation problems, low Apgar scores <7 or treatment in NICU

## Maternal factors

Information from the Utilisation study (Part 2) will inform the selection of maternal factors included in the Safety study

- Maternal age at birth in completed years.
- Parity
- Highest maternal education
- Socioeconomic status (SES) at birth, or at the start of pregnancy (dependent on when measured in DAP sources)
- Smoking status – at start of pregnancy: Non-smoker, smoker
- Substance misuse (where available) – based on referrals for addiction/treatment
- Alcohol use during pregnancy - yes/no (non-abstainer/abstainer).
- Heavy alcohol use (yes/no)
- Pre-pregnancy/first antenatal visit BMI

## Case- control study

**Covariates available in the case-control study are:**

- Registry
- Birth year
- Maternal age at birth in completed years
- Co-medication
- Maternal illness before and during pregnancy

## 8.4. Data sources

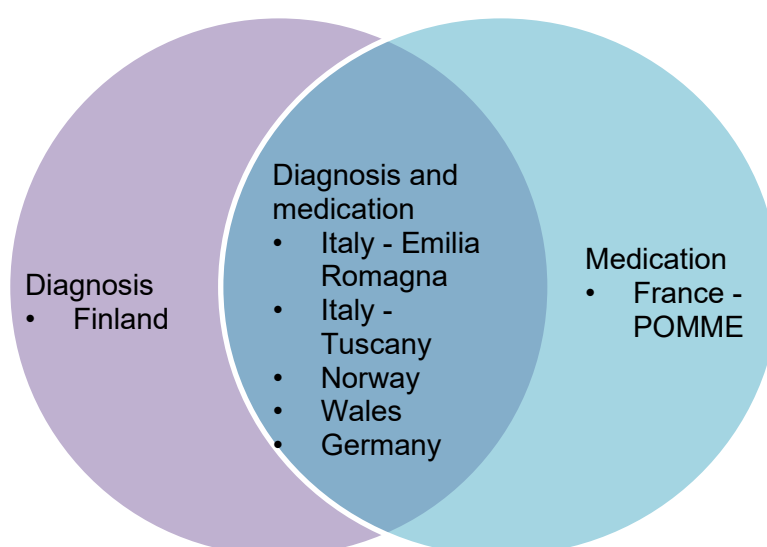
Data from healthcare and administrative databases will be used where available. Databases will be selected based upon availability of variables and data quality results from data characterisation undertaken when creating the IMI ConcePTION FAIR Data Catalogue. Different data sources may be used for different aspects of the project. **Table 1** shows the

time period and number of pregnancies covered for the potential data sources contributing to the medication utilisation study (pending data characterisation results).

Details of the neurodevelopmental outcomes available from each data source are shown in Table 5. ADHD may be identified based on 1) diagnosis only, 2) medication use and diagnosis and 3) medication use only, depending on the data source, as shown Figure 4 below. The rates of ADHD diagnosis produced using these three methods to identify cases will be compared in Part 1 and based on this a decision will be made whether to include all these data sources when examining risk of ADHD. We will also examine heterogeneity to assess if the results should be combined i.e. it is not valid to combine results if heterogeneity is high.

To increase the specificity of ASD and ADHD, a diagnosis should be present in a child's records at least once if it is recorded by a specialist and at least twice if it is recorded by a non-specialist before the child is considered as having that diagnosis. This will exclude the instances where a child is evaluated to rule out a diagnosis (Hjorth et al., 2019). For ADHD two recorded diagnoses by a non-specialist or a single diagnosis combined with a prescription for an ADHD medication would be sufficient. Where possible any diagnoses with an explicit qualifier "ruled out" or "suspected" will be excluded.

*Figure 4 Identification of ADHD across data sources<sup>6</sup>*



<sup>6</sup> EFEMERIS has no information on ADHD.

Table 5 Details of neurodevelopmental outcomes available in each data source

DAP	Infant development at 24 months		ASD, ADHD and ID diagnoses up to 7 years of age				ADHD medication use up to 7 years of age	
			Primary care diagnoses ICD-10, Read, ICPC-2		Hospital outpatient/mental health service diagnoses ICD-10			
	Years available	Children (1,000)	Years available	Children with 7 years of follow-up (1,000)	Years available	Children with 7 years of follow-up (1,000)	Years available	Children with 7 years of follow-up (1,000)
<b>Finland</b>			2012-2019	53	1996-2019	848		
<b>EFEMERIS database</b>	2004-2019 <sup>7</sup>	136						
<b>POMME database</b>	2010 and 2015 <sup>7</sup>	18					2010	8
<b>Italy – Emilia Romagna</b>					2010-2019	114	2004-2019	324
<b>Italy - Tuscany</b>					2010-2019	90	2003-2019	300
<b>Norway</b>					2008-2019	300	2004-2019	540
<b>Wales<sup>8</sup></b>	2000-2020 <sup>9</sup>	660	2000-2020	365	2000-2020	462	2000-2020	365
<b>Germany</b>	2006-2019 <sup>10</sup>	1,335	Primary care does not exist in health system		2006-2019	555	2006-2019	555
<b>Total sample</b>		<b>2,131</b>		<b>418</b>		<b>2,369</b>		<b>2,110</b>

<sup>7</sup> Certificates completed at 24 months by a general practitioner or a paediatrician - include 14 items designed to detect children at risk of psychomotor development abnormalities

<sup>8</sup> Sample sizes assume GP data available for 79% of population

<sup>9</sup> Health Visitor child health developmental examinations at 27 months which assess vision, audio, locomotion, manipulation, behaviour and speech. Assessments are recorded as satisfactory, problem, observe, treatment, referral or not done

<sup>10</sup> ICD-10 codes recorded during standard care or 'early developmental assessments'.

The data sources with breastfeeding data, and how and when this is measured, are listed in Table 6 along with the neurodevelopmental outcomes available in the subset of data sources contributing to the breastfeeding sub-study. As can be seen from this table the breastfeeding information is available for the same or fewer years than neurodevelopmental outcomes.

*Table 6 Details of breastfeeding measurement in each data source, years and number of children with breast feeding information available, years and number of children with both breastfeeding and neurodevelopmental outcome(s) available*

Country	Breastfeeding information	Breastfeeding Years (1,000 children)	ND outcome(s) available	Breastfeeding and ND outcome(s) available Years (1,000 children <sup>11</sup> )
France	Health certificates completed during mandatory medical examinations at 8 days, 9 months and 24 months old record breastfeeding (Yes/No), duration of breastfeeding (in weeks) and duration of exclusive breastfeeding (weeks)	2004-2019 (156)	Infant motor development at 2 years  ADHD medication use	EFEMERIS 2004-2019 (136)  POMME 2010 and 2015 cohorts (18)
Italy – Tuscany	How the new-born was fed during the hospital stay. Only breast milk; breast milk with the addition of water or other liquids other than milk, breast milk and infant formula, infant formula.	2003-2019 (480)	ASD, ADHD, ID disorders (ICD diagnosis)  ADHD medication use	2010-2019 (90)  2003-2019 (300)
Wales	Health visitors record at birth, 10 days, 6 weeks and 6 months - 'any' breastfeeding	2005-2020 (630)	Infant development  ASD, ADHD and ID disorder (ICD diagnosis)  ADHD medication use	2005-2019 (540)  2005-2019 (Outpatient – 315) (Primary care diagnoses 249)  2005-2019 (Primary care medication use – 249)

The individual registries which contribute to the EUROMediCAT central database, and which have agreed to take part in ConcePTION are listed in Table 2 along with the years covered and number of CA cases.

<sup>11</sup> Estimates assume infant development assessed at 2 years with 7 years of follow-up for ADHD and ASD.



Table 7 gives an overview of data sources and their contribution to the different parts of the study.

*Table 7 Data sources and their contribution to aspects of the study*

		Medication utilisation (Cohort study)	Risk of adverse ND outcomes (Cohort study)	Risk of MCA (Case-control study with malformed controls)
Germany	GePaRD	✓	✓	
Finland	Care Register for Health Care, Register of Primary Health Care visits, Prescription Registry, Medical Birth Register, Register of Congenital Malformations	✓	✓	
France	EFEMERIS database	✓ ± BF	✓ BF	✓
	POMME database (France)	<sup>12</sup>	✓ BF	
Italy Emilia Romagna	SINPIA ER (Neuropsychiatry service for childhood and young people), SISM (regional mental health service), CEDAP (births), AFO/FED (dispensation of medications in community pharmacies/dispensations of medications from hospital pharmacies for outpatient use), SDO Scheda di dimissione ospedaliera (Hospital Discharge Record), CA registry (Emilia Romagna)	✓	✓	✓
Italy Tuscany	SALM – mental health services, CAP and CAP2 – birth registry, SPF – dispensation of medications in community pharmacies, FED – dispensations of medications from hospital pharmacies for outpatient use (Tuscany, Italy), CA registry (Tuscany)	✓ BF	✓ BF	✓
Norway	Norwegian Patient Registry (NPR), Norwegian Prescription Database (NorPD), Medical Birth Registry of Norway (MBRN)	✓	✓	

<sup>12</sup> Not included in the medication utilisation study as POMME is a subsample of EFEMERIS.

UK Wales	In-patient and out-patient PEDW records, Primary Care GP dataset, National Community Child Health Database (NCCHD), CARIS congenital anomaly registry (Wales, United Kingdom)	✓ BF	✓ BF	✓
	EUROmediCAT Central Database (Multi-National)			✓

BF= Breastfeeding sub study

### 8.5. Study size

Despite having a source population of more than six million births in **Part 2** (Medication utilisation, **Table 1**) sample size will be an issue in **Part 3 (Medication safety)**. See **Section 8.9** study power.

Neurodevelopmental outcomes are available for a more limited time period than medication exposure in pregnancy, reducing the available sample size (**Table 1**). Delayed infant development requires at least two years of follow-up. ASD, ADHD and learning disability or disorders of intellectual development require a much longer follow-up period.

Breastfeeding data are available in a limited number of data sources and the available sample in the breastfeeding sub-study will be severely limited with at most two data sources containing information on the same neurodevelopmental outcome and breastfeeding (see Table 6).

Some subgroups of MCA are rare and the risk of MCA will only be examined in subgroups with at least 3 exposed cases. With fewer exposed cases a case series will be conducted.

### 8.6. Data management

All data have been prospectively recorded and are available via electronic health databases or administrative systems. In some countries several registries are linked using the personal identification number of each citizen in the country (Finland, Norway) or anonymisation of this (Wales).

ConcePTION will work using a distributed network approach, with a common protocol for data characterization, a common data model and common analytics. Individual case data will remain with the local data access providers (DAPs). Analysis scripts written in Stata, and double coded in R, will be sent to the DAPs to run on their local data. The results of the analysis scripts consisting of only highly aggregated results or effect estimates will be submitted by the DAPs to the ConcePTION Secure Data Platform. This platform can only be accessed by ConcePTION members taking part in the study.

For **Part 3** two forms of data will be included in the EUROmediCAT Central Database: a) individual case data transmitted yearly to the EUROmediCAT Central Database (most participating registries) and b) aggregate data tables requested for this study to supplement the central database. The latter data are being requested from NCARDS for England, from Sweden, and from EFEMERIS in France. These aggregate tables will be combined with the individual level data for the analysis at Ulster University.

### 8.7. Data analysis

Each DAP will run the centrally produced analysis scripts on their own data, and upload **aggregated results or effect estimates** to the ConcePTION platform for meta-analyses by the postdoc researcher.

## Part 1: Develop algorithms to identify exposures and outcomes

Descriptive statistics will be used to characterise the contents of variables containing information on maternal depression, adverse neurodevelopmental outcomes and breastfeeding. Algorithms will be developed and then used to determine the prevalence of maternal depression or adverse neurodevelopmental outcomes in each data source. These will be stratified by factors which may influence the ability of an algorithm to identify the outcome such as year, age, gender. See Appendix 2, Appendix 9 and Appendix 10 for more detail.

## Part 2 (Medication utilisation)

Descriptive analysis: categorical variables will be summarized by frequencies and proportions of each modality, including the proportion of missing data. Mean, standard deviation and error, median and interquartile range will be provided for continuous variables. 95% Confidence intervals (CI) will be estimated [using Normal approximation for quantitative relevant parameters]. Cells with small numbers will be collapsed. See Table 8 below for an overview of the population groups and measures of disease/ exposures to be included in analysis.

Each DAP will conduct univariate and multivariate logistic regression locally based on an agreed SAP. The SAP will provide more details on modelling, including the longitudinal k-means clustering, described in **Section 8.3**.

*Table 8 Overview of the population groups and measures of disease/ exposures to be included in analysis*

Objective	Population	Measures of disease/exposure	Stratification
Depression in the WCBA population	WCBA with at least 2 records of antidepressant medication prescription or dispensation / WCBA without depression or treatment	Prevalence rate, (95% CI) (use of antidepressant medication)	Overall, by calendar year and by type of SSRI/SNRI
Pregnancy in the population with depression	Pregnant women with at least 2 records of antidepressant medication prescription or dispensation in 3 months before, during and 3 months after pregnancy / WCBA with depression or treatment	Incidence rate, (95% CI) (pregnancy among WCBA	Overall and by calendar year
Single record of antidepressant medication	Pregnant women with a single record of antidepressant medication prescription or dispensation i.e. non-renewal (or refilling) of prescription/ dispensation)	Prevalence rate, (95% CI)	Presence of depression diagnosis.  Overall and by calendar year

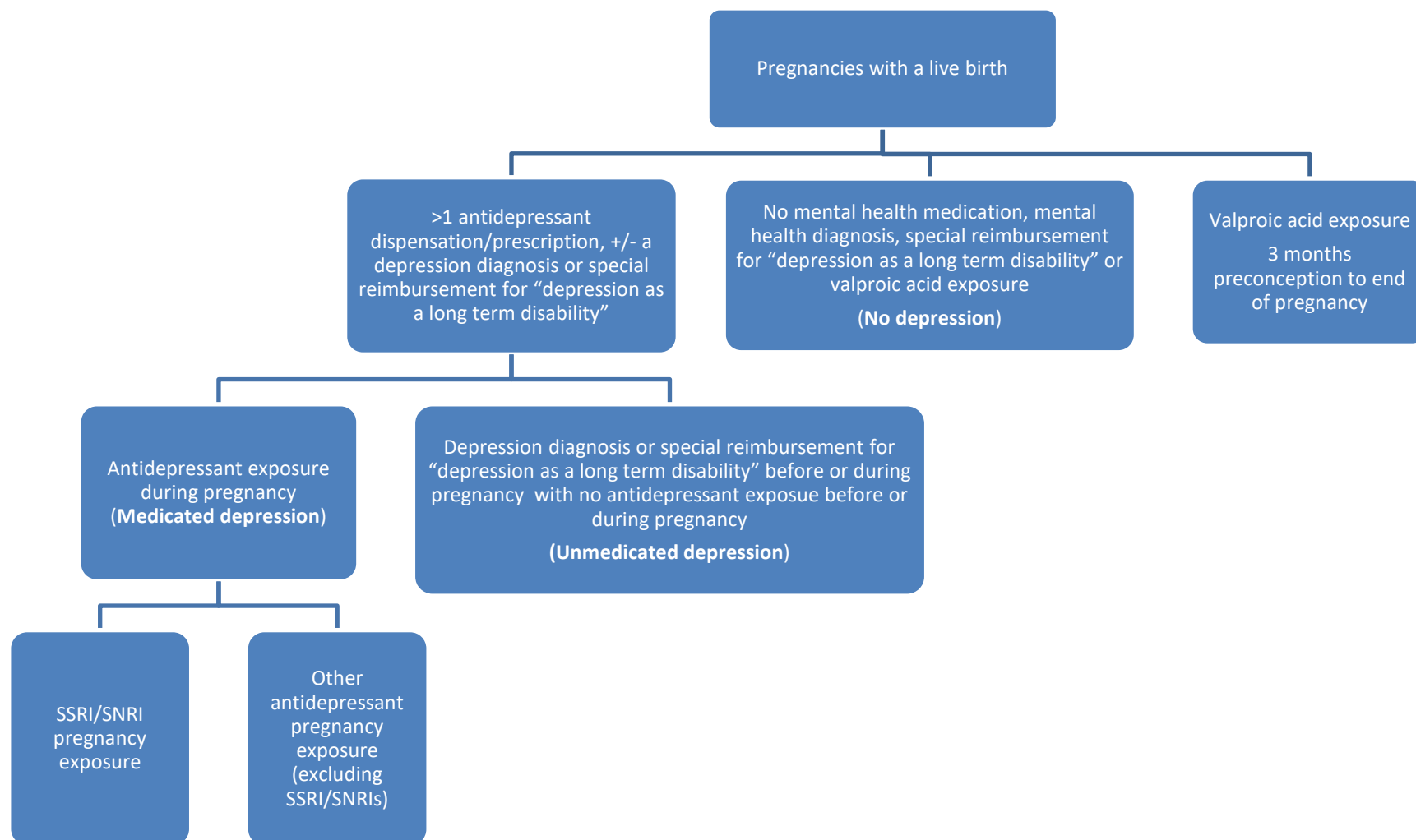
Use of antidepressant medication among pregnant women	(MAIN POPULATION)  Pregnant women with at least 2 records of antidepressant medication prescription or dispensation in 3 months before, during and 3 months after pregnancy / Pregnant women without depression or treatment (general population of pregnant women)	Prevalence rate, (95% CI) (depression (with or without a diagnosis record) among pregnant women, before, during and after pregnancy)	Presence of depression diagnosis,  Time windows of interest  Overall, by calendar year and by type of SSRI/ SNRI
Utilisation patterns among pregnant women	MAIN POPULATION	Discontinuation  Switching  Adherence	By SSRI type

### Part 3 (Medication safety)

#### Cohort study

The study population will be divided into a number of groups. medicated depression, unmedicated depression and no depression, see Figure 5 below.

Figure 5 Population groups of interest



## Descriptive analysis

Maternal baseline characteristics (e.g. age, SES, smoking status, parity) will be summarized for each data source and for each group/cohort using descriptive statistics. Frequency tables including numbers and proportions will be generated for categorical variables. Mean, standard deviation, median and interquartile range and range will be provided for continuous variables.

## Primary analysis

Each DAP will conduct univariate and multivariate logistic, poisson, or linear regression and Cox proportional hazards regression on their data source, based on an agreed SAP and a common script. If possible within the ConcePTION platform, this will also include advanced confounder adjustment methods, including propensity score methods, marginal structural models and inverse-probability-of-treatment weighting (IPTW) as appropriate to mitigate measured confounding.

When combining data from multiple DAPs, meta-analysis will be used to pool effect estimates using the random-effects model. The meta-analysis on aggregate data will allow for adjustment for country-optimized covariates (See Appendix 13).

## Comparison groups

The risk of adverse neurodevelopmental outcomes following:

- SSRI/SNRI pregnancy exposure: Pregnancies with SSRI/SNRI exposure, with or without a depression diagnosis/special reimbursement for “depression as a long term disability”, three months before through to the end of pregnancy
- Other antidepressant pregnancy exposure: Pregnancies with other antidepressant exposure (Non-SSRI/SNRI), with or without a depression diagnosis/special reimbursement, from three months before pregnancy through to the end of pregnancy

will be compared with:

1. Pregnant women with a depression diagnosis or special reimbursement for “depression as a long term disability” before pregnancy with no exposure to antidepressants before or during pregnancy OR pregnant women with or without a diagnosis of depression who discontinued antidepressants at least 3 months before pregnancy and during pregnancy (“Unmedicated disease comparator”)
2. Pregnancies with no history of mental health medication, valproate exposure, or mental health diagnosis from a year before pregnancy through to the end of pregnancy (“Population comparison group”)

Valproic acid exposure three months before and during pregnancy will be used as a positive control, see later section on ‘**Valproic acid**’.

Some DAPs may not be able to use diagnosis information when creating the ‘unmedicated disease comparator’ and will rely on pre-pregnancy antidepressant exposures to create this group.

## Analysis of Time varying confounders

Maternal depression is a time varying confounder affected by prior SSRI/SNRI treatment. If it is possible to identify maternal depression, over time, in the administrative datasets, and if possible within the ConcePTION platform, methods such as inverse-probability-of-treatment weighting, will be used to adjust for the confounding effect of depression, but not for the effect of SSRI/SNRI exposure on depression. This is dependent on whether the algorithms to identify maternal depression, developed in Part 1, can identify common time intervals across the data sources for e.g. 6 months or a year before pregnancy.

### *Ever/never exposure analysis*

To estimate associations with “ever being exposed to SSRI/SNRI” in pregnancy and adverse neurodevelopmental outcomes crude and weighted analyses will be used. In the weighted analysis, adjustment for a sufficient set of confounders (defined using literature search and DAGs) will be done via the use of the inverse probability of treatment weight (IPTW), using the propensity score. Logistic regression models will be fitted to estimate the probability of ‘SSRI/SNRI ever exposure’, relative to the two comparison groups, given the set of sufficient confounders. If data allow, the hazard ratio (HR) for adverse neurodevelopmental outcomes, crude and weighted Cox regression analyses with robust standard errors, will be conducted using child age as time scale.

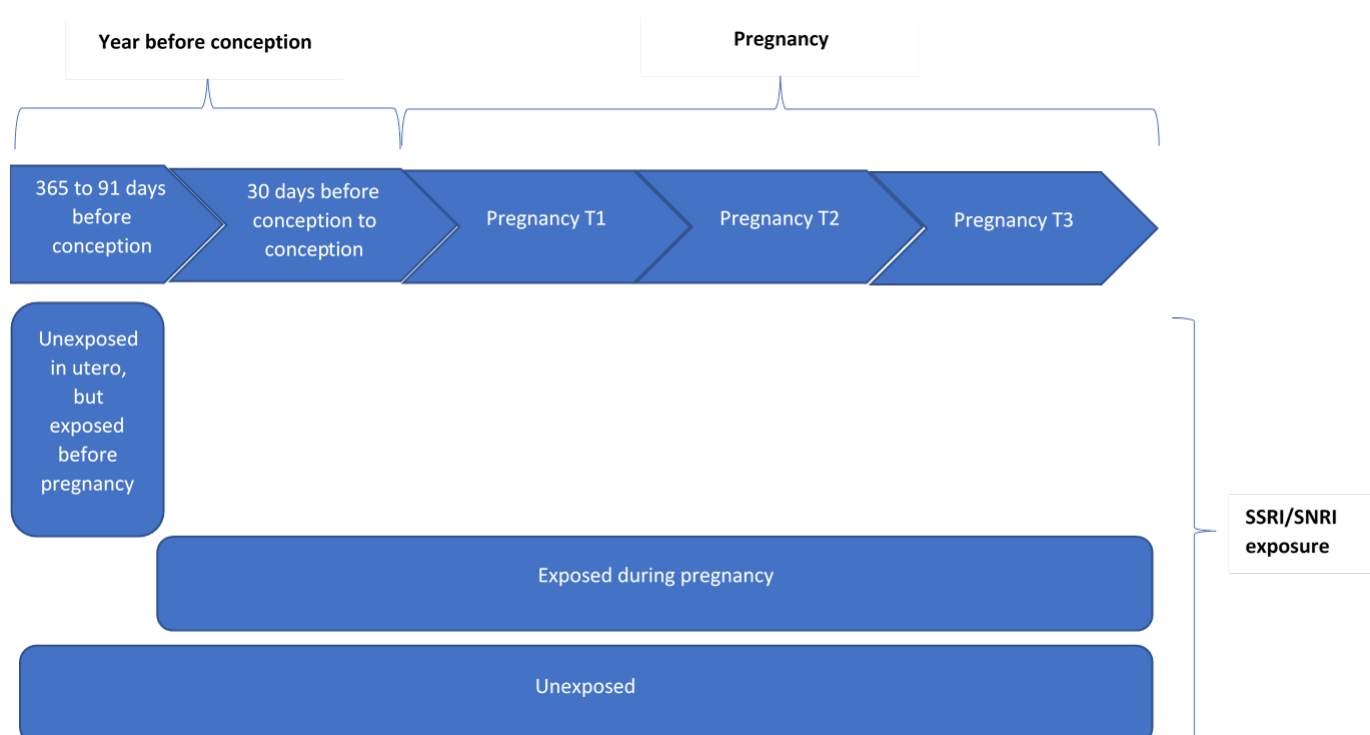
### *Timing of exposure analysis*

To estimate associations by timing of exposure (see Figure 6), we will fit marginal structural models (MSM) to account for i) time-varying SSRI/SNRI exposure; ii) time-varying confounders (i.e. depression diagnosis) which are affected by prior SSRI/SNRI treatment. We will estimate the probability of SSRI/SNRI treatment using a pooled logistic regression in which the outcome is current treatment with an SSRI/SNRI in early, mid or late pregnancy, and covariates are maternal baseline factors, time-varying and time-fixed confounders. If data allow, we will then derive stabilized IPTW for each pregnancy at each time point. Marginal structural Cox models with robust standard errors will be fitted applying the IPTW, as described earlier.

### *Duration of exposure analysis*

To estimate associations by duration of exposure, both crude and weighted analyses will be conducted, as for the ever/never exposure analysis. Logistic regression models will be first fit to estimate the probability of ‘SSRI/SNRI exposure’ identified in **part 2** relative to the two comparison groups, given the set of sufficient confounders. Cox models with robust standard errors will be fit applying the IPTW, as described earlier.

Figure 6 Exposure time periods for use in negative control and disease comparator analysis



## Sub-analyses

### *P-gp substrate/ inhibitors and BCRP substrate/ inhibitors*

The list of P-gp substrate/ inhibitors and BCRP substrate/ inhibitors associated with SSRI/SNRI exposures will be updated during the project. Based on the information available to date, within those exposed to SSRI/SNRI during pregnancy the impact of P-gp substrate/ inhibitors and BCRP substrate/ inhibitors on the risk of adverse neurodevelopmental outcomes will be assessed by examining the risk of adverse outcomes in the below groups, where exposure numbers allow.

#### P-gp substrate/ inhibitors

Monotherapy with an SSRI/SNRI which is a P-gp substrate (SSRI/SNRI-P-gp-S) vs. an SSRI/SNRI-P-gp-S, and another medication which is a P-gp substrate or inhibitor:

- Citalopram monotherapy (allowing other medications prescribed so long as they are not listed as P-gp substrates or inhibitors) compared with...
- Citalopram co-prescribed with a medication that is a P-gp substrate or inhibitor (allowing one or more medications that are P-gp substrates or inhibitors)

Monotherapy with an SSRI/SNRI that is a P-gp substrate (SSRI/SNRI-P-gp-S) vs. an SSRI/SNRI-P-gp-S and another medication that is a P-gp inhibitor:

- Citalopram monotherapy (allowing other medications prescribed so long as they are not listed as P-gp substrates or inhibitors) compared with...
- Citalopram co-prescribed with a medication that is a P-gp inhibitor (allowing one or more medications that are P-gp inhibitors)



## BCRP substrate/ inhibitors

Monotherapy with an SSRI/SNRI that is a BCRP substrate (SSRI/SNRI -BCRP-S) vs. an SSRI/SNRI-BCRP-S and another medication that is a BCRP substrate or inhibitor:

- Paroxetine monotherapy (allowing other medications prescribed so long as they are not listed as BCRP substrates or inhibitors) compared with...
- Paroxetine co-prescribed with a medication that is a BCRP substrate or inhibitor (allowing one or more medications that are BCRP substrates or inhibitors)

Monotherapy with an SSRI/SNRI that is a BCRP substrate (SSRI/SNRI -BCRP-S) vs. an SSRI/SNRI-BCRP-S and another medication that is a BCRP inhibitor:

- Paroxetine monotherapy (allowing other medications prescribed so long as they are not listed as BCRP substrates or inhibitors) compared with....
- Paroxetine co-prescribed with a medication that is a BCRP inhibitor (allowing one or more medications that are BCRP inhibitors)

At present no analysis of the P-gp inhibitors (fluvoxamine or sertraline) is planned but this may change once the list of P-gp substrate/ inhibitors and BCRP substrate/ inhibitors is updated.

## Missing data

The proportion of missing data will be described for each variable by birth year and patterns of missingness will be explored by cross-tabulating variables with missing data against exposure and outcome (Lupattelli, Wood and Nordeng, 2019). Depending on the pattern of missing data, and what is feasible within the ConcePTION platform, complete case analysis or imputation of missing values, such as single imputation or multiple imputation, will be used (Sterne *et al.*, 2009; Lupattelli, Wood and Nordeng, 2019).

## Sensitivity analyses

Several sensitivity analyses will be performed to assess the robustness of results. It is anticipated that the below will be conducted but additional sensitivity analyses may be needed once data are characterised and preliminary results available.

- Restrict analysis to those exposed 30 days before LMP to end of pregnancy – instead of 90 days before LMP to end of pregnancy
- Restrict to the first pregnancy for women with more than one pregnancy in the study period
- Include those with a single diagnosis of ASD or ADHD (instead of at least two diagnoses or one diagnosis and no ADHD medication)
- Include pregnant women with one SSRI/SNRI in the exposure window (3 months before, and throughout pregnancy)
- Restrict to those who used SSRIs/SNRIs between 365 and 182 days before conception (instead of 365-90 days before conception) to allow for possible epigenetic changes by drug exposures.

Table 9 gives an overview of the data analysis for the cohort study. It should be noted that the analysis for the cohort study is dependent on the results from Part 1 as well as the ability of DAPs to run analyses on individual data. Limited resources and time constraints may affect the amount of analysis that can be performed by each DAP, so we will prioritise what can be done in the time available.

Table 9 Overview of data analysis according to objective in Part 3

Objective	Study design	Cohorts	Outcome	Exposure	Stratification	Statistical method	Measure of association
<b>Main analysis<sup>13</sup></b>							
a	Cohort	Pregnant women with depression	Adverse ND outcomes	SSRI/SNRIs (as defined in Exposure section 8.3)	By type of SNRI/SNRI	Logistic regression, Poisson regression, Kaplan-Meier and Cox proportional-hazard regression model	Odds Ratio (OR) and 95%CI, Relative Risks (RR) and 95% CI and Hazard Ratio (HR) and 95% CI
b	Cohort	Pregnant women with SSRI/SNRIs exposure	Adverse ND outcomes	SSRI/SNRIs (as defined in Exposure section 8.3)	Co-medication with P-gp substrate/inhibitors or BCRP substrate/inhibitors	Logistic regression, Poisson regression, Kaplan-Meier and Cox proportional-hazard regression model	Odds Ratio (OR) and 95%CI, Relative Risks (RR) and 95% CI and Hazard Ratio (HR) and 95% CI

<sup>13</sup> Analysis of time varying confounders uses same statistical techniques as the main analysis

## Breastfeeding sub-study

With the exception of the breastfeeding variables, this sub-study will be confined to existing variables.

- a. Description of data available, with timeframes, in each country
- b. Selection of a common outcome measure, likely 4-8 weeks
- c. Investigate selected factors associated with breastfeeding status including specified prescription medications and diagnoses e.g. Associations with breastfeeding at this time point (illness [depression in DP 1.2], prescriptions of SSRI/ SNRI/antidepressants in trimester 1 but not 2 & 3, prescriptions in trimesters 2 or 3, unmedicated depression). Covariates: SES, age, BMI, SGA, gestational age, smoking, parity (primip / multip). Sensitivity analyses: exclude substance misuse/heavy alcohol use, multiples (including twins), congenital anomalies.
- d. Breastfeeding as a predictor of neurodevelopmental outcomes. Analyses as above:
  1. with and without breastfeeding variable to test for the possibility of breastfeeding being a mediator variable.
  2. with a breastfeeding \* antidepressant interaction variable to test moderation
  3. with prescription of SSRI/ SNRI/ antidepressants during lactation to test confounding
- e. mediator analysis if conditions are met i.e. positive results in c & d1 above.
- f. collider bias - prevalence of breastfeeding in the included and excluded infants to test for selection and potential collider bias (Wales data only).

Table 10 below gives an overview of the data analysis plan.

*Table 10 Overview of breast-feeding data analysis*

Objective	Population	Frequencies and proportions	Stratification	Measure of association
Prevalence of breast-feeding	A. women with depression treated  i.e. at least 2 records of antidepressant medication prescribed or dispensed)	N (%)	by presence of diagnosis of depression, (before and during the pregnancy of interest),  overall and by calendar year,  at the time of birth and during the post-natal period	A/C Unadjusted OR (95% CI)
Prevalence of breast-feeding	B. women without any antidepressant medication, with depression (unmedicated depression)	N (%)	during the post-natal period, overall and by calendar year	B/C Unadjusted OR (95% CI)
Prevalence of breast-feeding	C. women without any antidepressant medication, without depression (general population)	N (%)	during the post-natal period, overall and by calendar year	
	D. women with medication but no diagnosis of depression			D/C

## Valproic acid

The risk of ASD, ADHD, learning disability or disorders of intellectual development and delayed infant development among pregnancies with **valproic acid exposure** in the three months before pregnancy through to the end of pregnancy will be **compared to** the risk in the **population comparison group**.

### Case-control study

Three analytic approaches will be taken:

- Case-malformed control study with prior hypothesis
- Case-malformed control study without prior hypothesis
- Case series review (where less than 20 exposures per medication are recorded in the database).

Case-malformed control study with prior hypothesis.

Cases will be registrations with a congenital anomaly for which a published signal exists in the literature relating to the class of medication investigated. A preliminary list, which will be updated before the analysis, is included in Appendix 14. Controls will be all other registrations divided into non-genetic registrations and genetic syndrome registrations (i.e. two control groups). The non-genetic registrations will be the primary comparison group. If the non-genetic group is small due to a large number of registrations being assigned as cases, the two control groups may be combined.

Odds Ratios (95%CI) will be calculated comparing the proportion of exposures to the medication(s) of interest in the case group to the control group. Results will be shown for subgroups with at least 3 exposed cases.

#### Case-malformed control study without prior hypothesis

Each EUROCAT subgroup included in the non-genetic control group as described above will be considered a “case” group in turn, compared with all other (non-genetic) controls. Where there are no prior hypotheses, this will be the main analysis. If this analysis reveals a specific association between a EUROCAT subgroup and the medication of interest, a sensitivity analysis will be performed in the prior hypothesis design above, excluding that anomaly from the control group.

Odds ratios will be calculated with 95%CI, with adjustment for multiple testing by controlling the False Discovery Rate using the method proposed by Benjamini and Yekutieli (2001) (Benjamini and Yekutieli, 2001). Results will be shown for subgroups with at least 3 exposed cases across all DAPs and where small number restrictions allow.

#### Case series review.

When the number of registrations exposed to a medication is very low (below 20), and there is no prior signal to investigate, the series of exposed registrations will be reviewed for evidence of unusual MCA patterns (e.g. multiple MCAs, rare MCAs), and to contribute to the case report literature. It is expected that most such cases may be chance associations with the medication in question.

Case lists will be reviewed by a panel (epidemiologist, medical geneticist, pharmacologist). If a finding of concern is made, registries will be asked to find out more information about exposure (e.g. exact timing, dose) where possible.

Case reviews will be published in such a way that no identifiable information is included. All publications will be reviewed by participating registries before submission to check disclosure risks.

### **8.8. Quality control**

The studies will be conducted in line with the ENCePP Code of Conduct for scientific independence and transparency, and the FAIR (Findable, Accessible, Interoperable, Reusable) principles of the ConcePTION project.

Each DAP will be responsible for the extraction, transformation, and loading (ETL) of their original data to the ConcePTION Common Data Model (CDM). Standardized scripts will be written by the group of statisticians in R for data characterization, and sent, along with instructions, to participating DAPs using the ConcePTION task management system.

The DAPs are responsible for converting their data to the CDM using their preferred software and subsequently running the provided R script against the CDM-converted data. The results of the R-script will be submitted to a computing platform that can be accessed remotely by DAPs and ConcePTION partners using authentication. Access to each DAP's results on the platform will be limited to the DAP, WP1 public partner statisticians, and WP7 public partner statisticians. Results can only be used following approval from each respective DAP.

Data quality will be assessed according to a clear framework based on the ADVANCE database characterization process, the United States FDA Sentinel System data quality indicators the Observational Health Data Sciences and Informatics (OHDSI) data quality dashboard (in development), and EUROCAT indicators for population-based healthcare data sources. The data quality and characterization checks described below will take place in collaboration with partners. All data will remain local and only summary measures described below will be inspected in collaboration with WP7 partners and the task force for data transformation. This process will proceed iteratively in collaboration with each DAP until consensus on fitness for purpose has been reached between WP7 and the DAP. The result of this consensus process and some core results will be made available on the catalogue in a private area for inspection by investigators and DAPs. For all indicators and characterization output resulting in a cell count less than 5, counts will not be reported and will be replaced with "<5" programmatically to meet small number restrictions where applicable.

EUROmediCAT data will also be characterized and sent to each registry for approval and a decision taken, in agreement with the registry, that they are "fit for purpose". Since the exposure-MCA events are rare, data cleaning will consist of sending lists of exposed registrations to each participating registry to confirm the exposure, the outcome (MCA), and the timing of exposure (first trimester). The text information transmitted with exposed registrations regarding exposure, diagnosis, family history and general information will also be examined for relevant information. All cases of teratogenic syndromes should be individually assessed before exclusion, to check for the coding of the medication of interest as an embryopathy.

Level 1 data checks review the completeness and content of each variable in each table of the ConcePTION CDM to ensure that the required variables contain data and conform to the formats specified by the CDM specifications (e.g., data types, variable lengths, formats, acceptable values, etc.).

This is a check conducted in collaboration with DAPs to verify that the ETL procedure to convert from source data to the ConcePTION CDM has been completed as expected. Formats for all values will be assessed and compared to a list of acceptable formats. Frequency tables of variables with finite allowable values will be created to identify unacceptable values.

Level 2 data checks assess the logical relationship and integrity of data values within a variable or between two or more variables within and between tables. Examples of this type of check include: prostate cancer diagnoses in female subjects, observations occurring after a recorded death date, very high birth weight in combination with preterm birth, etc. In this check, we will assess records occurring outside of recorded person time (i.e. before birth, after death, or outside of recorded observation periods).

Level 3 checks will quantify subpopulations of interest. Counts of codes extracted to identify each event and exposure of interest will be calculated overall and by calendar year.

Following completion of level 1, 2 and 3 checks, WP7 will review results with DAPs and assess any detected errors.

## **8.9. Limitations**

A severe limitation will be not having access to case data to test models.

### Ascertainment of exposure

Reliance on prescription or dispensing records means that it is not possible to tell if a mother took the medication which was prescribed/dispensed. Also, the assumption of daily dose intake based on the DDD may incorrectly estimate the treatment length associated with a specific prescription/dispensation date. Both limitations may lead to misclassification of exposure status overall and/or by pregnancy trimester because some women may not take the medication or may stockpile the medication and take it later. Women in SSRI/SNRI exposed group who do not adhere to their prescribed medications will have similar outcomes to those in the untreated group with depression, minimising any differences between groups.

Some of the P-gp or BCRP transporter substrates (S) or inhibitors (I) do not require a prescription. The use of these over the counter medications will therefore be underestimated in the administrative prescribing data sources. This would lead to an underestimation of their effect.

Few data sources collect breastfeeding information and those which do often collect limited information such as breastfeeding at birth. Initiation of breastfeeding is however usually regarded as indicating intention, rather than successful breastfeeding (Fiona McAndrew, Jane Thompson, Lydia Fellows, Alice Large, 2012).

### Ascertainment of disease and disease severity

The indication for the medication is not comprehensively available in any of the prescribing databases in this study. Administrative databases may lack, or incompletely record, clinical details such as indications for prescriptions and severity of illness. If identification of maternal mental illness, is based on hospital diagnoses only it will be limited to the more severely affected (Morales *et al.*, 2018). In some countries clinicians may be reluctant to record a depression diagnosis, and instead may record depression symptoms, as the diagnosis triggers a minimal required follow-up or because it has implications for the employment or insurance status of the patient. This may mean women with depression are under identified in some data sources. Some pre-pregnancy depression diagnoses may be missed as women may have been diagnosed before the start of the period used here to identify pre-pregnancy depression. This will be less of an issue for pregnancy and post-pregnancy depression as women are monitored much more closely by the healthcare system during and immediately following pregnancy than they are pre-pregnancy. The clinical course of depression such as worsening or improving symptoms and resolution of depression / depressive symptoms, will also be difficult to follow in the limited information available in the administrative datasets. Likewise, the success of antidepressant treatment may not be obvious so when interpreting the results it must be remembered that poorly controlled depression among the SSRI exposed group may further confound results (Fitton *et al.*, 2020).

There will be some degree of under ascertainment in relation to the neurodevelopmental outcomes of interest as children who receive a diagnosis of ASD/ADHD in a private healthcare setting will not necessarily be identified as a case in the administrative healthcare

datasets. Similarly, children whose ASD, ADHD or delayed infant development was undiagnosed at the end of follow-up will not be identified as a case. Children with symptoms of these conditions but who do not quite meet the diagnostic criteria would not be detected in this study. Those who are identified at a younger age are likely to be the more severely affected and this may bias towards non- exposure causes such as genetic diagnoses. Approaches to neurodevelopment diagnosis may vary across included countries and even regions of a specific country. The years of follow up across data sources also varies which may also introduce a source of bias when comparing rates across databases.

The use of medication for ADHD across Europe will vary and this in turn will affect the ability to identify ADHD in those data sources where medication is the only indicator of ADHD. Some medications, such as bupropion or modafinil, may be used off label to treat ADHD. As such we may misclassify such children as not having ADHD if there is no diagnosis information. This will be rare though and is preferable to classifying all children taking these medications as having ADHD.

### Limited/missing covariate information

The age of diagnosis of ASD, ADHD, disorders of intellectual development and delayed infant development might be affected by external and extraneous factors. If these factors are differentially distributed in exposed and unexposed groups, the actual associations may be biased. We will adjust for some factors such as maternal SES which may influence age of diagnosis to reduce the bias to some extent. However, we cannot rule out the confounding effects of unmeasured factors. Administrative databases may also lack, or incompletely record, confounding variables such as illicit drug use, alcohol consumption or smoking status. When available such information is often reliant on maternal self-report. Social desirability bias, a bias that tends to be important when the questions deal with socially desirable (or undesirable) attitudes and behaviours (Grimm, 2010), may make women reluctant to admit their true alcohol (Lange *et al.*, 2014), smoking and illicit drug use. Indeed, few studies have been able to adjust for the effect of illegal drug use when examining outcomes following SSRI exposure (Fitton *et al.*, 2020). Illicit/recreational drug use is typically not well captured in administrative data. It may be possible to identify those diagnosed with problems, but not casual users or even regular users with no problems. The definition of 'illegal' drug use may vary across countries and some drugs which may be abused can also be prescribed such as methadone (in drug rehabilitation programmes) and dihydrocodeine, diazepam etc. as part of patient care.

We shall not explore paternal exposure, maternal sibships, family histories or environmental exposures, due to limited resources and limitations of the data.

Covariate information available in the EUROmediCAT database is limited.

### Study power

#### Part 3: Cohort study

The prevalence of maternal depression, SSRI/SNRI use and adverse neurodevelopmental outcomes are shown below, see Table 11.



*Table 11 Prevalence of maternal depression, SSRI/SNRI use and adverse neurodevelopmental outcomes used in the sample size calculations*

<b>Mother</b>	
Maternal depression	10-20% (Gorman, Kao and Chambers, 2012; Charlton <i>et al.</i> , 2015; Zoega <i>et al.</i> , 2015; Molenaar <i>et al.</i> , 2020)
SSRI/SNRI used at some stage during pregnancy	1-10% (Gorman, Kao and Chambers, 2012; Charlton <i>et al.</i> , 2015; Zoega <i>et al.</i> , 2015; Molenaar <i>et al.</i> , 2020)
Sodium valproate used at some stage during pregnancy	0.02-0.1% (Hurault-Delarue <i>et al.</i> , 2019; Julia <i>et al.</i> , 2021)
<b>Child</b>	
ADHD	3–5 % (Polanczyk <i>et al.</i> , 2014, 2015)
ASD aged 7-9 years	0.4-2.0% (Posada de la Paz, 2018)
ID disorders	1-1.5% (Maulik <i>et al.</i> , 2011; McKenzie <i>et al.</i> , 2016)
Delayed infant development	Will be identified in <b>Part 1</b> .

Using the prevalence of outcomes above and sample size calculations below with 80% power and type I error rate of 0.05:

If 5% of women use SSRI/SNRIs during pregnancy to detect a 50% increased risk: for ASD/ID disorders, we would require a sample size of around 75,000 and for ADHD 14,000 children (see figures below).

If 1% of women use SSRI/SNRIs during pregnancy to detect a 50% increased risk: for ASD/ID disorders, we would require a sample size of around 360,000 and for ADHD 68,000 children (see figures below).

If 0.1% of women use a specific SSRI, SNRI or sodium valproate during pregnancy to detect a 50% increased risk: for ASD/ID disorders, we require a sample size of around 3.5 million and for ADHD 67,500 children (see figures below).

Cohort study sample sizes – 80% study power and type I error rate of 0.05

Study sample size when 5% of the study population are using SSRI/SNRI medications

		<b>Baseline prevalence of Outcome</b>				
		<b>0.01%</b>	<b>0.1%</b>	<b>1%</b>	<b>5%</b>	<b>10%</b>
<b>Risk Ratio</b>	<b>1.1</b>	170,048,707	17,029,023	1,687,055	323,324	152,857
	<b>1.2</b>	43,888,044	4,384,587	434,241	83,099	39,206
	<b>1.5</b>	7,610,713	760,263	75,218	14,324	6,713
	<b>2</b>	2,133,487	213,082	21,041	3,971	1,836
	<b>5</b>	209,512	20,896	2,035	357	146

Study sample size when 1% of the study population are using SSRI/SNRI medications

		<b>Baseline prevalence of Outcome</b>				
		<b>0.01%</b>	<b>0.1%</b>	<b>1%</b>	<b>5%</b>	<b>10%</b>
<b>Risk Ratio</b>	<b>1.1</b>	816,484,080	81,572,607	8,081,460	1,548,911	732,340
	<b>1.2</b>	209,883,964	20,968,283	2,076,714	397,462	187,553

	<b>1.5</b>	36,211,891	3,617,363	357,910	68,179	31,960
	<b>2</b>	10,065,884	1,005,338	99,283	18,742	8,672
	<b>5</b>	946,776	94,426	9,191	1,609	655

Study sample size when 0.1% of the study population are using a specific SSRI or SNRI medication or sodium valproate

		<b>Baseline prevalence of Outcome</b>				
		<b>0.01%</b>	<b>0.1%</b>	<b>1%</b>	<b>5%</b>	<b>10%</b>
<b>Risk Ratio</b>	<b>1.1</b>	8,088,321,488	808,081,490	80,057,486	15,344,223	7,255,043
	<b>1.2</b>	2,078,385,997	207,639,542	20,564,892	3,936,015	1,857,381
	<b>1.5</b>	358,172,230	35,779,422	3,540,137	674,401	316,157
	<b>2</b>	99,366,025	9,924,276	980,096	185,033	85,616
	<b>5</b>	9,246,765	922,213	89,749	15,708	6,378

### Part 3: Case-control study

The sample size available will vary with the signal anomalies being examined (case group) and the control group used (non-signal or genetic control groups). Analyses will only be performed for subgroups with at least 3 exposed cases.

## 9. Other aspects

### Ethical considerations

An umbrella protocol covering the five demonstration projects was circulated to the DAPs to enable them to get local ethical approval (where applicable) and to use their data in the demonstration projects.

We will present the protocol to an independent clinical expert with experience in treating pregnant women with depression for input in the SAP and discussion of results.

This project is based on secondary use of data, and will follow the ENCePP Code of Conduct, Revision 4 ([http://www.encepp.eu/code\\_of\\_conduct/documents/ENCEPPCodeofConduct.pdf](http://www.encepp.eu/code_of_conduct/documents/ENCEPPCodeofConduct.pdf)) to ensure transparency and high scientific standards. If an industry partner's company manufactures antidepressants, he/she will only be involved up to the protocol development stage i.e. they will not be involved in the analysis/ interpretation of results.

## 10. Protection of human subjects

The project will follow the EU General Data Protection Regulation as well as all ethical and institutional regulations relevant for each data source in the project. Each DAP will ensure that rules and regulations are followed and that required approvals are obtained. Databases may require approval indicating that informed consent is waived and the rationale for this decision will be maintained. The protocol and waiver of informed consent will be reviewed and approved by the appropriate authority (e.g. Research Ethics Board/ Institutional Review Board/Data Protection Officer) before study start. Copies of all approvals will be stored in the ConcePTION secure platform. DAPs will ensure that sensitive data are stored and analysed

at a local secure platform (GDPR compliant). In some instances, this may include a Data Protection Impact Assessment performed by the appropriate Data Protection Officer.

Prior to use of the EUROMediCAT central database, all registries must give approval to use their data in the study. In addition, this study will be submitted to the University of Ulster ethics committee for ethical approval. All registries are responsible for ethics permission in their own areas, but as no additional data than is usually collected by the registry, no problems are foreseen. All data are held anonymously in the EUROCAT Central Registry, within University of Ulster, Newtownabbey. No sensitive data will be taken outside the Central Registry and EUROCAT data handling policies will be adhered to at all times.

#### Low numbers

Some DAPs such as the SAIL databank (Wales) will only provide data with the requirement that aggregate data on fewer than 5 people are not released. SAIL prohibits the public release of numbers 1-4 in any data category (except 'information missing'). This applies to all documents in the public domain and communications outside secure links (e.g. emails). This not only applies to text and tables, but also to reporting that could lead to the derivation of a low number in any category, for example:

1. Where an unadjusted OR or RR is reported for a contingency table, and the denominators and numerator in the larger category are available, it is easy to calculate the missing value.
2. Where a proportion is reported in a figure or graph or table, and the total number of cases is reported either in the same report or another report or publication, the number can be calculated.
3. Where numbers in categories across Europe are low\*, they only have permission to say that 'Wales contributed data'. It is a breach of their conditions of approval to say 'Wales contributed cases'.

\*low can only be defined with reference to the number of cases and countries.

In Wales European projects have permission to pass low numbers (1-4) to the centre responsible for analysis, via secure links to authorised colleagues on the above conditions. These numbers are to be aggregated before reporting.

<https://www.ncbi.nlm.nih.gov/books/NBK350762/>

## **11. Management and reporting of adverse events/adverse reactions**

This study will adhere to the International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practice <https://www.pharmacoepi.org/resources/policies/guidelines-08027/>. Since this is a non-interventional study design which is based on secondary data use, reporting of Adverse Events and Adverse Drug Reactions is not required.

## **12. Plans for disseminating and communicating study results**

The results of this study will be published as scientific papers in peer-reviewed journals. Small numbers will not be published from DAPs in countries where the data protection legislation prohibits this for e.g. if numbers less than 5 or 8 cannot be reported.

Preparation of such manuscripts will be prepared independently by the investigators and in accordance with the current guidelines of STrengthening the Reporting of OBservational

studies in Epidemiology (STROBE), the ENCePP standards (European Medicines Agency, 2018) and EMA guidelines (European Medicines Agency, 2020). The ConcePTION Management Board will review draft manuscripts and provide comments prior to submission of the manuscript for publication.

The following funding disclosure will be used:

The publication is part of the activities within the ConcePTION project. It has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 821520. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.”

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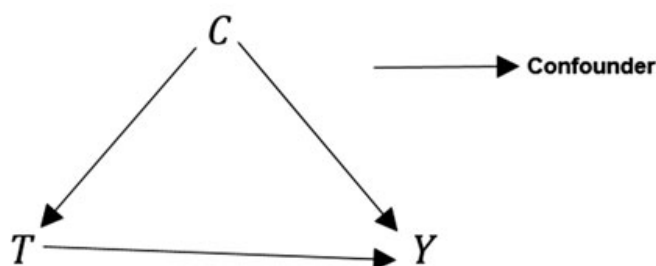
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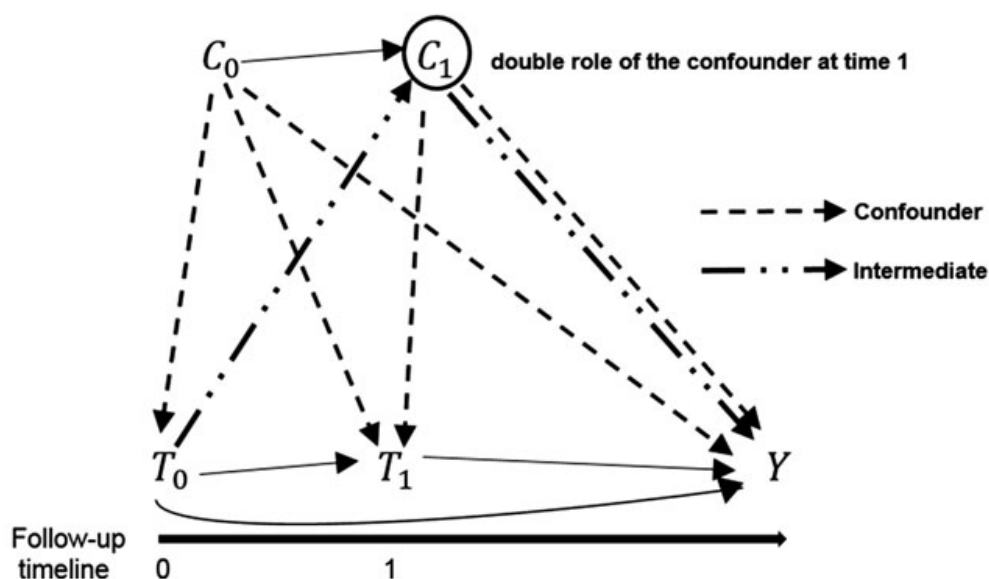
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Appendix 1 Directed acyclic graphs showing confounding and time varying confounding  
**DAG A: Confounder at a single time point (cross-sectional studies)**



**DAG B: Time-varying confounder (longitudinal studies)**



DAG A: Relationship between a confounder variable  $C$ , a treatment variable  $T$ , and an outcome variable  $Y$  in a time point study. DAG B: Relationships between a time - varying exposure, a time varying confounder (which also acts as an intermediate factor), and an outcome variable in a longitudinal study. The double role of the confounder level  $C_1$  is indicated by drawing a double arrow. The observations at each time point of the time-varying exposure and the time - varying confounder are indicated, respectively, with  $T_0$ ,  $T_1$ ,  $C_0$ , and  $C_1$  since they are measured at time 0 and at time 1. The variable  $Y$  indicates the outcome. For simplicity of the graphical representations, in DAG A and in DAG B a variable representing the set of potential unmeasured confounders has been omitted (Pazzagli et al., 2018).

## Appendix 2 Identification of maternal depression

### Identification of maternal depression and mental illness

Underlying maternal mental illness in pregnancy and/or the postpartum period has been shown to be associated with suboptimal behavioural, cognitive, and socio-emotional development (Field, 2011; Kingston, Tough and Whitfield, 2012; Kingston and Tough, 2014; Kobayashi *et al.*, 2016; Kaplan *et al.*, 2017; Wood *et al.*, 2018; Halvorsen *et al.*, 2019) raising the potential for confounding by indication. Both maternal depression, and antidepressant use, may change over time. Maternal depression therefore has the potential to be a time-varying confounder when estimating the risk of adverse neurodevelopmental outcomes following antidepressant exposure during pregnancy (Mansournia *et al.*, 2017b). There are two distinct types of time-varying confounders: (1) time-varying confounding not affected by prior treatment, and (2) time-varying confounding affected by prior treatment (Burcu and Oehrlein, 2016). Conventional statistical methods can introduce bias in the presence of time varying confounding (Mansournia *et al.*, 2017b) particularly time-varying confounding affected by prior treatment (Burcu and Oehrlein, 2016). As maternal depression is a time varying confounder affected by prior SSRI/SNRI treatment appropriate statistical methods should be used to adjust for the confounding effect of depression, but not for the effect of SSRI/SNRI exposure on depression. In order to do this however it must be possible to identify maternal depression, over time, in the administrative datasets used.

A range of algorithms have been published and validated to identify depression in primary care (Spettell *et al.*, 2003; John *et al.*, 2016; Doktorchik *et al.*, 2019), hospital discharge diagnosis records (Fiest *et al.*, 2014) and claims data (Solberg *et al.*, 2006). These tend to be database specific and there is no definitive gold standard algorithm. A systematic review by Townsend *et al.* found that including pharmacy records indicating an antidepressant prescription tends to increase sensitivity by capturing more patients with depression. As antidepressants are not just prescribed for depression it comes at the expense of false positive cases that diminish the positive predictive value (PPV) (Townsend *et al.*, 2012). Spettell *et al.* recommended the use of at least two diagnoses, two prescriptions for an antidepressant or one prescription and a diagnosis (Spettell *et al.*, 2003). The use of 1 inpatient or two outpatient codes within a year has also been shown to improve the PPV (Spettell *et al.*, 2003; Solberg *et al.*, 2006). There is evidence of decreasing use of diagnostic codes in favour of symptom codes in the UK (Rait *et al.*, 2009; John *et al.*, 2016). The most suitable algorithms for detecting depression in administrative data will vary depending on the nature of the data (primary care, hospital, claims etc.) and on the context. For surveillance purposes, the most inclusive algorithms will ensure that as few affected individuals are missed as possible. In contrast where diagnostic certainty is required more restrictive algorithms are preferable (Townsend *et al.*, 2012; Fiest *et al.*, 2014). The impact of different algorithms to determine depression, and depression timing, will be explored. It is important to note that IMI ConcePTION does not have access to patients or their medical charts, although some DAPs may review a sub-sample of charts as a validation check. Therefore, validation activities cannot compare algorithm-identified cases to a gold standard. Standard accuracy measures such as positive-predictive value cannot be produced. Instead, changes in prevalence across various dimensions (calendar time, maternal age etc), consistency with published estimates obtained from traditionally validated work, and expert opinion will be used to determine face validity.

Across the data sources contributing to this project maternal depression may be recorded in a number of ways, see Table 1 below. The estimated sample available across the DAPs is included in Appendix 2.

Table 1 Depression information across DAPs

Data Access Provider (Births with medication exposure available)	Years with medication exposure in pregnancy	Primary care diagnoses	Inpatient diagnoses	Outpatient diagnoses	Prescriber speciality	Other information to identify depression
EFEMERIS & POMME	2004-2009  2010 and 2015	None	ICD-10 if hospitalised in the public University Hospital of Toulouse ONLY DURING PREGNANCY 2004-2019	None	Yes	Special reimbursement for “depression as a long term disability”
Finland	1996-2019	ICPC2 from 2012	ICD-10 1996-2019	ICD-10 1996-2019	Only available in Finnish. Variable changed, uncertain availability of this information 2015 onwards.	
GePaRD	2006-2019	Primary care does not exist in health system.	ICD-10-GM 2004-2019	ICD-10-GM 2004-2019	Yes	
Italy - Emilia Romagna	2004-2019	None	ICD-9-CM 2004-2019	ICD-10 2013-2019	No	
Italy – Tuscany	2003-2019	None	ICD-9-CM 2003-2019	None	No	

Norway	2004-2019	None	ICD-10 2008-2019	ICD-10 2008-2019	Yes	
Wales	1998-2019	Read codes 2000- ~ 79% of population covered	ICD-10 2000-	ICD-10 2000-	No	

**NOTE:** maternal depression information does not necessarily cover the same period as that with medication exposure available.

When validating maternal depression the aims are to:

1. To compare a range of algorithms to identify depression
2. To determine how the prevalence of depression varies in the pre-pregnancy, pregnancy and post-natal periods based on the algorithms used to identify depression

### Depression diagnosis codes

In Finland and Wales medication use, primary care and hospital inpatient and outpatient diagnoses will be available. In GePaRD and Norway medication use and hospital inpatient and outpatient diagnoses will be available. In Tuscany medication and hospital inpatient diagnosis only will be available. In Emilia Romagna only medication use and outpatient mental health service diagnoses are available. In EFEMERIS/POMME medication use and hospital inpatient diagnoses from three months before and during pregnancy will be available as well as special reimbursement for “depression as a long term disability”. In all other data sources information should be available pre, during and post pregnancy.

Three categories of maternal depression will be examined based on the below codes:

### **Depression**

- ICD-9: Major Depressive Disorder, single episode (296.2), Major Depressive Disorder, recurrent episode (296.3), Dysthymic Disorder/neurotic depression (300.4) Depressive Disorder not elsewhere Classified (311), Mental disorders complicating pregnancy childbirth or the puerperium (648.4).
- ICD-10: depressive episode (F32), Recurrent depressive disorder (F33), dysthymia (F34.1), mixed anxiety and depressive disorder (F41.2), postnatal/postpartum depression (F53.0).
- ICPC2: It is therefore not possible to distinguish those who had just depression in ICPC2. Depressive disorder code includes depressive neurosis/psychosis; mixed anxiety and depression; puerperal/postnatal depression; reactive depression) (P76).
- Read codes: depression diagnosis, symptom and review codes, see Appendix 1 (to be updated).

Data characterisation by WP7 will reveal if the level of detail recorded provides information on severity and/or type of depression. This will be indicated by the number of digits available in ICD or Read codes. ICPC2 does not indicate severity of depression and it does not have different codes for depression and anxiety – P76 includes depression but also mixed anxiety and depression. In Finland, while ICPC2 is the official system used physicians still use ICD10. Some regions only use ICPC2 but ICD10 will still capture a lot of diagnoses.

The number of depression diagnosis codes and median age at time of first diagnosis will be examined, see Table 2. This will be done for each data set/table which records diagnoses within a DAP. This will facilitate a comparison between primary care, outpatient and inpatient diagnoses. In Finland where both ICD10 and ICPC2 diagnoses may be recorded in primary care there should be a) a table for ICPC2, b) a table for ICD10 and c) a table for ICPC2 and ICD10). Tables to be produced for women of childbearing age with the cohort entry date the latest of the date when they joined the database, the date of their 15th birthday or 1st of Jan of the earliest year of data available in the data source. The cohort exit date will be the earliest of the date they left the database, date of death, the date of their 49th birthday or 31st of December of the last full year of data available in the data source. For Finland who only have women who had a pregnancy the table will be produced for this sample only. In EFEMERIS/POMME and the medical birth registries (such as in Finland or Norway) where a

woman is in the dataset during her pregnancy this table is not applicable. Instead, the median, and IQR, number of depression diagnoses will be requested.

*Table 2 Number of depression diagnosis codes among women of childbearing age (to be completed for each data source which records diagnoses within a DAP).*

<b>Data source/table name</b>		<b>Origin of diagnosis (Primary care, Inpatient, Outpatient)</b>	
<b>Number of depression diagnostic codes</b>	<b>Total number of women N</b>	<b>Median time in study population and Inter Quartile Range (Years)</b>	<b>Median age of women at time of first diagnostic code and Inter-Quartile Range (Years)</b>
<b>0</b>			
<b>1</b>			
<b>2+</b>			
<b>Total</b>			

For each data source within a DAP the median time between first and second depression diagnosis and Inter-Quartile Range (Years) will be calculated, see Table 3.

*Table 3 Median time between first and second depression diagnosis, and Inter-Quartile Range, for women of childbearing age*

<b>Number of depression diagnostic codes</b>	<b>Median time between first and second depression diagnosis and Inter-Quartile Range (Years)</b>
<b>Depression</b>	

#### Antidepressant medication use

All data sources record maternal medication exposure based on prescriptions issued or dispensed. Antidepressants will be identified by ATC codes starting N06A. The number of diagnosis codes, and how this relates to medication, and special reimbursement for “depression as a long term disability” in EFEMERIS/POMME, will be examined among women of childbearing age, or the pregnant population in Finland and EFEMERIS/POMME, as per Table 4 below.



*Table 4 Number of depression diagnosis codes by medication and special reimbursement for “depression as a long term disability” (EFEMERIS/POMME only) across linked datasets within each DAP.*

Number of Depression diagnostic codes	Number of women with					Total number of women
	No antidepressant medication	≥ 1 Antidepressant medication	>1 Antidepressant medication	Special reimbursement for “depression as a long term disability”	>1 Antidepressant and special reimbursement for “depression as a long term disability”	
<b>0</b>						
<b>1</b>						
<b>2+</b>						
<b>Total</b>						

Within each DAP the medication use, diagnosis will be combined as below, see Table 5. Special reimbursement for “depression as a long term disability” is specific to EFEMERIS/POMME and will only be used in this DAP. At least two prescriptions/dispensations for an antidepressant are required before a woman is considered to have depression based on medication use.

*Table 5 Algorithms to identify depression*

Algorithm	Medication	Diagnosis codes	Other measure
<b>Depression only</b>			
D1	>1 antidepressant medication		
D2		≥1 Diagnosis code	
D3			Special reimbursement
D4	>1 antidepressant medication or ≥1 diagnosis code or Special reimbursement		

Each of the tables below will be completed for the four groups below (where available):

- Women of childbearing age
- Women with a pregnancy
  - Pre-pregnancy depression – one year before pregnancy up to three months before the date of conception
  - Pregnancy depression – from three months before or during pregnancy
  - Depression in the post-natal period (depression or post-natal depression) – depression during the first years after delivery

This will be done for each algorithm to determine if the prevalence is internally stable and consistent over calendar year and woman’s age in each DAP. The prevalence seen will be also be compared to that in the published literature. In EFEMERIS only the estimate of pregnancy depression will be possible.

*Table 6 Prevalence over time per 1,000 women for each algorithm separately*

	Algorithm Number	Number of women with diagnoses according to algorithm	Number of women in study population	Prevalence per 1,000 women	95% Confidence Interval of Prevalence per 1,000 women <sup>14</sup>
1996	D1				
1997					
	....				
	....				
2018					
2019					
1996	D2				
1997					

<sup>14</sup> Confidence intervals to be calculated using the Wilson score method

	....				
	....				
2018					
2019					
	Etc.				

Table 7 Prevalence stratified by age and calendar period per 1,000 women for each algorithm separately

<b>Year in study</b>	<b>Age of women</b>	<b>Algorithm Number</b>	<b>Number of women in study population</b>	<b>Number of women with diagnoses according to algorithm</b>	<b>Prevalence per 1,000 women</b>	<b>95% Confidence Interval of Prevalence per 1,000 women<sup>17</sup></b>
1996-2000	15-19	D1				
1996-2000	20-24	D1				
1996-2000	25-29	D1				
1996-2000	30-34	D1				
1996-2000	35-39	D1				
1996-2000	40-44	D1				
1996-2000	45-49	D1				
2001-2004	15-19	D1				
2001-2004	20-24	D1				
2001-2004	25-29	D1				
2001-2004	30-34	D1				

2001- 2004	35-39	D1				
2001- 2004	40-44	D1				
2001- 2004	45-49	D1				
2005- 2009	15-19	D1				
2005- 2009	20-24	D1				
2005- 2009	25-29	D1				
2005- 2009	30-34	D1				
2005- 2009	35-39	D1				
2005- 2009	40-44	D1				
2005- 2009	45-49	D1				
2010- 2014	15-19	D1				
2010- 2014	20-24	D1				
2010- 2014	25-29	D1				
2010- 2014	30-34	D1				
2010- 2014	35-39	D1				
2010- 2014	40-44	D1				
2010- 2014	45-49	D1				

2015-2019	15-19	D1				
2015-2019	20-24	D1				
2015-2019	25-29	D1				
2015-2019	30-34	D1				
2015-2019	35-39	D1				
2015-2019	40-44	D1				
2015-2019	45-49	D1				
2005-2009	15-19	D1				
		.....				
2015-2019	45-49	###				

Cells will be collapsed if small numbers are an issue.

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### Appendix 1 Read Codes for Depression

Eu32.	[X]Depressive episode
Eu320	[X]Mild depressive episode
Eu321	[X]Moderate depressive episode
Eu322	[X]Severe depressive episode without psychotic symptoms
Eu323	[X]Severe depressive episode with psychotic symptoms
Eu324	[X]Mild depression
Eu325	[X]Major depression, mild
Eu326	[X]Major depression, moderately severe
Eu327	[X]Major depression, severe without psychotic symptoms
Eu328	[X]Major depression, severe with psychotic symptoms
Eu329	[X]Single major depressive episode, severe, with psychosis, psychosis in remission
Eu32A	[X]Recurrent major depressive episodes, severe, with psychosis, psychosis in remission
Eu32B	[X]Antenatal depression
Eu32y	[X]Other depressive episodes
Eu32z	[X]Depressive episode, unspecified
E2B..	Depressive disorder NEC
E2B0.	Postviral depression
E2B1.	Chronic depression
1B17.	Depressed
	(no sub levels)
1B1U.	Symptoms of depression
	(no sub levels)
	Depressed
1BT..	mood
	(no sub levels)
9H9..	Mental health annual physical examination done
9H90.	Depression annual review
9H91.	Depression medication review
9H92.	Depression interim review

*Appendix 2 Sample size across DAPs*

DAP	Medication exposure in pregnancy		Primary care diagnoses		Inpatient diagnoses		Outpatient diagnoses	
	Years available	Total births (1,000)	Years available	Total births (1,000)	Years available	Total births (1,000)	Years available	Total births (1,000)
<b>Finland</b>	1996-2019	1,575	2012-2019	424	1996-2019	1,575	1996-2019	1,575
<b>EFEMERIS database</b>	2004-2019	156			2004-2019	156		
<b>POMME database</b>	2010 and 2015	18			2010 and 2015	18		
<b>Italy – Emilia Romagna</b>	2004-2019	573			2004-2019	573	2013-2019	260
<b>Italy - Tuscany</b>	2003-2019	480			2003-2019	480		
<b>Norway</b>	2004-2019	890			2008-2019	720	2008-2019	720
<b>Wales</b>	1998-2020	726	2000-2020 <sup>15</sup>	521.4	2000-2020	660	2000-2020	660
<b>Germany</b>	2006-2019	1,335	Primary care does not exist in health system		2004-2019	1,335	2004-2019	1,335
<b>Total sample</b>		5,735		945		5,499		4,500

<sup>15</sup> Assuming 79% of population of Wales have GP data



### Appendix 3 Attention Deficit Hyperactivity Disorder (ADHD)

ADHD is characterized by a persistent pattern (at least 6 months) of inattention and/or hyperactivity-impulsivity, with onset during the developmental period, typically early to mid-childhood (Fayyad *et al.*, 2017). The degree of inattention and hyperactivity-impulsivity is outside the limits of typical variation expected for age and level of intellectual functioning and significantly interferes with academic or social functioning. Inattention refers to significant difficulties in sustaining attention to tasks that do not provide a high level of stimulation or frequent rewards, distractibility and problems with organization. Hyperactivity refers to excessive motor activity and difficulties with remaining still, most evident in structured situations that require behavioural self-control. Impulsivity is a tendency to act in response to immediate stimuli, without deliberation or consideration of the risks and consequences. The relative balance and the specific manifestations of inattentive and hyperactive-impulsive characteristics varies across individuals and may change over the course of development. To be diagnosed, the behaviour pattern must be clearly observable in more than two settings and impact on everyday functioning.

#### 1. Synonyms / lay terms used

- ☐ ADHD
- ☐ Attention deficits disorder with hyperactivity
- ☐ Attention deficit hyperactivity disorder
- ☐ Attention deficit syndrome with hyperactivity
- ☐ Hyperkinetic disorder

#### 2. Laboratory tests done specific for event

None. Genetic testing may be undertaken to rule out other conditions.

#### 3. Diagnostic tests done specific for event

Diagnostic practices are variable across countries. Diagnosis may be made as part of a multidisciplinary team or by an individual clinician. Information collected to inform the diagnostic process also varies by what information is collected and who this information comes from. At a minimum there is a direct observation of the child by the diagnosing clinician/ team and information on early development and daily functioning collected from parents and educators. Psychometric questionnaires may also be utilized and include the Child Behaviour Checklist (CBCL), Conner's Rating Scales or the Vanderbilt ADHD Rating Scale. Cognitive attention, IQ and other cognitive skills such as language functioning may also be assessed to determine any comorbid difficulties.

Diagnosis maybe based on the guidance in the Diagnostic and Statistical Manual of Mental Disorders, which is now on its 5th edition, rather than on ICD-11 categories.

#### 4. Medications used to treat

Attention Deficit Hyperactivity Disorder can be treated with stimulant medications which include: Methylphenidate (N06BA04), dexamethylphenidate (N06BA11), lisdexamfetamine (N06BA12), atomoxetine (N06BA09) and guanfacine (C02AC02).

Stimulant medication is not always used and instead environmental or behavioural management techniques are utilised.

#### 5. Setting (outpatient specialist, in-hospital, GP, emergency room) where condition will be most frequently /reliably diagnosed

Specialist outpatient appointments. There is often an observation of the child in the home and/or school environment.

**ADHD ICD-10, ICD-9, ICPC2 and Read codes**

ICD-10	Description	Comments
<b>F90</b>	A group of disorders characterized by an early onset (usually in the first five years of life), lack of persistence in activities that require cognitive involvement, and a tendency to move from one activity to another without completing any one, together with disorganized, ill-regulated, and excessive activity. Several other abnormalities may be associated. Hyperkinetic children are often reckless and impulsive, prone to accidents, and find themselves in disciplinary trouble because of unthinking breaches of rules rather than deliberate defiance.	Using this parent code will not allow for the differentiation between inattentive and hyperactive types
Hyp erki neti c dis ord ers		
F90 .0	Disturbance of activity and attention. Attention deficit disorder with hyperactivity, hyperactivity disorder, syndrome with hyperactivity	
F90 .1	Hyperkinetic conduct disorder. Hyperkinetic disorder associated with conduct disorder	
F90 .8	Other hyperkinetic disorder	
F90 .9	Hyperkinetic disorder, unspecified. Hyperkinetic syndrome not otherwise specified	
ICD-9		
<b>314</b>	A disorder characterized by a marked pattern of inattention and/or hyperactivity-impulsivity that is inconsistent with developmental level and clearly interferes with functioning in at least two settings (e.g. At home and at school). At least some of the symptoms must be present before the age of 7 years	Using this parent code will not allow for the differentiation between inattentive and hyperactive types
Atte ntio n defi cit dis ord er		
314	Attention deficit disorder without mention of hyperactivity	
314 .1	Attention deficit disorder with hyperactivity	
314 .8	Other specified manifestations of hyperkinetic syndrome	
ICPC-2(The Directorate of eHealth, 2021)		
P81	Hyperkinetic disorder - attention deficit disorder (ADD); hyperactivity. Early onset of a lack of persistence in activities requiring cognitive involvement, with a tendency to move from one activity to another without completing any one, with disorganised and ill-regulated behaviour, and excessive activity	Excludes hyperkinetic disorder with adolescent onset P23; learning disorder P24. ICD-10 equivalent F90.0; F90.1; F90.8; F90.9.
Read codes		
	To be defined in <b>Part 1</b> with input from DAP.	

## Appendix 4 Autistic Spectrum Disorders

ASD is characterized by persistent deficits in the ability to initiate and to sustain reciprocal social interaction and social communication, and by a range of restricted, repetitive, and inflexible patterns of behaviour and interests (Ousley and Cermak, 2014; Masi et al., 2017). The onset of the disorder occurs during the developmental period, typically in early childhood, but symptoms may not become fully manifest until later, when social demands exceed limited capacities. Deficits are sufficiently severe to cause impairment in personal, family, social, educational, occupational or other important areas of functioning and are usually a pervasive feature of the individual's functioning observable in all settings, although they may vary according to social, educational, or other context. Individuals along the spectrum exhibit a full range of intellectual functioning and language abilities.

### 1. Synonyms / lay terms used

- ☐ Autism
- ☐ Autism syndrome
- ☐ Infantile autism
- ☐ 'ASD'
- ☐ Asperger's syndrome
- ☐ Pervasive developmental disorder
- ☐ Autistic disorder

### 2. Laboratory tests done specific for event

None. Genetic testing may be undertaken to rule out other conditions.

### 3. Diagnostic tests done specific for event

Diagnostic practices are variable across countries. Diagnosis may be made as part of a multidisciplinary team or by an individual clinician. Information collected to inform the diagnostic process also varies by what information is collected and who this information comes from. At a minimum there is a direct observation of the child by the diagnosing clinician/ team and information on early development and daily functioning collected from parents and educators. Psychometric measurements may also be utilized and include the Modified Checklist for Autism in Toddlers (MCAT), Screening Tool for Autism in Toddlers and Young Children (STAT), Autism Diagnostic Observation Schedule (ADOS), Autism Diagnostic Interview-Revised (ADI-R) or the Childhood Autism Rating Scale (CARS). IQ and other cognitive skills such as language may also be assessed to determine any comorbid difficulties. Diagnosis may be based on the guidance in the Diagnostic and Statistical Manual of Mental Disorders, which is now on its 5th edition, rather than on ICD-11 categories.

### 4. Medications used to treat event

None. Certain medications may be used in the treatment of comorbid symptoms (e.g. melatonin for sleep difficulties), but none are specific enough to autism to be utilised as a proxy marker for this condition.

### 5. Setting (outpatient specialist, in-hospital, GP, emergency room) where condition will be most frequently /reliably diagnosed

Specialist outpatient appointments. There may also be some observation of the child in the home and/or school environment.

**ASD ICD-10, ICD-9, ICPC-2 and Read codes**

ICD-10	Description	Comments
<b>F84</b> Pervasive developmental disorders	A group of disorders characterized by qualitative abnormalities in reciprocal social interactions and in patterns of communication, and by a restricted, stereotyped, repetitive repertoire of interests and activities. These qualitative abnormalities are a pervasive feature of the individual's functioning in all situations.	Using the parent code F84 will be unreliable due to the wide variability of conditions included here, some of which are genetic in origin and therefore not linked to disease or medication teratogenicity. F84.3 includes a wide range of heterogeneous conditions including those arising from acquired brain injuries.
<b>F84.0</b> Childhood autism	A type of pervasive developmental disorder that is defined by: (a) the presence of abnormal or impaired development that is manifest before the age of three years, and (b) the characteristic type of abnormal functioning in all the three areas of psychopathology: reciprocal social interaction, communication, and restricted, stereotyped, repetitive behaviour. In addition to these specific diagnostic features, a range of other nonspecific problems are common, such as phobias, sleeping and eating disturbances, temper tantrums, and (self-directed) aggression.	
<b>F84.1</b> Atypical Autism	A type of pervasive developmental disorder that differs from childhood autism either in age of onset or in failing to fulfil all three sets of diagnostic criteria. This subcategory should be used when there is abnormal and impaired development that is present only after age three years, and a lack of sufficient demonstrable abnormalities in one or two of the three areas of psychopathology required for the diagnosis of autism (namely, reciprocal social interactions, communication, and restricted, stereotyped, repetitive behaviour) in spite of characteristic abnormalities in the other area(s). Atypical autism arises most often in profoundly retarded individuals and in individuals with a severe specific developmental disorder of receptive language. Includes typical childhood psychosis and mental retardation with autistic features.	
<b>F84.3</b> Other childhood disintegrative disorder	A type of pervasive developmental disorder that is defined by a period of entirely normal development before the onset of the disorder, followed by a definite loss of previously acquired skills in several areas of development over the course of a few months. Typically, this is accompanied by a general loss of interest in the environment,	

		by stereotyped, repetitive motor mannerisms, and by autistic-like abnormalities in social interaction and communication. In some cases the disorder can be shown to be due to some associated encephalopathy but the diagnosis should be made on the behavioural features. Includes dementia infantilis, disintegrative psychosis and Heller syndrome (childhood disintegrative disorder).	
	<b>F84.4</b> Overactive disorder associated with mental retardation and stereotyped movements	An ill-defined disorder of uncertain nosological validity. The category is designed to include a group of children with severe mental retardation (IQ below 35) who show major problems in hyperactivity and in attention, as well as stereotyped behaviours.	
	<b>F84.5</b> Asperger's Syndrome	A disorder of uncertain nosological validity, characterized by the same type of qualitative abnormalities of reciprocal social interaction that typify autism, together with a restricted, stereotyped, repetitive repertoire of interests and activities. It differs from autism primarily in the fact that there is no general delay or retardation in language or in cognitive development. This disorder is often associated with marked clumsiness. There is a strong tendency for the abnormalities to persist into adolescence and adult life. Psychotic episodes occasionally occur in early adult life.	
	<b>F84.8</b> Other pervasive developmental disorders		
	<b>F84.9</b> Pervasive developmental disorder, unspecified		
<b>ICD- 9</b>			
		Description	Comments
	299 Autistic Disorder	Disorder beginning in childhood marked by the presence of markedly abnormal or impaired development in social interaction and communication and a markedly restricted repertoire of activity and interest; manifestations of the disorder vary greatly depending on the developmental level and chronological age of the individual.	Note infantile psychoses would not be grouped with autism in recent times
	<b>299.0</b> Autistic disorder	Applies to, Childhood autism, Infantile psychosis, Kanner's syndrome	Other specific codes under 299 code

			for non-autism conditions such as Heller's syndrome
<b>299.8</b> Other specified pervasive developmental disorders	Neuropsychiatric disorder whose major manifestation is an inability to interact socially; other features include poor verbal and motor skills, singlemindedness, and social withdrawal. Syndrome or disorder usually first diagnosed in childhood, characterized by severe and sustained impairment in social interactions and restricted, repetitive patterns of behaviours, interests, and activities. Syndrome or disorder usually first diagnosed in childhood, characterized by severe and sustained impairment in social interactions and restricted, repetitive patterns of behaviours, interests, and activities.		
<b>299.80</b> Other specified pervasive developmental disorders, current or active state			
<b>299.81</b> Other specified pervasive developmental disorders, residual state			
<b>299.90</b> Unspecified pervasive developmental disorder	A category of developmental disorders characterized by impaired communication and socialization skills. The impairments are incongruent with the individual's developmental level or mental age. Group of disorders characterized by delays in the development of socialization and communication skills; typical age of onset is before 3 years of age; symptoms may include problems with using and understanding language; difficulty relating to people, objects, and events; unusual play with toys and other objects; difficulty with changes in routine or familiar surroundings, and repetitive body movements or behaviour patterns; autism is the most characteristic and best studied pdd; other types of pdd include Asperger syndrome, childhood disintegrative disorder, and Rett syndrome; prefer nts where possible Broad term for disorders, usually first diagnosed in children prior to age 4, characterized by severe and profound impairment in social interaction, communication, and the presence of		Note genetic conditions will also be included in this code

		stereotyped behaviours, interests, and activities. Compare developmental disabilities. These disorders can be associated with general medical or genetic conditions	
<b>ICPC-2</b> (The Directorate of eHealth, 2021)			
	P99	Psychological disorders other - autism; neurosis NOS.	ICD10 equivalent - F48.1; F48.8; F48.9; F53.8; F53.9; F54; F59; F84.0; F84.1; F84.2; F84.3; F84.4; F84.5; F84.8; F84.9; F88; F89; F99
<b>Read codes</b>			
		To be defined in <b>Part 1</b> with input from DAP.	

## Appendix 5 Learning disability or disorders of intellectual development

### 1. Synonyms / lay terms used

- Mental retardation (or 'retarded')
- Intellectual impairment
- Low IQ
- Incomplete development of the mind
- Feeble-mindedness
- Mental sub normality

### 2. Laboratory tests done specific for event

None. Genetic testing may be undertaken to rule out this as being part of a wider syndrome such as a genetic syndrome.

### 3. Diagnostic tests done specific for event

Diagnostic practices are variable across countries. Diagnosis may be made as part of a multidisciplinary team or by an individual clinician. Information collected to inform the diagnostic process also varies by what information is collected and who this information comes from. At a minimum there is a direct observation of the child by the diagnosing clinician/ team and information on early development and daily functioning collected from parents and educators. If the level of impairment is very obvious no psychometric assessments are utilized however other cases may require an assessment of intellectual functioning. The score from this assessment is called the intelligence quotient (IQ). Other cognitive skills are also likely to be assessed to inform on the extent of the difficulty across cognitive functioning. Learning disability is heterogenous in terms of presentation and aetiologies. Whilst ICD codes are available for 'mild', 'moderate', 'severe' and 'profound' learning disability, these collectively only represent the most severe of cases (despite the utilization of the term 'mild') and a substantial impact on daily functioning can be found with IQ levels slightly above these cut offs.

### 4. Drugs used to treat event

None. Medications may be used to treat comorbidities but not this condition directly.

### 5. Procedures used specific for event treatment

Treatment will be non-medicinal in nature and will vary substantially between countries.

### 6. Setting (outpatient specialist, in-hospital, GP, emergency room) where condition will be most frequently /reliably diagnosed

Specialist outpatient appointments. There is often an observation of the child in the home and/or school environment.

### 7. ICD-9, ICD-10, ICPC2 and Read codes

ICD-10		
<b>F70-F79 Mental retardation</b>	<b>Description</b>	<b>Comments</b>
<b>F70</b> Mild mental retardation	Approximate IQ range of 50 to 69 (in adults, mental age from 9 to under 12 years). Likely to result in some learning difficulties in school. Many adults will be	



		able to work and maintain good social relationships and contribute to society.	
<b>F70.0</b> Mild mental retardation with the statement of no, or minimal, impairment of behaviour		Mild mental retardation with no or very minimal impairment to behaviour	
<b>F70.1</b> Mild mental retardation : significant impairment of behaviour requiring attention or treatment		Mild mental retardation plus a significant impairment of behaviour requiring attention or treatment	
<b>F70.8</b> Mild mental retardation : other impairments of behaviour		Mild mental retardation with other impairments of behaviour	
<b>F70.9</b> Mild mental retardation without mention of impairment of behaviour		Mild mental retardation without mention of impairment of behaviour	
<b>F71</b> Moderate mental retardation		Approximate IQ range of 35 to 49 (in adults, mental age from 6 to under 9 years). Likely to result in marked developmental delays in childhood but most can learn to develop some degree of independence in self-care and acquire adequate communication and academic skills. Adults will need varying degrees of support to live and work in the community.	
<b>F71.0</b> Moderate mental retardation with the statement of no, or minimal, impairment of behaviour		Moderate mental retardation with the statement of no, or minimal, impairment of behaviour	
<b>F71.1</b> Moderate mental retardation : significant impairment of behaviour requiring attention or treatment		Moderate mental retardation with a significant impairment of behaviour requiring attention or treatment	
<b>F71.8</b> Moderate mental retardation : other impairments of behaviour		Moderate mental retardation with other impairments of behaviour	
<b>F71.9</b> Moderate mental retardation		Moderate mental retardation without mention of impairment of behaviour	

	without mention of impairment of behaviour		
	<b>F72</b> Severe mental retardation	Approximate IQ range of 20 to 34 (in adults, mental age from 3 to under 6 years). Likely to result in continuous need of support.	
	<b>F72.0</b> Severe mental retardation with the statement of no, or minimal, impairment of behaviour	Severe mental retardation with no or minimal impairment of behaviour	
	<b>F72.1</b> Severe mental retardation : significant impairment of behaviour requiring attention or treatment	Severe mental retardation with significant impairment of behaviour requiring attention or treatment	
	<b>F72.8</b> Severe mental retardation : other impairments of behaviour	Severe mental retardation with other impairments	
	<b>F72.9</b> Severe mental retardation without mention of impairment of behaviour	Severe mental retardation without mention of impairment of behaviour	
	<b>73.0</b> Profound mental retardation	IQ under 20 (in adults, mental age below 3 years). Results in severe limitation in self-care, continence, communication and mobility.	
	<b>F73.0</b> Profound mental retardation with the statement of no, or minimal, impairment of behaviour	Profound mental retardation with no or minimal impairment of behaviour	
	<b>F73.1</b> Profound mental retardation : significant impairment of behaviour requiring attention or treatment	Profound mental retardation with significant impairment of behaviour requiring attention or treatment	
	<b>F73.8</b> Profound mental retardation : other impairments of behaviour	Profound mental retardation with other impairments of behaviour	
	<b>F73.9</b> Profound mental retardation without mention of	Profound mental retardation without mention of impairment of behaviour	

	impairment of behaviour		
	<b>F78</b> Other mental retardation	Other mental retardation; no further specification given	
	<b>F78.0</b> Other mental retardation with the statement of no, or minimal, impairment of behaviour	Other mental retardation with no or minimal impairment of behaviour	
	<b>F78.1</b> Other mental retardation : significant impairment of behaviour requiring attention or treatment	Other mental retardation with significant impairment of behaviour requiring attention or treatment	
	<b>F78.8</b> Other mental retardation : other impairments of behaviour	Other mental retardation: other impairments of behaviour	
	<b>F78.9</b> Other mental retardation without mention of impairment of behaviour	Other mental retardation without mention of impairment of behaviour	
	<b>F79</b> Unspecified mental retardation	Including 'sub normality' and deficiency not otherwise specified	
	<b>F79.0</b> Unspecified mental retardation with the statement of no, or minimal, impairment of behaviour	Unspecified mental retardation with the statement of no, or minimal, impairment of behaviour	
	<b>F79.1</b> Unspecified mental retardation : significant impairment of behaviour requiring attention or treatment	Unspecified mental retardation : significant impairment of behaviour requiring attention or treatment	
	<b>F79.8</b> Unspecified mental retardation : other impairments of behaviour	Unspecified mental retardation with other impairments of behaviour	
	<b>F79.9</b> Unspecified mental retardation without mention of impairment of behaviour	Unspecified mental retardation without mention of impairment of behaviour	
<b>ICD-09</b>			
<b>317-319 Intellectual Disabilities</b>			
	<b>Description</b>	<b>Comments</b>	

	<b>317</b> Mild intellectual disabilities	Intellectual disability with IQ 50-70	US versions use the term mental retardation
	<b>318</b> Other specified intellectual disabilities	None specified intellectual disabilities	
	<b>318.0</b> Moderate intellectual disabilities	Intellectual disability with IQ 35-49	
	<b>318.1</b> Severe intellectual disabilities	Severe intellectual disabilities IQ 20-34	
	<b>318.3</b> Profound intellectual disabilities	Profound intellectual disability IQ less than 20	
	<b>319</b> Unspecified intellectual disabilities	Subnormal intellectual functioning which originates during the developmental period; multiple potential aetiologies, including genetic defects and perinatal insults; intelligence quotient (iq) scores are commonly used to determine whether an individual is mentally retarded; iq scores between 70 and 79 are in the borderline mentally retarded range and scores below 67 are in the retarded range	
<b>ICPC-2(The Directorate of eHealth, 2021)</b>			
<b>P85</b>		Mental retardation. Arrested/incomplete development of the mind with impairment of skills during the developmental period, and a low overall level of intelligence, with/without impairment of behaviour. Excludes mental retardation due to CA.	ICD10 equivalent: F70.0; F70.1; F70.8; F70.9; F71.0; F71.1; F71.8; F71.9; F72.0; F72.1; F72.8; F72.9; F73.0; F73.1; F73.8; F73.9; F78.0; F78.1; F78.8; F78.9; F79.0; F79.1; F79.8; F79.9
<b>Read codes</b>			
		To be defined in <b>Part 1</b> with input from DAP.	

### Appendix 6 EFEMERIS/POMME developmental assessments

Original name	Meaning	Data dictionary in English (if useful)	Percentage of completeness (2004-2018)	Comment
M9_JOUE_COUCOU	able to play 'peek-a-boo'	0 = no 1 = yes	82%	
M9_MOTRICITE_MEMBRES	Limb motor skill	0 = no 1 = yes	83%	Measures the symmetric motor function, two by two, of the limbs. It assesses the global motor function and coordination of the child.
M9_POINTE_DOIGT	able to point the finger	0 = no 1 = yes	81%	
M9_REAGIT_PRENOM	reaction to own name	0 = no 1 = yes	98%	
M9_SE_DEPLACE	Able to move around	0 = no 1 = yes	98%	
M9_SAISIE_OBJET	Able to grab an object	0 = no 1 = yes	89%	
M9_REPETE_SYLLABE	able to repeat a syllable	0 = no 1 = yes	98%	
M9_TIENT_ASSIS	Able to stay seated	0 = no 1 = yes	98%	
M24_OBEIT_ORDRE	able to understand a simple instruction	0=no 1=yes	98%	
M24_NOMME_IMAGE	able to name a picture	0=no 1=yes	98%	
M24_SUPERPOSE_OBJET	Able to place something on top of something else	0=no 1=yes	98%	
M24_ASSOCIE_2_MOTS	able to associate two words	0=no 1=yes	81%	
M24_MOTRICITE_MEMBRES	Limb motor skill	0=no 1=yes	81%	
M24_MARCHE_ACQUISE	Able to walk	0=no 1=yes	98%	
M24_AGE_MARCHE_ACQUISE	Age at first step		86%	In month

### Appendix 7: List of teratogenic medications

A detailed list of teratogenic exposures and diseases is currently under development by the University of Swansea. When finalised, the list of teratogenic exposures relevant to neurodevelopmental outcomes and congenital anomalies will be included in the SSRI study SAP and reported in the analysis.

Table 1. WP2 List of medications with an association with disruption of structural organ development or growth.

Medication	Physical affects
<b>Oral retinoid</b>	
Acitretin	Multiple malformations including central nervous system abnormalities, orofacial clefts, cardiovascular, skeletal, limb and ear. Facial dysmorphia.
Alitretinoin	
Bexarotene	
Isotretinoin	
Tretinoin	
<b>Antiepileptic/ anticonvulsants</b>	
Carbamazepine	Variable by individual medication type but include cardiovascular (phenobarbital, primidone, valproate), neural tube (valproate, carbamazepine), skeletal (valproate), orofacial cleft (topiramate, valproate) and limb (valproate). Facial dysmorphia (phenytoin, carbamazepine, valproate). Growth disruption (topiramte).
Phenytoin	
Fosphenytoin	
Primidone	
Topiramate	
Valproate	
Phenobarbital	
<b>Antithyroid</b>	
Carbimazole	Multiple malformation including skin defects including aplasia cutis, choanal atresia, esophageal atresia, other malformations of the gastrointestinal tract. Facial dysmorphia.
Methimazole	
<b>Anticoagulant</b>	
Coumarin	Multiple malformations including nasal hypoplasia, stippled epiphyses, skeletal and digital. Growth disruption. Facial dysmorphia.
Phenindione	
Warfarin	
Acenocoumarol	
<b>Immunosuppressive</b>	
Mycophenolate	Multiple malformations including orofacial cleft, microtia, external auditory canal atresia, micrognathia, cardiovascular, oesophageal atresia.
Methotrexate and Aminopterin	Multiple malformations including skeletal, cardiovascular, urogenital, holoprosencephaly. Growth disruption.

## Appendix 8 Information items of interest to this project

Information item	
<b>Pregnancy timing</b>	
Pregnancy timing	<input checked="" type="checkbox"/>
<b>Medication exposure</b>	
<b>Source of medication information</b>	
Primary care/General practitioner	<input checked="" type="checkbox"/>
Inpatient	<input type="checkbox"/>
Outpatient specialist	<input type="checkbox"/>
Prescription records (prescribed or dispensed)	<input checked="" type="checkbox"/>
Private prescriptions – private healthcare	<input type="checkbox"/>
Maternal self-report	<input type="checkbox"/>
<b>Details of medication</b>	
Name/ATC code of medication of interest	<input checked="" type="checkbox"/>
Date of issued/dispensed prescription, administration or used	<input checked="" type="checkbox"/>
Strength	<input type="checkbox"/>
Dosage – amount taken per day	<input type="checkbox"/>
Frequency – per day	<input type="checkbox"/>
Formulation (oral, injection, cream etc).	<input type="checkbox"/>
DDD dispensed	<input type="checkbox"/>
Quantity prescribed or dispensed (tablets)	<input type="checkbox"/>
Prescriber specialty	<input type="checkbox"/>
Co-medications	<input checked="" type="checkbox"/>
<b>Maternal disease/medication indication</b>	
<b>Diagnosis</b>	
Diagnosis in healthcare database e.g. ICD10	<input checked="" type="checkbox"/>
Diagnosis in disease registry	<input type="checkbox"/>
Type of ward where the diagnosis was given	<input type="checkbox"/>
Intervention in healthcare database as surrogate for disease	<input type="checkbox"/>
Healthcare admission as surrogate for disease/disease severity	<input type="checkbox"/>
<b>Severity of disease</b>	
Health care visit pattern	<input type="checkbox"/>
Co-morbid diagnosis/diagnoses	<input checked="" type="checkbox"/>
Co-morbidity – Infection – COVID-19	<input type="checkbox"/>
<b>Outcomes</b>	
<b>Maternal pregnancy outcomes</b>	
Spontaneous abortions	<input checked="" type="checkbox"/>
Termination of pregnancy - elective	<input checked="" type="checkbox"/>
Termination of pregnancy - for fetal anomaly	<input checked="" type="checkbox"/>
Pregnancy related conditions e.g. GD, preeclampsia, hypertension	<input checked="" type="checkbox"/>
Mode of delivery	<input type="checkbox"/>
Maternal death	<input checked="" type="checkbox"/>
Maternal diagnoses postpartum (e.g. stroke, infection, psychosis, death)	<input checked="" type="checkbox"/>
<b>Perinatal outcomes</b>	

Live birth: normal	<input checked="" type="checkbox"/>
Stillbirth	<input checked="" type="checkbox"/>
Neonatal death	<input checked="" type="checkbox"/>
Major congenital anomalies	<input checked="" type="checkbox"/>
Gestational age at delivery/preterm birth	<input checked="" type="checkbox"/>
Small for gestational age/ IUGR	<input type="checkbox"/>
Birth weight	<input checked="" type="checkbox"/>
Head circumference	<input type="checkbox"/>
Length at birth	<input type="checkbox"/>
Apgar score (5, 10 minutes)	<input type="checkbox"/>
Admission to Neonatal Intensive Care Unit	<input type="checkbox"/>
<b>Childhood outcomes</b>	
Death - infant or childhood	<input checked="" type="checkbox"/>
Health visitor/public health nurse records	<input type="checkbox"/>
Growth in childhood	<input type="checkbox"/>
Diagnosis in a specialist disease registry	<input type="checkbox"/>
Healthcare diagnosis records – ADHD, ASD	<input checked="" type="checkbox"/>
Referrals to specialists	<input type="checkbox"/>
Hospital admissions during childhood	<input type="checkbox"/>
Childhood prescriptions	<input type="checkbox"/>
Registered disability in child	<input type="checkbox"/>
Academic results and school performance	<input type="checkbox"/>
Special educational needs/educational support	<input checked="" type="checkbox"/>
Psychometric measurements	<input checked="" type="checkbox"/>
<b>Confounders/covariates</b>	
Folic acid - pre-conception, first trimester, none	<input type="checkbox"/>
Assisted conception	<input type="checkbox"/>
Maternal age at delivery	<input checked="" type="checkbox"/>
Maternal socioeconomic status –or occupation, employment, income, education etc.	<input type="checkbox"/>
Smoking status – prior to/ during pregnancy	<input type="checkbox"/>
Alcohol consumption – during pregnancy	<input type="checkbox"/>
Substance misuse - during pregnancy	<input type="checkbox"/>
Body mass index	<input type="checkbox"/>
Parity	<input type="checkbox"/>
Plurality	<input checked="" type="checkbox"/>
Breast feeding	<input checked="" type="checkbox"/>
Paternal medication	<input type="checkbox"/>
Family structure (linkage to siblings)	<input type="checkbox"/>

☒ required

☐ desirable



## Appendix 9 Subtask 1.3.3 – Neurodevelopment

### ADHD Tables

#### Table naming convention

- Table Number\_ *Country\_Data base name* \_Table description
  - The person creating the tables will need to provide information about the country, database, and dates, indicated by *red, italicized text*.
  - Information on birth cohort years in the table will need to be provided by the person working with the data. This information is indicated by *red, italicized text* in the table.

#### Source Cohort definition (Cohort that gives rise to the identification of patients with ADHD)

- All children (< 18 years) born to mothers with pregnancy medication exposure data available (to be defined by the Work Package 7 Common Data Model and the DP1.2. protocol, “Study Population”)
  - Children should be captured in the database for at least 28 days

#### Algorithm information

Algorithms adopted from [Lindemann et al 2017](#)

- Algorithm 1: One **specialist code** for ADHD provided
  - Index date: Date of specialist diagnosis (may occur during hospital admission or specialist outpatient clinic visit, for example); any diagnosis with an explicit qualifier of “ruled out” or “suspected” should not be considered.
- Algorithm 2: Two **non-specialist codes** for ADHD that are at least 28 days apart, but within 1.5 years
  - Index date: Date of second non-specialist diagnosis. Where available and applicable, any diagnosis with an explicit qualifier of “ruled out” or “suspected” should not be considered.
- Algorithm 3: One **non-specialist code** and 1 at least dispensing/prescription for ADHD medication within a year of diagnosis
  - Index date: The later of either the non-specialist code or medication dispensing; any diagnosis with an explicit qualifier of “ruled out” or “suspected” should not be considered.
- Algorithm 4: For countries where an ADHD medication must be 1<sup>st</sup> prescribed by specialist (5 of the 6 countries in this study. In GePaRD stimulants and non-stimulants prescribed by a specialist) only one medication is required.
  - In this case the index date is the first medication dispensing.

In GePaRD for non-stimulants prescribed by a non-specialist, at least two dispensings/prescriptions within 120 days

- Index date: Date of the second qualifying dispensing/medication

The identification of disease classification and medication codes will depend on the database being used and will need to be agreed upon prior to programming. The mock tables provide ICD-10 diagnosis codes and ATC medication codes. The table footnotes will need to be updated based on what is available for the database.

#### Calculation of prevalence

- *Numerator*: The child will be considered to have ADHD upon completion of the algorithm requirements. For example, Algorithm 2 requires two outpatient diagnoses. For Algorithm 2, the child will be considered to have ADHD on the second outpatient diagnosis. Because ADHD is a chronic disease, the child will be assumed to have ADHD for the remainder of their time in the study population.
- *Denominator*: The denominator should include all children present at least 28 days in the defined period. For example, Table 4 examines the prevalence of ADHD. In the prevalence calculation for Birth Cohort 1, the denominator should include all children born in within the defined birth years. In Table 5, the denominator should include all children in the birth cohort during a given calendar year.

#### Source of ND diagnosis and confidence in this

Data access providers (DAP) were contacted to gather information on how neurodevelopmental disorders are diagnosed in their countries/health care systems. The below table summarises the responses.

Table 12 Source of ND diagnosis and confidence

DAP	Specialist diagnosis/Rx (CONFIDENT in Dx)	Non-specialist diagnosis	Note
<p><b>Finland</b></p> <p><b>EFEMERIS/POMME database</b></p> <p><b>Emilia Romagna and Tuscany</b></p>	<p>Hospital inpatient or outpatient diagnoses.</p> <p><u>No medication use available for children in this study</u> but ADHD medication would be started by specialists (if available).</p> <p>ADHD diagnosis is made by a child psychiatrist, paediatrician or a neurologist. The FIRST prescription must come from one of these specialists working in an hospital (or from a hospital sleep centre). The prescription can be renewed by GPs or private paediatricians or psychiatrists. Methylphenydate is the only medication marketed for ADHD in France and is prescribed for a maximum of 28 days on a special form.</p> <p>Mental Health Databank -Only child neuropsychiatrists (NPI) can confirm the diagnosis. A qualified phycologist can do it, but a NPI visit is strongly recommended.</p> <p>Medications always started by a specialist in specific centers "Centri Prescrittori" dedicated to the prescription of medications. Methylphenidate and atomoxetine are recommended, both prescribed by a specialist. Other medications are not really considered. Patients receive the first dose of methylphenidate in a day hospital which will be recorded in the day hospital system.</p>	<p>GPs recommended to refer to a child psychiatrist, paediatrician or a neurologist for diagnosis.</p> <p>No primary care available.</p>	<p>VISIT_OCCURRENCE and EVENTS record diagnoses in secondary/tertiary and primary care. meaning_of_visit can be used to determine the setting where a diagnosis was recorded.</p>
<b>Norway</b>	<p>Outpatient diagnoses in Norwegian Patient Registry (NPR)</p> <p>Prescription (both stimulant and non-stimulant) indicates specialist diagnosis.</p>	<p>Primary care diagnoses in Norway Control and Payment of Primary Health Care Refunds (KUHR)</p>	

<b>SAIL</b>	<p>Prescription indicates specialist diagnosis – including non-stimulant prescriptions (atomoxetine, guanfacine).</p> <p>Originate in outpatient data but recorded in primary care following letters to GP from specialist. No way to tell if diagnosis in primary care has originated from a specialist or GP suspicion.</p>	Primary care	Could exclude read codes for 'referral' and potentially those with 'suspected'
<b>GePaRD</b>	<p>Hospital diagnosis</p> <p>Outpatient diagnosis – specialist (e.g. child and adolescent psychiatrist)</p> <p>Prescription of a stimulant indicates specialist diagnosis.</p> <p>Non-stimulant medications (atomoxetine, guanfacine) started by a specialist.</p>	<p>Outpatient diagnosis - GP, paediatrician, psychotherapists and all other specialties</p> <p>Non-stimulant medications (atomoxetine, guanfacine) started by a non-specialist.</p>	<p>Can exclude diagnoses "ruled out" or "suspected" – the variables to do this are included in the CDM.</p> <p>Specialist is recorded and can be used to distinguish between specialist and non-specialist outpatient diagnoses.</p> <p>Prescribers speciality available in the data to distinguish between non-stimulant medications started by a specialist or non-specialist.</p>

# Algorithm Tables

**Table 1\_Germany\_GePaRd\_ADHD** Diagnoses the in the Source Cohort during **DD-MON-YYYY** through **DD-MON-YYYY**

	Total number of children N=#			Time in study population <sup>a</sup> (months) Median (IQR) Mean (SD)			Age at first diagnostic code (years) Median (IQR) Mean (SD)			Time between diagnosis codes (months) Median (IQR) Mean (SD)		
Number of ADHD diagnostic codes <sup>b</sup>	F	M	Total	F	M	Total	F	M	Total	F	M	Total
0	n	n	n	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	NA	NA	NA	NA	NA	NA
1	n	n	n	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	NA	NA	NA
2	n	n	n	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)
3+	n	n	n	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)

F= Female; IQR= Inter-quartile range; M=Male; Med= Median; NA= Not applicable; SD= Standard deviation

<sup>a</sup> Time in source cohort calculated from first diagnosis

<sup>b</sup> ICD-10 diagnosis codes for ADHD: F90.0, F90.1, F90.8, F90.9

**Table 2** *Germany\_GePaRd* ADHD Medication (treatment) by Diagnoses in the Source Cohort during *DD-MON-YYYY* through *DD-MON-YYYY*

	Total number of children with no ADHD Medication <sup>b</sup> N=#			Total number of children with ≥ 1 ADHD Medication <sup>b</sup> N=#			Time between 1 <sup>st</sup> ADHD dx and 1 <sup>st</sup> ADHD medication (months) Median (IQR) Mean (SD)		
Number of ADHD diagnostic codes <sup>a</sup>	Females	Males	Total	Females	Males	Total	Females	Males	Total
0	n	n	n	n	n	n	Not applicable	Not applicable	Not applicable
1	n	n	n	n	n	n	Median (IQR)  Mean (SD)	Median (IQR)  Mean (SD)	Median (IQR)  Mean (SD)
2	n	n	n	n	n	n	Median (IQR)  Mean (SD)	Median (IQR)  Mean (SD)	Median (IQR)  Mean (SD)
3+	n	n	n	n	n	n	Median (IQR)  Mean (SD)	Median (IQR)  Mean (SD)	Median (IQR)  Mean (SD)
Overall	n	n	n	n	n	n	Median (IQR)  Mean (SD)	Median (IQR)  Mean (SD)	Median (IQR)  Mean (SD)

IQR= Inter-quartile range

<sup>a</sup> ICD-10 diagnosis codes for ADHD: F90.0, F90.1, F90.8, F90.9

<sup>b</sup> ATC codes for ADHD medication: Amphetamine (N06BA01); Atomoxetine (N06BA09); Dexamfetamine Sulfate (N06BA02); Dexmethylphenidate (N06BA11); Guanfacine (C02AC02); Lisdexamfetamine (N06BA12); Methylphenidate (N06BA04); Modafinil (N06BA07); Racemic amphetamine sulfate (N06BA01)

**Table 3** *Germany GePaRd* ADHD Diagnosis Setting in the Source Cohort during *DD-MON-YYYY* through *DD-MON-YYYY*

			1 <sup>st</sup> ADHD Diagnosis n (%)		2 <sup>nd</sup> ADHD Diagnosis n (%)		3 <sup>rd</sup> ADHD Diagnosis n (%)	
			<i>Specialist</i>	<i>Non-Specialist</i>	<i>Specialist</i>	<i>Non-Specialist</i>	<i>Specialist</i>	<i>Non-Specialist</i>
Number of ADHD Diagnostic Codes <sup>a</sup>	1	Female	n (%)	n (%)				
		Male	n (%)	n (%)				
		Total	n (%)	n (%)				
	2	Female	n (%)	n (%)	n (%)	n (%)		
		Male	n (%)	n (%)	n (%)	n (%)		
		Total	n (%)	n (%)	n (%)	n (%)		
	3+	Female	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
		Male	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
		Total	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

<sup>a</sup>ICD-10 diagnosis codes for ADHD: F90.0, F90.1, F90.8, F90.9

**Table 4** *Germany\_GePaRd*\_Prevalence of ADHD per 1,000 Children (< 18 years) by birth cohort for data available from *DD-MON-YYYY* through *DD-MON-YYYY*

		<b>Algorithm #1</b>		<b>Algorithm #2</b>		<b>Algorithm #3</b>		<b>Algorithm #4</b>	
<b>Birth Cohort</b>	<b>Children in Source Cohort by birth years (n)</b>	<b>Children identified with ADHD (n)</b>	<b>Prevalence per 1,000 Children (95% CI)</b>	<b>Children identified with ADHD (n)</b>	<b>Prevalence per 1,000 Children (95% CI)</b>	<b>Children identified with ADHD (n)</b>	<b>Prevalence per 1,000 Children (95% CI)</b>	<b>Children identified with ADHD (n)</b>	<b>Prevalence per 1,000 Children (95% CI)</b>
1 (YYYY-YYYY)		n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)
2 (YYYY-YYYY)		n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)
3 (YYYY-YYYY)		n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)
4 (YYYY-YYYY)		n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)
5 (YYYY-YYYY)		n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)
.		.	.	.	.	.	.	.	.
.		.	.	.	.	.	.	.	.
.		.	.	.	.	.	.	.	.

**Table 5** *Germany\_GePaRd*\_Prevalence of ADHD per 1,000 Children (< 18 years) by age for data available from *DD-MON-YYYY* through *DD-MON-YYYY*

		<b>Algorithm #1</b>		<b>Algorithm #2</b>		<b>Algorithm #3</b>		<b>Algorithm #4</b>	
<b>Age</b>	<b>Children in Source Cohort by age (n)</b>	<b>Children identified with ADHD (n)</b>	<b>Prevalence per 1,000 Children (95% CI)</b>	<b>Children identified with ADHD (n)</b>	<b>Prevalence per 1,000 Children (95% CI)</b>	<b>Children identified with ADHD (n)</b>	<b>Prevalence per 1,000 Children (95% CI)</b>	<b>Children identified with ADHD (n)</b>	<b>Prevalence per 1,000 Children (95% CI)</b>
<5	n	n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)
<7	n	n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)
<13	n	n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)
<18	n	n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)

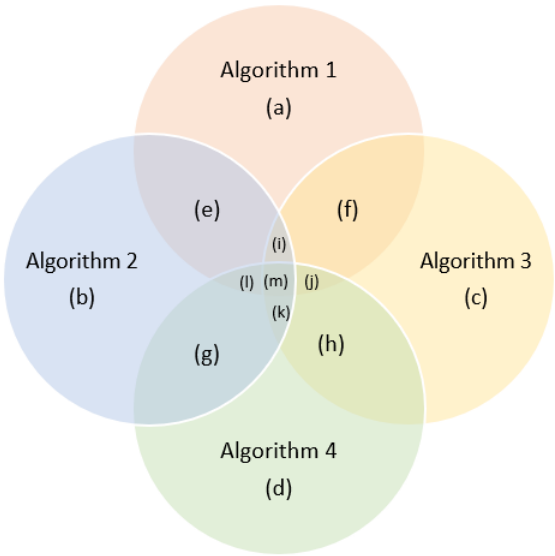
Total	n	n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)
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**Figure 1B\_ *Germany\_GePaRd*** Venn diagram displaying the number of children (<18 years) identified as having ADHD, by algorithm, data available from *DD-MON-YYYY* through *DD-MON-YYYY*

Section of Venn Diagram	Definition	n
a	The number of children identified by algorithm 1 but not by algorithms 2, 3, or 4	n
b	The number of children identified by algorithm 2 but not by algorithms 1, 3, or 4	n
c	The number of children identified by algorithm 3 but not by algorithms 1, 2, or 4	n
d	The number of children identified by algorithm 4 but not by algorithms 1, 2, or 3	n
e	The number of children identified by algorithms 1 and 2 but not algorithms 3 or 4	n
f	The number of children identified by algorithms 1 and 3 but not algorithms 2 or 4	n
g	The number of children identified by algorithms 2 and 4 but not algorithms 1 or 3	n
h	The number of children identified by algorithms 3 and 4 but not algorithms 1 or 2	n
i	The number of children identified by algorithms 1, 2, and 3, but not algorithm 4	n
j	The number of children identified by algorithms 1, 3, and 4, but not algorithm 2	n

k	The number of children identified by algorithms 2, 3, and 4, but not algorithm 1	n
l	The number of children identified by algorithms 1, 2, and 4, but not algorithm 3	n
m	The number of children identified by algorithms 1, 2, 3, and 4	n



## ASD Tables

### Table naming convention

- Table Number\_ *Country\_Data base name* \_Table description
  - The person creating the tables will need to provide information about the country, database, and dates, indicated by *red, italicized text*.
  - Information on birth cohort years in the table will need to be provided by the person working with the data. This information is indicated by *red, italicized text* in the table.

### Source Cohort definition (Cohort that gives rise to the identification of patients with ASD)

- All children (< 18 years) born to mothers with pregnancy medication exposure data available (the Work Package 7 Common Data Model and the DP1.2. protocol, “Study Population”)
  - Children should be captured in the database for at least 28 days

### Algorithm information

- Algorithm 1: One **specialist code** for ASD provided
  - Index date: Date of specialist diagnosis (may occur during hospital admission or specialist outpatient clinic visit, for example); any diagnosis with an explicit qualifier of “ruled out” or “suspected” should not be considered.
- Algorithm 2: Two **non-specialist codes** for ASD that are at least 28 days apart, but within 1.5 years
  - Index date: Date of second non-specialist diagnosis; any diagnosis with an explicit qualifier of “ruled out” or “suspected” should not be considered.

The identification of disease classification and medication codes will depend on the database being used and will need to be agreed upon prior to programming. The mock tables provide ICD-10 diagnosis codes and ATC medication codes. The table footnotes will need to be updated based on what is available for the database.

### Calculation of prevalence

- *Numerator*: The child will be considered to have ASD upon completion of the algorithm requirements. For example, Algorithm 2 requires two outpatient diagnoses. For Algorithm 2, the child will be considered to have ASD on the second outpatient diagnosis. Because ASD is a chronic disease, the child will be assumed to have ASD for the remainder of their time in the study population.
- *Denominator*: The denominator should include all children present at least one day in the defined period. For example, Table 4 examines the prevalence of ASD. In the prevalence calculation for Birth Cohort 1, the denominator should include all children born in within the defined birth years. In Table 5, the denominator should include all children in the birth cohort during a given calendar year.

### Source of ND diagnosis and confidence in this

Data access providers (DAP) were contacted to gather information on how neurodevelopmental disorders are diagnosed in their countries/health care systems. See **Table 12 Source of ND diagnosis and confidence** in ADHD tables for more information.

# Algorithm Tables

**Table 1\_Germany\_GePaRd\_** ASD Diagnoses the in the Source Cohort during **DD-MON-YYYY** through **DD-MON-YYYY**

	Total number of children N=#			Time in study population <sup>a</sup> (months) Median (IQR) Mean (SD)			Age at first diagnostic code (years) Median (IQR) Mean (SD)			Time between diagnosis codes (months) Median (IQR) Mean (SD)		
Number of ASD diagnostic codes <sup>b</sup>	F	M	Total	F	M	Total	F	M	Total	F	M	Total
0	n	n	n	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	NA	NA	NA	NA	NA	NA
1	n	n	n	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	NA	NA	NA
2	n	n	n	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)
3+	n	n	n	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)

F= Female; IQR= Inter-quartile range; M=Male; Med= Median; NA= Not applicable; SD= Standard deviation

<sup>a</sup> Time in source cohort calculated from first diagnosis

<sup>b</sup> ICD-10 diagnosis codes for ASD: F84.0, F84.1, F84.4, F84.5, F84.8, F84.9

**Table 2** *Germany GePaRd* ASD Diagnosis Setting in the Source Cohort during *DD-MON-YYYY* through *DD-MON-YYYY*

			<b>1<sup>st</sup> ASD Diagnosis</b> n (%)		<b>2<sup>nd</sup> ASD Diagnosis</b> n (%)		<b>3<sup>rd</sup> ASD Diagnosis</b> n (%)	
			<i>Specialist</i>	<i>Non-Specialist</i>	<i>Specialist</i>	<i>Non-Specialist</i>	<i>Specialist</i>	<i>Non-Specialist</i>
<b>Number of ASD Diagnostic Codes<sup>a</sup></b>	1	Female	n (%)	n (%)				
		Male	n (%)	n (%)				
		Total	n (%)	n (%)				
	2	Female	n (%)	n (%)	n (%)	n (%)		
		Male	n (%)	n (%)	n (%)	n (%)		
		Total	n (%)	n (%)	n (%)	n (%)		
	3+	Female	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
		Male	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
		Total	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

<sup>a</sup> ICD-10 diagnosis codes for ASD: F84.0, F84.1, F84.4, F84.5, F84.8, F84.9

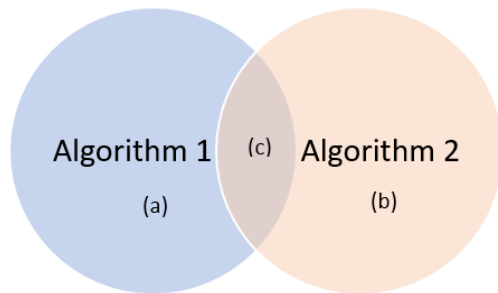
**Table 3** *Germany\_GePaRd*\_Prevalence of ASD per 1,000 Children (< 18 years) by birth cohort for data available from *DD-MON-YYYY* through *DD-MON-YYYY*

Birth Cohort	Children in Source Cohort by birth years (n)	<i>Algorithm #1</i>		<i>Algorithm #2</i>	
		Children identified with ASD (n)	Prevalence per 1,000 Children (95% CI)	Children identified with ASD (n)	Prevalence per 1,000 Children (95% CI)
1 ( <i>YYYY-YYYY</i> )		n	Prev (95% CI)	n	Prev (95% CI)
2 ( <i>YYYY-YYYY</i> )		n	Prev (95% CI)	n	Prev (95% CI)
3 ( <i>YYYY-YYYY</i> )		n	Prev (95% CI)	n	Prev (95% CI)
4 ( <i>YYYY-YYYY</i> )		n	Prev (95% CI)	n	Prev (95% CI)
5 ( <i>YYYY-YYYY</i> )		n	Prev (95% CI)	n	Prev (95% CI)
.		.	.	.	.
.		.	.	.	.
.		.	.	.	.

**Table 5** *Germany\_GePaRd*\_Prevalence of ASD per 1,000 Children (< 18 years) by age for data available from *DD-MON-YYYY* through *DD-MON-YYYY*

Age	Children in Source Cohort by age (n)	<i>Algorithm #1</i>		<i>Algorithm #2</i>	
		Children identified with ASD (n)	Prevalence per 1,000 Children (95% CI)	Children identified with ASD (n)	Prevalence per 1,000 Children (95% CI)
<5	n	n	Prev (95% CI)	n	Prev (95% CI)
<7	n	n	Prev (95% CI)	n	Prev (95% CI)
<13	n	n	Prev (95% CI)	n	Prev (95% CI)
<18	n	n	Prev (95% CI)	n	Prev (95% CI)
Total	n	n	Prev (95% CI)	n	Prev (95% CI)

**Figure 1B\_ *Germany\_GePaRd*** Venn diagram displaying the number of children (<18 years) identified as having ASD, by algorithm, data available from *DD-MON-YYYY* through *DD-MON-YYYY*



Section of Venn Diagram	Definition	n
a	The number of children identified by algorithm 1 but not by algorithm 2	n
b	The number of children identified by algorithm 2 but not by algorithm 1	n
c	The number of children identified by algorithms 1 and 2	n

## ID Tables

### Table naming convention

- Table Number\_ *Country\_Data base name* \_Table description
  - The person creating the tables will need to provide information about the country, database, and dates, indicated by *red, italicized text*.
  - Information on birth cohort years in the table will need to be provided by the person working with the data. This information is indicated by *red, italicized text* in the table.

### Source Cohort definition (Cohort that gives rise to the identification of patients with ID)

- All children (< 18 years) born to mothers with pregnancy medication exposure data available (the Work Package 7 Common Data Model and the DP1.2. protocol, “Study Population”)
  - Children should be captured in the database for at least 28 days

### Algorithm information

- Algorithm 1: One **specialist code** for ID provided
  - Index date: Date of specialist diagnosis (may occur during hospital admission or specialist outpatient clinic visit, for example); any diagnosis with an explicit qualifier of “ruled out” or “suspected” should not be considered.
- Algorithm 2: Two **non-specialist codes** for ID that are at least 28 days apart, but within 1.5 years
  - Index date: Date of second non-specialist diagnosis; any diagnosis with an explicit qualifier of “ruled out” or “suspected” should not be considered.

The identification of disease classification and medication codes will depend on the database being used and will need to be agreed upon prior to programming. The mock tables provide ICD-10 diagnosis codes and ATC medication codes. The table footnotes will need to be updated based on what is available for the database.

### Calculation of prevalence

- *Numerator*: The child will be considered to have ID upon completion of the algorithm requirements. For example, Algorithm 2 requires two outpatient diagnoses. For Algorithm 2, the child will be considered to have ID on the second outpatient diagnosis. Because ID is a chronic disease, the child will be assumed to have ID for the remainder of their time in the study population.
- *Denominator*: The denominator should include all children present at least one day in the defined period. For example, Table 4 examines the prevalence of ID. In the prevalence calculation for Birth Cohort 1, the denominator should include all children born in within the defined birth years. In Table 5, the denominator should include all children in the birth cohort during a given calendar year.

### Source of ND diagnosis and confidence in this

Data access providers (DAP) were contacted to gather information on how neurodevelopmental disorders are diagnosed in their countries/health care systems. See **Table 12 Source of ND diagnosis and confidence** in ADHD tables for more information.



## Algorithm Tables

**Table 1** *Germany\_GePaRd*\_ID Diagnoses the in the Source Cohort during *DD-MON-YYYY* through *DD-MON-YYYY*

	Total number of children N=#			Time in study population <sup>a</sup> (months) Median (IQR) Mean (SD)			Age at first diagnostic code (years) Median (IQR) Mean (SD)			Time between diagnosis codes (months) Median (IQR) Mean (SD)		
Number of ID diagnostic codes <sup>b</sup>	F	M	Total	F	M	Total	F	M	Total	F	M	Total
0	n	n	n	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	NA	NA	NA	NA	NA	NA
1	n	n	n	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	NA	NA	NA
2	n	n	n	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)
3+	n	n	n	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)

F= Female; IQR= Inter-quartile range; M=Male; Med= Median; NA= Not applicable; SD= Standard deviation

<sup>a</sup> Time in source cohort calculated from first diagnosis<sup>b</sup> ICD-10 diagnosis codes for ID: F70, F70.0, F70.1, F70.8, F70.9, F71, F71.0, F71.1, F71.8, F71.9, F72, F72.0, F72.1, F72.8, F72.9, F73.0, F73.1, F73.8, F73.9, F78, F78.1, F78.8, F78.9, F79, F79.0, F79.1, F79.8, F79.9

**Table 2** *Germany GePaRd* ID Diagnosis Setting in the Source Cohort during *DD-MON-YYYY* through *DD-MON-YYYY*

			1 <sup>st</sup> ID Diagnosis n (%)		2 <sup>nd</sup> ID Diagnosis n (%)		3 <sup>rd</sup> ID Diagnosis n (%)	
			Specialist	Non-Specialist	Specialist	Non-Specialist	Specialist	Non-Specialist
Number of ID Diagnostic Codes <sup>a</sup>	1	Female	n (%)	n (%)				
		Male	n (%)	n (%)				
		Total	n (%)	n (%)				
	2	Female	n (%)	n (%)	n (%)	n (%)		
		Male	n (%)	n (%)	n (%)	n (%)		
		Total	n (%)	n (%)	n (%)	n (%)		
	3+	Female	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
		Male	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
		Total	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

<sup>a</sup> ICD-10 diagnosis codes for ID: F70, F70.0, F70.1, F70.8, F70.9, F71, F71.0, F71.1, F71.8, F71.9, F72, F72.0, F72.1, F72.8, F72.9, F73.0, F73.1, F73.8, F73.9, F78, F78.1, F78.8, F78.9, F79, F79.0, F79.1, F79.8, F79.9

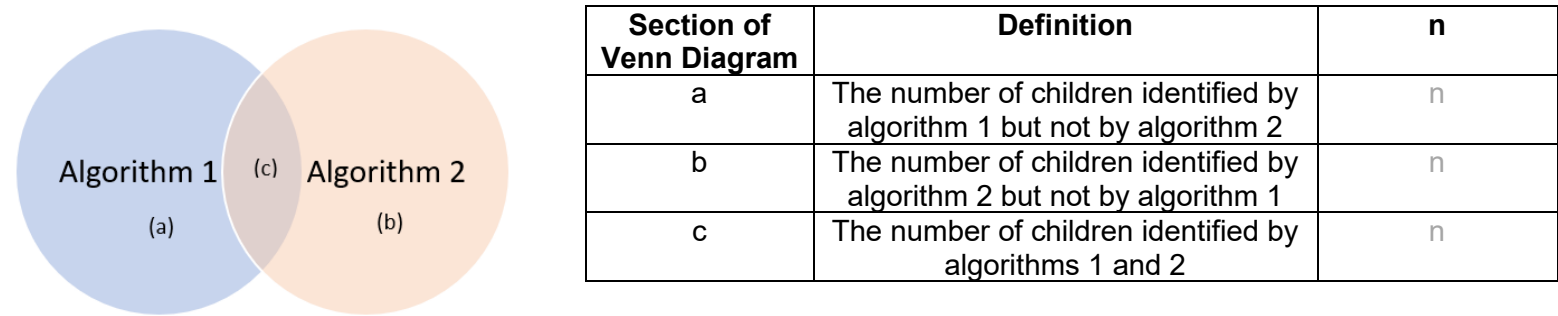
**Table 3** *Germany\_GePaRd*\_Prevalence of ID per 1,000 Children (< 18 years) by birth cohort for data available from *DD-MON-YYYY* through *DD-MON-YYYY*

Birth Cohort	Children in Source Cohort by birth years (n)	Algorithm #1		Algorithm #2	
		Children identified with ID (n)	Prevalence per 1,000 Children (95% CI)	Children identified with ID (n)	Prevalence per 1,000 Children (95% CI)
1 (YYYY-YYYY)		n	Prev (95% CI)	n	Prev (95% CI)
2 (YYYY-YYYY)		n	Prev (95% CI)	n	Prev (95% CI)
3 (YYYY-YYYY)		n	Prev (95% CI)	n	Prev (95% CI)
4 (YYYY-YYYY)		n	Prev (95% CI)	n	Prev (95% CI)
5 (YYYY-YYYY)		n	Prev (95% CI)	n	Prev (95% CI)
.		.	.	.	.
.		.	.	.	.
.		.	.	.	.

**Table 5** *Germany\_GePaRd*\_Prevalence of ID per 1,000 Children (< 18 years) by age for data available from *DD-MON-YYYY* through *DD-MON-YYYY*

Age	Children in Source Cohort by age (n)	Algorithm #1		Algorithm #2	
		Children identified with ID (n)	Prevalence per 1,000 Children (95% CI)	Children identified with ID (n)	Prevalence per 1,000 Children (95% CI)
<5	n	n	Prev (95% CI)	n	Prev (95% CI)
<7	n	n	Prev (95% CI)	n	Prev (95% CI)
<13	n	n	Prev (95% CI)	n	Prev (95% CI)
<18	n	n	Prev (95% CI)	n	Prev (95% CI)
Total	n	n	Prev (95% CI)	n	Prev (95% CI)

**Figure 1B\_ *Germany\_GePaRd*** Venn diagram displaying the number of children (<18 years) identified as having ID, by algorithm, data available from *DD-MON-YYYY* through *DD-MON-YYYY*



## Supplementary information on ND diagnosis Finland

- 1) In your health care system, are ADHD diagnoses in children confirmed by a specialist?

*My understanding is that ADHD diagnoses are only made by specialists i.e. children with symptoms suggestive for ADHD are referred to secondary/tertiary health care for confirmation.*

- 2) If a specialist recorded the diagnosis which data set would this be recorded in?

*In the ConcePTION CDM, we have mapped diagnoses from secondary/tertiary care 1996 onwards and diagnoses from primary health care 2011 onwards. These are both in VISIT\_OCCURRENCE and EVENTS data. You can distinguish between hospitalization/outpatient visit/primary care by my meaning\_of\_visit variable. However, we only have information during which visit diagnoses of interest was recorded. We do not have information when exactly the diagnoses was made and by whom.*

- 3) If a non-specialist recorded the diagnosis which data set would this be recorded in?

*Kindly see my response above.*

- 4) If a data set contains both specialist and non-specialist diagnoses, is there a variable to identify who had made the diagnosis?

*No. As I told previously, we do not know who exactly made the diagnoses. However, we have mapped variable specialty of visit in VISIT\_OCCURRENCE where you can e.g. find an admission to child or youth psychiatry.*

- 5) Would it be possible to exclude any diagnoses with an explicit qualifier “ruled out” or “suspected” in your data? If so, could you give an example of how we would do this (variables etc).

*No. This is the biggest problem in administrative data as it records everything. If, for instance, a clinician in the primary care considers ADHD and refers a child to secondary care, it is possible that a referral includes ADHD diagnosis code and then written text “suspected/suspicion” but the administrative database will only capture the diagnosis code. We know from previous validation studies that administrative health care data includes false positive diagnoses. Only possibility to clean these false-positives is to use algorithms which, for instance, require two diagnoses codes or one code and a drug or similar.*

- 6) Some countries will have specialist care/consultation only at hospital, others may have specialist’s consultation at the specialist’s practice (outside hospital). Could you give us some details on the setting where these disorders are typically identified and followed-up in your country?

*In Finland, hospital districts can organize the health care service the way they find it most meaningful. I would assume that the most common practice is that specialist consultation occurs at hospital/outpatient visit when the diagnoses is made. However, follow-up can also be in primary care. Even changes for drug dose can occur in primary care based on written instructions from a specialist.*

- 7) Would a non-specialist start ADHD medication, or would this always be done by a specialist?

*There is no medication use available for children in this study in Finland but ADHD medication would be started by specialists (if available).*

### **Emilia Romagna and Tuscany (response below from Emilia Romagna).**

1. In your health care system, are ADHD diagnoses in children confirmed by a specialist?

*Yes, in the Emilia Romagna Region (I think also in Italy) only the child neuropsychiatrist (NPI) can confirm the diagnosis. Also a qualified psychologist can do it, but a NPI visit is strongly recommended.*

2. If a specialist recorded the diagnosis which data set would this be recorded in?  
*NPI code ADHD using ICD-10, in a specific national register dedicated only to patients requiring pharmacological treatment. All the NPI visits (not only ADHD) and treatment are collected in a specific digitalized medical record system. NPI records all diagnoses in ICD10 (ADHD or autism and others) and this flow is available with specific permission from 2010.*

3. If a non-specialist recorded the diagnosis which data set would this be recorded in?

*NA*

4. If a data set contains both specialist and non-specialist diagnoses, is there a variable to identify who had made the diagnosis?

*NA*

5. Would it be possible to exclude any diagnoses with an explicit qualifier “ruled out” or “suspected” in your data? If so, could you give an example of how we would do this (variables etc).

*NA*

6. Some countries will have specialist care/consultation only at hospital, others may have specialist’s consultation at the specialist’s practice (outside hospital). Could you give us some details on the setting where these disorders are typically identified and followed-up in your country?

*Only outside hospital; admission only for first administration of Methylphenidate (day hospital system)*

7. Would a non-specialist start ADHD medication, or would this always be done by a specialist? *Always a specialist*

8. Is there any distinction made depending on the type of ADHD medication? For example, in Germany the stimulant ADHD medications need to be started by a specialist, but non-stimulant medications (atomoxetine, guanfacine) can be started by a non-specialist.

*There are specific centers "Centri Prescrittori" dedicated to the prescription of medications. Methylphenidate and atomoxetine are recommended, both prescribed by a specialist. Other medications are not really considered. Patients receive the first dose of methylphenidate in hospital.*

### **Norway**

1. In your health care system, are ADHD diagnoses in children confirmed by a specialist?

*Yes, we rely on diagnosis as given by specialists in child development. The national guidelines for the diagnostic and treatment of ADHD in children and other developmental*

*disorders state that if the GP suspects / observes possible symptoms of ADHD/other disorders, the child has to be referred to the specialist clinic.*

2. If a specialist recorded the diagnosis which data set would this be recorded in?

*Norwegian Patient Registry.*

3. If a non-specialist recorded the diagnosis which data set would this be recorded in?

*Norway Control and Payment of Health Reimbursement (KUHR) Database.*

4. If a data set contains both specialist and non-specialist diagnoses, is there a variable to identify who had made the diagnosis?

*Yes, the diagnoses given in primary vs secondary care stem from different registries, so we can distinguish between them. We may contain information on the specialty of the physician giving the diagnosis.*

5. Would it be possible to exclude any diagnoses with an explicit qualifier “ruled out” or “suspected” in your data? If so, could you give an example of how we would do this (variables etc).

*We cannot directly distinguish between “suspected” diagnoses and “verified” ones. National reports have however shown that for ADHD for example, 80% of the children with a specialist diagnosis in Norway also receive psychostimulant medication, supporting the fact that ADHD was most likely verified. Since children with suspected ADHD or other developmental issues by the GP are referred to a specialist (see my first reply), specialist diagnosis are most likely verified.*

6. Some countries will have specialist care/consultation only at hospital, others may have specialist’s consultation at the specialist’s practice (outside hospital). Could you give us some details on the setting where these disorders are typically identified and followed-up in your country?

*In Norway, children receive specialist care/consultations at district outpatient clinics, within the public healthcare system.*

7. Would a non-specialist start ADHD medication, or would this always be done by a specialist?

*For ADHD, GPs may still prescribe ADHD medications to children, but only after the first prescription has been issued by a specialist doctor.*

8. Is there any distinction made depending on the type of ADHD medication? For example, in Germany the stimulant ADHD medications need to be started by a specialist, but non-stimulant medications (atomoxetine, guanfacine) can be started by a non-specialist. *In Norway all medications for ADHD in children (i.e., both stimulants and non-stimulants) have to be initiated by a specialist.*

## SAIL

1. In your health care system, are ADHD diagnoses in children confirmed by a specialist?

*Prescriptions must be under specialist supervision ie. Diagnosis made by specialist. Dexamfetamine, lisdexamfetamine, atomoxetine & guanfacine must be initiated by specialists. In children, they are only licensed for ADHD. Therefore all these rxes will be associated with specialist diagnosis. This applies to methylphenidate in general, but some brands only carry this warning in EMC, not BNF. Only licensed from 6 years.*

2. If a specialist recorded the diagnosis which data set would this be recorded in?  
*A letter would be written to the GP, but finding the record of this would be difficult. There is a Read code.*
3. If a non-specialist recorded the diagnosis which data set would this be recorded in?  
*GP – primary care. It would likely be as given by the specialist.*
4. If a data set contains both specialist and non-specialist diagnoses, is there a variable to identify who had made the diagnosis?  
*The presence of the prescriptions indicates a specialist diagnosis. Only specialists can give this diagnosis.*
5. Would it be possible to exclude any diagnoses with an explicit qualifier “ruled out” or “suspected” in your data? If so, could you give an example of how we would do this (variables etc).  
*There are Read codes, but not sure how well this would be recorded.  
There are Read codes for referrals. However, not all referrals give a diagnosis. ADHD is difficult to rule out, but it is often too mild to be worth medicating. There is usually a trial without medication, often with referrals to groups (online these days). Not all of these are reimbursed, so may not be well recorded.*
6. Some countries will have specialist care/consultation only at hospital, others may have specialist’s consultation at the specialist’s practice (outside hospital). Could you give us some details on the setting where these disorders are typically identified and followed-up in your country?  
*Out-patients. Admissions v rare. Psychiatrist, paediatrician or specialist social worker or OT. Follow up rxes are from the GP.  
<https://www.nhs.uk/conditions/attention-deficit-hyperactivity-disorder-adhd/diagnosis/>  
There is some private practice, which is outside SAIL.*
7. If you have any additional comments that will explain how children are diagnosed with ADHD/ ASD or intellectual disability in your country, please let us know.  
*Autism is harder – not medicated. There are Read codes. Intellectual disability would be best as SEN in the education data. There is also the HV data: this was changed in 2015.*

### GePaRD

1. In your health care system, are ADHD diagnoses in children confirmed by a specialist?  
*A confirmation by a specialist is not required. We also don't see in our data if a pediatrician has a special qualification for ADHS diagnosis and therapy.*
2. If a specialist recorded the diagnosis which data set would this be recorded in?  
*Both in outpatient and hospital data.*
3. If a non-specialist recorded the diagnosis which data set would this be recorded in?  
*Outpatient data. Pediatricians are the first point of contact and should be counted as non-specialists.*
4. If a data set contains both specialist and non-specialist diagnoses, is there a variable to identify who had made the diagnosis?  
*Yes, the specialty of the physician is available.*



5. Would it be possible to exclude any diagnoses with an explicit qualifier “ruled out” or “suspected” in your data? If so, could you give an example of how we would do this (variables etc).

*Yes. The variables are included in the CDM.*

6. Some countries will have specialist care/consultation only at hospital, others may have specialist’s consultation at the specialist’s practice (outside hospital). Could you give us some details on the setting where these disorders are typically identified and *followed-up in your country?*

*ADHD is usually identified and followed-up in the outpatient setting by a pediatrician. Some patients will also see specialists or be even treated/diagnosed in the hospital setting.*

*Prescribing ADHD medication:*

*Non-stimulant ADHD medication (atomoxetine, guanfacine) can be prescribed by any physician to children without any further restrictions.*

*For stimulant medication (methylphenidate—about 94% of incident ADHD drugs [1]—, lisdexamfetamine, dexamfetamine), the following applies (according to the regulations of the Federal Joint Committee):*

*“The medicines must be prescribed only by a specialist in behavioral disorders in children and/or adolescents”*

*In this case, the “specialist” may also be a pediatrician, especially if they have undergone appropriate further training—which we cannot see in our data.*

*“In exceptional cases, primary care physicians may also provide follow-up prescriptions if it is ensured that supervision is provided by a behavioral health specialist.”*

*So, even GPs may prescribe stimulants, however, only when a specialist (see above) started medication—that sounds like what you heard from the other countries.*

*Percentage of incident diagnoses and incident ADHD meds by specialty:*

*Importantly—as in other countries—the child and adolescent psychiatrist is generally best qualified to diagnose and treat children with ND including ADHD.*

*In children aged 5–12 years, about 55% and 23% of incident diagnoses were made by pediatricians and child and adolescent psychiatrist, respectively [2]. However, among children aged 0–17 years, about 24% and 50% of incident ADHD medications were prescribed by pediatricians and child and adolescent psychiatrist, respectively [1].*

*My recommendation regarding assignment of German “specialists”:*

*When the incident diagnosis would be the outcome, I think the diagnosis from a child and adolescent psychiatrist is most reliable; then pediatricians and psychotherapists (which however, are only accounting for 2% of diagnoses [2]); then all other specialties—so, three categories would make sense, if possible; or “child and adolescent psychiatrist” as specialist and all others as non-specialists.*

*When the incident ADHD medication would be the outcome (which I would prefer if sample size allows), I think all specialties are to some extent reliable (as prescribing stimulants is generally already quite restricted). However, if assignment to “specialist” is necessary, I would include child and adolescent psychiatrist and pediatricians (as we do not know about how well they are trained).*

*By the way, the different requirements for starting ADHD medication—even within Europe—lead to extreme differences in the prevalence of ADHD medication use among children. For example, 0.5% of children in UK and almost 4% of children in the Netherlands had at least one prescription of ADHD medication (Germany: about 2%) [3].*

*[1] Scholle, O., Kollhorst, B., Riedel, O., & Bachmann, C. J. (2021). First-Time Users of ADHD Medication Among Children and Adolescents in Germany: An Evaluation of Adherence to Prescribing Guidelines Based on Claims Data. *Frontiers in Psychiatry*, 12, 653093. Retrieved from <https://doi.org/10.3389/fpsyt.2021.653093>*

- [2] Scholle, O., Fegert, J. M., Kollhorst, B., Öztürk, E. E., Riedel, O., & Kölch, M. (2020). Predictors for Receiving Medication and/or Psychotherapy in Children Newly Diagnosed With ADHD: A Longitudinal Population-Based Cohort Study. *Journal of Attention Disorders*, 24(2), 255–264. Retrieved from <https://doi.org/10.1177/1087054718816172>
- [3] Bachmann, C. J., Wijlaars, L. P., Kalverdijk, L. J., Burcu, M., Glaeske, G., Schuiling-Veninga, C. C. M., ... Zito, J. M. (2017). Trends in ADHD medication use in children and adolescents in five western countries, 2005–2012. *European Neuropsychopharmacology*, 27(5), 484–493. Retrieved from <https://doi.org/10.1016/j.euroneuro.2017.03.002>

### EFEMERIS/POMME (France )

*In France it is recommended that general practitioner's who think that a child is suffering from ADHD send it to a **child psychiatrist, a pediatrician or a neurologist**. The **FIRST prescription** must come from one of these specialist working in an **hospital** (or from a hospital sleep center). The prescription can be renewed by GPs or private pediatricians or psychiatrists. **Methylphenydate** is the only medication marketed for ADHD in France. It can be prescribed for a maximum of 28 days on a special form.*

## Appendix 10 Subtask 1.3.7 - Breastfeeding

### Task 1.3 Subtask 1.3.7 Breastfeeding

#### Version: 5

#### 1. Overview of ConcePTION WP1 Task 1.3 and Task 1.3.7

Task 1.3 has been set up to “To develop definitions and validate proposed algorithms to identify outcomes of interest, exposure and confounders and produce background and disease-specific prevalence rates of pregnancy outcomes”.

In Work Package 1, Task 1.2, a “pre-protocol” document was agreed which describes methodological approaches to medication safety studies in pregnancy, including the definitions of outcome, exposure and confounders. Task 1.3 will operationalise Task 1.2 in the databanks selected for Demonstration Projects. The 7 subtasks in Task 1.3 will aim to validate (e.g. from literature reviews, direct applications to DAPS or expert consultations etc.) the identification of specific outcomes in different health care databases.

This task is developed in conjunction with work designed to meet the aims of the Demonstration study: Exposure to SSRI/SNRI and depression in pregnancy and long-term childhood outcomes: the effect of modifying factors (copied below for reference): A medication utilisation and disease prevalence study will assess the prevalence of depression and the pattern of SSRI and SNRI (Serotonin and norepinephrine reuptake inhibitors) use in women before, during, and after pregnancy. Patterns of co-medication and breastfeeding will also be described plus variation by country, age, parity, socioeconomic, and educational status. A medication safety study will assess the risk of long-term neurodevelopmental outcomes in children, taking into account the mental health of the mother [over time,] breastfeeding, and other confounders. The impact of this study will be to help create evidence-based clinical guidelines on risks and benefits of antidepressant treatment in pregnancy and to establish appropriate methodology for post-marketing surveillance in relation to long term neurodevelopmental outcomes..

**Note to DAPs.** To meet the stated aims of task 1.3.7, the only additional data collection for this task is prevalence of breastfeeding (any) at time points to be agreed (likely birth, 4-6 weeks, ?6 months) and use of medication of interest in weeks 1-6 of infant’s life. Data will be described and used to explore existing outcomes and statistical techniques.

#### 2. Task 1.3 Aims

The aim of Task 1.3 is to make recommendations for future analyses in the Demonstration Projects. Specifically, this subtask should:

- Develop definitions and validate proposed algorithms to identify outcomes of interest, exposure and confounders;
- Produce background and disease-specific prevalence rates
- Develop the criteria for determining which DAPS have data suitable for analysis for the specified outcomes
- Provide recommendations on any specific analyses relating to the specified outcomes (if appropriate).

#### Aims of Task 1.3.7

1.3.7 will address the above aims for infant feeding by:

- Examining the availability, status, provenance and validity of breastfeeding data at any postnatal age in the databanks used in the demonstration projects and

- Investigating selected factors associated with breastfeeding status including specified prescription medications and diagnoses.

### 3. Rationale and background to 1.3.7

Suboptimal breastfeeding is one of the main threats to global health (Lawn et al 2014). The impact of breastfeeding on infants and mothers is well documented in epidemiological studies (Victora et al 2016). These include reductions in: infant mortality from infectious diseases, diarrhoea, respiratory infections, acute otitis media, asthma/ wheezing, malocclusion, obesity and type 2 diabetes; maternal breast and ovarian cancer, type 2 diabetes, necrotising enterocolitis and sudden infant death syndrome (Victora et al 2016). Accordingly, epidemiologists concerned with maternal, infant and child health need to consider the effect of breastfeeding. One of the few randomized control trials in breastfeeding, conducted in Belarus, indicated a positive impact on children's cognitive enhancement (Kramer, 2008), indicating that all studies of childhood 'cognitive performance' should consider how breastfeeding may influence these outcomes. Associations between infection in infancy and breastfeeding are also too large to be overlooked with one study observing reduced risks of admission for diarrhoea RR 0.28, 0.16-0.50 and for respiratory infections RR 0.43, 0.35-0.55 (Horta et al 2013).

Women using prescription medications are less likely to breastfeed, particularly if there is little information about the transfer of the medication to breastfed infants (Saha, 2015). Therefore, when evaluating infant and childhood outcomes, it is important to separate the effect of the exposure to medications *in utero* from the effect of 'not breastfeeding'. In Wales, antidepressant prescriptions in late pregnancy are associated with reduced breastfeeding prevalence at 6-8 weeks (aOR 0.81, 95%CI 0.67-0.98) (Jordan, 2019). In any subsequent follow up of this population, we shall need to account for this association. When applying this research, it will be important to define target behaviours: for example, should the emphasis be on prescription reduction or breastfeeding support? Linear relationships between economic deprivation and breastfeeding (Jordan, 2005; Jordan, 2009) and antidepressant prescribing (Jordan, 2019) are compounding socio-economic disadvantage, and introducing complexity into statistical models.

The physiology of lactation initiation is complex, and vulnerable to disruption by prescribed medications (Jordan et al 2005, 2009, 2019). Breastfeeding at 6, 12 or 26 weeks indicates a healthy dyad, and warrants consideration as an outcome measure. Initiation of breastfeeding is usually regarded as indicating intention, rather than successful breastfeeding (McAndrew, 2012).

#### Outcomes of interest (WHO 2018)

The outcomes of interest considered critical for decision-making included the following:

- early initiation of breastfeeding within one hour after birth
- any breastfeeding at 4–6 weeks
- exclusive breastfeeding at 4–6 weeks
- any breastfeeding at 6 months
- exclusive breastfeeding at 6 months
- giving any additional foods or fluids in the first 2 days after birth
- use of artificial teats and bottles in the first 6 months.

### 4. Research questions and objectives

The key objectives of Subtask 1.3.7 Breastfeeding are to:

1. Examine the availability, status, provenance and validity of breastfeeding data at any postnatal age in the databanks used by the databanks in the demonstration projects (DP)s.
2. Report on the definitions and terminology used when recording infant feeding in each data source (see Appendix 3: Breastfeeding glossary).
3. Investigate the extent to which selected prescription medications and recorded diagnoses are associated with breastfeeding status (initiation, at 6 weeks, and duration).
4. Explore the impact of factors associated with breastfeeding status (including maternal age at childbirth, SES, maternal and infant ill-health) to validate future analyses concerning breastfeeding and outcomes.
5. Compare breastfeeding rates and other data with external sources (section 7 below).

## 5. Study population

All pregnancies with a known live birth outcome and survival of mother and infant to time point of breastfeeding recorded in populations defined by each DP. Timing of pregnancy will be as in the DP/ umbrella standardization protocols.

## 6. Study variables

### a. Table 1. Study variables

Breastfeeding definition / outcome (no ICD10 codes)		
		Comments
Terms	“Breastfeeding OR Lactation OR Breastfe* OR Breast-fe* OR “Breast fe*” OR Lactat* OR “Infant feed*” OR “Infant Nutrition”	These terms are used in literature searches. They may be useful to search databanks.
Time points	Birth/ day 1,4- 6 weeks, 12 weeks, 26 weeks, 1 year As in database	Assume no initiation as infant ages. Feeding at all time points will be described as percentages / proportions. Feeding at 4-6 weeks will be subjected to inferential analyses.
Completeness	Exclusive, partial, any (see glossary for definitions)	We shall use ‘any’ breastfeeding in inferential analyses.

### b. 6.2 Factors affecting breastfeeding (Table 2 and 3 in excel file)

#### Maternal Factors

A small number of women are advised against breastfeeding (see limitations). We shall explore, descriptively, these exposures:

Clozapine (ATC N05AH02) in pregnancy

Lithium (ATC N05AN / N05AN01) in pregnancy)

Breast cancer (Wales only)

Breastfeeding is affected by demographics and lifestyle. The following factors will be as recorded in the DP and the breastfeeding rates will be described:

- Year of birth

- Maternal age
- SES (at birth)
- Parity (primip/ multip)
- Smoking (y/n)
- BMI
- Heavy alcohol use ever (y/no record)
- Substance misuse ever (y/no record) (Available in Wales only)
- Community mental health team referral ever (y/no record) (Available in Wales only)
- Mode of delivery-(Available in Wales only)

Other factors are discussed under 'limitations'. We believe it will be outside the scope of the project to collect data on variables such as mastitis.

**Infant Factors** We shall describe breastfeeding rates for infants at risk of 'not breastfeeding'.

- Infants with galactosaemia (ICD10=74.2) will be described but excluded from further analysis.
- Infants with congenital anomalies will be defined in all DPs. These infants will be excluded from the main analysis. The proportion of infants with congenital anomalies (any) and cleft palate who are breastfeeding will be described. The categories of anomalies to be described can be expanded where numbers permit e.g. Down syndrome.
- Preterm birth <32 and <37 weeks
- SGA <10<sup>th</sup> and <3<sup>rd</sup> centile (or equivalent in DAP)
- Twin or higher multiple
- Variables being defined in DP 2 (antidepressants)

### c. 6.3 Exposures

Exposures will be as defined by DPs (Table 2 and in excel file). Table 2, below will be repeated for each medication group or medication of interest.

**Table 2 : Exposures affecting breastfeeding**

<b>Exposures affecting breastfeeding</b>		
<i>Variable</i>	<i>Definition in words</i>	<i>Categorization</i>
Prescribed medications in pregnancy		Details as in rest of study
High dose	Maximum tablet strength	If in the DP
Other dose		
Co-prescriptions		If in the DP
Indication for prescription		
Medicated depression		
Unmedicated depression		
Co-morbidities		As in the DP
Discontinuation of prescription in T1		
Discontinuation of prescription pre-pregnancy		
Prescriptions in T2 or T3		

Prescriptions during breastfeeding weeks 1-6		
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\* Note. This may not be possible for all conditions, and is for discussion. We have previously published using 'depression medicated' and 'depression unmedicated'. This is confounded by severity of indication, and is predicated on the depression diathesis hypothesis; however, it represents one strategy to explore the contributions of both the medications and the condition.

## 7. Data Sources

### a. External Data

External databanks for comparisons: WHO 2019, UNICEF 2018, Theurich et al 2019, Bagci Bosi et al 2016, national statistics (e.g. NHS England 2020, Stats Wales 2019, Infant feeding survey). These surveys and NHS data records report breastfeeding rates at specified infant ages. The provenance of the data and data entry methods and any information on incentivisation (Bagci Bosi et al 2016) will be described.

Earlier work has explored the impact of: medications (any), antidepressants, AEDs and asthma medications on breastfeeding rates (Jordan et al in preparation has a review). There are also suggestions that infants exposed to AEDs *in utero* are protected from transgenerational ADRs; however, the only data identified to date are based on a volunteer cohort (Veiby et al 2013). We shall compare findings with the database studies identified in our literature search (in progress) (e.g. Ito et al 1995, Gorman & Chambers 2012, Kronenfeld et al 2018).

### b. Participating registries

The ConCePTION databanks working on this subtask of DP 1.2 will be France, Tuscany and Wales.

Table 2 Collaborators providing breastfeeding data in Task 1.3.7

REGISTER
<b>France</b>
EFEMERIS : Evaluation chez la Femme Enceinte des MEDicaments et de leurs RISques (Evaluation in Pregnant Women of MEDications and their RISK) Toulouse
<b>Italy</b>
Tuscany birth path for pregnancy Anna
<b>UK</b>
Wales, SAIL

## 8. Methods

### a. Information to be collected from databanks

Study variables are listed in section 6, above.

Issues such as timing of medication exposures will use the methods determined/specified by the DPs

We have surveyed the DPs with breastfeeding data, asking them to complete the table below.

Table 3. DAP survey

Specify how you plan to identify breastfeeding in your data source	
Search terms from the literature include:	

"Breastfeeding OR Lactation OR Breastfe* OR Breast-fe* OR "Breast fe*" OR Lactat* OR "Infant feed*" OR "Infant Nutrition"	
Specify the infant ages for data collection for breastfeeding	Initiation / birth 6, 12, 26 weeks, 1 year As in database
Specify the years of data collection	
Specify the extent of breasting e.g. exclusive, any	
Information from existing DP for rest of subtask.	

### **b. Analytic methods**

Tables are drafted in the attached excel file.

Cases to be excluded from analyses: infant not surviving to 6 weeks. Inferential analyses will exclude dyads with contra-indications to breastfeeding (maternal lithium, clozapine, infant galactosaemia). , Multiple pregnancies Will be treated as in rest of DP. See above and limitations, below.

#### **i. Descriptive aggregate results for all live births, breastfeeding:**

- a) At time points of birth or 1 day, 4-6 weeks and 6 months (if available), numbers of live and surviving births with any record of whether the mother breastfed at all.
- b) At time points of birth or 1 day, 4-6 weeks and 6 months (if available), numbers of live births who were breastfed exclusively or not. (if we have >1 country?)
- c) Distribution of all variables listed in 2 and in attached excel table 2

#### **ii. Descriptive aggregate results for those with breastfeeding information (inferential unadjusted) (Section 6, above):**

- d) Proportions not breastfeeding, breastfeeding any at 4-6 weeks are to be reported as in excel table 2:
  - Age of mother
  - Year of birth of baby
  - Mother's SES at birth
  - Maternal smoking in pregnancy
  - Maternal heavy alcohol use ever
  - Community mental health team referral ever
  - Parity
  - BMI
  - Twins / multiples
  - Maternal depression. If possible medicated and unmedicated.
  - Congenital anomalies
  - Preterm births <32 and <37 weeks
  - SGA < 3<sup>rd</sup> and 10<sup>th</sup> centile.
  - Medications listed according to DP. If possible, high dose and low dose.
  - Mode of delivery (Wales only)
  - Maternal substance misuse, ever (Wales only)

The categorisations and explicit definitions are provided for each maternal/child factor are outlined in task 1.2 Section 6, and in the umbrella protocol, the DP protocol and the standardisation protocol.



The above data will be presented separately for each DAP and, if appropriate, summary measures will be obtained across all DAPS. Numbers 1-4 will not be disclosed.

### iii. Comparison of breastfeeding rates with country-specific rates.

We shall describe breastfeeding rates in participating DAPs (Table 1 in excel file). We shall also tabulate comparisons with data collected by other sources for participating countries and all high-income countries (examples in table 4). (These comparisons will be illustrative, and not subjected to inferential analyses.

**Table 4 Examples of comparator data**

	UNICEF 2018				WHO 2019*	
Country	Year	Ever breastfed %	Year	Any breastfeeding 4-8 weeks %	Year	Infants exclusively breastfed for the first six months of life (%)
France	calculated 2016	63			-	-
Italy	calculated 2016	86			1999	5
UK	calculated 2016	81			2010	1
High income	Calculated 2016	79**			2016	~1
Wales (Stats Wales 2020)	2020	64.5	2020	39	2020	32
Scotland (2019)	2019	65	2019	43		-

\* From: GHO | By category | Exclusive breastfeeding under 6 months - Data by country (who.int)

\*\* 74% in USA, 54% in Ireland

We shall also describe the proportion of women initiating breastfeeding (recorded as breastfeeding at birth/ day 0/ day 1) who are not breastfeeding at 4-6 weeks. This will identify the women who tried to breastfeed, but with limited success. Women not intending to breastfeed rarely initiate breastfeeding (Jordan et al 2005). As described in Table 1 in excel file, this will be calculated from existing data, without additional variables.

### iv. Breastfeeding at 4-6 weeks (Inferential adjusted)

Outcome: Breastfeeding rates for specified time point (4-6 weeks). Excel sheet, tables 2a & 2b, lists possible covariates. Covariates to be entered as above.

Logistic regression models will be built, using covariates in section 6. Outcome variable will be 'any breastfeeding at 4-6 weeks'.

If there are sufficient data, we shall also explore an outcome variable 'change in breastfeeding status between birth and 4-6 weeks'. Dyads that did not initiate breastfeeding will be described and excluded from this analysis.

### v. Sensitivity analyses of cases excluded from analyses:

- Exposed to medication or disease posing greater risk than exposure under consideration, to be defined from above cross tabulations. These are likely to include: substance misuse, heavy alcohol use, insulin (as marker for type 1 diabetes), AEDs, antipsychotics.
- Infants at increased (but not 100%) risk of not breastfeeding: congenital anomalies, birth <32, <37 weeks, SGA <3<sup>rd</sup> centile.

Selection of exposures and conditions will be informed by earlier analyses. Data for Wales 2004-2010 are appended. These are copied from Jordan et al 2019, supplementary material.

#### **vi. A priori Subgroup analyses**

We shall examine the impact of antidepressants on breastfeeding rates in: 'At risk' women: substance misuse/ heavy alcohol use, insulin use, AED use, community mental health team clients, cancer, MS, lowest socio-economic status (5<sup>th</sup> Townsend quintile). Examples from Jordan et al 2016 indicate the impact of SSRI exposure on the rates of congenital anomalies in these vulnerable groups.

'At risk' infants: preterm <32, <37 weeks, SGA <3<sup>rd</sup> centile, congenital anomalies., twins, birth by section.

Some medications of interest in Conception (e.g. chemotherapies, monoclonal antibodies) are not recommended during breastfeeding. We anticipate undertaking an exploratory analysis in one database (Wales).

#### **vii. 7. Breastfeeding as a mediator or confounder**

For some outcomes e.g. neurodevelopment, breastfeeding may be a mediator, rather than a confounder. This will be explored by testing the impact of

- a) medication of interest (e.g. antidepressant, baclofen) on breastfeeding (as above)
- b) breastfeeding on outcome of interest (neurodevelopment, infections) (Jordan et al in preparation) DP 1.2 is planning to include breastfeeding as a covariate in the neurodevelopmental outcomes.

Should these conditions be met, we shall seek further funding to explore causal models.

### **9. Dissemination plan**

The results will also be used to identify the characteristics of women who do not breastfeed at 4-6 weeks despite initiation of breastfeeding. This behaviour pattern often indicates a willingness to breastfeed, but a difficulty in sustaining feeding. Characterisation of women most at risk will inform healthcare professionals as to which women need additional support.

Paper 1

Breastfeeding in 3 European countries: the impact of prescribed medications

Paper 2

Breastfeeding as a mediator or confounder in pharmacovigilance (section 7 above)

### **10. Limitations of task 1.3.7**

Information on infant feeding is rarely reported in pharmaco-epidemiological studies (Jordan et al in preparation). Breastfeeding is basically recommended for all mothers with few exceptions. This study will not be able to exclude all mothers with contraindications to

breastfeeding, but numbers will be low. We shall not be able to identify women diagnosed with open TB or HIV infections. Some medications of interest in Conception (e.g. chemotherapies, monoclonal antibodies) are not recommended during breastfeeding. We anticipate undertaking an exploratory analysis in just one database (Wales).

Breastfeeding is complicated by serious illness in infant or mother. It will not be possible to identify all dyads affected by serious illness, for example, we are unable to identify admissions to NICU. However, despite infant admission to intensive care, mothers are encouraged to breastfeed, and the rates of 'any breastfeeding' at 4 weeks of life in NICU (~60%) or discharge from NICU (~43%) are comparable with national rates (Akuma et al 2018). We are unable to identify use of milk banks (there are none in Wales), donor milk or wet nursing, which is often informal.

We acknowledge that discontinuation of breastfeeding is sometimes associated with mastitis (ICD10 codes: JB45 Infections of breast associated with childbirth, GB21 Inflammatory disorders of breast, GB21.Y Other specified inflammatory disorders of breast), particularly as breastfeeding progresses, but we may not have resources to explore this. Return to work is a further consideration, but this is relatively unusual before 6 weeks in Europe. It is very difficult to explore this and other social factors in electronic data.

Breastfeeding data is as reported by mothers or carers to or observed by health visitors, nurses, midwives or data collected. No reimbursement is associated with these data. As with many variables in Conception (smoking, alcohol use) we are unable to explore any social desirability response.

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## 12. Appendices

Appendix 1 Infants at increased risk of not breastfeeding. (from Jordan et al 2019, S2 file)

Table B1. Infants exposed to Insulin or Anti-epileptic drugs [AEDs]

	exclusions = anomalies + TOPFAs [n=113316]					exclusions = anomalies + TOPFAs [n=113316]				
	insulin in trimester 1					AEDs in trimester 1				
	Exposed n [%]	% without unknown outcome	Unexposed n [%]	% without unknown outcome	unadjusted OR [95% CI]	Exposed n [%]	% without unknown outcome	Unexposed n [%]	% without unknown outcome	unadjusted OR [95% CI]
<b>Breastfeeding 2004-2010</b>										
<b>at birth</b>										
Yes	165 [23.98]	45.83	25,930 [23.02]	52.3	0.77 [0.63, 0.95]	226 [19.42]	40.5	25,869 [23.07]	52.38	0.62 [0.52, 0.73]
No	195 [28.34]	54.17	23654 [21]	47.7		332 [28.52]	59.5	23,517 [20.97]	47.62	
Total without unknowns	360 [52.33]	100	49,584 [44.02]	100		558 [47.94]	100	49,386 [44.03]	100	
Unknown	328 [47.67]		63,044 [55.98]			606 [52.06]		62,766 [55.97]		
Total	688 [100]		112,628 [100]			1164 [100]		112,152 [100]		
<b>at 6-8 weeks</b>										
Yes	75 [10.9]	25	13,102 [11.63]	32.59	0.69 [0.53, 0.90]	84 [7.22]	19.31	13,093 [11.67]	32.68	0.49 [0.39, 0.63]
No	225 [32.7]	75	27100 [24.06]	67.41		351 [30.15]	80.69	26,974 [24.05]	67.32	
Total without unknowns	300 [43.6]	100	40,202 [35.69]	100		435 [37.37]	100	40,067 [35.73]	100	
Unknown	388 [56.4]		72,426 [64.31]			729 [62.63]		72,085 [64.27]		
Total	688 [100]		112,628 [100]			1164 [100]		112,152 [100]		

**Table B2. Infants exposed to coumarins or heavy drinking or substance misuse (exclusions = anomalies + TOPFAs [n=113316])**

	coumarins [anticoagulants] in trimester 1					heavy drinking/ substance misuse				
	Exposed n [%]	% without unknown outcomes	Unexposed n [%]	% without unknown outcomes	unadjusted OR [95% CI]	Exposed n [%]	% without unknown outcomes	Unexposed n [%]	% without unknown outcomes	unadjusted OR [95% CI]
<b>Breastfeeding 2004-2010</b>										
at birth										
Yes	57 [14.92]	39.58	26,038 [23.06]	52.29	0.60 [0.43, 0.84]	294 [16.38]	35.94	25,801 [23.14]	52.52	0.51 [0.44, 0.59]
No	87 [22.77]	60.42	23762 [21.04]	47.71		524 [29.19]	64.06	23,325 [20.92]	47.48	
Total without unknowns	144 [37.7]	100	49,800 [44.1]	100		818 [45.57]	100	49,126 [44.05]	100	
Unknown	238 [62.3]		63,134 [55.9]			977 [54.43]		62,395 [55.95]		
Total	382 [100]		112,934 [100]			1795 [100]		111,521 [100]		
at 6-8 weeks										
Yes	16 [4.19]	14.68	13161 [11.65]	32.58	0.36 [0.21, 0.61]	117 [6.52]	17.94	13,060 [11.71]	32.77	0.45 [0.37, 0.55]
No	93 [24.35]	85.32	27,232 [24.11]	67.42		535 [29.81]	82.06	26,790 [24.02]	67.23	
Total without unknowns	109 [28.53]	100	40,393 [35.77]	100		652 [36.32]	100	39,850 [35.73]	100	
Unknown	273 [71.47]		72,541 [64.23]			1143 [63.68]		71,671 [64.27]		
Total	382 [100]		112,934 [100]			1795 [100]		111,521 [100]		

Table B3. Infants excluded from the analysis: those with congenital anomalies or multiples

	exclusions = anomalies + TOPFAs [n=113316]					no exclusions [n=117717]				
	Multiples					anomalies including TOPFAs				
	Exposed n [%]	% without unknown outcomes	Unexposed n [%]	% without unknown outcomes	unadjusted OR [95% CI]	Exposed n [%]	% without unknown outcomes	Unexposed n [%]	% without unknown outcomes	unadjusted OR [95% CI]
<b>Breastfeeding 2004-2010</b>										
at birth										
Yes	487 [18.81]	52.14	25,608 [23.13]	52.25	1.00 [0.88, 1.13]	700 [15.91]	47.78	26,095 [23.03]	52.25	1.00 [0.88, 1.13]
No	447 [17.27]	47.86	23,402 [21.13]	47.75		765 [17.38]	52.22	23,849 [21.05]	47.75	
Total without unknowns	934 [36.08]	100	49,010 [44.26]	100		1465 [33.29]	100	49,944 [44.07]	100	
Unknown	1655 [63.92]		61,717 [55.74]			2936 [66.71]		63,372 [55.93]		
Total	2589 [100]		110,727 [100]			4401 [100]		113,316 [100]		
at 6-8 weeks										
Yes	196 [7.57]	25.42	12,981 [11.72]	32.67	0.70 [0.60, 0.83]	315 [7.16]	26.72	13,177 [11.63]	32.53	0.70 [0.60, 0.83]
No	575 [22.21]	74.58	26,750 [24.16]	67.33		864 [19.63]	73.28	27,325 [24.11]	67.47	
Total without unknowns	771 [29.78]	100	39,731 [35.88]	100		1179 [26.79]	100	40,502 [35.74]	100	
Unknown	1818 [70.22]		70,996 [64.12]			3222 [73.21]		72,814 [64.26]		
Total	2589 [100]		11,0727 [100]			4401 [100]		113,316 [100]		

## Appendix 2. Breastfeeding information From DP 1.2

Table 1 Region, time period and pregnancies covered for data sources used in this study (pending data characterisation results)

Region	Data sources (bold provide ND outcomes, italic breast feeding)	Time period	Pregnancies in period covered (1,000)
France			
Haute-Garonne	<b>EFEMERIS database</b>	2004-2017	137
Haute-Garonne	<b>POMME database</b>	Two birth cohorts (2010, 2015), both followed until end of 2017 (soon data on 2018 will be added)	18
Italy			
Tuscany	<b>SALM – mental health services</b> , CAP and CAP2 – <i>birth registry</i> , SPF – dispensation of medications in community pharmacies, FED – dispensations of medications from hospital pharmacies for outpatient use	2003- (2010 with ND outcomes)	480
United Kingdom			
Wales	<b>In-patient and out-patient PEDW records, Primary Care GP dataset, National Community Child Health Database (NCCHD)</b> , CARIS congenital anomaly registry	1998, breastfeeding 2005-	945



### Appendix 3: Breastfeeding Glossary

Breastfeeding as an outcome measure or confounder is not straightforward in terms of timing of recording and reporting. The infant feeding literature offers little consistency regarding the timing of data collection. Consequently, to compare data sets commonalities will need to be determined. Definitions of full and partial breastfeeding will need to be considered.

It is recognised that the WHO categories of breastfeeding do not allow finer distinctions; for example, they would classify as complementary feeding the mother giving an occasional formula feed, and therefore almost fully breastfeeding, and the mother giving an occasional breastfeed, and therefore almost exclusively formula feeding. In addition, the WHO definition of complementary feeding does not allow distinguishing between feeding with and without the use of formula. Monitoring systems, or more often operational research, willing to gain a better understanding of different patterns of infant feeding, may add categories to the WHO definitions, provided they use them anyway for international comparisons (EC 2008 p.11). Therefore, some databanks ask those entering data to estimate % breastmilk e.g. NHS Wales 2017.

Term	Definition	Reference	Notes
Breastfeeding	Breastmilk, including wet nurse or expressed milk via tube or cup or syringe	WHO 1991, 2008	
Completeness			
Exclusive / total	Infant receives only breast milk from his/her mother or a wet nurse, or expressed breast milk via tube, cup or syringe, and no other liquids or solids with the exception of drops or syrups consisting of vitamins, mineral supplements or medication.	EC 2008, based on WHO 1991, 2008	
	Only breastmilk or essential medications. <i>It is intended that milk feeding should be recorded as exclusive breast milk feeding even if solid food has been introduced if breast milk is the only source of fluids. As other drinks are introduced milk feeding should be recorded as combined milk feeding (predominant or partial as appropriate).</i>	NHS Wales 2017	
Predominant	Predominant breastfeeding: the infant's predominant source of nourishment is breast milk. However, the infant may also receive water and water-based drinks; Oral Rehydration Solution (ORS); drop and syrup forms of vitamins, minerals and medications; and ritual fluids (in limited quantities). With the exception of fruit juice and	EC 2008, based on WHO 1991, 2008	

	sugar-water, no food-based fluid is allowed under this definition.		
Full	Predominant or exclusive	EC 2008	Use this portmanteau term will avoid differences in data collection
Partial or mixed	Currently receiving breast milk (this may be expressed breast milk) at 6 weeks of age and who are also receiving formula milk or any other liquids or food.	NHS England 2014	
Complementary	Breastmilk plus solid or semi-solid foods or liquids, including non-human milk	WHO 1991, 2008	
Combined milk feeding – predominantly breast	>75% of the feeds in the previous 24 hours were breastfeeds	NHS Wales 2017	
Combined milk feeding – partially breast	75% or less of the feeds in previous 24 hours were breastfeeds	NHS Wales 2017	
Any	Full or complementary or combined	NHS Wales 2017	
Bottle feeding	Liquid or solid from a bottle with a teet, including breastmilk fed this way.	WHO 1991, 2008	Finland would not include bottle-fed breastmilk in this category
Artificial milk feeding	Formula milk and any other drink but no breast milk	NHS Wales 2017	
Other terms			
Continued breastfeeding	Breastfeeding (any) after 12 months	WHO 1991	
Galactagogue	A galactagogue is a material or action that stimulates milk production.	Lawrence 2011	
Infant formula	The Federal Food, Drug, and Cosmetic Act (FFDCA) defines infant formula as "a food which purports to be or is represented for special dietary use solely as a food for infants by reason of its simulation of human milk or its suitability as a complete or partial substitute for human milk" (FFDCA 201(z)). FDA regulations define infants as persons not more than 12 months old (Title 21, Code of	Source: Excerpted from Guidance for Industry: Frequently Asked Questions about FDA's Regulation of Infant Formula March 1, 2006. Cited in FDA 2018	

	Federal Regulations 21 CFR 105.3(e). 3 main types: modified bovine (or goat/ hircine) whey, soy (phyto-oestrogens may be problematic), hydrolysed “hypo-allergenic”. Not to be confused with ‘follow on’ milk, which is not regulated.		
Ritual fluids	Typically herbal preparations or teas. These may include water (boiled or otherwise) from the family source. They may be the 1 <sup>st</sup> intake, as colostrum is not always offered (considered unclean).	Davies-Aetugbo 1997	
Support	From the first feed, women should be offered skilled breastfeeding support (from a healthcare professional, mother-to-mother or peer support) to enable comfortable positioning of the mother and baby and to ensure that the baby attaches correctly to the breast to establish effective feeding and prevent concerns such as sore nipples. Extra support should be given following narcotics, general anaesthetics, sections, delayed skin-to-skin contact.	NICE 2014, 1.3.15	
Timely complementary feeding	Complementary feeding over 6 months	WHO 1991	
Weaning	Introducing solid foods or complementary feeding	NHS 2019	

### Outcomes of interest (WHO 2018)

The outcomes of interest considered critical for decision-making included the following:

- early initiation of breastfeeding within one hour after birth
- any breastfeeding at 4–6 weeks
- exclusive breastfeeding at 4–6 weeks
- any breastfeeding at 6 months
- exclusive breastfeeding at 6 months
- giving any additional foods or fluids in the first 2 days after birth
- use of artificial teats and bottles in the first 6 months.

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# Appendix 11 Medication, ATC code and P-gp or BCRP substrates (S) or inhibitors (I) status

Medication	ATC code	P-gp transporter substrate/ Inhibitor	BCRP transporter substrate/ Inhibitor
Ranitidine	A02BA02	S	
Famotidine	A02BA03	S	
Nizatidine	A02BA04	S	
Omeprazole	A02BC01	S,I	I
Pantoprazole	A02BC02	S,I	S,I
Lansoprazole	A02BC03	S,I	I
Rabeprazole	A02BC04	I	I
Loperamide	A07DA03	S,I	I
Sulfasalazine	A07EC01	S	S,I
Olsalazine	A07EC03	S	
Metformin	A10BA02	S	S
Pioglitazone	A10BG03		I
Sitagliptin	A10BH01	S,I	
Repaglinide	A10BX02	S,I	
Dipyridamole	B01AC07	S,I	S,I
Digoxin	C01AA05	S,I	
Flecainide	C01BC04	S,I	
Prazosin	C02CA01	S,I	S,I
Hydrochlorthiazide	C03AA03	S	
Furosemide	C03CA01		S,I
Spironolactone	C03DA01	I	
Propranolol	C07AA05	I	
Acebutolol	C07AB04	S	
Celiprolol	C07AB08	S,I	
Labetalol	C07AG01	S	
Carvedilol	C07AG02	S,I	
Amlodipine	C08CA01	S,I	I
Felodipine	C08CA02	I	
Isradipine	C08CA03	I	
Nifedipine	C08CA05	I	I
Verapamil	C08DA01	S,I	I
Diltiazem	C08DB01	S,I	
Simvastatin acid	C10AA01	S,I	I
Simvastatin	C10AA01	S,I	I
Lovastatin	C10AA02	S,I	
Fluvastatin	C10AA04	S	S,I
Atorvastatin	C10AA05	S,I	S,I
Rosuvastatin	C10AA07	S,I	S,I
Miconazole	G01AF04	I	

Bromocriptine	G02CB01	S	
Estradiol (17-beta)	G03CA03		I
Estriol	G03CA04	S	
Progesterone	G03DA04	I	
Dexamethasone	H02AB02	S	I
Methylprednisolone	H02AB04	S	I
Prednisolone	H02AB06	S	
Prednisone	H02AB07	S	
Hydrocortisone	H02AB09	S	
Dicloxacillin	J01CF01	S	
Trimethoprim	J01EA01	S	
Erythromycin	J01FA01	S,I	S
Roxithromycin	J01FA06	S,I	
Clarithromycin	J01FA09	S,I	
Azithromycin	J01FA10	S,I	
Telithromycin	J01FA15	S,I	
Ofloxacin	J01MA01		S
Ciprofloxacin	J01MA02	S	S
Norfloxacin	J01MA06		S
Levofloxacin	J01MA12	S, I	
Moxifloxacin	J01MA14	S	
Nitrofurantoin	J01XE01		S
Tedizolid	J01XX11		I
Ketokonazole	J02AB02	S,I	I
Ketoconazole	J02AB02	S,I	I
Itraconazole	J02AC02	I	
Famciclovir	J05AB09	S	
Oseltamivir	J05AH02	S,I	
Tamoxifen	L02BA01	S,I	
Anastrozole	L02BG03	S	
Letrozole	L02BG04	S	
Cyclosporine	L04AD01	S,I	I
Tacrolimus	L04AD02	S,I	I
Indomethacin	M01AB01	S,I	
Diclofenac	M01AB05		S,I
Meloxicam	M01AC06	I	
Naproxen	M01AE02	I	
Celecoxib	M01AH01	S,I	I
Rofecoxib	M01AH02	I	
Etoricoxib	M01AH05	I	
Diclofenac (topical)	M02AA15		S
Allopurinol	M04AA01		S
Oxycodone	N02AA05	S	

Buprenorphine	N02AE01	S	
Zolmitriptan	N02CC03	S	
Eletriptan	N02CC06	S	
Chlorpromazine	N05AA01	I	
Methotrimeprazine (levomepromazine)	N05AA02	I	
Fluphenazine	N05AB02	S,I	
Perphenazine	N05AB03	I	
Prochlorperazine	N05AB04		I
Thioridazine	N05AC02	I	I
Haloperidol	N05AD01	I	
Ziprasidone	N05AE04	I	
Chlorprothixene	N05AF03	I	I
Clozapine	N05AH02	I	
Quetiapine	N05AH04	I	
Risperidone	N05AX08	S,I	
Aripiprazole	N05AX12	I	I
Lorazepam	N05BA06	S	
Hydroxyzine	N05BB01	S	
Midazolam	N05CD08	I	
Amitriptyline	N06AA09	I	
Citalopram	N06AB04	S,I	
Paroxetine	N06AB05		S
Sertraline	N06AB06	I	
Fluvoxamine	N06AB06	I	
Bupropion	N06AX12	S	S
Tinidazole	P01AB02	I	
Fluticasone	R01AD08	S	
Lidocaine	R02AD02	I	
Budesonide	R03BA02	S	
Montelukast	R03DC03	I	
Cetirizine	R06AE07	S, I	
Levocetirizine	R06AE09	S	
Levocetirizine (R-cetirizine)	R06AE09	S	
Astemizole	R06AX11	S,I	
Terfenadine	R06AX12	S,I	
Loratadine	R06AX13	S	
Acrivastine	R06AX18	S	
Ebastine	R06AX22	I	
Fexofenadine (terfenadine carboxylate)	R06AX26	S	
Fexofenadine	R06AX26	S	
Desloratadine	R06AX27	S	
Desloratadine	R06AX27	S	

Prednisolone (local)	S01BA04	S	
Diclofenac (local)	S01BC03		S
Diclofenac	S01BC03		S



## Appendix 12 Covariates available across data sources

	Socioeconomic status (SES), maternal education	Ethnicity	Smoking / alcohol use	BMI	Parity
Finland registers	Mother's occupation (25% missing)	NA	smoking yes/no (recorded at the first antenatal visit)	available only 2004/2005 onwards with 2-5.1% missing	Available
France: EFEMERIS / POMME	Maternal occupation (employed Y/N, 16% missing), level of education (45% missing)	NA	yes/no during pregnancy (60% missing) alcohol use collected but difficult to interpret	NA	Available
Italy – Emilia Romagna	Maternal and paternal employment - maternal education and paternal education. Paternal data could have missing data. To check depending on year. In 2018 we had 4.1% (n=13239 missed values for pat edu, and 3.1% (1004) missed values for pat employment.	Available	Yes/no during pregnancy. if Yes: discontinued before pregnancy, when pregnancy discovered, continued during pregnancy	BMI to be derived	Available
Italy - Tuscany	Among cases with congenital anomalies 2005-2017: maternal employment (40% missing), maternal education (23% missing, among LB with CA 12% missing)	For cases with congenital anomalies: maternal country of birth (28% missing)	Among cases with congenital anomalies: smoking during pregnancy yes/no (26% missing), if yes, n° cigarettes/day (12% missing) alcohol yes/no (44% missing)	For cases with congenital anomalies (26% missing)	Available
Norwegian Registries	Maternal employment status	Maternal country of birth	Yes/no (86% complete)	50% missing	Available
Wales / SAIL linked datasets	SES at birth (100% complete). Based on Welsh Index of Multiple Deprivation (IMD) or Townsend	No data earlier years. Withheld later years, as sensitive.	Categories Codes for SUD or referral for heavy alcohol consumption / substance misuse Smoking >90% complete, but	BMI at start and end of pregnancy/ 1 <sup>st</sup> midwifery appointment ~90% complete from 2015.	~100% complete for primip / multip. After 3 <sup>rd</sup> child data unreliable and low numbers.

			has 'ex-smoker' category	60-70% complete earlier	
Germany / GePaRD	Deprivation index of place of living (complete 100%). Highest educational attainment based on occupational codes available for employees – missing for children, students and retired people	NA	Codes for alcohol abuse / P codes recording harm to child due to alcohol and smoking	Codes for obesity / underweight	To derive based on previous records of pregnancies

## Appendix 13 Meta Analytic Techniques for use in ConcePTION

Version: 4 :16/11/2020  
Joan Morris, Matt Pryce

### Purpose

The purpose of this document is to suggest possible methods for use by the different demonstration projects for pooling analytic results and aggregate data from the different databases in ConcePTION.

All DPs consist of

### **Medication Utilisation and Event/Outcome Definition Study:**

The aim of the medical utilisation study is to describe the frequency / quantity of prescriptions of specified medications in the database and in particular in pregnant women within the database. The aim of the event outcome definition study is to define specific algorithms to identify outcomes / events. This is likely to involve analysing prevalence of events/outcomes over time and possibly by pre-specified subgroups of interest, in particular pregnant women. But there may be additional information on, for example, groups defined according to socio-economic status

### **Medication Safety Study:**

The aim is to assess the safety in pregnancy of specified medications. Safety will be assessed using a range of outcomes and confounders and mediators are likely to be included in analyses.

It is expected that both study types will use similar meta-analytic techniques to analyse their results when appropriate. However, many of the results from these studies are expected to be database specific and therefore meta-analytic techniques will not be required.

### Appropriateness of Conducting a Meta-Analysis

Before combining results between countries, it is key that the effect estimates to be combined are logically comparable. The following questions should be considered before conducting any meta-analysis of effect estimates across countries:

- Are the outcome definitions being analysed by each country the same?
- Are the methods used to obtain exposure definitions comparable between countries?
- Do the countries have comparable medication utilisation profiles?
- Do the data sources being compared have any other underlying differences?

When extreme heterogeneity is present between countries, it would not be advisable to produce a combined effect estimate as its interpretable value is low and may be misinterpreted by readers.

### Use of Controls

When combining results from different data sources (especially if they are from different countries) it is highly recommended that all analyses include controls in order to reduce country specific differences. For example in table 1, when IQ scores in children born to women taking a specific medication the IQ score of children of women not exposed to the medication should be also analysed as it will vary by data source.

Table 1: Example of using control data in analysis

Database	Mean Score Exposed	Mean Score Controls	Difference in mean score (E-C)	Ratio of mean scores (E/C)
<b>A</b>	100	110	10	1.1
<b>B</b>	100	105	5	1.05
<b>C</b>	80	88	8	1.1
<b>Meta-analysis all studies</b>	Exposed	Control	Diff	Ratio

The ideal measure to summarize across data sources may either be the difference in scores compared to unexposed babies or the ratio of scores. This depends on which you believe to be most relevant. In general it is not advised to combine all the exposed mean scores and then to combine all the control mean scores. This will introduce more variation in the models. with a confidence interval for this difference or the ratio of scores – the difference could be on an arithmetic (the actual difference) or log scale (the proportional difference). Similarly, when analysing the occurrence of SGA, the ideal comparison would be the increased odds of SGA compared to unexposed pregnancies.

#### Random Effects vs Fixed Effects

When conducting meta-analyses, most methods fall into one of two categories, fixed effect models or random effect models. Fixed effects models assume that the true effect being estimated in each country is the same. However, random effect models assume that the true effect being estimated varies between countries and so the estimates will also vary. The model accounts for this by assuming these estimates will follow a distribution around the true effect (usually a normal distribution). Which models are used should be decided prior to analysing the data.

#### Bias

When performing meta-analysis, it is recommended that the STATA programs metabias and metafunnel are run to examine potential bias in estimates. This may not be applicable in this situation when you are analysing data from different data sources rather than from published studies. So it is not essential to run these.

#### Effects of Covariates

The biggest challenge in this analysis is that it is not likely to be possible to fit individual models to the data in each data source, to examine the fit of the data and to adapt the models for each data source. As the data will vary between data sources this means that many may not have the same complete set of covariates. It will need to be decided if multivariate models can be fitted or whether adjusting for each covariate separately may provide sufficient information. If you have access to at least one data base the whole range of models can be fitted and then inferences can be made about the model fitting to other data sets.

#### Summary of Meta-Analysis Techniques and Procedures in STATA

1. METAN – Meta-analysis of binary or continuous data with fixed or random effects and by subgroups

```
metan tdeath tnodeath cdeath cnodeath
```

```
metan tsample tmean tsd csample cmean csd,
```

```
metan logor selogor
```

```
metan mean semean
```

```
metan mean lowerci upperci
```

```
metan percent lowerci upperci (see metaprop below)
```

2. METAAN - Similar to metan, but a greater range of estimation methods and different inputs :

metaan eff SEeff,

metaan eff effvar, varc

3. METAPROP– Meta-analysis of proportions with fixed or random effects and by subgroups[1]

4. (ftt Calculate the pooled estimate after Freeman-Tukey Double Arcsine Transformation)

metaprop num denom, ftt

But this has been identified as prone to errors[2] so see also GLMM procedure in STATA

5. METAREG : Meta-analysis of binary or continuous data with fixed or random effects relating value(s) of each study to the observed relative riskor mean

metareg logrr latitude, wsse(selogrr)

metareg smd abstract duration itt, wsse(sesmd) permute(10000)

6. MVMETA : Meta-analysis of several variables simultaneously and can include regression[3]

mvmeta b V

b : set of variables all starting with b for example if looking at related factors such as diagnosis other maternal diseases : diabetes , epilepsy, other all as binary variables you would code them b1 , b2 and b3 and do a meta-analysis of the 3 beta's simultaneously.

Additional programs in STATA

7. XTPOISSON : Analysing counts with random effects / mixed effects models[4]

- a. Can use small time intervals and then model risk(an event occurring within time interval) against potential confounders etc. Gives greater flexibility to use of multilevel models

- b. Stsplit in STATA will create a data set of small time intervals

8. GLST : Generalized Least Squares for trend estimation of summarized dose-response data[5, 6]

glst depvar dose [indepvars] , se(varname) cov(n cases)

Can use to model changes in log(rr) according to dose. So could have potential when looking at SES categories for instance.

9. MEGLM : Multilevel mixed-effects generalized linear model

These can be used to overcome the issues in METAPROP for count data and can also be specified using MELOGIT or MEPOISSON

Meta-analysis of survival curves

The analysis of survival curves is a different situation as there will be estimated probabilities of survival for a set of different time points. These probabilities are all highly correlated and hence should not ideally be analysed without including information about these correlations.

#### 1. Use of MVMETA

The survival probabilities can be combined if there are only 2 or 3 time points. You may need to use the Freeman-Tukey double arcsine transformation to stabilize the variances first.

## 2. Multivariate meta-analysis on conditional probabilities [7]

MetaSurv in R does this:

- i. Calculate probability survival up to fixed time points conditional on survival up to that time point as the conditioning means that the estimates are not correlated
- ii. Combine these probabilities
- iii. Multiply these together to get overall estimate

However, MetaSurv includes a continuity correction of 0.5, which creates bias for combining small samples sizes. SGUL are writing a program that will include a smaller continuity correction that will reduce the bias.

## 3. Bayesian multivariate meta-analysis on conditional probabilities

A Bayesian version of the method proposed by Combescure has been developed by SGUL but is currently being assessed in comparison with Frequentist methods.

Potential Issues: Mainly Small Numbers

### 1. Continuous Measures

Generally OK particularly if analysing means as you can always estimate a mean and its se if you have at least two data points – the lack of data will usually be reflected in the variance. However, if you only have two data points and they are extremely close then the variance may be very low. You do need to examine all your data carefully.

### 2. Proportions and Odds Ratios

This can be very problematic as you may have no events and hence 0 in specific cells. Many programs either drop all data from that database or else automatically insert a 0.5 and carry on. You need to check what is happening with this. If there are several databases with this issue it may have a large effect on your overall estimates. There is a difference between medication not being prescribed in a country and hence no events with exposure for that medication in the country with no events occurring when the medication is being prescribed. The FTT transformation in METAPROP may introduce bias especially if your databases vary greatly in size.

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## Appendix 14 SSRI/SNRI signal anomalies identified in the literature

Evidence for increased risk following SSRI exposure is conflicting with some studies finding no increased risk. A number of signals have been identified:

### SSRIs

- all major malformations combined, aOR 1.13, 95% CI 1.06-1.20 (Furu et al., 2015)
- Anencephaly aOR 2.4, 95% CI 1.1-5.1 (Alwan et al., 2007)
- Hydrocephalus RR 2.7, 95% CI 1.5-4.6 (Munch et al., 2014)
- congenital heart defects aOR 1.15, 95% CI 1.05-1.26 (Furu et al., 2015); use throughout first trimester aOR 2.01, 95% CI 1.60 to 2.53; paused SSRI use aOR 1.85, 95% CI 1.07 to 3.20 (Jimenez-Solem et al., 2012).
  - septal heart defects, aOR 2.04 (95% CI 1.53 to 2.72), paused exposure, aOR 2.56 (95% CI 1.41 to 4.64)(Jimenez-Solem et al., 2012)
  - right ventricular outflow tract obstructions, aOR 1.48, 95% CI 1.15-1.89 (Furu et al., 2015)
  - atrial and ventricular septal defects, aOR 1.17, 95% CI 1.05-1.31 (Furu et al., 2015)
- Cystic kidney disease (OR 2.83, 95% CI 1.14–7.04(Colvin et al., 2011); OR 2.39, 95% CI 1.09-4.54 (M Reis and Källén, 2010)
- omphalocele, aOR 2.11, 95% CI 1.01-4.39 (Furu et al., 2015)
- Lower limb reduction (OR 4.20, 95% CI 1.27-13.93) (Colvin et al., 2011)
- Club foot aOR 1.8, 95% CI 1.1-2.8 (Yazdy et al., 2014); aOR 1.34, 95% CI 1.05-1.71 (Furu et al., 2015); aOR 2.2, 95% CI 1.4-3.6 (Louik et al., 2007)
- Craniosynostosis aOR 2.5, 95% CI 1.5-4.0 (Alwan et al., 2007)

### Citalopram

- All major congenital malformations aOR 1.36, 95% CI 1.08-1.73; aOR 1.19, 95% CI 1.07-1.31) (Furu et al., 2015)
- craniosynostosis aOR 3.95, 95% CI 2.08-7.52 (Bérard et al., 2017)
- neural tube defects aOR 2.46, 95% CI 1.20-5.07 (Malm et al., 2011)
- congenital heart defects, odds ratio 2.09, 95% CI 1.25-3.51) (Jordan et al., 2016)
  - Septal defects OR 2.52, 95% CI 1.04-6.10 (Pedersen et al., 2009); OR 1.68, 95% CI 1.15-3.0 (Jimenez-Solem et al., 2012)
  - patent ductus arteriosus (OR 5.5, 95% CI, 2.3-13.6 based on 5 exposed cases) (Colvin et al., 2011)
  - and right ventricular outflow tract obstruction (aOR 1.65, 95% CI 1.10-2.48). (Furu et al., 2015)
  - tetralogy of Fallot (N=2, aOR 4.41, 95% CI 1.02-19.15) (Wemakor et al., 2015)
  - Ebstein anomaly (N=1, aOR 12.36, 95% CI 1.61-95.15) (Wemakor et al., 2015)
- abdominal wall defects OR 3.52, 95% CI 1.56-7.91(Jordan et al., 2016)
  - gastroschisis (aOR 5.10, 95% CI 1.46-17.75) (Wemakor et al., 2015)
- omphalocele aOR 2.8, 95% CI 1.3-5.7 (Alwan et al., 2007)
- Congenital urinary tract when pregnancies in non-depressed women were used as the control aOR 2.07, 95% CI 1.10-3.92 for urinary (Ban et al., 2014).
  - hypospadias aOR 3.21, 95% CI 1.56-6.60 (Wemakor et al., 2015); OR 1.69, 95% CI 1.04-2.73 (Jordan et al., 2016)
- digestive system defects when pregnancies in non-depressed women were used as the control aOR 2.60, 95% CI 1.07-6.32 (Ban et al., 2014).
- musculoskeletal defects aOR 1.92, 95% CI 1.40-2.61 (Bérard et al., 2017)

- lower limb abnormalities (OR 9.8, 95% CI 2.3-41.4 (Colvin et al., 2011))

#### Escitalopram

Escitalopram is the active enantiomer of citalopram – Reprotox authors argue that this should produce the same results as citalopram

- Ebstein anomaly (N=1, aOR 34.19, 95% CI 4.09-286.04) (Jimenez-Solem et al., 2012)
- atrial septal defects (aOR 3.31, 95% CI 1.11-9.90) (Jimenez-Solem et al., 2012)
  - atrial septal defects without severe congenital heart malformations (N=5, aOR 3.62, 95% CI 1.21-10.83) (Jimenez-Solem et al., 2012)
- atrioventricular septal defects (OR 8.71, 95% CI 1.21-62.64) (Jimenez-Solem et al., 2012)
- club foot aOR 2.9, 95% CI 1.1-7.2 (Yazdy et al., 2014) ; (aOR 3.88, 95% CI 1.19-12.69) (Wemakor et al., 2015); OR 2.18, 95% CI 1.16-4.07) (Jordan et al., 2016)

#### Fluoxetine

- all major malformations combined (aOR 1.25, 95% CI 1.10-1.42) (Furu et al., 2015)
- neural tube defects, odds ratio 2.57, 95% CI 1.21-5.46 (Jordan et al., 2016)
- Ear/face and neck (OR 4.39, 95% CI 1.40-13.79) (Colvin et al., 2011)
- cardiovascular malformations aOR 4.47; 95% CI 1.31-15.27 (Diav-Citrin et al., 2008); (aOR 1.34, 95% CI 1.10-1.63) (Furu et al., 2015)
  - tetralogy of Fallot (aOR 5.03, 95% CI 1.73-14.58) (Wemakor et al., 2015)
  - atrial and ventricular septal defects (aOR 1.45, 95% CI 1.15-1.84) (Furu et al., 2015)
  - atrial septal defects OR 2.53, 95% CI 1.2-5.32 (Jimenez-Solem et al., 2012)
  - right ventricular outflow tract obstructions (aOR 1.95, 95% CI 1.17-3.25) (Furu et al., 2015); (posterior odds ratio 2.0, 95% CI 1.4-3.1) (Wemakor et al., 2015)
  - patent ductus arteriosus OR, 5.9; 95% CI, 1.5–24.0 (Colvin et al., 2011)
  - Isolated ventricular septal defect (aOR 2.03, 95% CI 1.28-3.21) (Malm et al., 2011)
- Digestive (OR 3.08, 95% CI 1.27-7.48) (Colvin et al., 2011)
- pyloric stenosis OR 8.7, 95% CI 2.3–33.2 (Bakker, De Walle, et al., 2010)
- protective for genital defects when pregnancies in non-depressed women were used as the control aOR 0.38, 95% CI 0.16-0.93 (Ban et al., 2014)
- renal dysplasia (aOR 5.76, 95% CI 2.54-13.08) (Wemakor et al., 2015)
- craniosynostosis (aOR 2.8, 95% CI 1.3-6.1) (Alwan et al., 2007); posterior odds ratio 1.9, 95% CI 1.1-3.0 (Wemakor et al., 2015)

#### Sertraline

- anencephaly (aOR 3.2, 95% CI 1.1-9.3) (Wemakor et al., 2015)



- cardiac malformations (OR 3.0, 95% CI 1.4-6.4) (Kornum et al., 2010); aOR 2.01, 95% CI 1.60-2.53 (Jimenez-Solem et al., 2012)
  - severe congenital heart defects aOR 2.88, 95% CI 1.09-7.61 (Wemakor et al., 2015)
  - Ebstein's anomaly (1 exposed case) aOR 16.42, 95% CI 2.10-128.38 (Wemakor et al., 2015)
  - septal defects aOR 1.34, 95% CI 1.02-1.76 (Bérard et al., 2015); OR 3.25, 95% CI 1.21-8.75 (Pedersen et al., 2009); OR 3.3, 95% CI 1.5-7.5 (Kornum et al., 2010)
  - ventricular septal defects OR 3.6, 95% CI 1.86-6.96 (Jimenez-Solem et al., 2012)
  - atrial septal defects OR 2.85, 95% CI 1.35-5.99 (Jimenez-Solem et al., 2012)
- respiratory system defects when pregnancies in non-depressed women were used as controls (aOR 4.04, 95% CI 1.00-16.27, P=0.049)(Ban et al., 2014); unspecified respiratory system defects (aOR 3.73, 95% CI 1.18-11.82)(Colvin et al., 2011)
- Omphalocele aOR 5.7, 95% CI 1.6-20.7 (Louik et al., 2007)
- anal atresia aOR 2.47, 95% CI 1.09-5.57(Furu et al., 2015); aOR 4.4, 95% CI 1.2-16.4 (Louik et al., 2007)
- limb reduction defects aOR 3.9, 95% CI 1.1-13.5 (Louik et al., 2007)
- craniosynostosis (aOR 2.03, 95% CI 1.09-3.75, N=3) (Bérard et al., 2015)
- clubfoot aOR 1.76, 95% CI 1.10-2.81(Furu et al., 2015); aOR 3.05, 95% CI 1.09-8.52 (Wemakor et al., 2015)

#### Paroxetine

- All congenital malformation aOR 1.89, 95% CI 1.20-2.98 (Cole et al., 2007)
- neural tube defects OR 3.3, 95% CI 1.1-10.4 (Yazdy et al., 2014); aOR 3.3, 95% CI 1.1-10.4 (Louik et al., 2007)
  - anencephaly OR 3.2, 95% CI 1.1-9.3 (Werler et al., 2018); posterior odds ratio 3.2, 95% CI 1.6-6.2(Reefhuis et al., 2015), aOR 5.1, 95% CI 1.7-15.3 (Alwan et al., 2007)
- Eye (RR 2.36, 95% CI 1.20-4.66) (Davis et al., 2007)
- congenital heart defects, odds ratio 1.76, 95% CI 1.09-2.85 (Jordan et al., 2016); aOR 1.45, 95% CI 1.12-1.88 (Bérard et al., 2017); OR 1.63, 95% CI 1.17-2.27(Källén et al., 2013); OR 1.66, 95% CI 1.09-2.53 (M. Reis and Källén, 2010); OR 2.22, 95% CI 1.39-3.55(Källén and Otterblad Olausson, 2006); OR 1.63, 95% CI 1.05-2.53 (Källén et al., 2007); OR 2.93, 95% CI 1.52-5.13 (Källén et al., 2007); congenital heart defects when pregnancies in non-depressed women were used as the control (aOR 1.78, 95% CI 1.09-2.88)(Ban et al., 2014)
  - septal defects aOR 1.92, 95% CI 1.09-3.37 (Bérard et al., 2016); atrial or ventricular septal defect was 3.23, 95% CI 1.30-6.65 (Källén et al., 2007)
  - atrial septal defects OR 3.51, 95% CI 1.57-7.87 (Jimenez-Solem et al., 2012); aOR 5.7; 95% CI, 1.4-23.7(Bakker, Kerstjens-Frederikse, et al., 2010); posterior odds ratio 1.8, 95% CI 1.1-3.0 (Reefhuis et al., 2015)
  - ventricular septal defect OR 2.61, 95% CI 1.47-4.62 (Jordan et al., 2016); aOR 1.91, 95% CI 1.03-3.98 (Bérard et al., 2016)
  - ventricular septal defects without severe congenital heart defects aOR 2.12, 95% CI 1.15-3.92(Bérard et al., 2016)
  - right ventricular outflow tract obstruction aOR 2.54, 95% CI 1.31-4.90 (Furu et al., 2015); aOR 4.68, 95% CI 1.48-14.74 (Malm et al., 2011); OR 3.3, 95% CI 1.3-8.8 (Yazdy et al., 2014); posterior odds ratio 2.4, 95% CI 1.4-3.9(Reefhuis et al., 2015); OR 2.5, 95% CI 1.0-6.0 (Werler et al., 2018)
  - conotruncal and major arch anomalies aOR 2.27, 95% CI 1.01-5.07 (Furu et al., 2015)

- anomalies of pulmonary artery OR 19.94, 95% CI 6.00-66.22 (Colvin et al., 2010, 2011)
- clubfoot OR 5.8, 95% CI 2.6-12.8 (Yazdy et al., 2014); aOR 5.8, 95% CI 2.6-12.8 (Louik et al., 2007)
- gastroschisis posterior odds ratio 2.5, 95% CI 1.2-4.8 (Reefhuis et al., 2015); OR 2.9, 95% CI 1.0-8.4 (Werler et al., 2018), aOR 2.9, 95% CI 1.0-8.4 (Alwan et al., 2007)
- omphalocele OR 8.1, 95% CI 3.1-20.8 (Werler et al., 2018); posterior odds ratio 3.5, 95% CI 1.3-8.0 (Reefhuis et al., 2015), aOR 8.1, 95% CI 3.1-20.8 (Alwan et al., 2007)
- hypospadias OR 2.45, 95% CI 1.12-4.64 (M. Reis and Källén, 2010)
- undescended testes OR 2.8, 95% CI 1.0-7.8 (Yazdy et al., 2014)

## SNRIs

### Venlafaxine

- anencephaly, aOR 6.3, 95% CI 1.5-20.2 (Polen et al., 2013)
- cleft palate, aOR 3.3, 95% CI 1.1-8.8 (Polen et al., 2013)
- atrial septal defect, aOR 3.1, 95% CI 1.3-7.4 (11 exposed cases) (Polen et al., 2013)
- left ventricular outflow tract defects, aOR 3.3, 95% CI 1.2-8.2 (9 exposed cases, 6 of which were coarctation of the aorta) (Polen et al., 2013)
- respiratory system defects aOR 2.17, 95% CI 1.07-4.38 (Bérard et al., 2017)
- gastroschisis aOR 5.7, 95% CI 1.8-15.9 (Polen et al., 2013); aOR 3.5, 95% CI 1.4-8.4 (Werler et al., 2018)

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## Appendix 15 ENCePP checklist for study protocols

### ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

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

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

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

**Study title:** Exposure to SSRI/SNRI and depression in pregnancy and long-term childhood outcomes: the effect of modifying factors.

**EU PAS Register® number:**  
**Study reference number (if applicable):**

<b>Section 1: Milestones</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection <sup>16</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.2
1.1.2 End of data collection <sup>17</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.2
1.1.3 Progress report(s)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	5
1.1.4 Interim report(s)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	5
1.1.5 Registration in the EU PAS Register®	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	5
1.1.6 Final report of study results.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	5

Comments:

<sup>16</sup> Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

<sup>17</sup> Date from which the analytical dataset is completely available.

<b><u>Section 2: Research question</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
2.1 Does the formulation of the research question and objectives clearly explain:	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6
2.1.2 The objective(s) of the study?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7
2.1.5 If applicable, that there is no <i>a priori</i> hypothesis?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

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<b><u>Section 3: Study design</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.3
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.7
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	10

Comments:

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<b><u>Section 4: Source and study populations</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
4.1 Is the source population described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.2 and 8.4
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.2
4.2.2 Age and sex	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.2
4.2.3 Country of origin	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.2 and 8.4
4.2.4 Disease/indication	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7, 8.3

<b><u>Section 4: Source and study populations</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
4.2.5 Duration of follow-up	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.2 and 8.3
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.2

Comments:

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<b><u>Section 5: Exposure definition and measurement</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.3
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.3
5.3 Is exposure categorised according to time windows?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.3
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Duration 8.3
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.3
5.6 Is (are) (an) appropriate comparator(s) identified?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.7

Comments:

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<b><u>Section 6: Outcome definition and measurement</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.3
6.2 Does the protocol describe how the outcomes are defined and measured?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.3, appendix 3-6 and 11.
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.3 and appendix 3-6 and 11
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

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<b><u>Section 7: Bias</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.7
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.7

Comments:

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<b><u>Section 8: Effect measure modification</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.3 and 8.7

Comments:

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<b><u>Section 9: Data sources</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.4
9.1.3 Covariates and other characteristics?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.3, 8.4, Appendix 14
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.3 and appendix 14
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.3 and appendix 13



<b><u>Section 9: Data sources</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.3, appendices 3-6
9.3.3 Covariates and other characteristics?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.3 and appendices 10, 12
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.6

Comments:

<b><u>Section 10: Analysis plan</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
10.1 Are the statistical methods and the reason for their choice described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.7
10.2 Is study size and/or statistical precision estimated?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.5 and 8.9
10.3 Are descriptive analyses included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.7 and appendix 10-12
10.4 Are stratified analyses included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.7
10.5 Does the plan describe methods for analytic control of confounding?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.7
10.6 Does the plan describe methods for analytic control of outcome misclassification?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.7
10.7 Does the plan describe methods for handling missing data?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.7
10.8 Are relevant sensitivity analyses described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.7

Comments:

<b><u>Section 11: Data management and quality control</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.6
11.2 Are methods of quality assurance described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.8
11.3 Is there a system in place for independent review of study results?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9

Comments:

We have an independent clinical expert on the team to comment on the results and papers arising from this study

<b><u>Section 12: Limitations</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	8.9
12.1.2 Information bias?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.9, appendices 10-12

Comments:

<b><u>Section 13: Ethical/data protection issues</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9
13.2 Has any outcome of an ethical review procedure been addressed?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
13.3 Have data protection requirements been described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9

Comments:

<b><u>Section 14: Amendments and deviations</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
14.1 Does the protocol include a section to document amendments and deviations?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	4

Comments:

<b><u>Section 15: Plans for communication of study results</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	11
15.2 Are plans described for disseminating study results externally, including publication?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	11

Comments:

Name of the main author of the protocol:

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Date: 01/10/2021

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# concePTION

## SAFETY EVIDENCE ECOSYSTEM

### Protocol

DP3. Novel statistics to handle rare diseases and small sample sizes using Bayesian techniques: Application to Multiple Sclerosis (MS) and Systemic Lupus Erythematosus (SLE) in pregnancy

This study will be conducted within the ConcePTION project of the Innovative Medicines Initiative under grant agreement No 821520

<b>Title</b>	Novel statistics to handle rare diseases and small sample sizes using Bayesian techniques: Application to MS and SLE in pregnancy
<b>Protocol version identifier</b>	1.0
<b>Date of last version of protocol</b>	1/10/2021
<b>EU PAS register number</b>	Study will be registered in the EU PAS register.
<b>Active substance</b>	<b>SLE:</b> Antiprotozoals (P01), Immunosuppressants (L04A), Antineoplastic agents (L01), Corticosteroids for systemic use (H02)  <b>MS:</b> Immunosuppressants (L04A), Antineoplastic agents (L01), Nervous system drugs (N07X), Immunostimulants (L03A)

<b>Medicinal product</b>	<p><b>SLE:</b> Hydroxychloroquine (ATC: P01BA02), Chloroquine (ATC: P01BA01), Azathioprine (ATC: L04AX01), Mycophenolate (ATC: L04AA06), Cyclophosphamide (ATC: L01AA01), Ciclosporin (ATC: L04AD01), Mepacrine (ATC: P01AX05), Tacrolimus (ATC: L04AD02), Belimumab (ATC: L04AA26), Rituximab (ATC: L01XC02), Prednisolone (ATC: H02AB06), Prednisone (ATC: H02AB07), Methylprednisolone (ATC: H02AB04/H02BX01/S01CA08)</p> <p><b>MS:</b> Alemtuzumab (ATC: L04AA34), Azathioprine (ATC: L04AX01), Cladribine (ATC: L04AA40), Daclizumab (ATC: L04AC01), Dimethyl fumarate (ATC: N07XX09), Fingolimod (ATC: L04AA27), Glatiramer (ATC: L04AA07), Glatiramer acetate (ATC: L03AX13), Interferon beta-1a (ATC: L03AB07), Interferon beta-1b (ATC: L03AB08), Mitoxantrone (ATC: L01DB07), Natalizumab (ATC: L04AA23), Ocrelizumab (ATC: L04AA36), Peginterferon beta-1a (ATC: L03AB13), Rituximab (ATC: L01XC02), Teriflunomide (ATC: L04AA31), Ofatumumab (ATC: L01XC10), Siponimod (ATC: L04AA42), Ozanimod (ATC: L04AA38), Methotrexate (ATC: L04AX03)</p>
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<p><b>Research question and objectives</b></p>	<p>The aim of the study is to evaluate the safety to the mother and child of medications that are used by women suffering from SLE or MS during pregnancy using novel statistical methods. The ConcePTION platform will be used to analyse data from multinational cohort studies based on secondary data sources and the following studies will be undertaken.</p> <p><b>Identification of the most appropriate algorithm for the following outcomes; MS, SLE, childhood infections (subtask 1.3.4 and 1.3.6):</b> To derive the most appropriate algorithms to identify MS, SLE, childhood infections in selected data sources on the ConcePTION platform. These algorithms will initially be used to determine which data sources have data suitable for analysis in the safety study.</p> <p><b>Medication utilisation study objective:</b> To evaluate the utilisation trends and patterns of exposures in women with SLE and MS (a) of childbearing age and (b) in pregnant women before, during and after pregnancy. Medication utilisation will be compared across data sources.</p> <p><b>Medication safety study objective:</b> To evaluate the safety to the mother and child of medications that are used by women suffering from SLE or MS during pregnancy. Analytic results from across the data sources will be combined using novel meta-analytic techniques to overcome the issue of small numbers that will occur due to rare exposures and outcomes being studied.</p> <p><b>EUROmediCAT safety study objective:</b> To evaluate any increased risk of the occurrence of a major congenital malformation associated with first trimester exposure to medications that are used by women suffering from SLE or MS during pregnancy. EUROmediCAT data will be used to perform case-malformed analyses and to compile case series of congenital anomaly cases to identify possible safety indicators.</p>
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<b>Country(-ies) of study</b>	Finland (Nationwide), France (Nationwide + MS registry, Haute Garonne), Germany (~ 17% Nationwide), Italy (Emilia Romagna, Tuscany), Norway (Nationwide), Spain (Valencian Region), Wales (Nationwide + MS registry).
<b>Author(s)</b>	Professor Joan Morris, Dr. Yvonne Geissbühler, Dr. Sandra Lopez-Leon, Dr Christine Damase-Michel, E-mail: jmorris@sgul.ac.uk yvonne.geissbuehler@novartis.com sandra.lopez@novartis.com christine.damase-michel@univ-tlse3.fr

## Table of Contents

1. List of abbreviations .....	7
2. Responsible parties .....	9
3. Abstract.....	10
4. Amendments and updates.....	14
5. Milestones.....	15
6. Rationale and background .....	15
7. Research question and objectives.....	17
8. Research methods.....	17
8.1. Study design .....	17
8.2. Data sources.....	18
* Data sources from other countries (e.g. the Swedish registries), may be included, pending on results from the Data characterization (WP7).....	19
8.3. Setting .....	20
8.3.1 Study Period .....	20
* Data sources from other countries (e.g. the Swedish registries), may be included, pending on results from the Data characterization (WP7).....	20
8.3.2 Identification Period .....	20
8.3.3 Study populations .....	20
8.3.3.1 Pregnancy cohort .....	20
8.3.3.2 Foetus cohort .....	22
8.3.3.3 Live birth cohort.....	22
8.3.3.4 Women of childbearing age cohort .....	22
8.4. Variables.....	24
8.4.1 Disease indication .....	24
8.4.2 Medications.....	24
8.4.3 Maternal outcomes.....	25
8.4.4 Pregnancy outcomes.....	25
8.4.5 Birth/Neonatal outcomes .....	26
8.4.6 Outcomes in children under 2 years of age .....	26
8.4.7 Covariates .....	26
8.5. Study size .....	43
8.6. Data management .....	46
8.7. Data analysis .....	47
8.7.1 Drug utilisation.....	47
8.7.2 Medication safety .....	48
8.7.3 EUROMediCAT safety study .....	49



8.7.4	Missing data .....	49
8.7.5	Combining results .....	49
8.8.	Quality control .....	50
8.9.	Limitations of the research methods .....	51
9.	Protection of human subjects and reporting of adverse events/adverse reactions.....	53
10.	Plans for disseminating and communicating study results.....	54
11.	References .....	54
12.	Appendices .....	57
12.1.	Appendix I – Data source information.....	57
	Data sources from other countries (e.g. the Swedish registries), may be included, pending on results from the Data characterization (WP7).....	62
12.2.	Appendix II – Outcome availability .....	63
12.3.	Appendix III – Covariate availability.....	64
	Data sources from other countries (e.g. the Swedish registries), may be included, pending on results from the Data characterization (WP7).....	64
12.4.	Appendix IV – Medication information.....	65
12.5.	Appendix V – Medication exposures that will be considered for exclusion from pregnancy safety cohort.....	71
12.6.	Appendix VI - Covariate definitions .....	72
12.7.	Appendix VII Subtask 1.3.6 – Identifying MS and SLE in Health Care Databases .....	73
12.8.	AppendixVIII :.....	73
	Known risks of transgenerational adverse drug reactions .....	73
12.9.	Appendix IX Subtask 1.3.4 - Identification of Childhood Infections in Health Care Databases	

## 1. List of abbreviations

Abbrev.	Term
ATC	Anatomical Therapeutic Chemical
BICLA	BILAG-Based Composite Lupus Assessment
BILAG	British Isles Lupus Assessment Group
BPE	Bordeaux PharmacoEpi
CDM	Common Data Model
CI	Confidence Intervals
DAP	Data Access Provider
DDD	Defined Daily Dose
DMARD	Disease Modifying Anti-Rheumatic Drug
DSL	DerSimonian-Laird Method
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EncePP	European network of centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EUROCAT	European network of population-based registries for the epidemiological surveillance of congenital anomalies
FAIR	Findable, Accessible, Interoperable, and Reusable
FERR	University of Ferrara
FISABIO	Foundation for the Promotion of Health and Biomedical Research of Valencian Region
GA	Gestational Age
ICD-8/9/10	International Classification of Diseases 8 <sup>th</sup> /9 <sup>th</sup> /10 <sup>th</sup> Revision
IP	Industry Partner
LFA-REAL	Lupus Foundation of America rapid evaluation of activity in lupus
MA	Meta-analysis
MH	Mantel-Haenszel method
MS	Multiple Sclerosis
NIHW	Finnish Institute for Health and Welfare
ORs	Odds Ratios
PP	Public Partner

SAP	Statistical Analysis Plan
SGA	Small-for-Gestational Age
SLE	Systemic Lupus Erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SNDS	Système National des Données de Santé
SSPGA	SELENA SLEDAI Physician's Global Assessment
SRI	SLE Responder Index
TOPFA	Termination Of Pregnancy for Fetal Anomaly
UCL	University College London
WHO	World Health Organization

## 2. Responsible parties

Name	Role	Working institution/company
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<b>Christine Damase-Michel</b>	Lead PP from January 2022	University Hospital of Toulouse, F
<b>Yvonne Geissbühler</b>	Lead IP – protocol development	Novartis
<b>Kerstin Hellwig</b>	Clinician expert: MS	
<b>Sandra Vukusic</b>	Clinician expert: MS	
<b>Ian Giles</b>	Clinical Expert: SLE	Centre for Rheumatology, Rayne Institute, UCL
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<b>Sandra Lopez-Leon</b>	Pharmacoepidemiology expert in Neuroscience	Novartis
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<b>Maarit Leinonen</b>	DAP Finland	NIHW Finnish Institute for Health and Welfare, Finland
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### 3. Abstract

<b>Title</b>	Novel statistics to handle rare diseases and small sample sizes using Bayesian techniques: Application to MS and SLE in pregnancy
<b>Author(s)</b>	Professor Joan Morris, Dr. Yvonne Geissbühler, Dr. Sandra Lopez-Leon, Dr. Christine Damase-Michel
<b>Rationale and Background</b>  <b>Number</b>	Multiple Sclerosis and Systemic Lupus Erythematosus often have remitting-relapsing natural histories that include sporadic and unpredictable episodes that may be severely disabling. These diseases have relatively low prevalence rates, but both are much more common in women than men and are frequently diagnosed during women's childbearing years. In both diseases, women experience disease relapses / flares and are treated with the aim of either preventing new disease relapses / flares or controlling a disease relapse / flare. The treatments aimed at preventing relapses / flares are important during pregnancy as relapses increase disease progression and for SLE disease severity/flaring is considered to be associated with adverse pregnancy outcomes.

<b>Research question and objectives</b>	<p>The ultimate aim of the study is to use novel methods of analysis concerning the synthesis of information from disparate data sources to provide data about medications that are used by women suffering from rare diseases such as SLE or MS, on their safety in pregnancy to the mother and child. There are two initial steps which are to identify algorithms and to assess the medication use in pregnant MS or SLE patients.</p> <p><b>Identification of the most appropriate algorithm for the following outcomes; MS, SLE, childhood infections (subtask 1.3.4 and 1.3.6):</b> These studies aim to identify the algorithms to be recommended for use in the ConcePTION medication utilization and safety studies on women with MS or SLE and for medication safety studies investigating neonatal, infant and childhood infections and to use these to produce prevalence rates in the data sources and to confirm which data sources have data suitable for analysis in the safety studies.</p>
	<p><b>Medication utilisation studies:</b> The utilisation trends and patterns of medications in patients with SLE and MS before and during pregnancy will be investigated within these studies. Prevalences amongst women of childbearing age and pregnant women will be calculated. Medication utilisation before, during and after pregnancy will be reviewed and compared across data sources.</p> <p><b>Medication safety studies:</b> The safety of medications used during pregnancy to treat patients with SLE and MS will be investigated within these studies. Maternal, pregnancy and childhood outcomes will be assessed and results from across Europe will be combined using meta-analytic techniques.</p> <p><b>EUROmediCAT safety study:</b> EUROmediCAT data will be used to perform case-malformed analyses and to compile case series of congenital anomaly cases to identify possible safety indications.</p>
<b>Data sources</b>	<p>Finland (Nationwide), France (Nationwide + MS registry, Haute Garonne), Germany (~17% Nationwide), Italy (Emilia Romagna, Tuscany), Norway (Nationwide), Spain (Valencian Region), Wales (Nationwide + MS registry), EUROmediCAT central registry. Data Access Providers (DAPs) for other data sources (e.g. the Swedish registers), may be included pending on results</p>

	from the Data characterization (WP7).
<b>Study design</b>	<p><b>Algorithm identification, drug utilisation and safety studies:</b> These studies are multinational cohort studies using secondary data sources.</p> <p><b>EUROmediCAT safety study:</b> This will be a case-malformed analysis and a multinational case series.</p>
<b>Study period</b>	The overall study period will run from 1 January 1998 until 31 December 2019. Some data sources will not provide data for the entire study period and data up to the end of 2019 may be incomplete in some data sources owing to the time and nature of data collection.
<b>Study population</b>	<p><b>Algorithm identification (MS, SLE), drug utilisation studies:</b> The study population will be all women aged between 15 and 49 years during the study period in each of the data sources.</p> <p><b>Drug safety studies:</b> All pregnancies during the study period from women with MS or SLE and those without aged between 15 and 49 at the time of LMP.</p> <p><b>Algorithm identification study childhood infection:</b> The study population will consist of all live births occurring during the study period in each of the data sources</p> <p><b>EUROmediCAT safety study:</b> All live births, still births and TOPFA with a major congenital anomaly.</p>

<p><b>Variables</b></p>	<p><b>Disease:</b> Multiple Sclerosis and Systemic Lupus Erythematosus</p> <p><b>Exposure:</b> Medications used to treat Multiple Sclerosis and Systemic Lupus Erythematosus will be identified for their respective studies using the Anatomical Therapeutic Chemical classification system (ATC) or using procedural codes.</p> <p><b>Outcomes:</b> Preeclampsia, gestational diabetes, still births, spontaneous abortions, live births, elective terminations, ectopic pregnancy, small for gestational age, large for gestational age, major congenital malformations (Overall and by organ system), neonatal stroke, neonatal death, neonatal infections, pre-term live birth, infant death and infant infections and infections in children up to two years of age.</p> <p><b>Covariates (if available):</b> Maternal age, parity, year of birth, maternal body mass index, smoking during pregnancy, alcohol consumption during pregnancy, comedications (disease specific and general teratogens), comorbidities (disease specific), disease severity (if feasible), breastfeeding (when available), socioeconomic status and ethnicity.</p>
<p><b>Study size</b></p>	<p>The nine contributing data sources capture approximately 28 million women of child bearing age and 8.9 million pregnancies.</p> <p>EUROmediCAT has data on 31,626 congenital anomaly cases with one or more medication exposures in the first trimester of pregnancy.</p>



<p><b>Data Analysis</b></p>	<p><b>Algorithm identification studies:</b> These studies will assess different algorithms to define MS, SLE and childhood infections, calculate their prevalence (MS, SLE) or incidence (infections) and informally compare it to the published literature.</p> <p><b>Drug utilisation studies:</b> The drug utilisations studies will estimate the prevalence of medications used to treat MS and SLE among pregnant women and women of child bearing age with MS or SLE. Prevalence amongst pregnancies will be estimated prior to, during and (if available) after pregnancy. An age-matched cohort of women will be used to assess the role pregnancy plays in drug utilisation. Treatments will be reviewed individually, in combinations and as groups.</p> <p><b>Drug safety studies:</b> The drug safety studies will estimate the prevalence of maternal, pregnancy, birth/neonatal and childhood outcomes among women with MS and SLE. These studies will review the effect of MS/SLE has on these outcomes and the safety of each treatment with respect to each outcome among women with MS/SLE will be estimated by comparing exposed women with MS/SLE to unexposed women with MS/SLE. Exposure will be classified into two groups, exposure during the first trimester and exposure during pregnancy only after the first trimester.</p> <p>Novel techniques for dealing with pooling results from small sample sizes such as Bayesian modelling will be investigated.</p> <p><b>EUROmedICAT safety study:</b> Case-malformed control analysis will be performed to estimate the relative odds of a specific anomaly given 1<sup>st</sup> trimester exposure to a medication. For medications with few exposures, case series will document the occurrence of specific anomalies.</p>
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#### 4. Amendments and updates

Not applicable

## 5. Milestones

Milestone	Planned date
Registration in the EU PAS register	Date: October2021
Final report of study results	Date: March 2024

## 6. Rationale and background

When evaluating the safety of specific medications during pregnancy, the quantity and quality of available information can be a limitation. This limitation is amplified when considering medications used to treat relatively rare diseases or treatments new to the market. As a result of the sparse data, studies investigating medication utilisation and safety for rare disease treatments before and during pregnancy may require data from several data sources for sufficient power. The ConcePTION platform offers a tool which enables us to conduct both drug utilisation and drug safety studies on a range of data sources from countries across Europe. As many countries are not able to share individual case data, the platform will provide the aggregate data or analytic results from each data source and meta-analyses on the aggregate data must be performed.

When conducting meta-analyses on analytic results, there are two areas in which bias may be introduced into an estimate. The first is within the individual country level models. When individual data source sample sizes are very small, limitations are imposed both on the level of complexity that the statistical models can take and on the accuracy of each model's assumptions. For example, if multi-level models are used, over-parametrisation may occur in small datasets<sup>1</sup>, and even simpler models tend to rely on asymptotic principles in their estimation processes, introducing bias when samples sizes are small<sup>2</sup>. Alternative, more robust methods such as the use of a penalized likelihood<sup>2</sup> or using the bootstrap method<sup>3</sup> aim at either relaxing some of the distributional assumptions the models make or reducing the influence of sample size. Model adjustments such as altering the continuity correction<sup>4</sup> or outcome transformation<sup>5</sup> can also be used to help model fitting and reduce the bias in the effect and precision estimates.

Secondly, bias can also arise in the meta-analytic process. Common meta-analytic methods rely on asymptotic principles, which falter when applied to rare events<sup>6</sup>. Methods such as Mantel-Haenszel

(MH) method<sup>7</sup> or the DerSimonian-Laird method (DSL)<sup>8</sup> have been used in prior literature to combine results across countries<sup>9-12</sup>. However, more robust alternatives exist when dealing with sparse data such as the use of Bayesian modelling<sup>13</sup>.

The motivating example of this demonstration project is the treatment of multiple sclerosis (MS) and systemic lupus erythematosus (SLE) during pregnancy. Both SLE and MS have disease courses that include sporadic and unpredictable episodes that are severely disabling. The diseases have relatively low prevalence rates, but both are much more common in women than men and are frequently diagnosed during a women's childbearing years<sup>14,15</sup>. The prevalence of MS amongst the general population varies from a prevalence of 58 per 100,000 in central Europe, rising to 120 per 100,000 in the Nordic countries, whilst that of SLE is around 80 per 100,000<sup>14-16</sup>. In both diseases, women experience disease relapses / flares and are treated with the aim of either preventing new disease relapses / flares or controlling a disease relapse / flare. The treatments aimed at preventing relapses / flares are important during pregnancy as relapses increase disease progression and for SLE disease severity/flaring is considered to be associated with adverse pregnancy outcomes<sup>17</sup>. However, during pregnancy women with SLE or MS commonly discontinue their medications due to fears that the medications may lead to adverse pregnancy outcomes<sup>18,19</sup> and due to drug labelling recommending drug discontinuation before pregnancy but also because remission is relatively common.

With disease flares, medications and even pregnancy itself affecting a woman's risk of adverse maternal, pregnancy and childhood outcomes, reliable safety data are required for women with SLE and MS to safely navigate pregnancy.

### **Identification of the most appropriate algorithms**

As an initial step before starting with the drug utilization and safety studies, to define the MS and SLE cohorts, several published algorithms to identify patients with SLE or MS will be assessed in the different data sources (details are provided in the protocol in appendix VII) with the aim of identifying the best performing algorithm for use in the drug utilization and safety studies.

As one of the childhood outcomes of the safety study is neonate, infant and childhood infections the best performing algorithm to identify childhood infections in population-based databases (details are provided in the protocol in appendix VIII) will also be identified.

## 7. Research question and objectives

### Research question

The aim of the study is to use novel methods of analysis concerning the synthesis of information from disparate data sources to provide information about medications that are commonly used by women with SLE or MS on their use during pregnancy and their safety in pregnancy to the mother and child.

### Objectives

#### **Drug Utilisation Studies (MS – DU, SLE – DU)**

1. To determine the extent to which pregnancy influences medication utilisation in women with MS or SLE.
2. To determine whether medication utilisation differs between data sources in women with MS and SLE.

#### **Drug Safety Studies (MS – DS, SLE – DS)**

3. To evaluate the safety of specific medications used by women with MS or SLE in pregnancy with respect to maternal, pregnancy and childhood outcomes.
4. To evaluate the effect that MS/SLE has on adverse pregnancy outcomes.

#### **EUROmediCAT case series study (EMC – CS)**

5. To evaluate if there are any associations of specific congenital anomalies with medications used by women with MS or SLE in the first trimester of pregnancy.

## 8. Research methods

### **8.1. Study design**

These studies are multinational cohort studies using secondary data sources. Utilisation of the medications used to treat SLE and MS (See Section 9.4.2) will be analysed using the methods outlined in Section 9.7. Safety studies will then be conducted, assessing the risk of experiencing the outcomes listed in Section 9.4.3-9.4.6. By using data from across Europe, this study will be able to increase the number of cases of SLE and MS that are analysed and will provide insight into the utilisation and safety of medications used in these disease areas across Europe.

## 8.2. Data sources

This project will analyse data from nine data sources within seven European countries. Key information on the nine data sources is provided in Table 1, however, further detail can be found in Appendix I. In addition, the EUROMedCAT database will be used to conduct the case series study on congenital anomalies.

**Table 1 – Data sources to be used in SLE/MS studies\***

<u>Country</u>	<u>Data coverage</u>	<u>Registries used</u>	<u>Start of available data</u>	<u>Number of pregnancies</u>	<u>Selected for MS studies</u>	<u>Selected for SLE studies</u>
Finland	Nationwide	Care Register for Health Care (HILMO) Register of Primary Health Care visits (Avohilmo) Medical Birth Register Register of Congenital Malformations	01/01/1998	1,506,000	Yes	No
France	Nationwide	SNDS	01/07/2005	300,000	Yes	Yes
France	Haute Garonne	EFEMERIS POMME	01/01/2015	137,600	Yes	Yes
Germany	Nationwide (~17%)	GePaRD (claims data)	01/01/2005	1,500,000	Yes	Yes
Italy	Emilia Romagna	Inhabitant registry Drug dispensations from community pharmacies and from hospital pharmacies Hospital discharge records Emergency admissions Outpatient services Birth registry	2005	525,000	Yes	Yes

		IMER Registry of Congenital anomalies				
Italy	Tuscany	Inhabitant registry Drug dispensations from community pharmacies and from hospital pharmacies Hospital discharge records Emergency admissions Outpatient services Birth registry Congenital anomaly register	2005	400,000	Yes	Yes
Norway	Nationwide	The Norwegian Prescription Database (NorPD) The Medical Birth Registry of Norway (MBRN) The Norwegian Patient Registry (NPR)	01/01/2008	830,000	Yes	Yes
Spain	Valencian Region	Prescription and dispensations dataset Hospital discharge records Mortality registry Perinatal mortality registry Congenital anomalies registry Birth registry	01/01/2010	440,000	Yes	Yes
Wales	Nationwide	SAIL MS registry	01/01/1998	350,000	Yes	No

\* Data sources from other countries (e.g. the Swedish registries), may be included, pending on results from the Data characterization (WP7)

## 8.3. Setting

### 8.3.1 Study Period

The overall study period will run from 1 January 1998 until 31 December 2019, with data sources providing data between the dates outlined in Table 2. For EUROmedicAT the study period starts 1 January 1995.

**Table 2 – Data source start and end dates\***

Country	Region	Start date	End date
Finland	Nation-wide	01/01/1998	31/12/2018
France	Haute-Garonne	01/07/2005	31/12/2019
France	Nation-wide	01/01/2015	31/12/2020
Germany	Nation-wide (~17%)	01/01/2005	31/12/2018
Italy	Emilia Romagna	2005	31/12/2019
Italy	Tuscany	2005	31/12/2019
Norway	Nation-wide	01/01/2008	31/12/2019
Spain	Valencian Region	01/01/2010	31/12/2019
UK	Wales	01/01/1998	31/12/2020
EUROmedicAT	Multinational	01/01/1995	31/12/2019

*\* Data sources from other countries (e.g. the Swedish registries), may be included, pending on results from the Data characterization (WP7)*

### 8.3.2 Identification Period

As described in more detail in section 9.3.3.1 the identification period starts 3 – 12 months after the beginning of the study period and ends 3 months before the end of the study period or at the end of the study period depending on prescription data availability in the respective data source.

### 8.3.3 Study populations

Algorithms to identify pregnancies and the best estimates for the start and end dates of a pregnancy within each data source will be developed by WP7 within the ConcePTION platform. All available pregnancies will be identified within each of the data sources during the study period.

#### 8.3.3.1 Pregnancy cohort

The pregnancy cohort will contain all pregnancies in which the mother has met the below inclusion/exclusion criteria. The cohort will be divided into 3 sub-cohorts containing pregnancies from women with a) MS or b) SLE and c) women without MS or SLE. The first two sub-cohorts will be used in the DU study to identify the prevalence of medication exposures during pregnancy and all three cohorts will be used in the Safety study.

Inclusion/exclusion criteria

Pregnant women will require the following prescription data for their pregnancy to be considered eligible for inclusion in the pregnancy cohort:

- 3 or 12 months of prescription data prior to their pregnancy (depending on data source)
- Prescription data throughout their pregnancy
- 3 months of prescription data after their pregnancy given the mother did not die during birth (depending on data source)

Whether the woman requires 3 or 12 months of prescription data prior to pregnancy depends on the information their data source is providing to ConcePTION. Table 3 outlines which months before and during pregnancy are available for each data source. Women from the data sources providing prescription data for 12 months prior to pregnancy will require 12 months of prescription data prior to pregnancy for the pregnancy to be considered eligible. Women from data sources only providing prescription data for the 3 months prior to pregnancy will only require 3 months of prescription data prior to pregnancy for the pregnancy to be considered eligible for the pregnancy cohort.

Women from data sources which are not providing data post pregnancy will not be required to have 3 months of prescription data post pregnancy for their pregnancy to be eligible for the cohort.

**Table 3 – Availability of prescription data before and during pregnancy by data source\***

<b>Data Source</b>	<b>12 months prior to pregnancy</b>	<b>3 months prior to pregnancy</b>	<b>During pregnancy</b>	<b>3 months after pregnancy</b>
Finland	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
France (Haute Garonne)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
France (SNDS)	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Germany	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Italy (Emilia Romagna)	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Italy (Tuscany)	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Norway	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Spain (Valencian Region)	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
UK (Wales)	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
EUROmedICAT	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

\* Data sources from other countries (e.g. the Swedish registries), may be included, pending on results from the Data characterization (WP7)

In addition, only mothers aged 15-49 at the time of LMP will be able to contribute pregnancies to this cohort.



#### **8.3.3.2 Foetus cohort**

The foetus cohort will contain all fetuses from the pregnancies included within the Pregnancy cohort (Section 9.3.3.1). It will contain fetuses born from singleton/multiple births and mothers are able to contribute multiple pregnancies/fetuses to the cohort. The cohort will contain fetuses from women with MS or SLE and fetuses from women without MS or SLE. In addition, fetuses exposed to the teratogens listed in Appendix V during the 3 months prior to LMP or at any time during the pregnancy will be excluded from the safety study. A fetus is considered exposed to a teratogen if the mother has a prescription for the teratogen with a dispensation or prescription date in the above period.

The foetus cohort will be used within the DS studies to review the safety of medications with respect to maternal, pregnancy, birth, neonatal and infant outcomes. This cohort will also be used to review the effect of disease on the same outcomes.

Three subpopulations will be identified from within this cohort, they are the following:

- MS fetus cohort – Any fetus within the Foetus cohort whose mother had MS diagnosed at or prior to LMP.
- SLE fetus cohort – Any fetus within the Foetus cohort whose mother had SLE diagnosed at or prior to LMP.
- No MS or SLE fetus cohort – Any fetus within the Foetus cohort whose mother did not have an MS or SLE diagnosis prior to or at any time during her pregnancy.

#### **8.3.3.3 Live birth cohort**

The live birth cohort will consist of all live born neonates/infants who have been successfully linked to their mothers. This cohort will be used to review the birth / neonatal, infant and childhood outcomes outlined in Section 9.4.5-9.4.6.

#### **8.3.3.4 Women of childbearing age cohort**

To review the effects of pregnancy on drug utilisation, matched cohorts of women of childbearing age will be used. Two matched cohorts will be produced, one matching each woman who provided pregnancies to the MS pregnancy cohort to a woman of childbearing age with MS and the other matching a woman who provided a pregnancy to the SLE pregnancy cohort to a woman of childbearing age with SLE. Each matched cohort will be a 4:1 matching based on age at LMP within each data source and calendar year.

To be eligible for matching the woman must be present within the given data source for the entire period of follow up of the matched mother (12/3 months prior, throughout pregnancy and (if available) 3 months after pregnancy). Additionally, she must be aged 15-49 at the time of matched mothers' pregnancy and she must not have had a pregnancy during the matched follow-up period. Each matched woman of childbearing age will then be allocated the same 3-month periods of exposure as her matched counterpart.

Non-pregnant women of childbearing age cannot be picked up in all data sources. Table 4 outlines which data sources are able to pick up women of childbearing age.

**Table 4 – Availability of women of childbearing age by data source\***

<b>Data Source</b>	<b>Women of childbearing age</b>
Finland	<input type="checkbox"/>
France (Haute Garonne)	<input type="checkbox"/>
France (SNDS)	<input checked="" type="checkbox"/>
Germany	<input checked="" type="checkbox"/>
Italy (Emilia Romagna)	<input checked="" type="checkbox"/>
Italy (Tuscany)	<input checked="" type="checkbox"/>
Norway	<input checked="" type="checkbox"/>
Spain (Valencian Region)	<input checked="" type="checkbox"/>
UK (Wales)	<input checked="" type="checkbox"/>
EUROmedicAT	<input type="checkbox"/>

\* Data sources from other countries (e.g. the Swedish registries), may be included, pending on results from the Data characterization (WP7)

## 8.4. Variables

### 8.4.1 Disease indication

Diagnosis algorithms are to be investigated as part of the algorithm identification studies mentioned in section 7. The algorithms being considered for SLE and MS comprise of the ICD-9/ICD-10 diagnosis codes from hospital, outpatient or primary care records or a combination of ICD-9/ICD-10 codes and prescription records. The ICD codes to be used are listed in Table 5.

**Table 5 - ICD codes for SLE and MS**

Disease	Coding system	Code
SLE	ICD-9	710.0
	ICD-10	M32
MS	ICD-9	340
	ICD-10	G35

In addition, for Wales MS registry data is available and therefore MS will be identified by presence in the register, and compared with the diagnoses in the databank. Membership of the MS registry is voluntary, and it is likely to be very incomplete, so formal analyses will be based on the same criteria as applied to the other data banks.

### 8.4.2 Medications

Exposure to medications in all studies will be classified according to the Anatomical Therapeutic Chemical (ATC) classification system or by country specific procedural codes.

The medications used in the treatment of SLE which will be reviewed are outlined in Table 6. Each medication will be reviewed individually and by group. Certain medication combinations will also be reviewed in the DU study.

**Table 6 - ATC codes for SLE medications**

Group	Drug	ATC
Antimalarials	Hydroxychloroquine	P01BA02
	Chloroquine	P01BA01
	Mepacrine	P01AX05
Corticosteroids	Prednisone/Prednisolone	H02AB06/H02AB07
	Methylprednisolone	H02AB04/H02BX01/ S01CA08
Traditional immunosuppressants	Azathioprine	L04AX01

	Mycophenolate	L04AA06
	Cyclophosphamide	L01AA01
	Ciclosporin	L04AD01
	Tacrolimus	L04AD02
Biologics	Belimumab	L04AA26
	Rituximab	L01XC02

The medications used in the treatment of MS which will be reviewed are outlined in Table 7.

**Table 7 - ATC codes for MS medications**

Medication	ATC code
Alemtuzumab	L04AA34
Azathioprine	L04AX01
Cladribine	L04AA40
Daclizumab	L04AC01
Dimethyl fumarate	N07XX09
Fingolimod	L04AA27
Glatiramer	L04AA07
Glatiramer acetate	L03AX13
Interferon beta-1a	L03AB07
Interferon beta-1b	L03AB08
Methotrexate	L04AX03
Mitoxantrone	L01DB07
Natalizumab	L04AA23
Ocrelizumab	L04AA36
Ofatumumab	L01XC10
Ozanimod	L04AA38
Peginterferon beta-1a	L03AB13
Rituximab	L01XC02
Teriflunomide	L04AA31

Further information on administration techniques, locations, common dosages and treatment patterns found in literature are detailed in Appendix IV.

### **8.4.3 Maternal outcomes**

Algorithms will be developed in the ConcePTION consortium to identify the following maternal outcomes that will be investigated:

- Preeclampsia
- Gestational diabetes

### **8.4.4 Pregnancy outcomes**

Algorithms will be developed in the ConcePTION consortium to identify the following pregnancy outcomes that will be investigated:

- Still birth
- Spontaneous abortions
- Live births
- Elective terminations
- Ectopic pregnancy

#### **8.4.5 Birth/Neonatal outcomes**

Algorithms will be developed in the ConcePTION consortium to identify the following birth/neonatal outcomes that will be investigated:

- SGA
- LGA
- Major congenital malformations
- Malformations split by organ system
  - (Cardiac malformations; Nervous system malformations; Eye malformations; Ear, face and neck malformations; Congenital heart defects; Respiratory malformations; Oro-facial clefts; Digestive system malformations; Abdominal wall defects; Urinary defects; Genital malformations; Limb malformations; Other anomalies/syndromes; Chromosomal defects)
- Pre-term birth
- Neonatal stroke
- Neonatal death
- Neonatal infections

#### **8.4.6 Outcomes in children under 2 years of age**

Algorithms will be developed in the ConcePTION consortium to identify the following outcomes in children under 2 years of age (if data is available) that will be investigated:

- Infant death (0 – 1 year)
- Death of child (> 1 – 2 years) (if data is available)
- Infant infections (0 – 1 year)
- Childhood infections (> 1 – 2 years) (if data is available)

#### **8.4.7 Covariates**

Each data source being analysed within this project has a varied list of potential covariates which may influence or bias safety data. Below is outlined all of the potential confounding and effect modifying covariates which will be searched for in each data source. Where present, each covariate will be dealt with appropriately within the safety analyses, this may include excluding women if required.

- Maternal age at LMP
- Parity
- Year of birth
- BMI (Mother) at LMP or 1<sup>st</sup> midwife visit (if available)
- Smoking during pregnancy
- Alcohol consumption during pregnancy
- Prophylactic treatment during pregnancy (inclusion will depend on the country's reimbursement scheme) (table 8)

**Table 8 Prophylactic treatments during pregnancy**

<b>Treatment</b>	<b>ATC code</b>
VITAMIN B12 AND FOLIC ACID	B03B
Iron in combination with folic acid	B03AD
Folic acid and derivatives	B03BB
Folic acid	B03BB01
Folic acid, combinations	B03BB51
Iron, multivitamins and folic acid	B03AE02
Iron, vitamin B12 and folic acid	B03AE01
Iron preparations	B03A
Iron and multivitamins	B03AE03
Iron, multivitamins and minerals	B03AE04
Multivitamins and iron	A11AA01
VITAMIN B1, PLAIN AND IN COMBINATION WITH VITAMIN B6 AND B12	A11D
Vitamin B1 in combination with vitamin B6 and/or vitamin B12	A11DB
Vitamin B12 (cyanocobalamin and analogues)	B03BA

- Teratogenic comedications (Appendix V)
- Disease severity at time of LMP (if available) (MS: EDSS, SLE: SLEDAI, BILAG, SRI, BICLA, SSPGA,

LFA-REAL)

- breastfeeding
- Socioeconomic status
- MS comorbidities / symptoms and comedications (table 9)
- SLE comorbidities and comedications (table 10)

**Table 9 MS comorbidities / symptoms and comedications including ATC codes**

Comorbidity	Comedication	ATC code
Spasticity	Antispastics	M03B
	Baclofen	M03BX01
	Tizanidine	M03BX02
	Gabapentin (potentially)	N03AX12
	Botulinum toxin A (severe cases)	M03AX01
Fatigue	Amantadine	N04BB01
	4-aminopyridine	N03AF01
	3,4-diaminopyridine	N07XX05
	Pemoline	N06BA05
	L-carnitine	A16AA01
	Modafinil	N06BA07
MS-related Pain Syndromes	Amitriptyline	>N06AA09
	Carbamazepine	N03AF01
	Gabapentin	N03AX12
	Lamotrigine	N03AX09
	Pregabalin	N03AX16
	Paracetamol combo, excl psycholeptics combo, w/ psycholeptics	N02BE01 N02BE51 N02BE71
	NSAID Butylpyrazolidines	M01AA01 M01AA02 M01AA03 M01AA05 M01AA06

	Acetic acid derivatives	M01AB01
		M01AB02
		M01AB03
		M01AB04
		M01AB05
		M01AB06
		M01AB07
		M01AB08
		M01AB09
		M01AB10
		M01AB11
		M01AB12
		M01AB13
		M01AB14
		M01AB15
		M01AB16
		M01AB17
		M01AB51
		M01AB55
	Oxicams	M01AC01
		M01AC02
		M01AC03
		M01AC04
		M01AC05
		M01AC06
		M01AC56
	Propionic acid derivatives	M01AE01
		M01AE02
		M01AE03
		M01AE04
		M01AE05
		M01AE06
		M01AE07
		M01AE08



		M01AE09
		M01AE10
		M01AE11
		M01AE12
		M01AE13
		M01AE14
		M01AE15
		M01AE16
		M01AE17
		M01AE18
		M01AE51
		M01AE52
		M01AE53
		M01AE56
	Fenamates	M01AG01
		M01AG02
		M01AG03
		M01AG04
		M01AH01
		M01AH02
		M01AH03
		M01AH04
		M01AH05
		M01AH06
		M01AH07
		M01AX01
	Other	M01AX02
		M01AX04
		M01AX05
		M01AX07
		M01AX12
		M01AX13
		M01AX14
		M01AX17

		M01AX18 M01AX21 M01AX22 M01AX23 M01AX24 M01AX25 M01AX26 M01AX68
Bladder Symptoms	Trospium chloride	G04BD09
	Tolterodine	G04BD07
	Oxybutynin	G04BD04
	Propiverine	G04BD06
	Solifenacin	G04BD08
	Darifenacin	G04BD10
Neurogenic Bowel Dysfunction	Laxatives Contact Laxatives	A06AB01 A06AB02 A06AB03 A06AB04 A06AB05 A06AB06 A06AB07 A06AB08 A06AB09 A06AB20 A06AB30 A06AB52 A06AB53 A06AB56 A06AB57 A06AB58
	Bulk-forming laxatives	A06AC01 A06AC02 A06AC03

	Osmotically acting laxatives	A06AC04 A06AC05 A06AC06 A06AC07 A06AC08 A06AC51 A06AC53 A06AC55 A06AD01 A06AD02 A06AD03 A06AD04 A06AD10 A06AD11 A06AD12 A06AD13 A06AD14 A06AD15 A06AD16 A06AD17 A06AD18 A06AD19 A06AD21 A06AD61 A06AD65
case	Botulinum toxin A	M03AX01
Sexual Dysfunction	Tibolone	G03CX01
Ataxia / Tremor	Beta blockers	C07AA** C07AB** C07AG** C07BA** C07BB** C07BG** C07CA**

		C07CB** C07CG** C07DA** C07DB** C07DG** C07EA** C07EB** C07FB** C07FX**
	Antiepileptics	N03A***
	Primidone	N03AA03
	Clonazepam	N03AE01
	Carbamazepine	N03AF01
Cognitive Dysfunction	no specific recommendation	
Depression	Antidepressants	
	Tricyclic antidepressants	N06AA01 N06AA02 N06AA03 N06AA04 N06AA06 N06AA09 N06AA10 N06AA11 N06AA12
	SSRI	N06AB02 N06AB03 N06AB04 N06AB05 N06AB06 N06AB07 N06AB08 N06AB09 N06AB10
	Noradrenalin reuptake inhibitors	N06AX16 N06AX21 N06AX23
	MAO A	N06AG02 N06AG03

Paroxysmal Symptoms	Antiepileptics	N03A***
	Carbamazepine	N03AF01
	Gabapentin	N03AX12
Trigeminal Neuralgia	Antiepileptics	N03A***
	Carbamazepine	N03AF01
	Oxcarbazepine	N03AF02
	Gabapentin	N03AX12
	Lamotrigine	N03AX09
	Baclofen	M03BX01
	Amitriptyline	N06AA09
	Pimozide	N05AG02
Other Paroxysmal Symptoms	Antiepileptics	N03A***
	Carbamazepine	N03AF01
Oculomotor Symptoms	Gabapentin	N03AX12
	Memantine	N06DX01
	Baclofen	M03BX01
Dysarthria / Dysphonia	Botulinum toxin A (potentially)	M03AX01
Dysphagia	Anticholinergics	N04A***
	Botulinum toxin A	M03AX01
Epileptic Seizures	Antiepileptics	N03A***
<b>Symptoms</b>		
Relapses	Corticosteroids	H02AB01 H02AB02 H02AB03 H02AB04 H02AB05 H02AB06 H02AB07 H02AB08 H02AB09 H02AB10 H02AB11 H02AB12 H02AB13 H02AB14 H02AB15 H02AB17 H02AA01

		H02AA02 H02AA03 H02BX01
Gait issues	Dalfampridine	N07XX07

\*\*/\*\* all the codes that appear are included

**Table 10 SLE comorbidities and comedications including ATC codes**

Comorbidity	Comedication	ATC code
Joint pain/ synovitis	Glucocorticoids	H02AB01 H02AB02 H02AB03 H02AB04 H02AB05 H02AB06 H02AB07 H02AB08 H02AB09 H02AB10 H02AB11 H02AB12 H02AB13 H02AB14 H02AB15 H02AB17
	NSAID Butylpyrazolidines  Acetic acid derivatives	M01AA01 M01AA02 M01AA03 M01AA05 M01AA06 M01AB01 M01AB02 M01AB03 M01AB04 M01AB05

		M01AB06
		M01AB07
		M01AB08
		M01AB09
		M01AB10
		M01AB11
		M01AB12
		M01AB13
		M01AB14
		M01AB15
		M01AB16
		M01AB17
		M01AB51
		M01AB55
	Oxicams	M01AC01
		M01AC02
		M01AC03
		M01AC04
		M01AC05
		M01AC06
		M01AC56
	Propionic acid derivatives	M01AE01
		M01AE02
		M01AE03
		M01AE04
		M01AE05
		M01AE06
		M01AE07
		M01AE08
		M01AE09
		M01AE10
		M01AE11
		M01AE12
		M01AE13

	Fenamates	M01AE14
		M01AE15
		M01AE16
		M01AE17
		M01AE18
		M01AE51
		M01AE52
		M01AE53
		M01AE56
		M01AG01
		M01AG02
		M01AG03
		M01AG04
		M01AH01
		M01AH02
		M01AH03
		M01AH04
		M01AH05
		M01AH06
		M01AH07
	Other	M01AX01
		M01AX02
		M01AX04
		M01AX05
		M01AX07
		M01AX12
		M01AX13
		M01AX14
		M01AX17
		M01AX18
		M01AX21
		M01AX22
		M01AX23
		M01AX24



		M01AX25 M01AX26 M01AX68
Osteopenia/ osteoporosis	Vitamin D Bisphosphonate	A11CC M05BA
Accelerated atherosclerosis	Statins       + lipid modifying agent       + other drug class	C10AA01 C10AA02 C10AA03 C10AA04 C10AA05 C10AA06 C10AA07 C10AA08  C10BA01 C10BA02 C10BA03 C10BA04 C10BA05 C10BA06 C10BA07 C10BA08 C10BA09  C10BX01 C10BX02 C10BX03 C10BX04 C10BX05 C10BX06 C10BX07 C10BX08 C10BX09 C10BX10

		C10BX11 C10BX12 C10BX13 C10BX14 C10BX15 C10BX16 C10BX17 C10BX18
	Hydroxychloroquine	P01BA02
Pulmonary hypertension	Prostacyclin pathway agonists (epoprostenol, treprostinil, iloprost, selexipag),	B01AC09 B01AC21 B01AC11 B01AC27
	Endothelin receptor antagonists (ambrisentan, bosentan, macitentan)	C02KX02 C02KX01 C02KX04
	nitric oxide (NO)	R07AX01
	Guanosine monophosphate (cGMP) enhancers (phosphodiesterase 5 inhibitors [PDE5Is; sildenafil, tadalafil]),	G04BE08 G04BE03
	Calcium channel blockers (CCBs; nifedipine, diltiazem) Dihydropyridines	C08CA01 C08CA02 C08CA03 C08CA04 C08CA05 C08CA06 C08CA07 C08CA08 C08CA09 C08CA10 C08CA11 C08CA12

	Phenylalkylamines	C08CA13 C08CA14 C08CA15 C08CA16
	Benzothiazepines	C08DA01 C08DA02  C08DB01
Antiphospholipid syndrome	Warfarin	B01AA03
	Heparin	B01AB01
	Vitamin K antagonists	B01AA
	Fondaparinux	B01AX05
Skin, joint, muscle involvement	Hydroxychloroquine	P01BA02
	Chloroquine	P01BA01
	Glucocorticoids	H02AB01 H02AB02 H02AB03 H02AB04 H02AB05 H02AB06 H02AB07 H02AB08 H02AB09 H02AB10 H02AB11 H02AB12 H02AB13 H02AB14 H02AB15 H02AB17
	Prednisone	A07EA03

	Immunosuppressive agent (e.g Azathioprine methotrexate                      mycophenolate cyclophosphamide rituxoimab)	L01BA01  L01BA03  L01BA04  L01BA05  L04AA06
Cutaneous	Topical corticosteroids	D07
	Topical calcineurin inhibitors	L04AD01  L04AD02  L04AD03
Nephritis	Mycophenolate	L04AA06
	Cyclophosphamide	L01AA01
	Glucocorticoids	H02AB01  H02AB02  H02AB03  H02AB04  H02AB05  H02AB06  H02AB07  H02AB08  H02AB09  H02AB10  H02AB11  H02AB12  H02AB13  H02AB14  H02AB15  H02AB17
	ACE inhibitors	C09A
	Angiotensin II receptor blockers	C09C
Peptic ulcer	Proton pump inhibitors	A02BC01  A02BC02  A02BC03  A02BC04  A02BC05



		H02AB05
		H02AB06
		H02AB07
		H02AB08
		H02AB09
		H02AB10
		H02AB11
		H02AB12
		H02AB13
		H02AB14
		H02AB15
		H02AB17
Raynaud's	Amlodipine	C08CA01

## 8.5. Study size

Table 11 approximates the number of women with SLE or MS we expect to find within each data source. The prevalence of MS in the general population was assumed to be between 58 and 120 per 100,000 in countries included in this study, whilst the prevalence of SLE was assumed to be around 80 per 100,000<sup>14,15</sup>. The number of pregnancies expected within each data source has been estimated either by the DAPs or by assuming that the number of pregnancies within a data source are 25% of the number of women of child bearing age within the data source. Prevalence of SLE or MS within pregnancies is assumed to be the same as in the general population.

Nine data sources are providing information for MS and seven data sources are providing information for SLE. In total, approximately 10,000 pregnancies from women with MS and 5,000 pregnancies from women with SLE will be identified.

Prevalence of medications are expected to vary greatly amongst our study population, but are expected to be lower than in the general MS/SLE population as women are more likely to discontinue treatments before or during pregnancy<sup>18</sup>. The study will only have the power to predict large risk differences. For example, major congenital anomalies have a prevalence of approximately 2%<sup>20</sup> across Europe, this would mean, with a medication prevalence of 5%, we would require 10,373 women with MS/SLE to be in the study to detect a doubling of risk. Or given a medication prevalence of 10%, we would require 5583 women with MS/SLE in the study to detect a doubling of risk.

**Table 11 – Sample size estimations for SLE and MS studies\***

		MS		SLE	
Data source	Number of pregnancies in period covered (2005 – 2019)	Prevalence of MS per 100,000 <sup>1</sup>	Estimated number of pregnancies in women with MS	Prevalence of SLE per 100,000 <sup>2</sup>	Estimated number of pregnancies in women with SLE
Finland	1,506,000	107	1,611	80	-
France - Nationwide	300,000	117	351	80	240
France – Haute Garonne	137,600	117	161	80	110
Germany	1,500,000	113	1,695	80	1,200
Italy - Tuscany	525,000	92	483	80	420
Italy – Emilia Romagna	400,000	92	368	80	320
Norway	830,000	120	996	80	664
Spain – Valencian Region	440,000	58	255	80	352
Wales	350,000	168	388	80	-
Total	5,998,600	-	6,308	-	3,306

<sup>1</sup> Prevalence estimates from Kingland et al ref 14

<sup>2</sup> Prevalence estimate from Rees et al ref 15

\* Data sources from other countries (e.g. the Swedish registries), may be included, pending on results from the Data characterization (WP7)





## 8.6. Data management

All data have been prospectively collected and will be analysed retrospectively. They are available through population based electronic health registries and claims data bases. In some countries several registries are linked using the personal identification number of each citizen in the country (Norway, Finland). The exception is the EUROmediCAT central registry, which contains case data from all the individual contributing registries. This registry will be treated as one single data source.

Data management and analysis will be done in each individual country/region using the ConcePTION common data model (CDM). Data will remain in the country of origin, and only aggregated data and analytic results will be delivered to the ConcePTION platform.

Each DAP, will perform the following tasks:

- 1) Obtain required ethical and legal permissions to use the data in this project
- 2) Extract and transform the data locally into ConcePTION CDM
- 3) Check and run script distributed to the DAP by the ConcePTION coordinating centre
- 4) Run standard scripts to check data quality (quality assessment of data)
- 5) Run the scripts for this specific study (iteratively)
- 6) Send aggregated results to the remote ConcePTION Secure Platform.

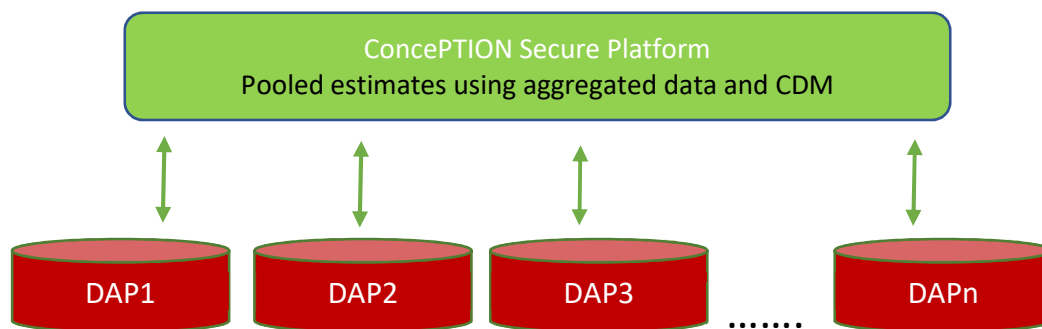


Figure 1: Data flow in ConcePTION. DAP: Data access provider. CDM: Common data model

## 8.7. Data analysis

Statistical analyses will be carried out in three steps. Firstly, pilot modelling of the SAP will be carried out on the Norwegian linked registry data (SGUL). Secondly, scripts will be re-coded in R (UMUC) and sent to all DAPs through the ConcePTION task management system. Thirdly, analytic results will be combined on the ConcePTION platform. Final results will be downloaded from the ConcePTION platform after being checked to ensure identifiability of any individual is prevented and small number suppression applied if necessary.

### 8.7.1 Drug utilisation

For both SLE and MS, medications include those taken as oral tablets, those being administered by intravenous injection and those requiring intravenous infusions. Consequently, the provenance of the prescriptions will include primary care, out-patient visits and also inpatient stays. The drug utilisation studies within this project will use the ATC codes listed in Tables 6 and 7 as well as country specific procedure codes (when appropriate) to identify prescriptions to each medication of interest.

#### Defining exposure

For a foetus to be considered exposed to medication X within the drug utilisation study the mother must have had a prescription to medication X with a dispensation date within the period of interest. For Wales only prescription date will be available. The periods of interest are three-month periods starting before a woman's LMP and ending after the pregnancy. These can be seen in Table 12. The matched women of childbearing age will be allocated equal exposure classifications using the calendar dates in the pregnant woman they are matched to.

**Table 12 – Definitions of pregnancy periods**

Pregnancy period	Definition
9-12 months prior to LMP	365-295 days prior to LMP
6-9 months prior to LMP	294-183 days prior to LMP
3-6 months prior to LMP	182-91 days prior to LMP
0-3 months prior to LMP	90 days prior to LMP
Any use during pregnancy	From LMP to end date of pregnancy
First trimester of pregnancy	As defined by WP7
Second trimester of pregnancy	As defined by WP7
Third trimester of pregnancy	As defined by WP7
0-3 months after pregnancy	90 days after end date of pregnancy

### Analysis

To assess the drug utilisation patterns during pregnancy of women with MS and SLE, the MS and SLE drug utilisation studies will include only women with MS or SLE respectively. Each study will count the number of pregnancies with maternal exposure to each medication by pregnancy period for pregnant women and by equivalent dates for matched controls (Table 9) to generate the respective prevalence's. Frequencies and prevalence's will be tabulated by calendar year and by age at LMP (or equivalent date). Formal comparisons between pregnant women and the non-pregnant women will be performed.

#### **8.7.2 Medication safety**

To investigate the effects of the medications outlined in Section 9.4.2 on pregnancy related outcomes in women with SLE/MS, descriptive analyses using tabulations and plots of the covariates, outcomes and exposure groups will be generated. Exposure will be identified primarily by using dispensation dates of prescriptions during the time period of interest (for example the first trimester). Sensitivity analyses will be conducted using additional information such as prescription length and half-life of the medication to include any drugs dispensed prior to the first trimester (exposure during the peri-LMP period) that might affect the foetus in the first trimester due to still being taken during the first trimester or due to their half live. Univariable logistic regression models between outcomes and categorised covariates will be fitted to evaluate the relationships held between each covariate and each outcome.

Medication safety will be analysed by comparing women with SLE or MS (depending on the study) who are exposed to a specific medication/medication combination with either women with SLE or MS who are unexposed to any medication of interest at any time during pregnancy. Two exposure periods are of interest for these safety studies, first trimester exposure and exposure during pregnancy only after the first trimester. In addition, both unexposed women with SLE or MS and all women with MS or SLE will be compared with women without either MS or SLE to estimate the association of each disease with adverse pregnancy outcomes.

To conduct these analyses, unadjusted logistic regression models between the exposures and outcomes of interest will be conducted, then a range of adjusted models will be run in order to account for confounders and effect modifiers. The variables adjusted for in each model will depend on the data availability and data quality of the covariates within each data source.

If a data source can provide one or two year's follow up on childhood infections (including neonatal

and infant infections) will be treated as time to event outcomes and Cox proportional hazard models will be run<sup>21</sup>.

### **8.7.3 EUROmediCAT safety study**

For each medication and specific anomaly, the proportion of exposures to the medication in cases with the specific anomaly will be compared to the proportion of exposures to the medication in a comparison group of other anomalies, with estimates reported using the proportional reporting ratio (PRR).

### **8.7.4 Missing data**

Missing data within each covariate and each outcome will be reviewed descriptively using tabulations of missingness. For each covariate missingness will be tabulated by outcome, exposure and by MS or SLE. For each outcome, missingness will be tabulated by covariate and by MS or SLE. This information will then be used to identify the most appropriate means of handling missing data within each model. Multivariable models will handle missing covariate data either by imputing the mean/mode of each covariate, or by using a complete case analysis. Univariable models will only be run using complete case analyses as the purpose of these models is descriptive. More complex imputation techniques such as multiple imputation will not be used within this project as the sample sizes within each country will not be sufficient to correctly fit the required predictive models.

### **8.7.5 Combining results**

Results from both the drug utilisation and drug safety studies may be compared across countries if appropriate. In the drug utilisation studies, appropriateness will be determined by considering the prescribing patterns of countries and subsets of countries may be used if certain countries use alternative prescribing strategies to the rest of the participants. Equally, only countries with similar data availability will be compared. For the drug safety studies, available data will once again be considered, however, further consideration will also be required as to how the outcomes are defined in each country.

To combine aggregated results from across countries accurately for MS and SLE, suitable meta-analytic techniques for sparse data must be employed. Adjustments to common meta-analytic techniques such as the Mantel-Haenszel method<sup>7</sup> or the DerSimonian Laird random effects

method<sup>8</sup> can be applied to help reduce the bias in detecting heterogeneity between treatment effects and the bias in the treatment effect itself<sup>6</sup>. Therefore, due to the heterogeneous nature of results across countries, this project will utilise an adjustment to the DSL method known as a simple average estimation method<sup>6</sup>. In the scenario that there is sufficient data to analyse any outcomes using time to event analyses, we will combine survival curves using a distribution-free approach for estimating summary survival curves with random effects<sup>22</sup>. Alternative Bayesian models, including hierarchical models are being investigated and may be applied if appropriate.

## **8.8. Quality control**

The studies will be conducted in line with the ENCePP Code of Conduct for scientific independence and transparency, and the FAIR (Findable, Accessible, Interoperable, Reusable) principles of the ConcePTION project.

Each data access provider will be responsible for the extraction, transformation, and loading of their original data to the ConcePTION CDM. Standardized scripts will be written by the group of statisticians in R for data characterization, to run against data in the ConcePTION common data model. R scripts plus instructions will be sent to participating DAPs using a task management system.

The DAP is responsible for converting data into the CDM using their preferred software and subsequently running the provided R script against the CDM-converted data. The results of the R-script will be submitted to a computing platform that can be accessed remotely by DAPs and ConcePTION partners and participating DAPs using authentication. Access to each DAP's results on the platform will be limited to the data access provider, WP1 public partner statisticians, and WP7 public partner statisticians.

Data quality will be assessed according to a clear framework based on the ADVANCE database characterization process, the United States FDA Sentinel System data quality indicators and the Observational Health Data Sciences and Informatics (OHDSI) data quality dashboard (in development). The data quality and characterization checks described below will take place in collaboration with partners. All data will remain local and only summary measures described below will be inspected in collaboration with WP7 partners and the task force for data transformation. This process will proceed iteratively in collaboration with each DAP until consensus on fitness for purpose has been reached between WP7 and the DAP, the result of this consensus process and some core results will be made available on the catalogue in a private area for inspection by investigators and DAPs. For all indicators and characterization output resulting in a cell count less than 5, counts will not be reported and will be

replaced with "<5" programmatically.

Level 1 data checks review the completeness and content of each variable in each table of the ConcePTION CDM to ensure that the required variables contain data and conform to the formats specified by the CDM specifications (e.g., data types, variable lengths, formats, acceptable values, etc.).

This is a check conducted in collaboration with DAPs to verify that the extract, transform, and load (ETL) procedure to convert from source data to the ConcePTION CDM has been completed as expected. Formats for all values will be assessed and compared to a list of acceptable formats. Frequency tables of variables with finite allowable values will be created to identify unacceptable values. Distributions of days and months of birth to assess any rounding will be constructed.

Level 2 data checks assess the logical relationship and integrity of data values within a variable or between two or more variables within and between tables. Examples of this type of check include: prostate cancer diagnoses in female subjects, observations occurring after a recorded death date, etc. In this check, we will assess records occurring outside of recorded person time (i.e. before birth, after death, or outside of recorded observation periods).

Following completion of level 1 and 2 checks, WP7 will review results with DAPs and assess any detected errors.

## **8.9. Limitations of the research methods**

### Secondary data

One of the key limitations of the planned research is inherent to secondary use of data studies (SUD): As data were collected for other purposes there is no control on what data are collected and how they are collected and how accurate the self-reported data are (e.g. smoking, alcohol, cannabis); particularly, there is no control over biases and not all biases in the data might be known<sup>23</sup>. Knowledge on how the data were collected and comparisons between analyses of data from different sources can help to identify and evaluate such potential biases. We shall have no information on other causes of adverse outcomes, including environmental pollution, genetic vulnerability, and substance misuse.

### Diagnosis information

Diagnosis algorithms are to be investigated during the ConcePTION platform data characterisation. The algorithms being considered for SLE and MS comprise either ICD-9/ICD-10 diagnostic codes or ICD-9/ICD-10 diagnosis codes and prescription records. As diagnosis codes and prescription data can be identified from a range of locations (Primary care, outpatient and hospital) countries which do not have access to certain areas of their health care system are likely to miss data containing diagnostic codes and maybe even the diagnosis itself. To account for this, during the identification of algorithms, each country will be reviewed separately and a range of algorithms will be considered and evaluated. For long-term conditions it is uncertain at present the length of time a woman needs to be in a data source to ensure her long-term condition is recorded and this will be evaluated. In addition, disease severity is an important confounder that is not likely to be accurately assessed when using the data sources without an MS registry.

### Exposure data

Each of the data sources in ConcePTION have limitations with respect to the available data they have on exposure to medications. One of the substantial limitations this study will face will be identifying medications which are commonly administered in hospital and medications given via infusions at outpatient clinics or as outpatients on wards. Each data source has its own limitations as to the prescriptions they pick up; this information is detailed in Appendix I. In addition to missing certain prescriptions, exposure will also be defined by making broad assumptions based on drug doses and timings and half-lives. Exposure algorithms will be tailored to suit the medication type and use, but availability of dose and prescription size information may be insufficient to use more complex algorithms to identify exposure and its timing. In addition, the presence of a prescription does not mean that the women actually took the medication and that this occurred at the time the prescription was issued or collected.

### Small numbers

As seen in Section 9.5, the number of women we expect to identify with SLE or MS is very low in some countries. As a result of this, we expect to encounter zero or very few exposures for certain newer medications in certain countries resulting in no occurrences of specific outcomes for these medications. Alternative methodology, including Bayesian modelling will be considered in these scenarios in order to include all data in the overall analyses. However, in some scenarios when total samples sizes are very small certain medication/outcomes combinations will not have the safety analyses conducted on them as the results will not provide reliable evidence.

### Multiplicity

One consequence of conducting such a broad and wide-reaching exploratory study is having to deal with multiplicity. The general principle around multiplicity is that if you test for enough associations then some will come back significant even if no true association exists. This is not an issue we can directly avoid; however, all interpretations will be treated with great caution and it needs to be emphasised that these results will only highlight possible areas of concern and not provide conclusive evidence that pregnancy outcomes are caused by a medication.

## **9. Protection of human subjects and reporting of adverse events/adverse reactions**

### **- Regulatory and Ethical Compliance**

This study is non-interventional, based on secondary use of pre-existing data. Therefore, as per the EMA Guideline on Good Pharmacovigilance Practices [Module VI—Management and reporting of adverse reactions to medicinal products (Rev1) 2014], the reporting of suspected adverse reactions in the form of individual case safety reports (ICSRs) is not required. Reports of adverse events/reactions should be summarized as part of any interim analysis and in the final study report unless the protocol provides differently. This data characterization is not considered as a PASS because the aim is not of “identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, nor of measuring the effectiveness of risk management measures.” While the data characterization is being conducted, the marketing authority holder (MAH) shall monitor the results generated and consider its implications for the risk-benefit balance of the medicinal product concerned. Any new information which might influence the evaluation of this risk-benefit balance shall be communicated to the competent authorities of Member States in which the medicinal product has been authorized. The channel for communicating this information is the notification of an Emerging Safety Issue.

This study is compliant with the provisions of the ENCePP Code of Conduct, Revision 4.

### **- Informed Consent**

Data bases with an Institutional Review Board (IRB) approval indicating that informed consent from individuals is waived and the rationale for this decision will be maintained.

### **- Responsibilities of the Investigator and IRB/IEC/REB**

The protocol and waiver of informed consent must be reviewed and approved by a properly constituted



institutional review board/independent ethics committee/research ethics board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol has been approved by the IRB/IEC/REB and waiver of informed consent must be given to the principal investigator before study initiation.

## 10. Plans for disseminating and communicating study results

The results of this study will be published as ConcePTION report and scientific papers in peer-reviewed journals. These manuscripts will be prepared independently by the investigators and in accordance with the current guidelines of STrengthening the Reporting of OBservational studies in Epidemiology (STROBE), the ENCePP standards and EMA guidelines.

The following funding disclosure will be used:

*“The publication is part of the activities within the ConcePTION project. It has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 821520. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.”*

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## **12. Appendices**

### **12.1. Appendix I – Data source information**

Finland	
Time period	1998- 2018
Population	Pregnancies - Live births, stillbirths, induced abortions
Number of women of childbearing age (15-55)	-
Number of pregnancies	1,506,000
Quality of mother-baby linkage	-
Quality of Mother-prescription linkage	-
Databases for medications	<ul style="list-style-type: none"> <li>• Drug purchases and reimbursements from three months before to three months after pregnancy</li> </ul>
Sources of medication information	Community pharmacy reimbursement
Databases for diagnoses	<ul style="list-style-type: none"> <li>• Care Register for Health Care (HILMO)</li> <li>• Register of Primary Health Care visits (Avohilmo)</li> </ul>
Sources of diagnosis information	Hospital, outpatient and primary care
Databases for outcomes	<ul style="list-style-type: none"> <li>• Medical Birth Register</li> <li>• Register of Congenital Malformations</li> </ul>
Italy - Tuscany	
Time period	2004-2018
Population	People in the inhabitant register younger than 56 Pregnancies – Deliveries of a live child, or a still birth with a number gestational weeks equal or more than 22 which occurred in hospital.
Number of women of childbearing age (15-55)	900,000 (Approx)
Number of pregnancies	525,000
Quality of mother-baby linkage	-
Quality of Mother-prescription linkage	-
Databases for medications	<ul style="list-style-type: none"> <li>• Drug dispensations from community pharmacies and from hospital pharmacies</li> </ul>
Sources of medication information	Hospital, if not during hospital admission, outpatient, if administered by hospital pharmacy and primary care
Databases for diagnoses	<ul style="list-style-type: none"> <li>• Hospital discharge records</li> <li>• Emergency admissions</li> <li>• Outpatient services</li> </ul>
Sources of diagnosis information	Hospital and outpatient
Databases for outcomes	<ul style="list-style-type: none"> <li>• Birth registry</li> <li>• Spontaneous abortions</li> <li>• Induced terminations registry</li> <li>• Death registry</li> <li>• Congenital anomaly register</li> </ul>

Italy - Emilia Romagna	
Time period	2004-2018
Population	People in the inhabitant register younger than 56 Pregnancies – Deliveries of a live child, or a still birth with a number gestational weeks equal or more than 22 which occurred in hospital.
Number of women of childbearing age (15-55)	1,100,000 (Approx)
Number of pregnancies	400,000 (Approx)
Quality of mother-baby linkage	-
Quality of Mother-prescription linkage	-
Databases for medications	<ul style="list-style-type: none"> <li>• Drug dispensations from community pharmacies and from hospital pharmacies</li> </ul>
Sources of medication information	Hospital, if not during hospital admission, outpatient, if administered by hospital pharmacy and primary care
Databases for diagnoses	<ul style="list-style-type: none"> <li>• Hospital discharge records</li> <li>• Emergency admissions</li> <li>• Outpatient services</li> </ul>
Sources of diagnosis information	Hospital and outpatient
Databases for outcomes	<ul style="list-style-type: none"> <li>• Birth registry</li> <li>• Spontaneous abortions</li> <li>• Induced terminations registry</li> <li>• Death registry</li> <li>• Congenital anomaly register</li> </ul>
Norway	
Time period	2008- 2019
Population	Anyone with a record in both the patient registry or in the prescription database (composite variable to identify patients with a disease) Pregnancies - Any pregnancy 12 weeks GA or beyond (live, miscarriage, elective abortion, stillbirth)
Number of women of childbearing age (15-55)	1,473,000
Number of pregnancies	830,000
Quality of mother-baby linkage	>99%
Quality of Mother-prescription linkage	>99%
Databases for medications	<ul style="list-style-type: none"> <li>• The Norwegian Prescription Database (NorPD)</li> </ul>
Sources of medication information	Hospital (after amendment), outpatient, if administered by hospital pharmacy and primary care
Databases for diagnoses	<ul style="list-style-type: none"> <li>• The Norwegian Patient Registry (NPR)</li> </ul>
Sources of diagnosis information	Hospital and outpatient (secondary care only)

Databases for outcomes	<ul style="list-style-type: none"> <li>The Medical Birth Registry of Norway (MBRN)</li> </ul>
Spain - Valencian Region	
Time period	2010-2019
Population	<p>Birth Registry: Mother of livebirths in Valencian Region; Children livebirths in Valencian Region who accept to participate in the screening programme (almost the 98-99% of livebirths), people from another Region who are born in a Valencia Region's hospital and accept to participate will be included. Children from Valencian Region born in another region will be not included.</p> <p>Congenital anomalies Registry: Mother of livebirths and stillbirths in Valencian Region with at least one major congenial anomaly; Children livebirths, and cases of stillbirths or TOPFA (no mother identifier), with at least one major congenital anomaly.</p> <p>Hospital discharge database: Women with a hospital discharge; children with a hospital discharge.</p> <p>Prescription and dispensation database: Women with a prescription or dispensation being outpatient. Children with a prescription or dispensation being outpatient.</p>
Number of women of childbearing age (15-55)	1,250,000 (Approx)
Number of pregnancies	440,000
Quality of mother-baby linkage	-
Quality of Mother-prescription linkage	-
Databases for medications	<ul style="list-style-type: none"> <li>Prescription dataset</li> <li>Dispensations dataset</li> </ul>
Sources of medication information	Hospital, if not during hospital admission, outpatient, if administered by hospital pharmacy and primary care
Databases for diagnoses	<ul style="list-style-type: none"> <li>Hospital discharge records</li> </ul>
Sources of diagnosis information	Hospital
Databases for outcomes	<ul style="list-style-type: none"> <li>Mortality registry</li> <li>Congenital anomalies registry</li> <li>Birth registry</li> </ul>
France - Nationwide	
Time period	2015 - 2020
Population	<p>99% of the French population from birth (or immigration) to death (or emigration)</p> <p>Pregnancies – Live births, spontaneous abortions, maybe others</p>
Number of women of childbearing age (15-55)	-
Number of pregnancies	300,000
Quality of mother-baby linkage	Mother and baby linkage possible with limitations (linkage possible in 94-96%)
Quality of Mother-prescription linkage	-

Databases for medications	SNDS tables: <ul style="list-style-type: none"> <li>MEDICAMENT</li> <li>MS registry (OFSEP)</li> </ul>
Sources of medication information	Hospital, outpatient and primary care
Databases for diagnoses	SNDS tables: <ul style="list-style-type: none"> <li>DIAGNOSIS</li> </ul>
Sources of diagnosis information	Hospital and outpatient (?)
Databases for outcomes	SNDS – Outcomes at time of pregnancy OFSEP – Possible more outcomes but only live births
France – Haute Garonne	
Time period	2005-2019
Population	
Number of women of childbearing age (15-55)	-
Number of pregnancies	137,600
Quality of mother-baby linkage	-
Quality of Mother-prescription linkage	-
Databases for medications	EFEMERIS tables: <ul style="list-style-type: none"> <li>PRESCRIPTION</li> </ul> POMME tables: <ul style="list-style-type: none"> <li>MEDICAMENTS ENFANT</li> </ul>
Sources of medication information	Hospital, outpatient and primary care
Databases for diagnoses	EFEMERIS tables: <ul style="list-style-type: none"> <li>HOSPIT_MERE</li> </ul>
Sources of diagnosis information	Hospital
Databases for outcomes	EFEMERIS tables: <ul style="list-style-type: none"> <li>NAISSANCE</li> <li>INTERRUPTION</li> <li>MALFORMATION</li> </ul> POMME tables: <ul style="list-style-type: none"> <li>PRESTATIONS ENFANT</li> </ul>
Germany	
Time period	2005-2019
Population	Approximately 17% of the general population
Number of women of childbearing age (15-55)	6,250,000
Number of pregnancies	1,500,000
Quality of mother-baby linkage	-
Quality of Mother-prescription linkage	-
Databases for medications	GePaRD table:



	<ul style="list-style-type: none"> <li>• T_AMB_GO</li> <li>• T_PRESCRIPTION</li> <li>• T_PRESCR_COMP</li> </ul>
Sources of medication information	Hospital, medications available through procedure codes, outpatient and primary care
Databases for diagnoses	GePaRD tables: <ul style="list-style-type: none"> <li>• T_DMPS</li> <li>• T_INPATIENT</li> <li>• T_DIAG</li> <li>• T_AMBULANT</li> <li>• T_AMB_DIAG</li> </ul>
Sources of diagnosis information	Hospital and outpatient
Databases for outcomes	GePaRD tables: <ul style="list-style-type: none"> <li>• T_PREG</li> </ul>
Wales	
Time period	1998-2020
Population	National data with medication data from ~80% of Welsh GP practices Pregnancies: NCCHD, primary care and hospital admission data for miscarriage. From 2015, midwifery data set.
Number of women of childbearing age (15-55)	1,400,000
Number of pregnancies	350,000
Quality of mother-baby linkage	>99%
Quality of Mother-prescription linkage	Around 75%
Databases for medications	GP prescriptions MS register
Sources of medication information	Primary care and MS registry, possibly outpatient and hospital if recorded by GP.
Databases for diagnoses	Inpatient PEDW records Outpatient PEDW records MS register Primary care
Sources of diagnosis information	Primary care, outpatient and hospital, MS registry.
Databases for outcomes	ONS births Congenital anomaly register National Community Child Health Database (NCCHD) MS register Education database Primary care Hospital admissions and OPD – PEDW.

Data sources from other countries (e.g. the Swedish registries), may be included, pending on results from the Data characterization (WP7)

## 12.2. Appendix II – Outcome availability

DAP/Data source	Outcome							
	Preeclampsia	Maternal death	Gestational diabetes	Still birth	Spontaneous abortion	Live births	Elective terminations	Ectopic pregnancies
Finland	Y		Y			Y		
Tuscany	?		?			Y		
Emilia Romagna	?		?			Y		
Norway	Y	Y	Y	Y	Y	Y	Y	Y
Valencian Region	Y		Y			Y		
France - Nationwide	?		?			Y		
France – Haute Garonne	Y		Y			Y		
Germany	?		?			Y		
Wales	Just not sure how complete	Y	Not sure how complete primary care will be	Y 24 weeks	With regulators	Y	With regulators	With regulators

Data sources from other countries (e.g. the Swedish registries), may be included, pending on results from the Data characterization (WP7)

Data availability might change pending confirmation from the data access providers following data characterization

DAP/Data source	Outcome								
	SGA	LGA	Major congenital anomalies	Preterm birth	Neonatal stroke	Neonatal death	Neonatal infections	Infant death	Childhood infections <sup>1</sup>
Finland	Y		Y		?				Y
Tuscany	Y		Y		Y				?
Emilia Romagna	Y		Y		Y				?
Norway	Y		Y		Y				Y (secondary care only)
Valencian Region	Y		Y		Y				Y
France - Nationwide	Y?		N		Y?				N
France – Haute Garonne	Y		Y		Y				Y
Germany	?		?		Y				?
Wales	Y	Y	Y	Y	Y	Y	Y	Y	Y

<sup>1</sup>Childhood infections within the first two years of life

Data sources from other countries (e.g. the Swedish registries), may be included, pending on results from the Data characterization (WP7)

### 12.3. Appendix III – Covariate availability

DAP/Data source	Covariate								
	Maternal age	Parity	Year of birth	BMI	Smoking during pregnancy	Alcohol consumption during pregnancy	Comorbidities	Socioeconomic status	Ethnicity
Finland	Y	Y	Y	Y	Y	N	Y	Y	N
Tuscany	Y	Y	Y	Y	Y	N	Y	N	N
Emilia Romagna	Y	Y	Y	Y	Y	N	Y	N	N
Norway	Y	Y	Y	Y	Y	N	Y	Y: maternal employment status	N
Valencian Region	Y	Y	Y	N	Y	Y	Y	N	N
France - Nationwide	Y	-	Y	-	N	N	Y	N	N
France – Haute Garonne	Y	Y	Y	N	Y	Y	Y	N	N
Germany	-	-	Y	-	-	-	-	-	-
Wales	Y	Y	Y	Y incomplete ~75% pre 2015- 90% from 2015	Y as reported by woman	Y, from 2015 + heavy use as referred from 1998.	Y	Y	No governance for this. Poorly recorded.

Data sources from other countries (e.g. the Swedish registries), may be included, pending on results from the Data characterization (WP7)

## 12.4. Appendix IV – Medication information

SLE medication information							
Medication	ATC code	Doses	Administration technique	Is this medication prescribed continuously, to prevent disease progression or sporadically, to treat flares for example?	Half life	5 times half life	Define peri-LMP period as per label (needed use of effective contraception since last dose)
<b>Antimalarials</b>							
Hydroxychloroquine	P01BA02	200mg-400mg, 200mg per tablet	Oral	Continuous	22.4 days	112 days	3 months
Chloroquine	P01BA01		Oral	Continuous	1 to 2 months	5 to 10 months	No info in SmPC
Mepacrine	P01AX05		Oral	Continuous	5 to 14 days	25 to 70 days	
<b>Corticosteroids</b>							
Prednisolone	H02AB06	7.5mg/d - 30 mg/d Doses range and are tapered up/down		Continuous & Flare	2.1 to 3.5 hours	10.5 to 17.5 hours	-
Prednisone	H02AB07			Continuous & Flare	3 to 4 hours	15 to 20 hours	-
Methylprednisolone	H02AB04	1 g/day for 3 consecutive days is gold standard but less may be just as useful		Flare	2.1 to 3.5 hours	10.5 to 17.5 hours	-
<b>Traditional immunosuppressants</b>							
Azathioprine	L04AX01	50-150mg or 1-3mg/kg a day	Oral	Continuous	1 day	5 days	3 months

Mycophenolate	L04AA06	0.5g – 2g per day	Oral	Continuous	12 hours	60 hours	90 days
Cyclophosphamide	L01AA01	1-1.5g daily (oral) 750 mg/m <sup>2</sup> body mass index (Infusion)	Oral/Infusion	Flare	3 to 12 hours	15 to 60 hours	12 months
Ciclosporin	L04AD01		Oral	Continuous	8.4 to 27 hours	42 to 135 hours	
Tacrolimus	L04AD02	0.1 mg/kg per day, twice daily aiming at a blood concentration of TAC maintained within 5-15 ng/mL	Oral	Continuous	3.5 to 40.5 hours	17.5 to 202.5 hours	While pregnant
<b>Biologics</b>							
Belimumab	L04AA26	10 mg/kg every 2 weeks for 3 doses, then 10 mg/kg every 4 weeks, review treatment if no response within 6 months.	Infusion	Continuous	1.74 to 19.4 days	8.7 to 97 days	4 months
Rituximab	L01XC02	500mg, 2 infusions 1 week apart or 1g, 2 weeks apart	Infusion	Continuous	3 weeks	15 weeks	12 months

MS medication information							
Medication	ATC code	Doses	Administration technique	Which MS patients receive this medication?	Non pregnant adult elimination Half life	5 times half life	Define peri-LMP period as per label (needed use of effective contraception since last dose)
Alemtuzumab	L04AA34	-First treatment course: 12 mg IV over 4 hours daily for 5 consecutive days -Second treatment course: 12 mg IV	Intravenous infusion	RRMS, SPMS  Patients who have had an inadequate response	2 weeks	10 weeks	4 months

		over 4 hours daily for 3 consecutive days administered 12 months after the first treatment course -Maintenance dose: 12 mg IV over 4 hours daily for 3 consecutive days may be administered, if needed, at least 12 months after the last dose of the prior treatment course		to 2 or more drugs for MS			
Azathioprine	L04AX01	50-150mg or 1-3mg/kg a day	Oral	MS	6 hours	30 hours	No info in SmPC
Cladribine	L04AA40	-10 mg -cycle dosage as 1 or 2 tablets once daily over 4 or 5 consecutive days - is 3.5 mg per kg body weight administered orally and divided into 2 yearly treatment courses (1.75 mg per kg per treatment course)	Oral	RRMS; SPMS  For patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of MS	1 day	5 days	6 months
Daclizumab	L04AC01	150 mcg subcutaneously once a month	Subcutaneous injection	Relapsing forms of multiple sclerosis (MS) who have had an inadequate response to 2 or more drugs	21 days	105 days	No info in SmPC
Dimethyl fumarate	N07XX09	The starting dose for TECFIDERA is 120 mg twice a day orally. After 7 days, the dose should be increased to the maintenance dose of 240 mg twice a day orally.	Oral	RRMS, CIS, SPMS	1 hour	5 hours	No info in SmPC
Fingolimod	L04AA27	0.5 mg once daily (adults and pediatric patients 10 years of age and older weighing more than 40 kg) 0.25 mg once daily (pediatric patients 10 years of age and older	Oral	RRMS, CIS, SPMS	6 – 9 days	30 – 45 days	2 months

		weighing less than or equal to 40 kg)					
Glatiramer acetate	L03AX13 L04AA07	COPAXONE 20 mg per mL: administer once per day or COPAXONE 40 mg per mL: administer three times per week and at least 48 hours apart	Subcutaneous injection/Self-injectable	RRMS; SPMS, CIS	<b>1 hour</b>	5 hours	No info in SmPC
Interferon beta-1a	L03AB07	Rebif: either 22 mcg or 44 mcg three times per week Avonex: 30 micrograms once a week, may be started at a dose of 7.5 micrograms and the dose may be increased by 7.5 micrograms each week for the next three weeks	Rebif: Subcutaneous injection Avonex: Intramuscular injection	RRMS; SPMS, CIS	Rebif: 50 – 60 hours  Avonex: 10 hours	Rebif : 250 – 300 hours (10,42 – 12.5 days) Avonex : 50 hours (2,08 days)	Rebif / Avonex: None (If clinically needed, the use of Betaferon may be considered during pregnancy)
Interferon beta-1b	L03AB08	Starting dose is 0.0625 mg (0.25 mL) subcutaneously every other day, with dose increases over a six-week period to the recommended dose of 0.25 mg (1 mL) every other day	Subcutaneous injection	RMS	8 minutes to 4.3 hours	40 minutes – 21.5 hours	None (If clinically needed, the use of Betaferon may be considered during pregnancy)
Mitoxantrone	L01DB07	12 mg/m <sup>2</sup> short IV (5-15 minutes) infusion every 3 months	Intravenous infusion	RRMS, SPMS	25 – 215 hours	125 - 1075	No info in SmPC
Natalizumab	L04AA23	300 mg intravenous infusion over one hour every four weeks	Intravenous infusion	RRMS; SPMS, CIS	27 days	135 days	No info in SmPC
Ocrelizumab	L04AA36	Initial dose: 300 mg intravenous infusion, followed two weeks later by	Intravenous infusion	RRMS; SPMS, CIS, PPMS	26 days	130 days	12 months

		a second 300 mg intravenous infusion. Subsequent doses: single 600 mg intravenous infusion every 6 months.					
Peginterferon beta-1a	L03AB13	Day 1: 63 micrograms Day 15: 94 micrograms From day 29: 125 micrograms every 14 days	Subcutaneous injection	RRMS	78 hours	390 hours (16 days)	No info in SmPC
Rituximab	L01XC02		Intravenous infusion?	RRMS, PPMS	22 days	110 days	12 months
Teriflunomide	L04AA31	7 mg or 14 mg once daily	Oral	RRMS; SPMS, CIS	19 days	95 days	Between 8 months and 2 years (plasma conc below 0.02 mg/l)
Ofatumumab	L01XC10	Initial Dosing: 20 mg administered at Week 0, 1, and 2. (2.2) Subsequent Dosing: 20 mg administered monthly starting at Week 4.	Subcutaneous injection	RRMS; SPMS, CIS	17.6 days	88 days	6 months
Siponimod	L04AA42	Initiate with 5 days titration (0.25 mg – 1.25 mg Maintenance dose: 2mg once daily.	Oral	RRMS; SPMS, CIS	30 hours	150 hours (6.25 days)	10 days
Ozanimod	L04AA38	Maintenance dosage: 0.92 mg once daily	Oral	RRMS; SPMS, CIS	2 weeks	105 hours (5 days) 55 days	3 months
Methotrexate	L04AX03	Oral: 7-5 -25mg once per week	Oral, intravenous	RRMS, PRMS, SPMS	7 hours	35 hours	6 months

**Guidance:**



1. For those DMDs which have information in the label, this time period should be used as peri-LMP (last column)
2. For those DMDs with no information in the label, 5 times the half-life should be used
3. Interferons: 5 times half-life should be used
4. Teriflunomid: 2 years should be used
5. For those which provide a range the more conservative should be used

Rationale for using the information provided in the label where available:

This is more conservative and takes into consideration additional aspects other than the half-life like mechanism of action and the female reproductive system including time of ovum maturation.

## 12.5. Appendix V – Medication exposures that will be considered for exclusion from pregnancy safety cohort

List of medications with an association with disruption of structural organ development or growth<sup>15</sup>.

Medication (ATC)		Physical affects
Oral retinoid		
Acitretin	D05BB02	Multiple malformations including central nervous system abnormalities, orofacial clefts, cardiovascular, skeletal, limb and ear. Facial dysmorphia.
Alitretinoin	L01XF02/D11AH04	
Bexarotene	L01XF03	
Isotretinoin	D10AD04/D10BA01/ D10AD54	
Tretinoin	D10AD01/L01XF01/ D10AD51	
Antiepileptic/ anticonvulsants		
Carbamazepine	N03AF01	Variable by individual medication type but include cardiovascular (phenobarbital, primidone, valproate), neural tube (valproate, carbamazepine), skeletal (valproate), orofacial cleft (topiramate, valproate) and limb (valproate). Facial dysmorphia (phenytoin, carbamazepine, valproate). Growth disruption (topiramte).
Phenytoin	N03AB02	
Fosphenytoin	N03AB05	
Primidone	N03AA03	
Topiramate	N03AX11	
Valproate	N03AG01	
Phenobarbital	N03AA02	
Antithyroid		
Carbimazole	H03BB01	Multiple malformation including skin defects including aplasia cutis, choanal atresia, esophageal atresia, other malformations of the gastrointestinal tract. Facial dysmorphia.
Methimazole	H03BB02/H03BB52	
Anticoagulant		
Coumarin	?	Multiple malformations including nasal hypoplasia, stippled epiphyses, skeletal and digital. Growth disruption. Facial dysmorphia.
Phenindione	B01AA02	
Warfarin	B01AA03	
Acenocoumarol	B01AA07	

## **12.6. Appendix VI - Covariate definitions**

### Maternal age

Maternal age is the age of the mother at LMP

### Parity

Parity is defined as the number of times that a woman has given birth to a foetus with a gestational age of 22 weeks or more, regardless of whether the child was born alive or was stillborn.

### Year of birth

The year in which the pregnancy outcome occurred.

### BMI (Mother)

The body mass index (BMI) of the mother at the latest time prior to becoming pregnant or in the first trimester of pregnancy

### Smoking during pregnancy

If the mother smoked at any time during the pregnancy (Yes/No).

### Alcohol during pregnancy

If the mother drank alcohol at any time during the pregnancy (Yes/No).

### Comedications – SLE

See table 10

### Comedications – MS

See table 9 Comedications – General

The general comedications which are potentially teratogenic are outlined in Appendix V. Any exposure during or in the 3 months prior to pregnancy of any of these medications may lead to exclusion from the safety studies.

### Comorbidities – SLE

See table 10

### Comorbidities – MS

See table 9

### Disease severity

Disease severity for either SLE or MS is not typically available in population-based health care data sources. However, if available, MS disease severity will be classified using the Expanded Disability Status Scale (EDSS). SLE disease severity will be classified based on the SLE severity score developed by Garris et al <sup>24</sup>.

## 12.7. Appendix VII Subtask 1.3.6 – Identifying MS and SLE in Health Care Databases



Subtask%201.3.6%20Analysis%20plan%20.docx

ICD-10 code G35, ICD-9 code 340	Smith et al 2020
algorithm requiring two MS diagnoses at least 30 days apart in administrative health claims datasets.	Capkun et al 2015
<p>≥3 MS-related claims from any combination of inpatient, outpatient, or DMT use within 1 year</p> <p>DMT use was defined as prescriptions including interferon beta-1a, interferon beta-1b, glatiramer acetate, fingolimod, dimethyl fumarate, teriflunomide and natalizumab, with claims for natalizumab not included if the individual also had an ICD code for inflammatory bowel disease,</p>	Culpepper et al 2019
≥2 inpatient diagnoses or ≥3 outpatient diagnoses within a 1-year time period	

## 12.8. AppendixVIII : *Known risks of transgenerational adverse drug reactions*

### Purpose of this document

*These lists indicate which co-exposures should be accounted, depending on outcome of interest.*

**We advise:**

- **Identification**
- **Exclusion**
- **Separate reporting of excluded subjects**
- **Listing unidentifiable aetiologies in the study limitations**

Sensitivity analyses may be useful, where numbers are sufficient.

Lists have been compiled from secondary sources, and encompass regulatory documents (see bibliography). The length of the lists is due to the level of details in these sources: the problem for investigators is that omission of any aspect of multifactorial aetiologies may lead to inaccurate conclusions.

### How to accommodate known risks? Team note – for decisions

Suggest: Append this list to the umbrella protocol and the protocol paper.

**All DPs with anomalies as an outcome:**

- Identify all aetiologies listed using a common syntax across the 5 DPs, if possible.
- Report each exposure, even if we can only say <5 (or 0)
- Where the exposures cannot be ascertained, note each of these in the study limitations.
- Report each exposure against outcome(s) of interest as *a priori* subgroups, numbers & governance permitting (This is v important for the large groups e.g. diabetes, substance misuse (Jordan et al 2019.) Where this is impossible e.g. due to low numbers in exposures or exposed cases, note in the text &, if appropriate, limitations.
- Exclude all exposed (at risk) pregnancies from the relevant analyses (suggest together to minimize work)
- Consider confining this to the highest risk aetiologies (even if rare).
- Consider a sensitivity analysis with these included (Alternatively, reverse this, and make the first analysis 'all' and the sensitivity analysis 'without the pregnancies exposed to known or suspected teratogens / cause of adverse outcomes'.)
- If the medicines or conditions of interest are on the list, mention this in the introduction. (It makes no sense to exclude them.)

#### ***All DPs with other outcomes***

As above, for these outcomes

#### ***Alternative approach***

Check exposed cases for the less frequent and less likely aetiologies, whilst excluding & reporting the large groups (e.g. Jordan et al 2016, 2019).

#### **Rationale for this document**

When examining transgenerational adverse drug reactions, the agent under investigation and prescribed medicines in general, may not be the only exposure or aetiology. Accounting for these is discussed elsewhere (Damase et al, task 1.2, Jordan et al submitted).

Comedications are of interest in medication safety studies in pregnancy because of their potential to act as confounders, or moderators, or to interact with the medication(s) of interest in the study. The numbers of infants exposed and affected can be very small, but some outcomes are also rare, ***and very low numbers of co-exposed cases can affect the study's interpretation.***

For example, the association between anti-depressants and substance misuse may complicate the interpretation of the associations with adverse outcomes (Jordan et al 2016, 2019).

Confounders are associated with both the medication exposure of interest, and the outcome (congenital anomaly, neurodevelopment, preterm birth, SGA), so a preselection of potential priority confounders looks for known teratogens. Whether they will be associated with the medication exposure of interest depends on that medication and its indication. While the traditional way of dealing with confounders is to stratify by them in the statistical analysis, this is usually not possible due to the very small numbers of co-exposed cases. At the same time, one or two co-exposures can have a considerable impact on odds ratios based on few overall exposures. Therefore, an alternative strategy is to exclude any exposures in the pregnancy population to rare known teratogens (a very small proportion of all pregnancies), and to check for the presence in the study population of potentially influential cases of co-exposure to less well established teratogens. Interaction with the medication exposure of interest depends on the mechanism of action, and needs to be assessed on a study specific basis.

#### ***ATC and ICD10 codes are appended***

**Highest risks for major anomalies (all / any)**

Other adverse perinatal outcomes are listed below

***Exclude and report as a priori subgroups*****Medicines**

- Coumarins
- Valproic acid derivatives
- Other AEDs (Veronili et al 2017) Risks increase with combinations
  - Clobazam
  - Ethosuximide
  - Vigabatrin
  - Topiramate
  - Phenytoin – fosphenytoin likely similar risk (no oral formulation) (BNF 2021)
  - Phenobarbital
  - Primidone (a barbiturate)

**Other substances with high risks**

- Radiopharmaceuticals (0 found in EMC) V09 (a v long list, most of which will not be seen in the data)
- Heavy alcohol use (as referral)
- Substance misuse (as referral to services as deemed necessary by primary care teams)

**Conditions**

- Type 1 diabetes – as insulin in trimester 1

*All Medicines with a pregnancy prevention program – high risk*

? exclude and report numbers (v low) or check exposed cases?

- Thalidomide & analogues (were 0 in women <55 in Wales in EMC)
  - Thalidomide L04AX02
  - Lenalidomide L04AX04
  - Pomalidomide L04AX06
- Retinoids (oral)
  - Isotretinoin D10AD04, D10BA01, D10AD54
  - Acitretin D05BB02
  - Alitretinoin D11AH04, L01XX2
  - Tretinoin
- Pulmonary hypertension treatments (no PPP in BNF)
  - Ambrisentan C02KX02
  - Bosentan C02KX01
  - Macitentan C02KX04
  - Riociguat C02KX05
- Vismodegib L01XX43 (for skin cancers, no PPP in BNF)
- Immunosuppressants
  - Eculizumab L04AA25 (no PPP in BNF)
  - fingolimod L04AA27 (for MS) (no PPP in BNF)
  - mycophenolatemofetil / mycophenolic acid L04AA06
- cytotoxics
  - hydroxycarbamide L01XX05 (no PPP in BNF)
  - bexarotene
- immune modulators
  - leflunomide L04AA13 (no PPP in BNF)
- bisphosphonate
  - zoledronic acid M05BA08, M05BB08 (no PPP in BNF)
- eptotermin alfa M05BC02 (not in BNF)

**Risk is supported by considerable evidence, but less frequently used.**

*Options are 'exclude and report' or check exposed cases.*

**Medicines**

- Carbimazole (H03BB) (methimazole outside UK);
- Methotrexate (Aminopterin no longer marketed)
- Penicillamine
- Ribavirin J05AP01
- Griseofulvin D01AA08, D01BA01
- Fluconazole regular use @400-800mg/ day
- Exenatide (for type 2 diabetes)
- Antineoplastics / alkylating agents (e.g.cisplatin, cyclophosphamide, doxorubicin)
- Antimetabolites
- Progesterones
- Diethylstilbestrol
- Finasteride (for prostatic hyperplasia or alopecia in men, unlicensed for hirsutism in women)
- Iodine, including topical
- 

**Conditions conferring risks - list with codes below**

- PKU
- SLE
- Congenital anomaly in mother
- Congenital anomaly in maternal sibling
- CMV exposure
- Rubella exposure
- Chickenpox exposure
- Toxoplasmosis exposure
- Febrile illness (Graham 2020, Czeizel et al 2008) – I do not know how we'll find these – likely a limitation.

**Risk may be less but need to check**

**Meds**

- Carbamazepine (Veroniki et al 2017)
- Aminoglycosides (ototoxicity, nephrotoxicity, not structural birth defects)

**Other substances**

- Lindane P03AB02
- Pesticides (likely not recorded. P03 gives insect repellants, and treatments)
- Pollution, landfill etc

**Conditions**

Cancer diagnosis with an admission (likely unknown because of so many variations) This excludes some skin cancers, which are not usually associated with chemotherapy.

**Uncertain additional risk**

Consider checking

- SSRIs / SNRIs / other antidepressants
- Fluconazole single use – not regular use @400-800mg/ day
- gold salts, aurothiomalate (uncertain, no information in UKTIS)
- lithium (N05AN);
- corticosteroids: oral – clefts, inhaled - ?congenital cataracts (Garne et al 2016)
- ergot derivatives (ergotamine)
- statins BNF indicates a risk

- Methylene blue V03AB17, V04CG05 FDA category X. iv only for cyanide poisoning. BNF says 'no information'. V rarely needed & then in hospital *stat* dose.
- Tetracyclines (evidence in animal studies) teeth & bone staining, hepatotoxicity
- Levonorgestrel G03AC03, G03AD01, G03FA11, G03FB09, G03AA07, G03AB03 (a contraceptive) FDA category X, BNF says 'not known'
- Ulipristal G03AD02, G03XB02 (a contraceptive) FDA category X, BNF says 'little information'
- Colchicine
- Misoprostol (an abortifacient)
- Mifepristone (an abortifacient)
- Ondansetron (clefts)
- Rifaximin (animal data) for diarrhoea
- Sulfasalazine (BNF advises folate)
- Other folate antagonists (unproven): trimethoprim, triamterene, cimetidine
- Antipsychotics (Creeley & Denton 2019)
  - Pregabalin – N03AX16 (Bastow 2017)
- Oxcarbazepine (few data)

#### **Risk uncertain – likely no additional risk**

Lamotrigine (Veroniki et al 2017) N03AX09

Gabapentin (Veroniki et al 2017) N03AX12

Macrolides: erythromycin, clarithromycin, azithromycin - uncertain (MHRA 2021).

#### **SGA & preterm birth & teratogenic**

From Jordan et al 2019,

- insulin, AEDs & coumarins in T1 are also associated with preterm birth.
- AEDs with < 10<sup>th</sup> centile &
- Coumarins with < 3<sup>rd</sup> centile.
- Some AEDs (zonisamide, phenobarbital, topiramate [BNF 2021])

#### **Probably not teratogenic, but are foetotoxic or affect other outcomes**

- benzodiazepines, preterm birth and SGA only (Creeley & Denton 2019), however, triazolam (N05CD05) was category X (it is no longer prescribable, but may be in older records).
- Z drugs – SGA & preterm
- Antipsychotics – SGA
- Ergot derivatives – SGA & preterm birth
- atenolol / beta blockers IUGR
- oral corticosteroids (preterm birth, SGA) (Davies et al 2020)
- beta2 agonists SGA (Davies et al 2020)
- antidepressants SGA (Jordan et al 2019)
- angiotensin converting enzyme inhibitors or angiotensin II blockers (C09): trimesters 2 & 3 (includes Aliskiren C09XA02, C09XA53, C09XA52, C09XA54, C09DX02, FDA category X) (renal damage)
- aminoglycosides - ototoxic
- thyroxine (N03AA) – depends on correct replacement dose
- Oxytocin G02AC01, H01BB02, H01BB02 uterine contractions
- Trimethadione – foetal loss
- Misoprostol – foetal loss
- Danazol (all androgens) – virilization
- Pregabalin – SGA N03AX16 (Bastow 2017)
- NSAIDs (premature closure of *ductus arteriosus*)



## Neurodevelopment

Valproate

Other AEDs: phenytoin, carbamazepine

?SSRIs/ SNRIs

??oxytocin

?benzodiazepines

## Miscarriage (if this is an outcome)

- Auto-immune conditions, including thyroid disorders
- Febrile illness (Giakoumelou et al 2016) STD additional risk
- Intra-uterine infection, UTI
- Alcohol
- Smoking
- Substance misuse
- Obesity
- Chromosomal anomalies
- Diabetes
- Severe hypertension
- Severe renal disease
- NSAIDs
- Misoprostol
- Oxytocin
- ? stimulant laxatives
- Methotrexate
- Retinoids
- Radiation exposure
- Lead, mercury, arsenic, solvents, pesticides (likely a limitation)
- Anatomical anomalies (uterus or cervix)
- Polycystic ovaries
- Severe malnutrition
- Maternal age  
(<https://www.webmd.com/baby/4-common-causes-miscarriage#1>)
- Macrolides: erythromycin, claritromycin, azithromycin - uncertain (MHRA 2021).

Some agents with weak or conflicting evidence of foetotoxicity or teratogenicity have been omitted from these lists: morphine, codeine (not reported in standard works and well used); azoles (usually topical applications); antimalarials (evidence uncertain); antivirals (systemic use associated with severe illness); methylphenidate (uncertain); endothelin receptor antagonists (new); enzyme replacement therapy (uncertain, animal studies reported); monoclonal antibodies (associated with severe illness) (Gomes et al 2021).

## ATC and ICD10 codes lists

List 1 ATCs for highest risk medicines

Drug	Code
Coumarins	B01AA01
	B01AA02
	B01AA03
	B01AA04
	B01AA07
	B01AA08

Valproic acid derivatives	N03AG01
Clobazam	N05BA09
Ethosuximide	N03AD01
Combinations	N03AD51
Vigabatrin	N03AG04
Topiramate	N03AX11
Phenytoin	N03AB02
Combinations	N03AB52
Phenobarbital	N03AA02

List 2 ATCs for high risk medicines less frequently prescribed

<b>Medication</b>	<b>Code</b>
Carbimazole (methimazole)	H03BB01
Methotrexate	L01BA01 L04AX03
Fluconazole Topical	J02AC01 D01AC15
Exenatide	A10BJ01
Antineoplastics	L01****
Cyclophosphamide	L01AA01
Antimetabolites Folic Acid analogues (shown in next table) Purine analogues  Pyrimidine analogues	L01BA**  L01BB02 L01BB03 L01BB04 L01BB05 L01BB06 L01BB07 L01BC01 L01BC02 L01BC03 L01BC04 L01BC05 L01BC06 L01BC07 L01BC08 L01BC09 L01BC52 L01BC53 L01BC59
Progesterone Hydroxyprogesterone Medroxyprogesterone	G03DA04 G03DA03 G03DA02
Finasteride	D11AX10 G04CB01
<b>Iodine</b>	D08AG03 D03AX01 B03AA11 V09AX03 V09IX03 V09XA03





	J01AA05 J01AA06 J01AA07 J01AA08 J01AA09 J01AA10 J01AA11 J01AA12 J01AA13 J01AA14 J01AA15 J01AA20 J01AA56
Colchicine	M04AC01
Misoprostol  + NAPROXEN	A02BB01 G02AD06 M01AE56
Mifepristone Combinations	G03XB01 G03XB51
Ondansetron	A04AA01
Rifaximin	A07AA11 D06AX11
Sulfasalazine	A07EC01
Folate antagonists	L01BA01 L01BA03 L01BA04 L01BA05
Antipsychotics (from Creeley & Denton 2019), including Olanzapine Haloperidol Risperidone Quetiapine Aripiprazole Clozapine Risperidone Ziprasidone	N05AD01 N05AE04 N05AE05 N05AH02 N05AH03 N05AH04 N05AH05 N05AX08 N05AX12
Pregabalin	N03AX16

List 4 Conditions considered a risk for adverse outcomes – codes & references

Outcome	Code	Reference
Heavy alcohol	E5.x, F10.x, G62.1, I42.6, K29.2, K70.0, K70.3, K70.9, T51.x, Z50.2, Z71.4, Z72.1  O99.310 Alcohol use complicating pregnancy, unspecified trimester O99.311 Alcohol use complicating	Hsu MC, Wang CC, Huang LY, Lin CY, Lin FJ, Toh S. Effect of ICD-9-CM to ICD-10-CM coding system transition on identification of common conditions: An interrupted time series analysis. Pharmacoepidemiol Drug Saf. 2021

	<p>pregnancy, first trimester O99.312 Alcohol use complicating pregnancy, second trimester O99.313 Alcohol use complicating pregnancy, third trimester</p> <p>In cause-of-death statistics on alcohol related deaths following codes are included in the UK: E24.4, F10, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K85.2, K86.0, Q86.0, R78.0, X45, X65, Y15. <a href="https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/causesofdeath/bulletins/alcoholrelateddeathsintheunitedkingdom/registeredin2019#measuring-the-data">https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/causesofdeath/bulletins/alcoholrelateddeathsintheunitedkingdom/registeredin2019#measuring-the-data</a></p> <p>In Finland the list is as follows: F10, G31.2, G40.51, G62.1, G72.1, I42.6, K29.2, K70, K86.0, K85.2, O35.4, P04.3, Q86.0, X45 <a href="https://www.stat.fi/til/ksyyt/ksyyt_2018-11-12_luo_001_en.pdf">https://www.stat.fi/til/ksyyt/ksyyt_2018-11-12_luo_001_en.pdf</a></p>	<p>Jul 14. doi: 10.1002/pds.5330. Epub ahead of print. PMID: 34258812</p> <p><a href="https://icd.codes/icd10cm/O9931">https://icd.codes/icd10cm/O9931</a></p>
Drug abuse	<p>F11.x–F16.x, F18.x, F19.x, Z71.5, Z72.2</p> <p>O99.3 – non-specific</p>	<p>Hsu MC, Wang CC, Huang LY, Lin CY, Lin FJ, Toh S. Effect of ICD-9-CM to ICD-10-CM coding system transition on identification of common conditions: An interrupted time series analysis. Pharmacoepidemiol Drug Saf. 2021 Jul 14. doi: 10.1002/pds.5330. Epub ahead of print. PMID: 34258812</p>
smoking	<p>O99.33 pregnancy smoking F17.2 nicotine dependence Z72.0 tobacco use</p>	<p><a href="https://www.codingstrategies.com/pdf/Nicotine%20Coding%20Job%20Aid%202016.pdf">https://www.codingstrategies.com/pdf/Nicotine%20Coding%20Job%20Aid%202016.pdf</a></p>
PKU	E70.0	<p><a href="https://lhncbc.nlm.nih.gov/newbornscreeningcodes/nb/sc/condition/PKU.html">https://lhncbc.nlm.nih.gov/newbornscreeningcodes/nb/sc/condition/PKU.html</a></p>
SLE – CHD and all adverse outcomes	M32	<p>Vinet É, Pineau CA, Scott S, Clarke AE, Platt RW, Bernatsky S. Increased congenital heart defects in children born to women with systemic lupus erythematosus: results from the offspring of Systemic Lupus Erythematosus Mothers Registry Study. Circulation. 2015 Jan 13;131(2):149-56. doi: 10.1161/CIRCULATIONAHA.114.010027. Epub 2014 Oct 29. PMID: 25355915.</p> <p>Bundhun PK, Soogund MZ, Huang F. Impact of systemic</p>

		lupus erythematosus on maternal and fetal outcomes following pregnancy: A meta-analysis of studies published between years 2001-2016. J Autoimmun. 2017 May;79:17-27. doi: 10.1016/j.jaut.2017.02.009. Epub 2017 Feb 28. PMID: 28256367.
Family history of congenital malformations Maternal CHD  Affected siblings and twins	Z87.798	Liu S, Joseph KS, Lisonkova S, Rouleau J, Van den Hof M, Sauve R, et al. Association between maternal chronic conditions and congenital heart defects: a population-based cohort study. Circulation. 2013;128(6):583-9. doi: 10.1161/CIRCULATIONAHA.112.001054. PubMed PMID: 23812182 Brodwall K, Greve G, Leirgul E, Tell GS, Vollset SE, Øyen N. Recurrence of congenital heart defects among siblings-a nationwide study. Am J Med Genet A. 2017 Jun;173(6):1575-1585. doi: 10.1002/ajmg.a.38237. Epub 2017 Apr 19. PMID: 28425218.
Congenital CMV	P35.1	Barlinn R, Dudman SG, Trogstad L, Gibory M, Muller F, Magnus P, Rollag H. Maternal and congenital cytomegalovirus infections in a population-based pregnancy cohort study. APMIS. 2018 Dec;126(12):899-906. doi: 10.1111/apm.12899. Epub 2018 Oct 30. PMID: 30378168.
Rubella	B06	
Toxoplasma	B58	
Febrile illness	R50. 9 fever unspecified B50.9 Plasmodium falciparum A32.9 Listeria monocytogenes B17.2 Hepatitis E B00. 82 herpes simplex virus disease, B54 malaria, A90 Dengue, A75. 3 scrub typhus	<a href="https://www.ncbi.nlm.nih.gov/books/NBK525177/">https://www.ncbi.nlm.nih.gov/books/NBK525177/</a> Graham 2020, Czeizel et al 2008

	A01.00 typhoid fever severe. O86. 04 Obstetric sepsis.	
Cancer	Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin C00.x-C26.x, C30.x-C34.x, C37.x-C41.x, C43.x, C45.x-C58.x, C60.x-C76.x, C81.x-C85.x, C88.x, C90.x-C97.x Metastatic cancer C77.x-C80.x We have excluded D codes, as these may be false positives for cancer diagnosis.	Hsu MC, Wang CC, Huang LY, Lin CY, Lin FJ, Toh S. Effect of ICD-9-CM to ICD-10-CM coding system transition on identification of common conditions: An interrupted time series analysis. <i>Pharmacoepidemiol Drug Saf.</i> 2021 Jul 14. doi: 10.1002/pds.5330. Epub ahead of print. PMID: 34258812
Autoimmune conditions	Addison's disease E27.1, E27.2 Ankylosing spondylitis M45, M08.1 Behcet's disease M35.2 Buerger's syndrome M31.1B, DI7.31 Celiac disease K90.0 Crohn's disease K50 Dermatitis herpetiformis L13.0 Diabetes mellitus type E10 Dupuytren's disease M72.0 Erythema nodosum L52 Goodpasture's syndrome M31.0 Graves' disease E05.0 Guillain-Barre' syndrome G61.0 Haemolytic anaemia D59.0, D59.1 Hashimoto's thyroiditis E06.3 Henoch-Schoenlein purpura D69.0 ITP D69.3 Kawasaki syndrome M30.3 Localized lupus erythematosus L93 Localized scleroderma L94.0, L94.1, L94.3 Myasthenia gravis G70.0 Multiple sclerosis G35 Pemphigoid L12 Pernicious anaemia D51.0 Pemphigus foliaceus L10.2 Pemphigus vulgaris L10.0 Polyarteritis nodosa M30.0 Polymyositis/dermatomyositis M33 Primary biliary cirrhosis K74.3 Psoriasis L40 Rheumatic fever I00, I01 Rheumatoid arthritis M05, M06 Raynaud's phenomenon DI73.0 Reiter's disease M02.3 Sarcoidosis D86 Sjogren's syndrome M35.0 Sympathetic ophthalmia H44.1B Systemic lupus erythematosus M32 Systemic scleroderma M34	Harpsøe MC, Basit S, Andersson M, Nielsen NM, Frisch M, Wohlfahrt J, Nohr EA, Linneberg A, Jess T. Body mass index and risk of autoimmune diseases: a study within the Danish National Birth Cohort. <i>Int J Epidemiol.</i> 2014 Jun;43(3):843-55. doi: 10.1093/ije/dyu045. Epub 2014 Mar 7. PMID: 24609069.  Howley MM, Browne ML, Van Zutphen AR, et al. Maternal autoimmune disease and birth defects in the National Birth Defects Prevention Study. <i>Birth Defects Res A Clin Mol Teratol.</i> 2016;106(11):950-962. doi:10.1002/bdra.23527
UTI	Combination of diagnosis and	Germanos G, Light P, Zoorob



	<p>symptoms has higher PPV  Cystitis N30 Acute Cystitis N30.0, N30.00, N30.01 Other Chronic Cystitis N30.2, N30.20, N30.21 Other Cystitis N30.8, N30.80, N30.81 Cystitis Unspecified N30.9, N30.90, N30.91 UTI (site not specified) N39.0 Acute Pyelonephritis N10 Nonobstructive Reflux-Associated Chronic Pyelonephritis N11.0 Chronic Obstructive Pyelonephritis N11.1 Pyonephritis N13.6</p> <p>UTI Related Symptoms Pain Associated with Micturition R30 Dysuria R30.0 Frequency of Micturition R35.0 Urgency of Urination R39.15</p>	<p>R, et al. Validating Use of Electronic Health Data to Identify Patients with Urinary Tract Infections in Outpatient Settings. <i>Antibiotics</i> (Basel). 2020;9(9):536. Published 2020 Aug 25.  doi:10.3390/antibiotics9090536</p>
Obesity	E66.x	<p>Hsu MC, Wang CC, Huang LY, Lin CY, Lin FJ, Toh S. Effect of ICD-9-CM to ICD-10-CM coding system transition on identification of common conditions: An interrupted time series analysis. <i>Pharmacoepidemiol Drug Saf.</i> 2021 Jul 14. doi: 10.1002/pds.5330. Epub ahead of print. PMID: 34258812</p>
Chromosomal anomalies	Q90-Q99.9	
Diabetes	E10.x-E14.x	<p>Hsu MC, Wang CC, Huang LY, Lin CY, Lin FJ, Toh S. Effect of ICD-9-CM to ICD-10-CM coding system transition on identification of common conditions: An interrupted time series analysis. <i>Pharmacoepidemiol Drug Saf.</i> 2021 Jul 14. doi: 10.1002/pds.5330. Epub ahead of print. PMID: 34258812</p>
Severe hypertension	I10.x-I13.x, I15.x	<p>Hsu MC, Wang CC, Huang LY, Lin CY, Lin FJ, Toh S. Effect of ICD-9-CM to ICD-10-CM coding system transition on identification of common conditions: An interrupted time series analysis. <i>Pharmacoepidemiol Drug Saf.</i> 2021 Jul 14. doi: 10.1002/pds.5330. Epub ahead of print. PMID: 34258812</p>
Chronic renal disease	<p>CKD N18  CKD Stage 5 (eGFR &lt;15) N185</p>	<p>Leif Friberg, Alessandro</p>

	CKD Stage 4 (eGFR 15–29) N184 CKD Stage 3 (eGFR 30–59) N183 CKD Stage 2 (eGFR 60–89) N182 CKD Stage 1 (eGFR ≥90) N181 Acute renal failure N17 Unspecified renal failure N19 Dependence on renal dialysis Z992 Adjustment and management of vascular access device Z492 Procedure codes: Creation of arterio-venous fistula from artery in the upper limb PBL Repair surgery of arterio-venous fistula in the upper limb PBU Haemodialysis, chronic DR016 Peritoneal dialysis, chronic DR024	Gasparini, Juan Jesus Carrero, A scheme based on ICD-10 diagnoses and drug prescriptions to stage chronic kidney disease severity in healthcare administrative records, <i>Clinical Kidney          Journal</i> , Volume 11, Issue 2, April 2018, Pages 254–258, <a href="https://doi.org/10.1093/ckj/sfx085">https://doi.org/10.1093/ckj/sfx085</a>
Maternal age		<a href="https://www.webmd.com/baby/4-common-causes-miscarriage#1">https://www.webmd.com/baby/4-common-causes-miscarriage#1</a>
Toxic effects of substances nonmedicinal	T51 toxic effect of alcohol T52 toxic effects of organic solvents T53 toxic effect of halogen derivatives T54 Toxic effects of corrosive substances T56 Metals T57 Inorganic substance T58 Carbon monoxide T59 Other gases, fumes and vapors	
Anatomical anomalies (uterus or cervix)	Q51.9	
Polycystic ovaries	E28.2	
Malnutrition	E40-E46	

List 5 ATCs for former class X medicines

Medication	Code
Valproate	N03AG01
Methotrexate	L01BA01 L04AX03
Ribavirin	J05AP01
Triazolam	N05CD05
Bosentan	C02KX01
Aliskiren	C09XA02 C09XA53 C09XA52 C09XA54 C09DX02

Levonorgestrel	G03AC03 G03AD01 G03FA11 G03FB09 G03AA07 G03AB03
Ulipristal	G03AD02 G03XB02
Griseofulvin	D01AA08 D01BA01
Methylene blue	V03AB17 V04CG05
Oxytocin	G02AC01 H01BB02
Riociguat	C02KX05
Isotrenitoin	D10AD04 D10BA01 D10AD54

List 6 ATCs for medicines with a PPP

Medicine	Code
Thalidomide	L04AX02
Lenalidomide	L04AX04
Pomalidomide	L04AX06
Isotretinoin	D10AD04 D10BA01 D10AD54
Acitretin	D05BB02
Alitretinoin	D11AH04 L01XX2
Ambrisentan	C02KX02
Bosentan	C02KX01
Macetentan	C02KX04
Vismodegib	L01XX43
Eculizumab	L04AA25
Eptotermin alfa	L04AA25
Fingolimod	M05BC02
Hydroxycarbamide	L01XX05
Leflunomide	L04AA13
Mycophenolate mofetil/Mycophenolic acid	L04AA06
Zoledronic acid	M05BA08 M05BB08

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Sj 29.7.21/ 2.8.21 SJ,SL,HD 11.8.21, 17.8.21

### **Lists appended for reference (covered above)**

#### *Former FDA class X medications*

- Valproate N03AG01
- Methotrexate L01BA01, L04AX03
- Ribavirin J05AP01
- Triazolam N05CD05
- Bosentan C02KX01
- Aliskiren C09XA02, C09XA53, C09XA52, C09XA54, C09DX02
- Levonorgestrel G03AC03, G03AD01, G03FA11, G03FB09, G03AA07, G03AB03
- Ulipristal G03AD02, G03XB02
- Griseofulvin D01AA08, D01BA01
- Methylene blue V03AB17, V04CG05
- Oxytocin G02AC01, H01BB02, H01BB02, H01BB02
- Riociguat C02KX05
- Isotretinoin D10AD04, D10BA01, D10AD54

#### *Medications with a pregnancy prevention program*

- Thalidomide L04AX02
- Lenalidomide L04AX04
- Pomalidomide L04AX06
- Isotretinoin D10AD04, D10BA01, D10AD54
- Acitretin D05BB02
- Alitretinoin D11AH04, L01XX2
- Ambrisentan C02KX02
- Bosentan C02KX01
- Macitentan C02KX04
- Vismodegib L01XX43
- Eculizumab L04AA25
- eptoterminalfa M05BC02
- fingolimod L04AA27
- hydroxycarbamide L01XX05
- leflunomide L04AA13

- mycophenolatemofetil / mycophenolic acid L04AA06
- zoledronic acid M05BA08, M05BB08

Medication	Physical affects
Oral retinoid	
Acitretin	Multiple malformations including central nervous system abnormalities, orofacial clefts, cardiovascular, skeletal, limb and ear. Facial dysmorphia.
Alitretinoin	
Bexarotene	
Isotretinoin	
Tretinoin	
Antiepileptic/ anticonvulsants	
Carbamazepine	Variable by individual medication type but include cardiovascular (phenobarbital, primidone, valproate), neural tube (valproate, carbamazepine), skeletal (valproate), orofacial cleft (topiramate, valproate) and limb (valproate). Facial dysmorphia (phenytoin, carbamazepine, valproate). Growth disruption (topiramte).
Phenytoin	
Fosphenytoin	
Primidone	
Topiramate	
Valproate	
Phenobarbital	
Antithyroid	
Carbimazole	Multiple malformation including skin defects including aplasia cutis, choanal atresia, esophageal atresia, other malformations of the gastrointestinal tract. Facial dysmorphia.
Methimazole	
Anticoagulant	
Coumarin	Multiple malformations including nasal hypoplasia, stippled epiphyses, skeletal and digital. Growth disruption. Facial dysmorphia.
Phenindione	
Warfarin	
Acenocoumarol	
Immunosuppressive	
Mycophenolate	Multiple malformations including orofacial cleft, microtia, external auditory canal atresia, micrognathia, cardiovascular, oesophageal atresia.
Methotrexate and Aminopterin	Multiple malformations including skeletal, cardiovascular, urogenital, holoprosencephaly. Growth disruption.

#### Text from Jordan et al 2016

To minimise **confounding by co-exposure**, we achieved a relatively homogeneous population by excluding infants: 1) with EUROCAT coding[37] indicating known teratogenic syndromes (EUROCAT subgroups al82-84, al86) 2) exposed to medicines more closely associated with congenital anomalies than SSRIs during the 91 days either side of 1<sup>st</sup> day of LMP: anti-epileptic

drugs (AEDs) (N03)[61]; coumarins (B01AA), mainly warfarin[62]; insulins (A10A)[63]. We examined, but did not exclude, SSRI exposed cases for: 1) exposure to other potentially teratogenic prescription medicines 91 days either side of 1<sup>st</sup> day of LMP: systemic isotretinoin (D10BA); angiotensin converting enzyme inhibitors or angiotensin II blockers (C09); lithium (N05AN); benzodiazepines (N05BA); first generation antipsychotics (N05AA through N05AG); second generation antipsychotics (N05AH, N05AL, N05AX); carbimazole (H03BB); thyroxine (N03AA); medicines rarely prescribed in primary care but associated with anomalies: aminoglycosides, ergot derivatives, lindane, gold salts, penicillamine, methotrexate, chloroquine, radiopharmaceuticals[64]; 2) heavy alcohol use and substance misuse (Wales only); 3) maternal conditions indicating that the woman might not be considered to be from the normal healthy population: hospital admission for cancer; thyroid disorders; phenylketonuria; maternal congenital anomalies[65]; 4) maternal siblings with anomalies.

- AEDs,
- coumarins
- Anti-thyroid (methimazole not in UK)
- Diabetes is a risk factor for many outcomes.
- Heavy alcohol, substance misuse
- angiotensin converting enzyme inhibitors or angiotensin II blockers (C09);
- lithium (N05AN);
- benzodiazepines (N05BA);
- first generation antipsychotics (N05AA through N05AG);
- second generation antipsychotics (N05AH, N05AL, N05AX);
- carbimazole (H03BB); thyroxine (N03AA);
- medicines rarely prescribed in primary care but associated with anomalies: aminoglycosides, ergot derivatives, lindane, gold salts, penicillamine, methotrexate, retinoids (oral only), chloroquine, radiopharmaceuticals[64]; (Manual review of standard text)
- maternal conditions indicating that the woman might not be considered to be from the normal healthy population: hospital admission for cancer; thyroid disorders; SLE; phenylketonuria; maternal congenital anomalies[65];
- maternal siblings with anomalies (likely only for anomalies, and only within database timeframe).

## **12.9. Appendix IX Subtask 1.3.4 - Identification of Childhood Infections in Health Care Databases**



Task1.3.4%20Study  
%20Protocol%20Fin







# concePTION

## SAFETY EVIDENCE ECOSYSTEM

### Protocol

Demonstrating solutions for studying intermittent medication exposures in diseases with episodic manifestations during pregnancy: application to medication for migraine in pregnancy

This study will be conducted within the ConcePTION project of the Innovative Medicines Initiative under grant agreement No 821520

<b>Title</b>	Demonstrating solutions for studying intermittent medication exposures in diseases with episodic manifestations during pregnancy: application to medication for migraine in pregnancy
<b>Protocol version identifier</b>	1.0
<b>Date of last version of protocol</b>	30/09/2021
<b>EU PAS register number</b>	EUPAS 43409
<b>Active substance</b>	Primary exposure: Triptans (ATC: N02CC) Co-medications: analgesics; preventive anti-migraine therapy; antiemetics
<b>Medicinal product</b>	Sumatriptan (ATC: N02CC01), Naratriptan (ATC: N02CC02), Zolmitriptan (ATC: N02CC03), Rizatriptan (ATC: N02CC04), Almotriptan (ATC: N02CC05), Eletriptan (ATC: N02CC06), Frovatriptan (ATC: N02CC07)

<b>Research question and objectives</b>	<p>This study is based on electronic health care registry data from 9 health care data bases in 7 European countries between 2005 and 2019/most recent data available. The study is divided into a medication utilisation part, and a medication safety part. The objective are as follows:</p> <p><b>Medication utilisation study:</b> to describe drug utilization patterns in women with migraine over the course of pregnancy, focusing especially on intermittent migraine medication use, using triptans as the motivating example. Medication utilisation before, during and after pregnancy will be reviewed and compared across data sources.</p> <p><b>Medication safety study:</b> To study the association between prenatal exposure to triptans and adverse maternal and pregnancy outcomes. The potential impact of exposure misclassification on exposure-outcome associations will be assessed under a range of scenarios. Results from across data sources will be combined using meta-analytic techniques.</p>
<b>Country(-ies) of study</b>	Norway (Nationwide), Finland (Nationwide), France (Haute-Garonne), Italy (Emilia Romagna, Tuscany), Spain (Valencian Region), UK (Nationwide for CPRD and Wales for SAIL), Germany (~ 17% population coverage), and possibly other countries, all pending on results from the Data characterization (WP7).
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## Table of Contents

<b>List of abbreviations</b>	<b>6</b>
<b>1. Title</b>	<b>8</b>
<b>2. Responsible parties</b>	<b>8</b>
<b>3. Abstract</b>	<b>9</b>
<b>4. Amendments and updates</b>	<b>12</b>
<b>5. Milestones</b>	<b>12</b>
<b>6. Rationale and background</b>	<b>13</b>
<b>6.1. Background</b>	<b>13</b>
<b>6.2. Migraine – the motivating example</b>	<b>13</b>
<b>7. Research question and objectives</b>	<b>16</b>
<b>7.1. Medication Utilisation and Event Definition</b>	<b>16</b>
<b>7.1.1 Medication Utilisation</b>	<b>16</b>
<b>7.1.2 Event: Migraine</b>	<b>16</b>
<b>7.1.3 Maternal outcomes: Preeclampsia and Gestational diabetes</b>	<b>17</b>
<b>7.2. Medication Safety</b>	<b>17</b>
<b>8. Research methods</b>	<b>18</b>
<b>8.1. Study design</b>	<b>18</b>
<b>8.2. Setting</b>	<b>18</b>
<b>8.3. Variables</b>	<b>20</b>
<b>8.3.1 Exposures</b>	<b>20</b>
<b>8.3.1.1 Primary exposure</b>	<b>21</b>
<b>8.3.1.2 Comparison groups</b>	<b>21</b>
<b>8.3.1.3 Migraine co-medication</b>	<b>22</b>
<b>8.3.1.4 Co-morbidity with nausea</b>	<b>22</b>
<b>8.3.2 Events: Migraine</b>	<b>22</b>
<b>8.3.3 Adverse maternal outcomes</b>	<b>23</b>
<b>8.3.3.1 Preeclampsia</b>	<b>23</b>
<b>8.3.3.2 Gestational diabetes mellitus</b>	<b>24</b>
<b>8.3.4 Adverse pregnancy outcomes</b>	<b>24</b>
<b>8.3.5 Covariates</b>	<b>25</b>
<b>8.4. Data sources</b>	<b>25</b>
<b>8.5. Study size</b>	<b>29</b>

<b>8.6. Data management</b>	<b>30</b>
<b>8.6.1 Software and Hardware</b>	<b>32</b>
<b>8.6.3 Access</b>	<b>32</b>
<b>8.6.4 Archiving and record retention</b>	<b>32</b>
<b>8.7. Data analysis</b>	<b>33</b>
<b>8.7.1 Definitions and categorization of key variables</b>	<b>33</b>
<b>8.7.2 Descriptive analysis: Part 1 (Medication Utilisation and Event/Outcome Definition)</b>	<b>34</b>
<b>8.7.3 Analysis of exposure misclassification</b>	<b>35</b>
<b>8.7.4 Analytical approaches - Part 2. (Medication Safety)</b>	<b>36</b>
<b>8.7.5 Sensitivity analyses</b>	<b>36</b>
<b>8.7.6 Handling of missing data</b>	<b>37</b>
<b>8.7.7. Combining results</b>	<b>37</b>
<b>8.8. Quality control</b>	<b>37</b>
<b>8.9. Limitations of the research methods</b>	<b>39</b>
<b>9. Protection of human subjects</b>	<b>41</b>
<b>10. Management and reporting of adverse events/adverse reactions</b>	<b>41</b>
<b>11. Plans for disseminating and communicating study results</b>	<b>41</b>
<b>12. References</b>	<b>43</b>
<b>13. Annexes</b>	<b>47</b>
<b>13.1. Annex 1. List of stand-alone documents</b>	<b>47</b>
<b>13.2. Annex 2. ENCePP checklist for study protocols</b>	<b>48</b>
<b>13.3. Annex 3. Syntactically Harmonized Common Data Model</b>	<b>54</b>
<b>14. Appendixes</b>	<b>57</b>

## List of abbreviations

Abbrev.	Term
ARS	Agenzia regionale di sanità della Toscana
ACE	Angiotensin converting enzyme
ARB	Angiotensin II receptor blockers
ATC	Anatomical therapeutic chemical
bcRR	Bias-corrected Relative-Risk
BMI	Body mass index
BW	Birth weight
CDM	Common data model
CGRP	Calcitonin gene-related peptide
CI	Confidence intervals
CPRD	Clinical practice research datalink
DAG	Directed acyclic graph
DAP	Data access provider
DDD	Defined daily dose
EFEMERIS	Evaluation des Femmes Enceintes des médicaments et de leurs risques
EMA	European medicines agency
EncePPENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European union
EUROCAT	European network of population-based registries for the epidemiological surveillance of congenital anomalies
FcRn	Neonatal Fc receptor
FAIR	Findable, Accessible, Interoperable, and Reusable
FDA	Food and drug administration
FISABIO	The Foundation for the Promotion of Health and Biomedical Research of Valencian Region
GA	Gestational age
GDM	Gestational diabetes mellitus
GePaRD	German Pharmacoepidemiological Research Database
GP	General practitioner
GLST	Generalized Least Squares for trend
GVP	Guideline on good pharmacovigilance practices
ICD-8/9/10	International Classification of Diseases 8 <sup>th</sup> /9 <sup>th</sup> /10 <sup>th</sup> Revision
ICHD	International Classification of Headache Disorders
ICSR	Individual case safety report
IEC	Independent ethics committee
IPTW	Inverse Probability Treatment Weighting
IRB	Institutional Review Board
IUGR	Intrauterine Growth Restriction
LBW	Low birth weight

Abbrev.	Term
MA	Meta-analysis
MAH	Marketing authorization holder
MCA	Major congenital anomaly
MEGLM	Multilevel mixed-effects generalized linear model
MI	Multiple imputation
MICE	Multiple imputation by chained equations
MPR	Medication possession ratio
MSMs	Marginal structural models
NNH	Number needed to harm
NSAIDs	Nonsteroidal anti-inflammatory drugs
NVP	Nausea and vomiting in pregnancy
OHDSI	Observational Health Data Sciences and Informatics
ORs	Odds ratios
OTC	Over-the-counter
PASS	Post-authorisation safety study
PDC	Proportion of days covered
PE	Preeclampsia
PS	Propensity score
REB	Research ethics board
RR	Relative-risk
SAILS	Secure anonymised information linkage
SES	Socio-economic status
SGA	Small-for-gestational age
STROBE	Strengthening the reporting of observational studies in epidemiology
TOPFA	Termination of pregnancy for fetal anomaly
WHO	World health organization



## 1. Title

Demonstrating solutions for studying intermittent medication exposures in diseases with episodic manifestations during pregnancy: application to medication for migraine in pregnancy

## 2. Responsible parties

Responsible parties are:

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### 3. Abstract

#### Title

Demonstrating solutions for studying intermittent medication exposures in diseases with episodic manifestations during pregnancy: application to medicinal products for migraine in pregnancy

#### Main authors:

Prof. dr. Hedvig Nordeng, University of Oslo, Norway

Justine Benevent, CHUT/ University of Oslo, Norway

#### Rationale and background

Knowledge about benefits and harms related to pharmacological treatment of diseases with episodic manifestations has been inadequate for years due to the difficulties and lack of harmonization in assessing episodic medication use in pregnancy using records of prescription medicines. Management of migraine will be used as the motivating example. The issue is to move beyond the oversimplification of medication use into exposed or non-exposed, and consider intensity and timing of use in pregnancy, severity of the underlying illness, and concomitant medication use.

#### Research question and objectives

**Medication Utilisation Study and Event Definition:** The aim is to describe drug utilization patterns in women with migraine over the course of pregnancy, focusing especially on intermittent migraine medication use, using triptans as the motivating example. Medication utilisation before, during and after pregnancy will be reviewed and compared across data sources.

Another aim is to describe prevalence of two pregnancy-related events: preeclampsia (PE) and gestational diabetes (GDM), which are relevant for the underlying maternal migraine disorder.

**Medication Safety study:** The aim is to study the association between prenatal exposure to triptans/migraine medications and adverse maternal (i.e. PE and GDM) and pregnancy outcomes (e.g. major congenital anomalies, low birth weight (LBW)). The potential impact of exposure misclassification on exposure-outcome associations will be assessed under a range of scenarios. Results from across data sources will be combined using meta-analytic techniques.

#### Study design

This is a multinational cohort study.

#### Study period:

Start\*: 1-1-2005 or the first-year medication AND birth outcomes are available from the data source (whichever is the latest)

End: 31.12.2019/most recent date of the data source where medication AND birth outcome are available.

\*The study start period may vary across DAPs, depending on the available look back-time data on maternal migraine history.

#### Study population

The study population will include pregnant women and their children observed in one of the participating data sources for at least one day during the study period (01.01.04 – 31.12.19/last data availability).

Study populations will be grouped into different cohorts of women:

- 1) Women with migraine with a pregnancy with a known outcome (live and non-live outcomes) during the study time period (“Migraine population”).
- 2) Women without migraine with a pregnancy with a known outcome (live and non-live outcomes) during the study time period (“Population comparison group: no migraine, no migraine medication”)

### Variables

*Disease:* Migraine type (with or without aura) and migraine severity (algorithms; diagnostic and ATC codes)

*Exposure:* The exposure will be defined based on maternal record of one or more prescriptions (prescribed, dispensed or reimbursed) of triptans/migraine medications in pregnancy and during the year prior to pregnancy. These medications will be classified according to the Anatomical Therapeutic Chemical (ATC) classification system.

*Maternal outcomes:* hypertensive disorders, gestational diabetes

*Pregnancy outcomes:* major congenital anomaly, non-live births, preterm births, low birth weight, small for gestational age/ intrauterine growth restriction.

*Covariates:* Maternal age, parity, year of delivery, body mass index, smoking during pregnancy, educational level/SES, reproductive history, comorbidities and comedications.

Available variable information will vary across data sources. Covariates will be chosen based on the literature review and evaluated using Directed Acyclic Graphs (DAG).

### Data sources

The study will include data from 9 electronic health care registries in 7 European countries (Germany (DE), Finland (FI), France (FR), Italy (IT), Norway (NO), Spain (ES), United Kingdom (UK)\*:

- Germany: GePARD (20% population sample)
- France: EFEMERIS (Evaluation chez la Femme Enceinte des Médicaments et de leurs RISques) (Haute-Garonne)
- Italy: ARS Healthcare administrative (Tuscany)
- Italy: Healthcare administrative (Emilia Romagna)
- Norway: linkage of several registries (Nationwide)
- Finland: linkage of several registries (Nationwide)
- Spain: FISABIO (Valencian Region)
- UK: SAIL databank (Wales)
- UK: Clinical practice research datalink (CPRD) (8.5% sample of GP practices)

\*Data sources from other countries (e.g. the Swedish and Scottish registries), may be included, pending on results from the Data characterization (WP7).

### Study size

The nine contributing data sources capture approximately 5 million pregnancies, depending on the in- and exclusion criteria that will differ according to the objectives. We estimate to include 500,000 pregnancies among women with migraine, including 75,000 triptan exposed pregnancies.

The results of the part 1 (Medication Utilisation and Event Definition) will allow us to determine which migraine definitions to use and confounders to include, as well as to determine which analyses we have sufficient study power to analyse in the safety study in part 2 and inform bias analyses.

Power calculations showed that we can expect to be able to detect at least a 50% increased risk in cardiac anomalies (baseline prevalence: 1%) and in any major congenital anomaly (baseline prevalence: 2.3%) for exposures that are used by 10% of the migraine population given a migraine study sample of 500,000 migraine pregnant women.

### Data analysis

**Drug utilisation studies:** Descriptive analysis will include a wide range of drug utilization measures to describe intermittent medication use among women with migraine. Prevalence of medication use will be estimated prior to, during and after pregnancy. Treatments will be reviewed individually, in combinations and as groups.

**Drug safety studies:** The drug safety studies will estimate the prevalence of maternal and pregnancy outcomes among women with migraine according to disease severity and medication use. Uni- and multivariable regression models will be used to determine exposure-outcome associations as appropriate. Propensity score methods will be used to mitigate measured confounding. Timing of medication use in pregnancy as well as migraine type and severity will be considered. Comparison groups include a) unexposed women with migraine and b) population comparison group (no migraine, no migraine medication).

Data will be accessed in a distributed manner using a common protocol, the ConcePTION common data model (CDM) and common analytics developed through the ConcePTION collaboration. Data will be transformed locally to the ConcePTION CDM and analysed using R-scripts that are generated centrally. Results will be sent to the digital research environment (DRE) for pooling and will be presented separately for each data source and aggregated across data sources.

#### 4. Amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1	Date	Text	Text	Text
...	Date	Text	Text	Text

#### 5. Milestones

Milestone	Planned date
Registration in the EU PAS register	October 2021
Final report of study results	March 2023

## 6. Rationale and background

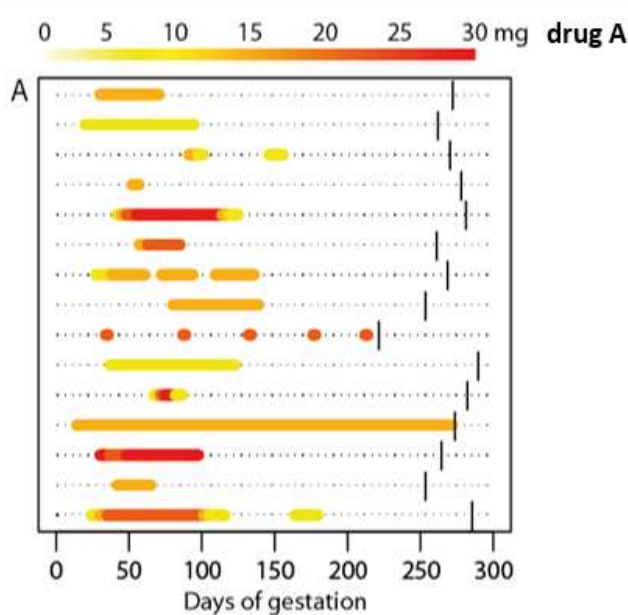
### 6.1. Background

Knowledge about the safety of medications used intermittently for diseases with episodic manifestations in pregnancy have been inadequate for years due to the methodological challenges of using prescription records to assess episodic medication use in pregnancy. In particular, diseases with episodic manifestations are often treated on “as needed” basis. In these situations, drug utilization patterns will be highly different from diseases treated continuously. That said, many chronic diseases are treated with a combination of continuous/daily medications *and* additional “add on” medication as needed (e.g. attacks or flares). The last type of medication is also defined as “intermittent medication use”.

In the situation of **intermittent medication exposure in pregnancy**, exposure will often vary over the course of pregnancy, with exposure episodes depending on a range of factors including fluctuation in disease activity, co-medication use and the women’s perception of her needs, drug risks and benefits. Understanding the drug utilization patterns for these drugs is especially important as it will inform choice of exposure definitions, exposure misclassification assessments and sensitivity analyses.

Custom plots that visualize for each patient their daily and cumulative filling pattern during pregnancy can be useful to identify the patterns of dispensing of medication used intermittently (see illustration). This can help researchers to choose between a range of drug utilization measures including the number of prescription fills, sum of defined daily doses (DDDs) across time periods (e.g. trimesters), and top 10% users in pregnancy<sup>1</sup>.

In medication safety studies, misclassifying some women as exposed whereas they were actually unexposed at the time of dispensing could lead to unpredictable biases that could give rise to either false-positive signals of adverse pregnancy outcomes or false-negative reassuring findings<sup>2</sup>. Several methods have been developed to handle or quantify **exposure misclassification** including probabilistic bias analysis<sup>3</sup> and calculation of the E-value<sup>4</sup>. In the safety part of this project, we will explore the potential impact of exposure misclassification on exposure-pregnancy outcome associations under a range of scenarios using several of these methods as well as results from the part 1 drug utilization study.



### 6.2. Migraine – the motivating example

To address this methodological issue, **migraine will be used as motivating example**.

This disorder is a relapsing-remitting pain condition. Migraine is the fourth leading cause of years

lived with disability among women at all ages, affecting approximately one out of five women of childbearing age<sup>5,6</sup>.

It is a neurological disorder which is characterised by a severe throbbing pain or a pulsing sensation, usually on one side of the head<sup>7</sup>. The International Headache Society (IHS) has classified two major subtypes: migraine without aura, and migraine with aura<sup>8</sup>. Migraine without aura is the most common migraine subtype, and is characterized by headache attacks lasting 4 to 72 hours. Headache attacks are accompanied by other symptoms including photophobia, phonophobia, nausea, and sometimes vomiting. Individuals with migraine with aura may experience in addition reversible focal neurological symptoms (**see Migraine Clinical definition in the Appendix II**). Migraine is most frequently diagnosed in outpatients. However, depending on severity patients can be treated in all settings: outpatient specialists such as neurologists, in-hospital, GPs or in the emergency room.

The frequency and severity of migraines changes during pregnancy: most women experience improvement of headache symptoms, but some women, especially migraine patients with aura experience a worsening of the migraine during pregnancy. Although migraine symptoms improve in one-half to three-fourths of pregnant women, symptoms recur in up to 55% of women within one month postpartum<sup>9</sup>, and up to 8% of women experience migraine throughout pregnancy<sup>10</sup>. If symptoms do not improve during the first trimester, migraines are likely to continue throughout pregnancy<sup>11</sup>. Migraine with aura has especially been associated with worsening or onset during pregnancy<sup>12,13</sup>.

A wide range of medications are used periodically and concomitantly for migraine including triptans and analgesics (paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids. One Norwegian questionnaire based study including 401 women with migraine found that 73.3% of them reported the use of migraine pharmacotherapy during pregnancy, of which triptans (71.1%), paracetamol (63.1%), and NSAIDs (60.1%) were the most frequently used agents<sup>14</sup>.

Triptans are the main focus of this study as they are the most frequently used rescue migraine medications in pregnancy. Prevalence estimates of triptan use during pregnancy among women with migraine vary between 15-25%<sup>15,16</sup>.

Agreement between self-reports and dispensed prescriptions of triptans has previously been described<sup>17</sup>. Harris *et al* found fair agreement (Cohen's kappa coefficient was 0.36) between dispensed triptans and self-reported use (considered as the reference) in the Norwegian Mother, Father and Child Cohort Study (MoBa). Sensitivity for the pregnancy period was 39.1% (95% CI 34.8-43.4) and specificity was 95.4% (95% CI 94.8-95.9). These estimates will be useful to parameterize our models. We will use estimates of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) from this study<sup>17</sup>, but expand on it by taking timing in pregnancy and prescription patterns into account.

The migraine attack intensity, frequency and duration are factors that can influence the dosage and quantity of anti-migraine medication taken during each episode. As there may be dose-response relationship(s) between the use of anti-migraine medication(s) in pregnancy and the risk of adverse pregnancy outcome(s), the intensity, frequency, and duration of medication

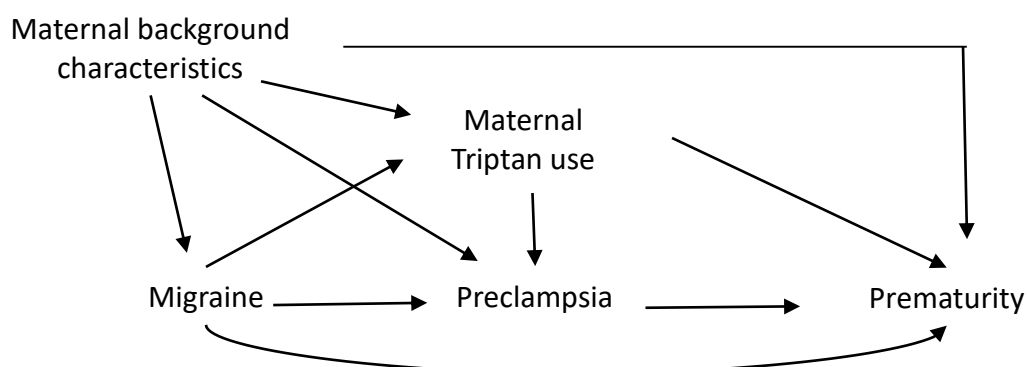
exposure(s) will be considered.

We will move beyond the oversimplification of medication use into exposed or non-exposed, and consider intensity and timing of medication use in pregnancy and/or and more complex medication regimens (e.g. migraine severity algorithms).

### The underlying migraine disease

The underlying maternal diseases will be one of the most important potential confounders to consider as migraine has been associated with an increased risk of adverse maternal and pregnancy outcomes, including preeclampsia and low birth weight<sup>18</sup>.

Prior studies have shown that women with migraine, especially migraine with aura, are at increased risk of hypertensive disorders<sup>19–21</sup>, preeclampsia<sup>22,23</sup> and insulin resistance, potentially increasing the risk of gestational diabetes<sup>24,25</sup>. Gestational hypertension and preeclampsia may also present themselves as symptoms of headache, and be misinterpreted as migraine (inverse association)<sup>26</sup>. Moreover, preeclampsia and gestational diabetes may potentially be important mediators of the risk of migraine on adverse pregnancy outcomes because they are in themselves risk factors for adverse pregnancy outcomes (e.g. preterm birth and low birth weight). An important issue will be to identify women with preeclampsia and gestational diabetes in order to consider the role of these potential mediators/effect modifiers.



### Medications used for migraine

The safety of medications to treat migraine in pregnancy, especially triptans, have been assessed in a few studies<sup>27–35</sup>. These studies, including one meta-analysis, did not find any increased risk of congenital anomalies after prenatal triptan exposure. A few of these studies found an increased risk of preeclampsia and preterm birth. It is, however, unclear whether these findings were confounded by the maternal underlying migraine disorder. Moreover, cases of intrauterine growth restriction (IUGR) and *in utero* death have been identified by the French pharmacovigilance system after use of high dose of triptans in pregnancy<sup>36</sup>, raising concerns about potential adverse vasoconstrictive properties of these drugs on pregnancy outcomes.

Knowledge about the safety of other medications used for prophylactic treatment of migraine stems from studies in non-pregnant populations, e.g. women with depression, hypertension or epilepsy, which may be comparable to their use for migraine prophylaxis.



For the newer migraine medications like the Calcitonin Gene-Related Peptide inhibitors (CGRP-inhibitors), however, the assessment of their safety in human pregnancy is limited<sup>37,38</sup>. Immunoglobulin antibodies cross the placenta through the neonatal Fc receptor (FcRn) in syncytiotrophoblast cells. During the first 20–22 weeks of pregnancy, FcRn is absent and therefore there is minimal active transfer of CGRP-inhibitors across the placenta. Placental transport, however, occurs progressively over the remaining course of pregnancy. Fetal exposure to a CGRP-inhibitor may occur during these periods, but the effect of CGRP blockade in a developing fetus is unknown. In a rat animal model, exposure to CGRP receptor antagonist resulted in elevated maternal rat blood pressure, a reduction in pup weight, and increased fetal mortality rate<sup>39</sup>. Consequently, we will study adverse pregnancy outcomes including congenital anomalies to confirm or refute prior safety signals.

## **7. Research question and objectives**

This is a ConcePTION demonstration project with an overarching goal of providing guidance on how to study intermittent medication exposures in diseases with episodic manifestation during pregnancy. Medications to treat migraine are used as motivating example.

This project is organized in two parts:

- Part 1. Medication Utilisation study and Event/Outcome Definition
- Part 2. Medication Safety study

The results from Part 1 will inform Part 2.

### **7.1. Medication Utilisation and Event Definition**

Results from this Part will inform decisions in Part 2, and focus on correctly defining exposure (i.e. migraine medication), the underlying disease (i.e. migraine) and selected outcomes associated with the underlying disease (i.e. preeclampsia and gestational diabetes).

#### **7.1.1 Medication Utilisation**

The aim is to describe drug prescription patterns of triptans/migraine medications and co-medications (cf 9.3.1. Exposure) over the course of pregnancy among women with migraine in the 12 months to 5 years period before last menstrual period (LMP) date (hereafter, “at baseline”).

The study research questions are:

1. How does use of triptans/migraine medications (acute and prophylactic) change over the course of a pregnancy (e.g. prior to, during, and after pregnancy), by migraine severity and type, and by database?
2. Which maternal factors are related to triptan/migraine medication utilization patterns in pregnancy (e.g. high use, discontinuation of pre-pregnancy treatment)?
3. Which medications are frequently use concomitantly with triptans/migraine medications in pregnancy?

#### **7.1.2 Event: Migraine**

The event/disease of particular focus in this study is migraine. Migraine severity will be classified based on migraine medication prescriptions prior to and during pregnancy (Appendix III). Migraine type will be determined by use of diagnostic codes, in particular to distinguish between migraine with or without aura and other form of headaches (Clinical definitions in Appendix II, Migraine event protocol).

The study research questions are, between the data sources:

1. What is the prevalence of migraine among pregnant women?
2. How do different algorithms to define migraine type and severity impact the prevalence of migraine among pregnant women?
3. Does the prevalence of migraine, migraine type and severity among pregnant women differ by maternal age and calendar year of LMP date (stratification)?

### **7.1.3 Maternal outcomes: Preeclampsia and Gestational diabetes**

Maternal outcomes of particular focus in this study are preeclampsia and gestational diabetes due to a possible association with the underlying migraine disorder, and as symptoms of preeclampsia may resemble a migrainous attack (reverse causation). They may also be important mediators of the risk of migraine on adverse pregnancy outcomes.

The study research questions are, between the data sources:

1. How do different algorithms to define a) Preeclampsia and b) Gestational diabetes impact the prevalence of these outcomes? And does it differ by maternal age and calendar year?
2. What is the prevalence of a) Preeclampsia and b) Gestational diabetes mellitus among women with migraine by migraine type, severity and treatments?
3. Is the association between migraine (type, severity and treatments) and GD and preeclampsia consistent by maternal age and calendar year?

Diagnostic codes for identification of migraine are presented in *Subtaks 1.3.5 study protocol: (Identification of Gestational diabetes & Preeclampsia in health care databases: Development of algorithms in multi-database studies and assessment by comparison of prevalence)*.

## **7.2. Medication Safety**

The second part will be a medication safety study.

The primary research questions are:

1. Is prenatal exposure to triptans associated with adverse maternal outcomes?
  - a. Hypertensive disorders (incl. preeclampsia)
  - a. Gestational diabetes (GD)
2. Is prenatal exposure to triptans associated with adverse pregnancy outcomes?
  - a. Congenital anomalies
  - b. Preterm birth
  - b. Non-live birth
  - c. Low birth weight/ SGA/ IUGR

We will consider intensity and timing of triptan use in pregnancy, severity of the underlying illness, and concomitant medication use. We will use several modelling approaches that will incorporate prior information about the magnitude and direction of exposure misclassification from Part 1.

The secondary research questions are, in the population of pregnant women with migraine at baseline:

1. Is prenatal exposure to major classes of antimigraine medications associated with adverse maternal outcomes?
  - a. Hypertensive disorders (incl. preeclampsia)
  - b. Gestational diabetes (GD)
2. Is prenatal exposure to major classes of antimigraine medications associated with adverse pregnancy outcomes?
  - d. Congenital anomalies
  - e. Preterm birth
  - c. Non-live birth
  - f. Low birth weight/ SGA/ IUGR

## **8. Research methods**

### **8.1. Study design**

These studies are multinational cohort studies using secondary data sources. Part 1 consist of a Drug Utilisation study and Part is a Drug Safety study. By using data from across Europe, these studies will be able to increase the number of pregnancies among women with migraine that are analysed and will provide insight into the utilisation and safety of medications used in migraine across Europe.

The source population will include pregnant women and their children observed in one of the participating data sources for 12 months (or at least the 3 months) before pregnancy and throughout the pregnancy during the study period (01.01.2005 – 31.12.19/last data availability). The 12 months look-back time will enable us to identify triptan prescription history as well as migraine diagnostic codes; whenever available in the data source, the look-back time for diagnostic codes is expanded to five years before LMP through LMP date. This information is crucial to identify migraine events at baseline for each pregnancy.

The pregnancy will be the unit of analysis.

### **8.2. Setting**

The overall study period will run from 1 January 2005 until 31 December 2019. Some data sources will not provide data for the entire study period, but instead provide data between the dates outlined below. The period in which pregnancies may be picked may be shorter than the dates in Table 1 due to additional data requirements for each pregnancy.

The study will include data from 9 or 11 data sources in 7 or 8 European countries (Germany, Finland, France, Italy, Norway, Spain, Sweden and UK) covering 5 million pregnancies across a

15-year time frame (Table 1). Data sources from other countries (e.g. the Swedish and Scottish registries), may be included, pending on results from the Data characterization (WP7). Data sources are described in section 9.4 and Appendix I.

**Table 1. Overview of data sources to be used for the study**

Country	Name Data source	Births per year (1000)	Start data End date	Pregnancies (2005-2019) (1000)	Type of data source	Diagnoses recordings	Birth registry data
Germany	GePaRD	100	01/01/2005 31/12/2018	1,500	Health insurance	GP, Specialist	Yes
Finland	Finish registries	60	01/01/2005 31/12/2018	900	Record linkage	Hospital	Yes
France	EFEMERIS	10	01/07/2005 31/12/2019	140	Cohort	Hospital	Yes
Italy	ARS	25	2005 31/12/2019	5	Record linkage	Hospital	Yes
Italy	IMER, Healthcare administrative	35	2005 31/12/2019	*	Record linkage	Hospital	Yes
Norway	Norwegian registries	55	01/01/2009 31/12/2019	605	Record linkage	Secondary care, GP	Yes
Spain-Valencian Region	Rare Diseases Research Unit from FISABIO	50	01/01/2011 31/12/2019	605 (2007-2019)	Record linkage	GP, specialist Hospital	Yes
UK	CPRD	*	*	*	Record linkage	GP	No
Wales, UK	SAIL	25	01/01/2005 31/12/2020	400	Record linkage databank	GP, Hospital	Yes
<b>Total</b>		<b>340</b>		<b>4.2</b>			

GP: General practitioner. WOCA: Women of childbearing age.

\*Preliminary counts / data not provided by the DAP.

## Study cohort

The pregnancy cohort will contain all pregnancies in which the woman has met the below inclusion/exclusion criteria.

The cohort will contain pregnancies from

- women with migraine at baseline, i.e. with migraine at least in the 12 months (or five years) period prior to through f LMP date
- women without migraine at baseline (population comparison group)

## Inclusion/exclusion criteria

Pregnant women will require the following prescription data for their pregnancy to be considered

eligible for inclusion in the pregnancy cohort:

- 12 or at least 3 months of prescription data prior to their pregnancy (depending on data source)
- Prescription data throughout their pregnancy
- Interval gap of at least 12 months between two consecutive pregnancies within same woman

Multiple pregnancies (e.g., twin, triplets) will be included in the drug utilisation study, but excluded in the drug safety study. Whether the woman requires 3 or 12 months of prescription data prior to pregnancy depends on the information their data source is providing to ConcePTION. Table 3 outlines which months around pregnancy are available for each data source. Women from the data sources providing prescription data for 12 months prior to pregnancy will require 12 months of prescription data prior to pregnancy for the pregnancy to be considered eligible. Women from data sources only providing prescription data for the 3 months prior to pregnancy will only require 3 months of prescription data prior to pregnancy for the pregnancy to be considered eligible for the pregnancy cohort.

#### Availability of prescription data around pregnancy by data source

Data Source	12 months prior to pregnancy	3 months prior to pregnancy	During pregnancy
Finland	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
France (Haute Garonne)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Germany	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Italy (Emilia Romagna)	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Italy (Tuscany)	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Norway	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Spain (Valencian Region)	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
UK (Wales)	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
UK (CPRD)	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>

### 8.3. Variables

#### 8.3.1 Exposures

The main exposure is triptans. Triptans are the most frequently used and prescribed medications for acute migraine; they are 5HT1B, 5-HT1D and 5-HT1F receptor agonists that act on the trigeminocervical complex and smooth muscle. However, more than 60% of the women using triptans switch to or restrict themselves to paracetamol only when they become pregnant<sup>40</sup>.

A wide range of other medications including analgesics (paracetamol, NSAIDS, opioids), antiemetics are used periodically and concomitantly to treat migraine attacks (see a table presenting medications used to treat migraine in Appendix III).

Medications will be classified according to the (ATC) classification system<sup>41</sup>. The population will be

selected based on maternal records of one or more prescriptions (prescribed, dispensed or reimbursed) before and during pregnancy. Exposure windows will be tailored to the outcome studied (for instance first trimester for MCA).

### **8.3.1.1 Primary exposure**

Triptans (ATC-code N02CC)

- N02CC01 sumatriptan
- N02CC02 naratriptan
- N02CC03 zolmitriptan
- N02CC04 rizatriptan
- N02CC05 almotriptan
- N02CC06 eletriptan
- N02CC07 frovatriptan

Specific analyses on medications at a substance level, before (at least three months prior to) and during pregnancy (at different trimesters in pregnancy) will be performed, as well as analysis on number of defined daily doses used, assuming one DDD per day. Moreover, reimbursement code, prescription category and prescriber information (e.g. specialization) will be included when available.

Extended use of triptans (i.e. headache medication overuse) will be defined as >15 DDDs described and dispensed/month (1 month = 30 days); this threshold of 15 DDDs was selected based on International Classification of Headache Disorders<sup>7</sup>. In sensitivity analysis, extended use of triptans will be defined as > 15 dosage units dispensed/month (1 month = 30 days), instead of DDDs.

### **8.3.1.2 Comparison groups**

The different comparison groups will be (see flowchart in Appendix IV):

Triptan exposed group	Pregnancies with a known outcome (live and non-live born infants) among women with migraine at baseline (i.e., with a migraine diagnosis in the five or at least one year prior to LMP though LMP date, or a triptan dispensed/prescribed during the year/3 months prior to pregnancy) with at least one triptan prescription during pregnancy This group by definition includes: - Prevalent users of triptans (i.e. continuers)
Triptans unexposed migraine comparison group	Pregnancies with a known outcome (live and non-live born infants) among women with migraine at baseline (i.e., with a migraine diagnosis in the five or at least one year prior to LMP though LMP date, or a triptan dispensed during the year/3 months prior to pregnancy) without triptan prescription during pregnancy Two categories are included in this group: - Triptans discontinuers during pregnancy - Non-users of triptans before nor during pregnancy
Non-migraine comparison group*	Pregnancies with a known outcome (live and non-live born infants) among women without migraine/triptan use prior to or during pregnancy

\*This group is considered only in the migraine algorithm characterization.

To better address the role of migraine severity, triptan continuers will be separately compared with triptan discontinuers and unexposed pregnancies with migraine at baseline.

### **8.3.1.3      *Migraine co-medication***

Migraine co-medication include both analgesics for acute use and preventive treatments. Many of them have also other indications than migraine.

Migraine acute treatments include non-migraine specific analgesics and antimigraine drugs:

- ATC code M01A (NSAIDs) (prescribed)
- ATC code N02BE01 (paracetamol) (prescribed)
- ATC code N02A (opioids)
- ATC code N02CA Ergot alkaloids

Preventive anti-migraine therapy

Although prophylactic medication, such as beta-blockers or anticonvulsants, are not recommended during pregnancy, around 10% of women have severe migraine during pregnancy and require prophylactic treatment<sup>42</sup>.

Preventive anti-migraine therapy are (Appendix III):

With migraine indication only	Requiring a migraine diagnosis in addition
N02CD (CGRP-antagonists) N02CX (other antimigraine preparations)	C07A (beta blockers) C08D (verapamil (C08DA01)) C09A (ACE-inhibitors) C09C (ARBs) M03AX (botulinum toxin) N03A (antiepileptics: topiramate (N03AX11), valproate (N0AG01)) N06AA (tricyclic antidepressants: amitriptyline) N07CA03 (flunarizine) N02CB Corticosteroid derivatives (short term prophylactic use)

### **8.3.1.4      *Co-morbidity with nausea***

Migrainous attacks will often be accompanied by nausea and a third of women with migraine suffer from Nausea and Vomiting in Pregnancy (NVP). We will therefore include the following medications ATC- and diagnostic codes:

- Antiemetics (e.g. ondansetron, metoclopramide, antihistamines used systemically) (ATC-codes A04AA01, A03FA01 and R06A) will be included as co-medications.
- NVP: ICD-10 diagnostic codes: 021 (Excessive vomiting in pregnancy). Read codes will be used for the UK. ICD-9 diagnostic codes will be used for Italy (Tuscany).

### **8.3.2 Events: Migraine**

An algorithm including diagnostic codes and ATC codes has been proposed to define incident migraine cohort (see Appendix V)<sup>43,44</sup>. Prevalence of migraineurs according to different migraine algorithms will be explored, and exposure-outcome association using these either though varying the exposure categorization or by stratifying, depending on results from Part 1.

### **Migraine types**

The International Classification of Headache Disorders (ICHD) I was proposed by the IHS and was first published in 1998. Since then, the classification has been modified several times (See Table 1 in Appendix II).

This classification includes:

- Migraine without aura
- Migraine with aura
- Medication overuse headache

### **Migraine severity**

Migraine severity will be defined according to migraine medication use prior to and during pregnancy as recommended in clinical guidelines<sup>45,46</sup>, and according to drug utilisation studies previously performed among women with migraine in pregnancy. (see Appendix V)<sup>43,44</sup>.

We will use different algorithms to identify migraine type and severity (**Migraine-event study protocol**).

Guidelines slightly vary according to the countries (in terms of criteria to initiate prophylactic treatment and of medications used as migraine prophylactic treatment)<sup>47-54</sup>. We will perform sub-analysis restricted to databases with diagnostic codes to avoid including women with cluster headaches who also may use some of the migraine medications (e.g. sumatriptan injections, verapamil, valproate, topiramate).

## **8.3.3 Adverse maternal outcomes**

We will have a special focus on maternal outcomes including preeclampsia and gestational diabetes. We will use diagnostic codes (e.g. ICD-codes, Read codes), medication codes (e.g. ATC codes) as defined and characterized in ConcePTION platform data characterization to identify the presence of these disorders. Algorithms used are described in **Subtaks 1.3.5 study protocol: Identification of Gestational diabetes & Preeclampsia in health care databases: Development of algorithms in multi-database studies and assessment by comparison of prevalence**.

### **8.3.3.1 Preeclampsia**

Pre-eclampsia is defined as new onset hypertension (>140 mm Hg systolic or >90 mm Hg diastolic) after 20 weeks of pregnancy and the coexistence of one or both of the following new-onset conditions:

- Proteinuria (urine protein:creatinine ratio  $\geq 30$  mg/mmol,
- Albumin/creatinine ratio  $\geq 8$  mg/mmol, or  $\geq 1$  g/L [2+] on dipstick testing)

We will use the preeclampsia event definitions developed in ConcePTION Subtaks 1.3.5.

Blood pressure above 140/90 mmHg requires pharmacological management: First choice:



Labetalol, second choice: nifedipine, third choice: methyldopa<sup>55</sup>.

### **8.3.3.2      *Gestational diabetes mellitus***

GD is defined as glucose intolerance with onset or first recognition in pregnancy. We will use the GD event definitions developed in ConcePTION Subtaks 1.3.5.

### **8.3.4 *Adverse pregnancy outcomes***

Diagnostic codes and quality indicators from the ConcePTION platform data characterization will be employed. We will use the same event definitions as in the ConcePTION clinical definition of pregnancy outcomes that will be mapped to the ConcePTION common data model. Sensitivity analysis varying the clinical event algorithm will be used to test robustness of findings.

#### *Primary outcomes*

##### **-      Major congenital anomalies**

The prevalence of major congenital anomalies among live-born infants is generally considered to be 2%-4%<sup>56</sup>. Prevalence of major congenital anomalies (including chromosomal anomalies) recorded by EUROCAT was 2.4% (2003-2007)<sup>57</sup>. All congenital anomalies will be classified and analysed according to the EUROCAT Classification (EUROCAT Subgroups of Congenital Anomalies). This includes diagnosis in the Q chapter of ICD-10 (and equivalent ICD-9 codes), but excludes a recognized list of minor anomalies, if isolated, as specified by EUROCAT. As recommended by European regulatory guidelines (GVP III)<sup>56</sup> and EUROCAT, congenital anomalies should be considered in both live and non-live births (e.g. TOPFA, stillbirths).

As recommended by these guidelines<sup>56</sup> we will use the following definitions:

$$\text{Live birth prevalence rate of MCA} = \frac{\text{Number of cases among live born infants}}{\text{Total number of live born infants}} * 1000$$

$$\text{Total prevalence rate of MCA} = \frac{\text{Number of cases among live, stillborn infants and TOPFA}}{\text{Total number of (live + non-live) infants}} * 1000$$

The numerator is the number of cases of the subject of interest. The denominator is the population from which the numerator comes.

#### *Analyses on organ class level:*

Besides studying combined MCA - if statistical power permits - congenital anomalies will be studied stratified by organ class (e.g. cardiovascular, oral clefts, etc.). EUROCAT subgroups will be used:

Cardiac malformations; Nervous system malformations; Eye malformations; Ear, face and neck malformations; Congenital heart defects; Respiratory malformations; Oro-facial clefts; Digestive system malformations; Abdominal wall defects; Urinary defects; Genital malformations; Limb malformations; Other anomalies/syndromes; Chromosomal defects.

We will provide estimates for the main subgroups of congenital anomalies to facilitate meta-analyses and increased study power. Congenital anomalies will be considered in both live and non-live births (i.e. TOPFAs and stillbirths), when available in the data source.

Only analyses for which we have sufficient a priori power (80%) to detect at least a 50% increase in the risk of the outcome in question will be performed, and analyses for groups of rare congenital anomalies will be essentially descriptive.

#### *Secondary outcomes:*

Immediate adverse pregnancy outcomes include a range of key outcomes routinely recorded in medical charts at birth and notifiable by law to national or regional birth registries in Europe. For this study, we will include the following immediate adverse pregnancy outcomes:

- non-live birth (y/n)
- preterm birth (y/n), GA (cont. in days)
- low birth weight (y/n), BW (cont. in gram, z-scores)
- small for gestational age/ intrauterine growth restriction

Definitions can be found in **Appendix VI** Pregnancy & neonatal outcome definitions

### **8.3.5 Covariates**

Covariates are chosen based on the literature review and evaluated using DAGs<sup>58</sup>. DAG is provided in appendix VIII. Each data source being analysed within this project has a varied list of potential covariates. Potential covariates/confounders may include:

- **Demographic characteristics:** geographic region (Germany, Finland, France, Tuscany, Emilia Romagna, Norway, Valencian Region/Spain, Wales/UK).
- **Maternal characteristics at start of pregnancy:** will be identified on the basis of information in the medical birth registry, and/or diagnosis codes recorded in patients' hospital discharge records, ATC codes in prescription registries depending on the availability in each of the DAPs, and include:
  - Maternal age at start of pregnancy
  - Parity
  - Year of LMP
  - BMI (e.g. obesity in the one year before pregnancy (BMI $\geq$ 30))

#### **Health related factors:**

- Reproductive history (e.g. previous spontaneous abortions, malformations, stillbirths)
- Comorbidities in the one year before pregnancy (e.g., depression, epilepsy)
- Comedications (disease specific and for NVP)

Availability and completeness of these variables will vary across data bases. List of covariates available according to each DAP in Appendix VII.

### **8.4. Data sources**

Data sources are population-based health care datasets (Table 1) that will be linked at person level.

Together they capture data on a source population of approximately 5 million pregnancies.

This project will utilize data from different countries with geographic spread across Europe using the ConcePTION platform and ConcePTION Common data model. Databases have been selected based upon availability of variables and data quality using the IMI ConcePTION FAIR Data Catalogue. A total of 9 data sources have been selected (See the list of all DAP in Appendix I):

- Germany: GePaRD (20% population sample)
- Finland: linkage of several registries (Nationwide)
- France: EFEMERIS (Haute-Garonne)
- Italy: ARS (Tuscany)
- Italy: Healthcare administrative (Emilia Romagna)
- Norway: linkage of several registries (Nationwide)
- Spain: FISABIO (Valencian Region)
- UK: CPRD (8.5% sample of GP practices in the UK (volunteer and paid))
- UK: SAIL databank (Wales)

Data sources from other countries (e.g. the Swedish and Scottish registries), may be included, pending on results from the Data characterization (WP7).

**A description of data sources participating in this project is given below (alphabetical order).**

#### ***Germany: GePaRD***

GePaRD is based on claims data from four statutory health insurance providers in Germany and currently includes information on approximately 25 million persons who have been insured with one of the participating providers since 2004 or later. Per data year, there is information on approximately 20% of the general population and all geographical regions of Germany are represented. In addition to demographic data, GePaRD contains information on dispensations of reimbursable prescription drugs as well as outpatient (i.e., from general practitioners and specialists) and inpatient services and diagnoses. **The Leibniz Institute for Prevention Research and Epidemiology – BIPS** will be Data Access Provider for the GePaRD data. GePaRD data have been used for vaccine safety studies and pregnancy studies. GePaRD is listed under the ENCePP resources database.

#### ***Finland: linkage of several registries (Nationwide)***

Universal health insurance coverage is accessible for all citizens and permanent residents in the country. Municipalities (currently around 200) are responsible for arranging and funding health care. Health services are divided into primary health care and specialized medical care. The data that THL provides access to is the majority of healthcare registries covering the whole population of Finland (around 5.6 million inhabitants). The core data of the Drugs and Pregnancy project includes data from Medical Birth Register, Register of Congenital Malformations and Register of Induced Abortions from 1996 onwards. Drugs and Pregnancy Database also includes following registries maintained by the Kela: Special refund codes and diagnoses three months before pregnancy to three months following delivery or abortion and drug purchases and reimbursements from three months before pregnancy to three months following delivery or abortion also 1996 onwards. The core data of the Drugs and Pregnancy currently includes all

pregnancies ending in delivery or induced abortion in 1996-2018 the total amount being around 1,5 million pregnancies. Additional data sources maintained or accessed by THL and mapped to ConcePTION CDM are Care Register for Health Care (HILMO), Register of Primary Health Care visits (Avohilmo), Finnish Cancer Registry and Cause of Death Registry for women diagnosed with cancer and for children up to one year of age. Data collection is mandatory by law and does not require informed consent from the recorded subjects. Data is stored on an individual level and can be linked by the personal identification number assigned to all citizens and permanent residents in Finland at birth or upon immigration.

#### ***France: EFEMERIS (Haute-Garonne)***

In 2005, EFEMERIS cohort was set up with the aim to evaluate the risks of medicine intake during pregnancy on fetus/newborn. EFEMERIS merges four databases: 1- the French health insurance database (drugs prescribed and reimbursed 3 months before and during pregnancy), 2- the mother and child protection center database (data on newborn health at 8 days, 9 months and 24 months), 3- the multidisciplinary prenatal diagnostic center database (data on TOPFAs), 4- data from the IT coding system of the hospital (PMSI) (hospital discharge data).

EFEMERIS is a cohort in general population that records anonymous data concerning more than 140,000 pregnancy outcomes, who delivered in Haute-Garonne between July 1<sup>st</sup>, 2004 and December 31<sup>th</sup>, 2018. EFEMERIS provides reliable data on period of exposure to medications, pregnancy terminations, and follow-up of babies until 2 years of age. The database is incremented each year with data on around 10 000 new pregnancies and their outcomes.

#### ***Italy: ARS database (Tuscany)***

The Italian National Healthcare System is organized at regional level: the national government sets standards of assistance and a tax-based funding for each region, and regional governments are responsible to provide to all their inhabitants. Tuscany is an Italian region, with around 3.6 million inhabitants. **The Agenzia Regionale di Sanita' della Toscana (ARS)** is a research institute of the Tuscany Region. The ARS database comprises all information that are collected by the Tuscany Region to account for the healthcare delivered to its inhabitants. Moreover, ARS collects data from regional initiatives. All the data in the ARS data source can be linked with each other at the individual level, through a pseudo-anonymous identifier. The ARS database routinely collects primary care and secondary care dispensing of drugs for community or outpatient use, and is able to link them at the individual level with hospital admissions, admissions to emergency care, records of exemptions from copayment, utilisation of diagnostic tests and procedures, causes of death, mental health services registry, birth registry, spontaneous abortion registry, induced terminations registry. Mother-child linkage is possible through the birth registry.

#### ***Italy: IMER Healthcare administrative (Emilia Romagna)***

The core data that Region Emilia Romagna has access to is the healthcare administrative database of the population of the Italian region of Emilia Romagna, that amounts to around 4.4 million inhabitants. UNIFE and Region Emilia Romagna collaborate for drug exposure analysis and to enrich the regional congenital anomaly registry and the rare disease registry (IMER).

Emilia Romagna Region use their DB for institutional purposes: economic evaluation, epidemiology and pharmacoepidemiology.

As is the case in every Italian region, the reason for entering the database is the registration with a primary care physician, which may happen upon immigration or upon birth; the reason for exiting the database is emigration or death. Emilia Romagna will map to the ConcePTION CDM the main columns of the most pertinent administrative databases (inhabitant registry, drug dispensations from community pharmacies and from hospital pharmacies, hospital discharge records, emergency admissions, outpatient services, exemptions from copayment, mental health services), and of the following additional registries: birth registry, death registry. UNIFE is Data access provider for Regione Emilia Romagna.

***Norwegian data: Linkage of nationwide registries University of Oslo***

The core data that UIO has access to is the health care administrative databases of the entire Norwegian population, which amounts to approximately 5.3 million inhabitants. Norway has a universal public health care system, consisting of primary health care services and specialist health care services. Many population-based health registries were established in the 1960s, with use of unique personal identifiers facilitating linkage between registries. The mandatory national health registries were established to maintain national functions. They are used for health analysis, health statistics, improving the quality of healthcare, research, administration and emergency preparedness. In Norway, the whole population is covered by the mandatory national health registries, i.e. the Medical Birth Registry, the National Patient Register (admission records to hospitals and specialist health care), and the National Prescription Registry (records on all prescriptions dispensed in Norway since 2004). The most commonly used registries are administrated by The Norwegian Institute of Public Health, The Norwegian Directorate of Health and Statistics Norway. Information about all Norwegian National Registries can be found here: [www.fhi.no/en/more/access-to-data/about-the-national-health-registries2/](http://www.fhi.no/en/more/access-to-data/about-the-national-health-registries2/) **University of Oslo** is Data Access Provider for the linked Norwegian registries in this project.

***Spain: FISABIO, Área de Investigación en Enfermedades Raras.***

**FISABIO integrates, as described in WP-7:** Prescription and dispensations dataset (GAIA), Morbidity through Hospital discharges database (CMBD), Mortality Registry (RMCV), Birth Registry (MetaB) and Congenital anomaly Registry (RPAC-CV).

A set of multiple, public, population-wide electronic databases for the Valencian Region will be used. Valencian Region is the fourth most populated Spanish region, with ≈5 million inhabitants and an annual birth cohort of 50 000 newborns, representing 10.7% of the Spanish population and around 1% of the European population. Together, all the included databases provide exhaustive longitudinal information including sociodemographic and administrative data (sex, age, nationality, etc.), clinical (diagnoses, procedures, etc.), drugs information (prescription, dispensation) and healthcare utilization data from hospital. It also includes a set of associated population databases and registries of significant care areas such as cancer, rare diseases, congenital anomalies and also public health databases from the population screening programmes. All electronic health systems use the ICD-9-CM and/or the ICD-10 and its derivatives. All the information in the databases can be linked at the individual level through a single personal identification code, the health number. The databases were initiated at different moments in time, but it is recommended to use them since 2010 (due to high quality improvements) until the last year available (it could differ between databases).

### ***United Kingdom: CPRD***

The Clinical Practice Research Datalink (CPRD) from the UK collates the computerized medical records of general practitioners (GPs) in the UK who act as the gatekeepers of healthcare and maintain patients' life-long electronic health records. As such they are responsible for primary healthcare and specialist referrals, and they also store information stemming from specialist referrals, and hospitalizations. GPs act as the first point of contact for any non-emergency health-related issues, which may then be managed within primary care and/or referred to secondary care as necessary. Secondary care teams also feedback information to GPs about their patients, including key diagnoses. The data recorded in the CPRD include demographic information, prescription details, clinical events, preventive care, specialist referrals, hospital admissions, and major outcomes, including death. The majority of the data are coded in Read Codes. Validation of data with original records (specialist letters) is also available.

The dataset is generalizable to the UK population based upon age, sex, socioeconomic class and national geographic coverage when GOLD & Aurum versions are used.

There are currently approximately 42 million patients (acceptable for research purposes) – of which 13 million are active (still alive and registered with the GP practice) – in approximately 1,700 practices (<https://cprd.com/Data>). Data include demographics, all GP/healthcare professional consultations (phone, letter, email, in surgery, at home), diagnoses and symptoms, laboratory test results, treatments, including all prescriptions, all data referrals to other care, hospital discharge summary (date and Read codes), hospital clinic summary, preventive treatment and immunizations, death (date and cause). For a proportion of the CPRD panel practices (>80%), the GPs have agreed to permit CPRD to link at patient level to the Hospital Episode Statistics (HES) data. CPRD is listed under the ENCePP resources database, access will be provided by **GSK**.

### ***United Kingdom: Wales, Swansea University***

The Secure Anonymised Information Linkage (SAIL) Databank sources, accesses, links and analyses prospectively collected routine health and population data, within a governed infrastructure that is safe and secure. All datasets are anonymised and encrypted by a third party, and returned to SAIL for linkage. Data are held on 5,400,000 people, since 1998. Data are available within 3 months of events. SAIL holds linkable, anonymised national datasets, including: Accident and emergency care from 2009, Critical care from 2016, Congenital Anomaly Register and Information Service for Wales (CARIS), In-patient and out-patient PEDW records, Maternity dataset from 2015 for additional data on childbirth, National Community Child Health Database (NCCHD, includes gestation (ultrasound), birth centiles, childbirth, infant feeding, developmental screening and vaccinations), National Pupil Database Wales (education attainment to 16), ONS births and deaths (compulsory registration), Primary care data (including all prescriptions and diagnoses) from ~75% of Welsh GP practices. **Swansea University** will be Data Access Provider for the SAIL data in this project.

## **8.5. Study size**

Overall, the source population will give rise to approximately 5 million pregnancies (Table 1). The prevalence of migraine in among women of childbearing age was assumed to be 10 per

100 in countries included in this study. The prevalence of triptan use is assumed to be 15% among women with migraine (conservative estimates). Given these diseases and triptan medication use prevalences, we estimate to include 500,000 pregnancies among women with migraine, including 75,000 triptan exposed pregnancies. The number of pregnancies expected within each data source has been estimated by the data source providers (DAPs).

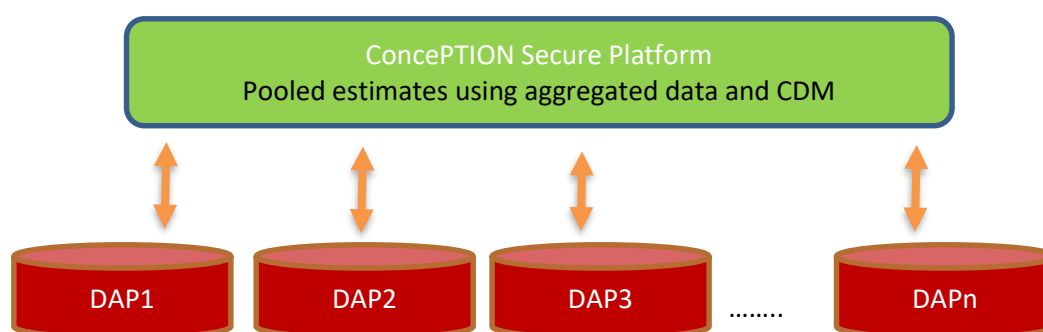
Per objective, the size of the study population will differ due to restrictions and matching that will deal with confounding.

## 8.6. Data management

Data management and analysis will be done in each individual country/region using the ConcePTION CDM. Data will remain in the country of origin, and only aggregated results will be delivered to the ConcePTION platform.

Each DAP will perform the following tasks:

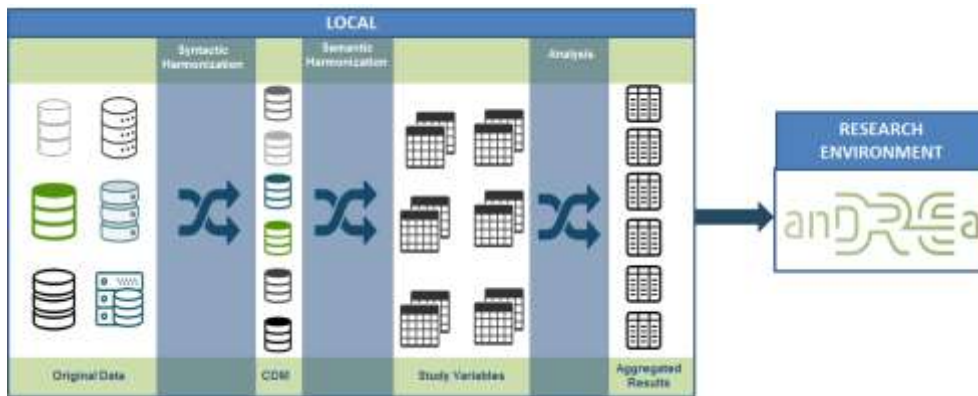
- 1) Obtain required ethical and legal permissions to use the data in this project
- 2) Extract and transform the data locally into ConcePTION CDM
- 3) Check and run scripts distributed to the DAP by the ConcePTION coordinating centre
- 4) Run standard scripts to assess data quality (data characterization)
- 5) Definition and operationalization of study variables for each DAP
- 6) Run the scripts for this specific study
- 7) Send aggregated results to the remote ConcePTION Secure Platform.



Data sources covering several million pregnancies

**Figure 1: Data flow in ConcePTION. DAP: Data access provider. CDM: Common data model**

The process for the data management plan is presented in **Figure 2**<sup>59</sup>. The data pipeline has been further specified in theoretical terms by Gini et al.<sup>60</sup> and further improved in the IMI-ConcePTION project ([www.imi-conception.eu/](http://www.imi-conception.eu/) Deliverable D7.5).



**Figure 2 Data management plan**

First, to harmonize the structure of the data sets held by each partner, a shared syntactic foundation is utilized. Syntactic foundation is described in **Annex 3** and refers to the syntactically harmonized CDM. In this common data model, data is represented in a common structure, but the content of the data remains in their original format, and the context where the data was originated (e.g. whether a code was collected during inpatient care, or during a primary care visit) is captured along with the data itself. The extraction, transform, and load (ETL) design will be shared on a searchable FAIR (Findable, Accessible, Interoperable, and Reusable) catalogue. The ConcePTION FAIR data catalogue is a metadata management tool designed to contain searchable metadata describing organizations that can provide access to specific data sources. Data quality checks will be conducted to assess the successfulness of the ETL process, to evaluate the completeness of the data sets as well as look into the logical relationship and integrity of the study variables (see **section 9.8 Quality Control**).

Second, to reconcile differences across terminologies, a shared semantic foundation is built for the definition of events under study by collecting relevant concepts in a structured fashion using a standardized event definition template. Based on the relevant diagnostic medical codes and keywords, as well as other relevant concepts (e.g. medications), one or more algorithms will be constructed to operationalize the identification and measurement of each event. Typically, a sensitive, or broad, set of codes and one specific, or narrow, set of codes, will be combined with the context where the medical codes are captured (e.g., inpatient care, emergency care, primary care), in a standardised yet flexible approach called *component strategy*.

These algorithms may differ per database, as the components that go into the study variable may differ<sup>61,62</sup>. Although external validation study will be done for this project, as there are no resources for this within the budget of the EMA tender, some validity of the data will be evaluated using comparisons with expected prevalence rates and expected associated risk factors. Wherever possible, the event definition sheet will specify prior validated algorithms and codes. Scripts for semantic harmonization will be developed in R, distributed to data access providers for local deployment, and shared on the catalogue. The impact of choices of different algorithms will be assessed quantitatively. This will result in a set of study variables which are both semantically and syntactically harmonized. An attempt at estimating validation indices for outcomes will be performed leveraging on the component strategy]



Third, following conversion to harmonized study variable sets, R scripts for generation of analytical datasets will be distributed to data access providers for local deployment.

The output of these scripts will then be uploaded to the Digital Research Environment (DRE) for aggregated analysis and visualization. The DRE is made available through UMCU ([www.andrea-consortium.org](http://www.andrea-consortium.org)). The DRE is a cloud based, globally available research environment where data is stored and organized securely and where researchers can collaborate ([www.andrea-consortium.org/azure-dre](http://www.andrea-consortium.org/azure-dre)).

### **8.6.1 Software and Hardware**

All final statistical computations will be performed on the DRE using R and/or STATA or SAS. Data access providers will have access to the workspace for verification of the scripts.

### **8.6.2 Storage**

Aggregated results, ETL specifications, and a repository of study scripts will be stored in the DRE.

### **8.6.3 Access**

Within the DRE, each project-specific area consists of a separate, secure folder, called a 'workspace'.

A workspace is a file system similar to a file system on a standard PC. Each workspace is completely secure, so researchers are in full control of their data. Each workspace has its own list of users, which can be managed by its administrators.

The architecture of the DRE allows researchers to use a solution within the boundaries of data management rules and regulations. Although General Data Protection Regulation (GDPR) and Good (Clinical) Research Practice still rely on researchers, the DRE offers tools to more easily control and monitor which activities take place within projects.

All researchers who need access to DRE are granted access to study-specific secure workspaces. Access to this workspace is only possible with double authentication using an ID and password together with the user's mobile phone for authentication. Access to workspaces within the anDREa research platform is granted at two levels: owner and researcher.

Upload of files is possible for all researchers with access to the workspace within the DRE. Download of files is only possible after requesting and receiving permission from the 'owner' of the workspace.

### **8.6.4 Archiving and record retention**

The final study aggregated results sets and statistical programs will be archived and stored on the DRE Sharepoint. The validation of the quality control (QC) of the statistical analysis will be documented. The final study protocol and possible amendments, the final statistical report, statistical programs and output files will be archived on a specific and secured drive centrally.

Documents that individually and collectively permit evaluation of the conduct of a study and the

quality of the data produced will be retained for a period of 5 years in accordance with GPP guidelines. These documents could be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement between study partners. It is the responsibility of the principal investigator to inform the other investigators/institutions as to when these documents no longer need to be retained. Study records or documents may also include the analyses files, syntaxes (usually stored at the site of the database), ETL specifications, and output of data quality checks.

## **8.7. Data analysis**

Analyses will be carried out through ConcePTION, which will work according to a distributed network approach, with a common data model and common statistical analysis plan. Data will remain local, and only aggregated results or effect estimates will be submitted for pooling. Statistical analyses will be carried out in two steps. Initial pilot modelling of the SAP will be carried out on the Norwegian linked registry data using STATA (UOSL), then scripts will be re-coded in R (UMUC), and sent to all DAPs through the ConcePTION task management system. Meta-analyses will be used to combine the aggregate data obtained from each DAP (SGUL).

### **8.7.1 Definitions and categorization of key variables**

Age groups will be defined based upon age at the start date of the pregnancy. Primary grouping will follow

- 15-24 years of age;
- 25-39 years of age;
- 40-55 years of age

#### Pregnancy start and end dates:

Pregnancy start and end dates will be assessed from medical birth registers for those data sources with access to a registry, while existing algorithms for defining start and end of pregnancy will be utilized in those data sources with an existing algorithm, novel algorithms will be developed if they do not exist to limit bias. Start of pregnancy is date of last menstrual period (LMP), end of pregnancy is the date of delivery or abortion (elective/spontaneous).

**Table Identification of pregnancies in data sources**

Country	Name Data source	Birth registry data	Data banks used to identify pregnancy start and end	Explanation
Germany	GePaRD	Yes	*	*
Finland	Finish registries	Yes	*	*
France	EFEMERIS	Yes	*	*
Italy	ARS	Yes	The CAP data bank records any delivery occurred in Tuscan hospitals of a live child, or a still birth with number gestational weeks longer or equal to 22. Recording is compulsory by national	Pregnancy end: Date of delivery Pregnancy start = Date of delivery – gestational length in weeks. Gestational length is estimated based on ultrasound examination.

Country	Name Data source	Birth registry data	Data banks used to identify pregnancy start and end	Explanation
			law and is sent yearly to the Ministry of Health.	
Italy	IMER, Healthcare administrative	Yes	*	*
Norway	Norwegian registries	Yes	The Norwegian Medical Birth Registry (MBRN). In MBRN, a record is created for any pregnancy of gestational age 12 weeks or beyond (live, miscarriage, elective abortion, stillbirth), at delivery.	A prompt in the MBRN. Start of pregnancy is date of last menstrual period (LMP). End of pregnancy is the date of delivery or abortion (elective/spontaneous). Pregnancy end: Date of delivery. Pregnancy start = Date of delivery – gestational length in days. Gestational length is estimated based on ultrasound examination.
Spain-Valencian Region	Rare Diseases Research Unit from FISABIO	Yes	*	*
UK	CPRD	No	*	*
Wales, UK	SAIL	Yes	*	*

\*Information not filled in by the DAP.

The period of pregnancy will be divided into trimesters. Across all analyses, the following definition of timing in pregnancy will be used:

Trimesters will be defined as follow (ACOG definition):

- Trimester 1: from the Last Menstrual Period (LMP) to day 97 after LMP;
- Trimester 2: from day 98 after LMP to day 195 after LMP;
- Trimester 3: from day 196 after LMP onwards.

The first 20 weeks of pregnancy: LMP to LMP+140 days

LMP: The first day of the LMP is estimated by subtracting the gestational age at delivery from the pregnancy end date. Due date, and thus, gestational length and LMP, is estimated by ultrasound, and only if unavailable, by the woman's recall of LMP.

### **8.7.2 Descriptive analysis: Part 1 (Medication Utilisation and Event/Outcome Definition)**

Maternal baseline characteristics (e.g. age, parity), at-risk medical conditions and pregnancy history will be summarized for each data source and for each cohort using descriptive statistics.

- Frequency tables including numbers and proportions will be generated for categorical variables (e.g. maternal age in categories, and at-risk medical conditions).
- Mean, standard error, median and interquartiles will be provided for continuous variables (e.g. maternal age).

## **Part 1. Medication Utilisation Definition**

The change in prevalence of triptans / each medication class used to treat migraine over the course of a pregnancy (during at least the 3 months prior to, during, and during the first 3 months after pregnancy if available in the datasource) and during pregnancy (1st, 2nd or 3rd trimester/first half vs. second half) will be described according to the data sources.

Medications, identified by outpatient prescription/dispensing codes will be evaluated by therapeutic classes (ATC-level 2) and if possible, by individual drugs (ATC-level 5).

The numerator will be the number of pregnancies having one or more dispensing/prescription (date of prescription/dispensing) of the specific medication within the given time-period. The denominator will be the number of pregnancies in that time period. The pregnancy will be identified and classified based on LMP date, which lies in a specific calendar year; this is done to avoid that pregnancies spanning over two years are counted twice in the proportion calculations.

We will consider the use of single medications (e.g. by calculating cumulative DDD, top 10% users) and more complex medication regimens (e.g. migraine polypharmacy, total number of migraine medication prescriptions). We will use data visualisation tools to describe patterns of drug utilisation throughout pregnancy.

We will describe discontinuations in pregnancy.

We will define several prescription pattern groups in which the probability that the woman actually took the prescribed and dispensed migraine medication may vary:

- Only one prescription during the different trimesters of gestation
- At least two prescriptions during pregnancy
- Medication overuse

We will use prior validation parameters about sensitivity and specificity of dispensed triptan prescription during pregnancy and by trimester<sup>17</sup> to generate hypothesis about those parameters in the different patterns groups.

**Part 1 Events/Migraine disease: will focus on descriptive analysis of prevalence and incidence measures.**

We will investigate the reporting and identification of study specific outcomes and covariates across multiple datasets, and interpret the findings in the context of the literature and expert review. This information will be used to discuss potential event/outcome misclassification, make recommendations about the inclusion of specific outcomes or covariates from data sources and to inform the analysis in the medication safety studies.

### ***8.7.3 Analysis of exposure misclassification***

We will address migraine medications exposure misclassification using probabilistic bias analysis methods.<sup>63–65</sup> Probabilistic bias analyses are sensitivity analyses that can assess the magnitude,

direction, and uncertainty of bias through the simulation of bias parameters.

We will use the sensitivity, specificity, PPV (positive predictive value) and NPV (negative predictive value) of dispensed triptan prescription during pregnancy according to the trimester and subsequently calculate the expected number of exposed women. We also will vary the sensitivity and specificity of triptan exposure during pregnancy according to the prescription pattern groups defined in part 1: a) Only one prescription during the different trimesters of gestation, b) At least two prescriptions during pregnancy, c) Medication overuse, d) Last month of gestation) as exposure misclassification may be different according to these utilization patterns. Then, we will generate probability distribution parameters (a simulation interval using for instance triangular, Beta and logistic regression; most commonly summarized as a 95% simulation interval containing bias-adjusted estimates with their 95% confidence intervals) for each group. We will then construct a new dataset with imputation of the values of exposure to triptans based on those parameters.

### **8.7.4 Analytical approaches - Part 2. (Medication Safety)**

In part 2, primary analyses will be carried out using multivariable linear regression, modified Poisson regression, and Cox proportional hazards regression (survival analysis) as appropriate, using robust standard errors. Advanced confounder adjustment methods, including propensity score methods and marginal structural models, will be used where appropriate to mitigate measured time-fixed and time-varying confounding.

First, unadjusted regression models between the exposures and outcomes of interest will be conducted, then a range of adjusted models will run in order to account for confounders and effect modifiers. The variables adjusted for in each model will depend on the data availability and data quality of the covariates within each data source.

For the meta-analysis of effects, effect estimates will be pooled using the random-effects model. The meta-analysis on aggregate data will allow for adjustment for country-optimized covariates (See Appendix IX: Meta analytic techniques for use in ConcePTION DPs).

Effect estimates will be presented both as relative and absolute risk estimates with CI describing the precision of the estimate (95% or 99% CI). For significant findings, the number of additional cases per 1000 (or 100 000) pregnancies (number needed to harm (NNH)) will be calculated.

We will stratify the population based on the migraine severity group at baseline (defined in the migraine-event protocol) and the type of migraine (with or without aura) at baseline. Adverse pregnancy outcomes will be compared among the different comparison groups (triptans continuers vs discontinuers, and vs unexposed with migraine comparison group) within each stratification group in order to disentangle the impact of the medication from that of the underlying illness.

### **8.7.5 Sensitivity analyses**

Several sensitivity analyses will be performed to assess the robustness of results:

- Varying the algorithm assessing migraine severity in women in order to consider the

recommendation in the different countries.

- As sumatriptan injection is also used to treat cluster headache, an analysis will be performed in databases that have diagnostic codes to describe the prevalence of cluster headache among women who are prescribed sumatriptan injection during pregnancy.
- Restrict to term pregnancies
- Restrict to single pregnancy for women participating more than once
- Restrict of congenital anomalies without including TOPFAs.

#### **8.7.6 Handling of missing data**

Patterns of missingness will be explored and handled as appropriate<sup>66</sup> in the following manner: Missing data within each covariate and each outcome will be reviewed descriptively using tabulations of missingness. For each covariate, missingness will be tabulated by outcome, exposure and disease status. For each outcome, missingness will be tabulated by covariate and disease status. This information will then be used to identify the most appropriate means of handling missing data within each model. Multivariable models will handle missing covariate data either by imputing the mean/mode of each covariate, or by using a complete case analysis. Univariable models will only be run using complete case analyses as the purpose of these models is descriptive. Multiple imputation will most likely not be used within this project as the sample sizes within each country will not be sufficient to correctly fit the required predictive models. If supported by ConcePTION tools, we will perform multiple imputation by chained equations (MICE) for missing values in covariates (if enough variables predictive of missing values are included in the imputation model). If not, we will conduct complete-case analysis. The conclusion so far from SCAN-AED (data from Norway, Sweden, Finland, Iceland and Denmark) is that some covariates from the birth registries are not missing at random (e.g. smoking, BMI).

#### **8.7.7. Combining results**

Results from both the drug utilisation and drug safety studies will be compared across data sources/countries if appropriate. Only countries with similar data availability will be compared. For the drug safety studies, available data will once again be considered, however, further consideration will also be required as to how the outcomes are defined in each country.

To combine aggregated results from across countries accurately for migraine, suitable meta-analytic techniques for sparse data must be employed. Adjustments to common Meta-analytic techniques such as the Mantel-Haenszel method<sup>67</sup> or the DerSimonian Laird random effects method<sup>68</sup> can be applied to help reduce the bias in detecting heterogeneity between treatment effects and the bias in the treatment effect itself<sup>69</sup>. Therefore, due to the heterogeneous nature of combine results across countries, this project will utilise an adjustment to the DSL method known as a simple average estimation method<sup>69</sup>.

### **8.8. Quality control**

The studies will be conducted in line with the ENCePP Code of Conduct for scientific independence and transparency, and the FAIR (Findable, Accessible, Interoperable, Reusable) principles of the ConcePTION project.

Each data access provider will be responsible for the extraction, transformation, and loading of their original data to the ConcePTION CDM. Standardized scripts will be written by the group of

statisticians in R for data characterization, to run against data in the ConcePTION common data model. R scripts plus instructions will be sent to participating DAPs using a task management system.

The DAP is responsible for converting data into the CDM using their preferred software and subsequently running the provided R script against the CDM-converted data. The results of the R-script will be submitted to a computing platform that can be accessed remotely by DAPs and ConcePTION partners and participating DAPs using authentication. Access to each DAP's results on the platform will be limited to the data access provider, WP1 public partner statisticians, and WP7 public partner statisticians.

Data quality will be assessed according to a clear framework based on the ADVANCE database characterization process<sup>70</sup>, the United States FDA Sentinel System data quality indicators<sup>71</sup> the Observational Health Data Sciences and Informatics (OHDSI) data quality dashboard (in development), and EUROCAT indicators for population-based healthcare data sources<sup>72</sup>. The data quality and characterization checks described below will take place in collaboration with partners. All data will remain local and only summary measures described below will be inspected in collaboration with WP7 partners and the task force for data transformation. This process will proceed iteratively in collaboration with each DAP until consensus on fitness for purpose has been reached between WP7 and the DAP, the result of this consensus process and some core results will be made available on the catalogue in a private area for inspection by investigators and DAPs. For all indicators and characterization output resulting in a cell count less than 5, counts will not be reported and will be replaced with "<5" programmatically.

All data sources with data in the EUROCAT CDM will be characterized according to the EUROCAT data quality indicators (<https://eu-rd-platform.jrc.ec.europa.eu/sites/default/files/DQI-List-of-Data-Quality-Indicators-since-2012.pdf>).

Level 1 data checks review the completeness and content of each variable in each table of the ConcePTION CDM to ensure that the required variables contain data and conform to the formats specified by the CDM specifications (e.g., data types, variable lengths, formats, acceptable values, etc.).

This is a check conducted in collaboration with DAPs to verify that the extract, transform, and load (ETL) procedure to convert from source data to the ConcePTION CDM has been completed as expected. Formats for all values will be assessed and compared to a list of acceptable formats. Frequency tables of variables with finite allowable values will be created to identify unacceptable values. Distributions of days and months of birth to assess any rounding will be constructed.

Level 2 data checks assess the logical relationship and integrity of data values within a variable or between two or more variables within and between tables. Examples of this type of check include: parents younger than 12 years old, observations occurring after a recorded death date, event dates outside observations periods etc. In this check, we will assess records occurring outside of recorded person time (i.e. before birth, after death, or outside of recorded observation periods).

Level 1 and 2 checks will be repeated until no errors are reported. Following completion of level 1 and 2 checks, WP7 will review results with DAPs and assess any detected errors.

## **8.9. Limitations of the research methods**

### **1. Secondary data**

One of the key limitations of the planned research is inherent to secondary use of data studies (SUD): there is no control on what data are collected and how they are collected and how accurate the self-reported data are (e.g. smoking); particularly, there is no control over biases and not all biases in the data might be known<sup>73</sup>. Knowledge on how the data were collected and comparisons between analyses of data from different sources can help to identify and evaluate such potential biases.

### **2. Diagnosis information**

Diagnosis algorithms are to be investigated during the ConcePTION platform data characterisation. The algorithms being considered for migraine comprise of either ICD-9/ICD-10 diagnostic codes or ICD-9/ICD-10 diagnosis codes and prescription records. As diagnosis codes and prescription data can be identified from a range of locations (Primary care, outpatient and hospital) countries which do not have access to certain areas of their health care system are likely to miss data containing diagnostic codes and maybe even the diagnosis itself. To account for this, during the identification of algorithms, each country will be reviewed separately and a range of algorithms will be considered and evaluated. At present, for long-term conditions, the length of time a woman needs to be in a data source to ensure her long-term condition is recorded is uncertain and will be evaluated. In addition, disease severity is an important confounder that is not likely to be accurately assessed when using the data sources.

### **3. Exposure information:**

Medications prescribed/dispensed are assumed to be taken. Moreover, information on when a woman took the medication if data is based on prescribing or dispensing, will be lacking. This gives a high risk of exposure misclassification. This project will address this by estimating the impact of exposure misclassification of triptan use on exposure-outcome associations, under a range of scenarios.

Information on patient-level data used in hospitals and other institutions will not be included in the data from prescription databases. This will create observation gaps and therefore there may be some cases classed as unexposed, who are actually treated in hospitals. However, most patients with migraine will not be admitted to hospital due to the disease. Hospital admission for status migrainous is expected, but the duration of admittance is short (1-3 days), and will probably vary by year and country and hospital region. Some treatments given in hospitals (e.g Botox treatments), may be missed.

**4. Over The Counter (OTC) medication:** Information about OTC medication is not recorded on an individual basis in the data sources, if they are not prescribed. Self-medication of mild analgesics (paracetamol) in pregnancy is expected to be high, self-medication with NSAIDs is expected to be lower as they are not recommended in pregnancy.

**5. Missing data/covariate information:** Information on maternal alcohol use or other substance abuse will not be available in this study, but it is a potential confounding factor. Heavy alcohol use may affect the risk of spontaneous abortion, and also other adverse pregnancy outcomes. Moreover, other covariate may have missing data, such as SES status, BMI.



6. Study power: Another challenge is the study power, and this limitation is recognized: even in a source population of over 5 million pregnancies, we will have limited power to study rare outcomes among pregnant women with migraine and the effect of migraine medications. For rare outcomes specifically related to severe migraine, however, we will have challenges, including sharing data with few cases/small counts. We expect to encounter zero or very few exposures for certain medications in certain countries resulting in no occurrences of specific outcomes for these medications.

Only analyses for which we have high a priori power (80%) to detect a two-fold increase in the risk of outcome in question will be performed, and analyses for very rare outcome will be essentially descriptive.

In the power calculations, the background prevalence rates of serious adverse pregnancy outcomes presented below was used.

Child	Prevalence (%)	Mother	Prevalence (%)
Preterm birth	6 - 10	Hypertensive disorders	5-10
Low birth weight	5	Gestational diabetes (GD)	5
Major congenital anomalies	2 - 4*	Preeclampsia	3
Cardiac anomaly	1	Stroke (any type)	0.1 - 0.2 per 1000

Using the prevalence of outcomes above and sample size calculations below, we will have the following: To detect a 50% increased risk for cardiac anomaly anomalies with 80% power and type I error rate of 0.05, we would require a sample size of around 360,000 pregnant women (see table below – examples in red). To assess maternal hypertensive disorders, a sample of around 32,000 pregnant women will be needed.

Cohort study sample sizes – 80% study power and type I error rate of 0.05

Study sample size when 1% of the study population are using a migraine medication

		Baseline prevalence of Outcome				
		0.01%	0.1%	1%	5%	10%
Risk Ratio	1.1	816,484,080	81,572,607	8,081,460	1,548,911	732,340
	1.2	209,883,964	20,968,283	2,076,714	397,462	187,553
	1.5	36,211,891	3,617,363	357,910	68,179	31,960
	2	10,065,884	1,005,338	99,283	18,742	8,672
	5	946,776	94,426	9,191	1,609	655

## 7. Multiplicity

One consequence of conducting such a broad and wide-reaching exploratory study is having to deal with multiplicity. The general principle around multiplicity is that if you test for enough associations then some will come back significant even if no true association exists. This is not an issue we can directly avoid; however, all interpretations will be treated with great caution and it needs to be emphasised that these results will only highlight possible areas of concern and not provide conclusive evidence that pregnancy outcomes are caused by a medication.

## **9. Protection of human subjects**

### **- Regulatory and Ethical Compliance**

This study is non-interventional, based on secondary use of data. Therefore, the reporting of suspected adverse reactions in the form of individual case safety reports (ICSRs) is not required. Reports of adverse events/reactions should be summarized as part of any interim analysis and in the final study report unless the protocol provides differently. This data characterization is not considered as a PASS because the aim is not of “identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, nor of measuring the effectiveness of risk management measures.” While the data characterization is being conducted, the marketing authorization holder (MAH) shall monitor the results generated and consider its implications for the risk-benefit balance of the medicinal product concerned. Any new information which might influence the evaluation of this risk-benefit balance shall be communicated to the competent authorities of Member States in which the medicinal product has been authorized. The channel for communicating this information is the notification of an Emerging Safety Issue.

This study is compliant with the provisions of the ENCePP Code of Conduct, Revision 4.

### **- Informed Consent**

Data bases with an Institutional Review Board (IRB) approval indicating that informed consent is waived and the rationale for this decision will be maintained.

### **- Responsibilities of the Investigator and IRB/IEC/REB**

The protocol and waiver of informed consent must be reviewed and approved by a properly constituted institutional review board/independent ethics committee/research ethics board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol has been approved by the IRB/IEC/REB and waiver of informed consent must be given to the principal investigator before study initiation.

## **10. Management and reporting of adverse events/adverse reactions**

As per the EMA Guideline on Good Pharmacovigilance Practices [Module VI–Management and reporting of adverse reactions to medicinal products (Rev1) 2014] for non-interventional study designs that are based on secondary use of data, individual reporting of adverse reactions is not required.

## **11. Plans for disseminating and communicating study results**

The results of this study will be published as ConcePTION report and scientific papers in peer-reviewed journals. Preparation of such manuscripts will be prepared independently by the investigators and in accordance with the current guidelines of STrengthening the Reporting of OBservational studies in Epidemiology (STROBE), the ENCePP standards and EMA guidelines.

The following funding disclosure will be used:

“The publication is part of the activities within the ConcePTION project. It has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 821520.

This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.”

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## 13. Annexes

### 13.1. Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1	Appendix I	04.10.2020	Databases and third-party DAPs
2	Appendix II	04.10.2020	Migraine clinical definition
3	Appendix III	04.10.2020	Medications used to treat migraine
4	Appendix IV	30.09.2021	Flowchart for the studied population
5	Appendix V	31.02.2021	Definitions of migraine severity groups and algorithm to define migraine patients in previous studies
6	Appendix VI	04.10.2020	Pregnancy & neonatal outcome definitions
7	Appendix VII	04.10.2020	Covariate items across DAPs
8	Appendix VIII	04.10.2020	Simplified Directed acyclic graph (DAG)
9	Appendix IX	04.10.2020	Meta analytic techniques for use in ConcePTION DPs



### 13.2. Annex 2. ENCePP checklist for study protocols

## ENCEPP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

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

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

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

**Study title:** Demonstrating solutions for studying intermittent medication exposures in diseases with episodic manifestations during pregnancy: application to medication for migraine in pregnancy

**EU PAS Register® number:**

**Study reference number (if applicable):**

<b>Section 1: Milestones</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection <sup>1</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.1
1.1.2 End of data collection <sup>2</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.1
1.1.3 Progress report(s)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	5
1.1.4 Interim report(s)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
1.1.5 Registration in the EU PAS Register®	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
1.1.6 Final report of study results.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	5

Comments:

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<sup>1</sup> Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

<sup>2</sup> Date from which the analytical dataset is completely available.

<b><u>Section 2: Research question</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
2.1 Does the formulation of the research question and objectives clearly explain:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	5
2.1.2 The objective(s) of the study?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7.7
2.1.5 If applicable, that there is no <i>a priori</i> hypothesis?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

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<b><u>Section 3: Study design</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.7
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.7
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	10

Comments:

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<b><u>Section 4: Source and study populations</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
4.1 Is the source population described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.1-8.2
4.2.2 Age and sex	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.1-8.2
4.2.3 Country of origin	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.1-8.2
4.2.4 Disease/indication	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.1-8.2
4.2.5 Duration of follow-up	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.1-8.2

<b><u>Section 4: Source and study populations</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.2

Comments:

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<b><u>Section 5: Exposure definition and measurement</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.3.1
5.3 Is exposure categorised according to time windows?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.3.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5.6 Is (are) (an) appropriate comparator(s) identified?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.3.1.2, 8.7

Comments:

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<b><u>Section 6: Outcome definition and measurement</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.3.3 and 8.3.4
6.2 Does the protocol describe how the outcomes are defined and measured?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.3.3 and 8.3.4
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.7
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYs, health care services utilisation, burden of disease or treatment, compliance, disease management)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not relevant

Comments:

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<b><u>Section 7: Bias</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.7
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.7

Comments:

<b><u>Section 8: Effect measure modification</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.7

Comments:

<b><u>Section 9: Data sources</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.9
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.9
9.1.3 Covariates and other characteristics?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.9
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Appendix XI
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Appendix XI
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Appendix XI
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CDM documents
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CDM documents
9.3.3 Covariates and other characteristics?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CDM docs

<b><u>Section 9: Data sources</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CDM docs

Comments:

<b><u>Section 10: Analysis plan</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
10.1 Are the statistical methods and the reason for their choice described?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.7
10.2 Is study size and/or statistical precision estimated?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.5
10.3 Are descriptive analyses included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.7
10.4 Are stratified analyses included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
10.5 Does the plan describe methods for analytic control of confounding?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.7
10.6 Does the plan describe methods for analytic control of outcome misclassification?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.7
10.7 Does the plan describe methods for handling missing data?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.7
10.8 Are relevant sensitivity analyses described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.7

Comments:

<b><u>Section 11: Data management and quality control</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.8
11.2 Are methods of quality assurance described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.8
11.3 Is there a system in place for independent review of study results?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.8

Comments:

<b><u>Section 12: Limitations</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.9
12.1.2 Information bias?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.9

<b><u>Section 12: Limitations</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.5

Comments:

<b><u>Section 13: Ethical/data protection issues</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9
13.2 Has any outcome of an ethical review procedure been addressed?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
13.3 Have data protection requirements been described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9

Comments:

<b><u>Section 14: Amendments and deviations</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
14.1 Does the protocol include a section to document amendments and deviations?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	4

Comments:

<b><u>Section 15: Plans for communication of study results</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	11
15.2 Are plans described for disseminating study results externally, including publication?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	11

Comments:

Name of the main author of the protocol: Professor Hedvig Nordeng,  
dr. Justine Benevent

Date: 30/September/2021

Signature: Professor Hedvig Nordeng, dr.  
Justine Benevent

### 13.3. Annex 3. Syntactically Harmonized Common Data Model

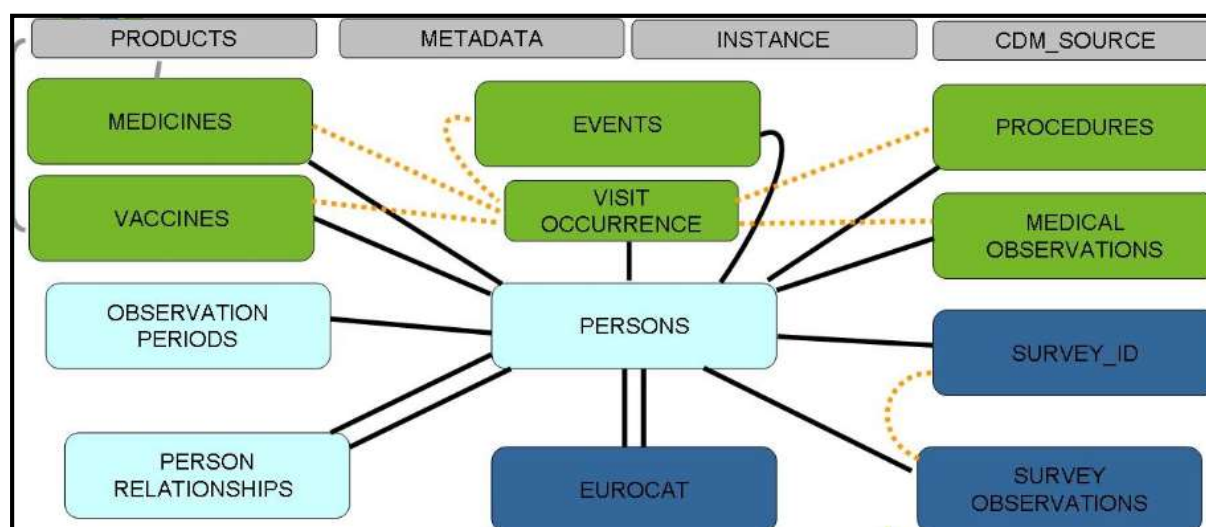


Figure. Schematic representation of the ConcePTION CDMv2.0

#### **METADATA TABLES**

The metadata tables contain data in a machine readable format which allows for processing of the data in the CDM. The CDM includes 4 tables in total:

##### **PRODUCTS**

Listing of national product codes for medicinal products. Contains a product ID foreign key to the DRUGS and VACCINES table. The PRODUCT\_CODE table contains detailed data on products at the package level.

##### **METADATA**

The metadata table contains indicators which can act as machine readable guides for code written against the CDM. For instance, whether data in the drug table represents prescription or dispensing.

##### **INSTANCE**

The instance table contains data on the specific instance of the ConcePTION CDM, such as tables and columns from source data which have been included.

##### **CDM\_SOURCE**

Contains high-level meta data describing the source data for the current instance such as the name of the source, data access provider, and date of last update.

-

#### **CURATED TABLES**

Curated tables differ from the other tables of the CDM in that data access providers are asked to create these tables using rule-based algorithms. These tables therefore represent a *syntactic* and *semantic* harmonization. The CDM includes 3 tables in total:

#### PERSON

One row of data per subject present in the data and meeting inclusion criteria for the CDM instance at any point during the study period. Data on each subject includes sex at the date of the instance creation, one date of birth, and one date of death (these may be derived using DAP-specific rules)

#### OBSERVATION\_PERIODS

One row per period during which a subject is present in the data source. This may be based upon registration in a geographical area, registration in a GP practice, presence in a registry, etc.

#### PERSON\_RELATIONSHIPS

Contains one row of data for each child present in the data and meeting inclusion for the CDM instance at any point during the study period, together with an identifier for the mother of the child and the father of the child if available.

-

#### **ROUTINE HEALTH DATA TABLES**

**Routine health care data tables capture data observed in the course of routine health care in hospitals, GP offices, pharmacies, outpatient clinics, etc. The CDM includes 6 tables in total:**

#### VISIT\_OCCURRENCE

Contains an identifier of a visit to allow for linkage of diagnoses, procedures, dispensings, etc in the same visit if this information is available in a data source.

#### EVENTS

Contains data on events indicated by a diagnosis code or free text. It contains one row per diagnosed event.

#### MEDICINES

One record per prescription or dispensing. Contains data required to estimate duration of exposure. Linkage to PRODUCT\_CODE table to access data on drugs at the package level.

#### PROCEDURES

Contains data on procedures ordered or completed. For those procedures with an associated result, results and units are recorded. It contains one row per procedure.

#### VACCINES

Contains data on vaccinations with one row per vaccine. Data on dose number for childhood vaccines and manufacturer are accommodated by this table.

#### MEDICAL\_OBSERVATIONS

Contains observations recorded during routine healthcare. Can be a result from a laboratory test, or physical measurement, but also level of education, or sex, or a pathology report. SARS-CoV-2 test results will be mapped under this Table.



### **SURVEILLANCE TABLES**

**Surveillance tables contain data collected for purposes beyond routine health care either for surveillance of specific events or for recording of detailed information related to a unit of observation such as a pregnancy or chronic illness. The CDM includes 3 tables in total:**

#### **EUROCAT**

Contains the EUROCAT or EUROmediCAT (a subset of the EUROCAT) table for those data access providers which have access to this standard table.

#### **SURVEY\_ID**

Contains metadata on observations contained in the SURVEY\_OBSERVATION table and allows for linkage between mothers and infants captured in a medical birth registry.

#### **SURVEY\_OBSERVATION**

Contains one row per observation in any survey or registry data table – such as a medical birth registry, well child program database, cancer registry, etc.

Full CDM specifications can be accessed here:

<https://drive.google.com/file/d/1hc-TBOfEzRBthGP78ZWla13C0RdhU7bK/view?usp=sharing>

Associated CDM vocabularies can be accessed here:

<https://docs.google.com/spreadsheets/u/0/d/1vPZwzQyJXlmmE1vvx3r1Jkw3Juz2DLjU9dKgEo8MijE/htmlview#>

## 14. Appendixes

### Appendix I: Databases and third-party DAPs

Country	Region	Data sources	DAP Name Name and Email of DAP contact person
Norway	Nation-wide	Linkage of three national registries	UOSL Prof. Hedvig Nordeng (h.m.e.nordeng@farmasi.uio.no)
Finland	Nation-wide	Linkage of several registries	THL Finnish Institute for Health and Welfare Maarit Leinonen (Maarit.leinonen@thl.fi)
France	Haute-Garonne	EFEMERIS database	CHUT Centre Hospitalier Universitaire de Toulouse Christine Damase-Michel (Christine.damase-michel@univ-tlse3.fr)
Italy	Tuscany	Healthcare administrative	ARS Agenzia regionale di sanità della Toscana Rosa Gini (rosa.gini@ars.toscana.it)
Italy	Emilia Romagna	IMER, Healthcare administrative	FERR Università degli Studi di Ferrara – University of Ferrara Amanda Neville (nvm@unife.it)
Spain	Valencian Region	FISABIO	FISABIO Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana. (Área de Investigación en Enfermedades Raras) Clara Caveró (cavero_cla@gva.es)
Germany	17% of population	GePaRD (Claims data)	BIPS Leibniz Institute for Prevention Research and Epidemiology Tania Schink (schink@leibniz-bips.de)
UK	Wales	SAIL Databank	USWAN University of Swansea Sue Jordan ( <a href="mailto:s.e.jordan@swansea.ac.uk">s.e.jordan@swansea.ac.uk</a> ) Daniel Thayer (d.d.thayer@swansea.ac.uk)
UK	GP records from 8.5% of the UK population	CPRD	GSK Keele Wurts ( <a href="mailto:keele.e.wurst@gsk.com">keele.e.wurst@gsk.com</a> ) Betsy Georgiou (mary.e.jones@gsk.com) Marianne Cunningham (marianne.9.cunnington@gsk.com)

## Appendix II: Migraine Clinical definition

The European Headache Federation defines the headache disorders of particular importance in primary care as follows:

**Table 1** The headache disorders of particular importance in primary care

Migraine	<ul style="list-style-type: none"> <li>• Usually episodic, occurring in 15–25% of the general population, in women more than men in a ratio of up to 3:1;</li> <li>• A chronic type is recognised, with headache occurring on more days than not</li> </ul>
Tension-type headache	<ul style="list-style-type: none"> <li>• Usually episodic, affecting most people from time to time but, in at least 10%, recurring frequently;</li> <li>• In up to 3% of adults and some children it is chronic, occurring on more days than not</li> </ul>
Cluster headache	<ul style="list-style-type: none"> <li>• Extremely intense and frequently recurring but short-lasting headache attacks, affecting up to 3 in 1000 men and up to 1 in 2000 women</li> </ul>
Medication-overuse headache	<ul style="list-style-type: none"> <li>• A secondary headache, but occurring only as a complication of a pre-existing headache disorder, usually migraine or tension-type headache, present on most days (<math>\geq 15</math> days/month) and affecting 1–2% of adults, women more than men, and about 0.5% of children and adolescents</li> </ul>

The international headache classification (ICHD-3) clinical criteria to define migraine with and without aura are (<https://ichd-3.org/>):

### ***Migraine without aura***

Adults with this disorder describe:

- recurrent episodic **moderate or severe headaches** which, *typically but not always*:
  - are **unilateral** and/or **pulsating**;
  - last (when untreated) from 4 h to 3 days;
  - are **associated with**:
    - nausea and/or vomiting;
    - photophobia, phonophobia and sometimes osmophobia;
  - are aggravated by routine physical activity, and **disabling**;
  - and during which they limit their activity and prefer **dark and quiet**;
- **freedom** from these symptoms **between attacks**.

In children:

- attacks may be shorter-lasting;
- headache is more often bilateral and less often pulsating;
- gastrointestinal disturbance is often more prominent.

### ***Migraine with aura***

This type affects about one third of people with migraine, although only a minority of these experience aura symptoms with every attack. It is characterised by:

- **aura** preceding or less commonly accompanying headache and consisting of **one or more neurological symptoms** (see Table 3)
- **headache** that is similar to migraine without aura, or may be rather featureless.

**Typical aura without headache** may occur in patients with a past history of migraine with aura.

### ***Chronic migraine***

This highly disabling migraine type develops, in a small minority of patients, from episodic migraine. Over time, attacks become more frequent, with **loss of clear periodicity**. Simultaneously, the specific characteristics of migraine become less pronounced.

**Table 3** Symptoms of aura (developing gradually over  $\geq 5$  min and usually resolving within 60 min)

Typical	<ul style="list-style-type: none"> <li>• <b>Visual symptoms</b> (occurring in &gt;90% of auras): usually a slowly-enlarging scintillating scotoma (patients may draw a jagged crescent if asked); <i>and/or</i></li> <li>• <b>Unilateral paraesthesiae</b> and/or numbness of hand, arm and/or face</li> </ul>
Less usual	<ul style="list-style-type: none"> <li>• Brainstem symptoms (eg, vertigo, tinnitus, diplopia, ataxia);</li> <li>• Speech and/or language disturbances</li> </ul>
Rare	<ul style="list-style-type: none"> <li>• Motor weakness</li> </ul>

## Appendix III: Medications used to treat migraine

### List of ATC codes of drugs used in the study

Drugs	ATC codes	OTC status	DDDs **
<b>Acute treatment – intermittent use*</b>			
<b>Triptans</b>			
Sumatriptan	N02CC01		20 mg
Naratriptan	N02CC02		2.5 mg
Zolmitriptan	N02CC03		2.5 mg
Rizatriptan	N02CC04		10 mg
Almotriptan	N02CC05		12.5 mg
Eletriptan	N02CC06		40 mg
Frovatriptan	N02CC07		2.5 mg
<b>Analgesics</b>			
Paracetamol	N02BE01	Yes	3 g
Codeine and paracetamol	N02AJ06		-
<b>NSAIDs</b>			
Ibuprofen	M01AE01	Yes	1.2 g
Diclofenac	M01AB05	Yes	0.1 g
Naproxen	M01AE02	Yes	0.5 g
Tolfenamic acid	M01AG02		0.3 g
<b>Antinauseants</b>			
Metoclopramide	A03FA01		30 mg
Doxylamine	R06AA09		25 mg
Meclozine	R06AE05	Yes	50 mg
Prochlorperazine	N05AB04		0.1 g
Promethazine	R06AD02		25 mg
Serotonin (5HT <sub>3</sub> ) antagonists	A04AA		
Ondansetron	A04AA01		16 mg
<b>Preventive treatment – continuous use*</b>			
<b>First line</b>			
Metoprolol	C07AB02		0.15 g
Propranolol	C07AA05		0.16 g
<b>Second line</b>			
Amitriptyline	N06AA09		75 mg
<b>Third line</b>			
Candesartan	C09CA06		8 mg
Topiramate	N03AX11		0.3 g
Valproic acid	N03AG01		1.5 g
Botulinum toxin	M03AX01		-
Pizotifen	N02CX01		1.5 mg
Clonidine	N02CX02		0.45 mg
Lisinopril	C09AA03		10 mg
Verapamil	C08DA01		0.24 g

<b>Calcitonin gene-related peptide (CGRP) antagonists</b>	N02C D		
Erenumab	N02C D01		2.5 mg
Galkanezumab	N02C D02		4 mg
Fremanezumab	N02C D03		7.5 mg

\*According to national clinical guidelines for treatment of women with migraine<sup>53,54</sup>. \*\* DDDs (defined daily dose) for the main indication in adults; administration route = oral <sup>41</sup>

### **Safety classification of migraine medications**

A comprehensive treatment approach of migraine during pregnancy includes the following pharmacological treatments<sup>45,46</sup>:

Medication	First Trimester	The second and early third trimesters	Late third trimester
Paracetamol			
Triptan	Majority of data indicating no risks	Majority of data indicating no risks	Majority of data indicating no risks
NSAIDs: ibuprofen, diclofenac, naproxen, tolfenam	Possible small increased risk of birth defects and miscarriage	Restrictive use is recommended: only occasional use up to Week 32	Week 32: Risk of adverse fetal and maternal effects
Monoclonal antibodies to CGRP	No Data. Theoretically no placental transfer.	No Data. Theoretically no placental transfer.	No Data.
Beta-blockers: Metoprolol, propranolol	Some reports of increased risk of certain birth defects.	Risk of fetal ARDs, for example slow heartbeat	Risk of fetal ARDs, for example slow heart rate, low blood sugar and low blood pressure
Tricyclic anti-depressants: amitriptyline	No evidence of teratogenic effects	A study shows an increased risk of preclampsia	Possible ADRs and withdrawal symptoms in newborns
Valproate (antiepileptic)	Increased risk of neural tube defects and other malformations. Contraindicated for migraine use in pregnancy.	The risk of severe developmental disorders. Contraindicated for migraine use in pregnancy.	The risk of severe developmental disorders. Contraindicated for migraine use in pregnancy.
Topiramate (antiepileptic)	Little data. Increased risk of lip-palate	Little data, but adverse effects on mental and motor functions cannot be excluded	Little data, but one cannot exclude adverse effects on mental and motor functions
Candesartan (AII blocker) and lisinopril (ACE inhibitor)	Increased risk of miscarriage, birth defects.	Increased risk of stillbirth, birth defects, and kidney damage for the fetus.	Increased risk of stillbirth, low amniotic fluid and kidney damage for the fetus.
Clonidine	Little data. Generally no evidence of teratogenic effect	Little data. Generally no evidence of teratogenic effect	Possible side effects in newborns using just before birth: sleep disorders, low blood pressure, low birth weight
Botulinum toxin	Little data. No evidence of being harmful to the mother or child.	Little data. No evidence of being harmful to the mother or child.	Little data. No evidence of being harmful to the mother or child.

Table based on Amundsen, S., et al. Updated information about use of candesartan / lisinopril, clonidine, botulinum toxin and monoclonal antibodies is added based on the available information October 2019.

Dark green: Can be used.

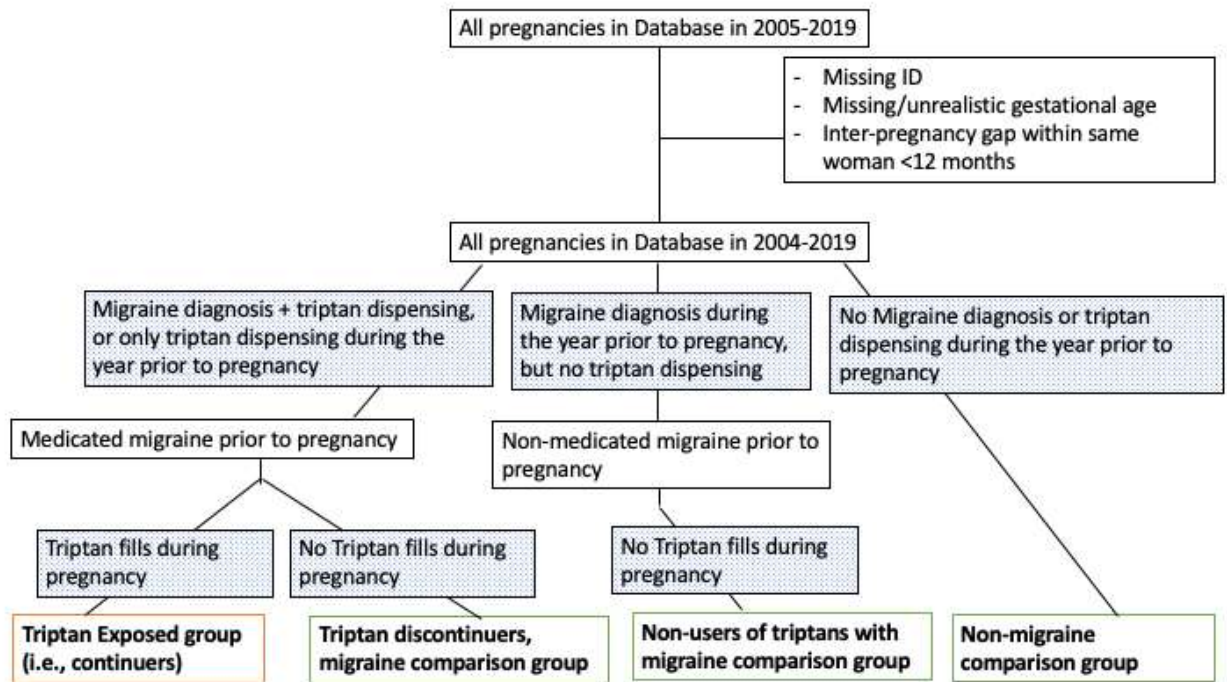
Light green: Medications may be used when needed, but there is either limited data, whether a particular period of pregnancy.

Yellow: Restrictive use is warranted. Risks during pregnancy cannot be excluded.

Red: Should not be used, unless where there is no other option and the women's need justifies the risks.

Accidental exposure of the fetus to drugs in the red field is no indication for elective abortion. However, we recommend referring to ultrasound/foetal diagnostics.

## Appendix IV: Flowchart for the studied populations



\*Triptan initiators during pregnancy (i.e. pregnancies with no triptan fills in the year prior to LMP, having one or more fills for triptans in pregnancy) are excluded from the study. Likewise, pregnancies within women having a new diagnosis of migraine in pregnancy, but no diagnosis history in the year prior to LMP, are excluded by design.

## Appendix V: Definitions of migraine severity groups and algorithm to define migraine patients in previous studies

Classification of severity according to prescription drug treatment. Migraine severity group according to Tauqeer et al. (In submission: Tauqeer et al. Perinatal Use of Triptans and Other Migraine Drugs – A Nation-wide Drug Utilisation Study.)

Severity	Migraine medication use
Mild	Sufficient effect using paracetamol and /or NSAIDs only.
Moderate	Use of triptans prior to and/or during pregnancy (excl. sumatriptan injection)
Severe	Sumatriptan injection prior to and/or during pregnancy and/or migraine prophylaxis prior to, but not during pregnancy.
Very severe*	Migraine prophylaxis in pregnancy

\*Drugs used for first line prophylaxis include Metoprolol & Propranolol. The second line includes Amitriptyline.

Drugs used for third line prophylaxis include Candesartan, Topiramate, Valproic acid, Botulinum toxin, Clonidine, Lisinopril, Flunarizine, Pizotifen & Verapamil, CGRP

Algorithm to define migraine patients according to Thomsen et al.:

Migraine cohort-defining diagnoses, events	ICD-8 code	ICD-10 code	ATC code
Migraine diagnosis (primary, secondary, inpatient, outpatient, emergency)		G43	
Migraine without aura		G430	
Migraine with aura		G431	
Specific acute or prophylactic migraine treatment			
Triptans			N02CC
Ergots			N02CA
Pizotifen			N02CX01
Flunarizine			N07CA03
<b>Exclusion criteria for incident migraine cohort (since 1977)</b>			
Migraine diagnosis or migraine-specific treatment	346	G43	N02CA, N02CX, N02CC, N07CA03
History of epilepsy or seizures since 1977 before or on cohort entry date (any hospital diagnosis)	345	G40, G41	N03 (since 2004)



## Appendix VI Pregnancy & neonatal outcome definitions

Terms for defining pregnancy and neonatal outcomes will be aligned with recommendations and current recognized standards:

- [Guideline on good pharmacovigilance practices \(GVP\). Product- or Population-Specific Considerations III: Pregnant and breastfeeding women](#). EMA/653036/2019 DRAFT FOR PUBLIC CONSULTATION, 4 December 2019 ([www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-good-pharmacovigilance-practices-product-population-specific-considerations-iii\\_en.pdf](http://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-good-pharmacovigilance-practices-product-population-specific-considerations-iii_en.pdf)):
- EuroPeriStat definitions and recommendations ([www.europeristat.com](http://www.europeristat.com))
- EUROCAT Classification ([EUROCAT Subgroups of Congenital Anomalies](#)).

The pregnancy events in are aligned with the definitions and are operationalized as in the IMI ConcePTION project. A brief overview of the definitions is given below.

**Pregnancy outcome:** End result of pregnancy, which includes ectopic pregnancy, miscarriage, foetal death, termination of pregnancy and live birth.

**Delivery:** Deliveries will be classified according to initiation type: Spontaneous, induction or Caesarian section. Place of delivery will be classified as at the maternity ward, at home (planned, unplanned) or at other place of delivery outside institution.

**Fetal death** (intrauterine death, *in utero* death): Death prior to complete expulsion or extraction from the mother of a foetus, irrespective of the duration of pregnancy. Early foetal death (before 22 completed weeks of gestation) is known as miscarriage, whereas late foetal death (after 22 completed weeks of gestation) is known as stillbirth.

**Spontaneous abortion/Miscarriage:** Spontaneous abortions or miscarriages are foetal losses before the gestational age or birthweight threshold for defining stillbirth. The definition of this indicator varies by country/data sources. According to EUROCAT, spontaneous abortions/miscarriages are foetal deaths <20 weeks. The WHO and the EMA define spontaneous abortion pregnancy ending spontaneously before 22 weeks of gestation (i.e. up to and including 21 6/7 weeks of gestation) (European Medicines Agency (EMA). Guideline on the exposure to medicinal products during pregnancy: Need for post-authorisation data. EMA, 2005. Accessed May 26, 2020. Available at: [https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-exposuremedicinal-products-during-pregnancy-need-post-authorisation-data\\_en.pdf](https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-exposuremedicinal-products-during-pregnancy-need-post-authorisation-data_en.pdf)).

The upcoming ICD-11 guidelines will likely define stillbirth from 22 weeks onwards with spontaneous abortion/miscarriage referring to deaths at <22 weeks.

Given that spontaneous abortions or miscarriages tend to occur early in pregnancy often these are often not recorded in register-based data sources. Women might not declare the occurrence of spontaneous abortion or this might be managed in emergency room or in primary health care. This leads to underestimation in pregnancy studies using register data.

**Termination of pregnancy** (induced abortion, elective abortion): Artificial interruption of pregnancy for any reason.

**Trimesters:** Trimester are usually defined as three months period where the first trimester covered the first 12 weeks of gestation. Trimesters will be defined as follow (ACOG definition):

- Trimester 1: from the Last Menstrual Period (LMP) to day 97 after LMP;
- Trimester 2: from day 98 after LMP to day 195 after LMP;
- Trimester 3: from day 196 after LMP onwards.

**Live birth:** Complete expulsion or extraction from the mother of a foetus, irrespective of the duration of the pregnancy, that, after such separation, breathes or shows any evidence of life.

**Gestational age:** Measure of the age of a pregnancy calculated from the first day of a woman's last menstrual period or as estimated by a more accurate method such as ultrasound. The method used needs to be clearly stated in any reporting. Gestational age is expressed in completed days or completed weeks (e.g. events occurring 280 to 286 days after the onset of the last menstrual period are considered to have occurred at 40 weeks of gestation).

**Birth weight:** Initial weight of the infant at birth.

**Preterm birth** (premature birth): Birth at less than 37 completed weeks (less than 259 days) of gestation.

**Term birth:** Birth at any time from 37 to less than 42 completed weeks (259 to 293 days) of gestation.

**Post-term birth:** Birth after 42 completed weeks of gestation or more (294 days or more).

**Low birth weight:** Body weight of the newborn at birth of less than 2,500 grams (up to and including 2,499 g).

**Intrauterine growth retardation** (IUGR) (small-for-gestational age): Observed weight of a live born infant or size of a foetus lower than expected, usually below the tenth percentile, on the basis of gestational age.

#### **Neonatal death / mortality:**

Neonatal mortality refers to death of a live-born baby within the first 28 days of life. Early neonatal mortality refers to the death of a live-born baby within the first seven days of life, while late neonatal mortality refers to death after 7 days until before 28 days.

#### **Terms for defining congenital anomalies (birth defects)**

Definitions and classifications are in line with EuroCat definitions and classifications (<https://euro-rd-platform.jrc.ec.europa.eu/sites/default/files/EUROCAT-Guide-1.3.pdf>):

***Congenital anomaly:*** Morphological, functional and/or biochemical developmental disturbance in the embryo or foetus whether detected at birth or not. The term congenital anomaly is broad and includes congenital abnormalities, foetopathies, genetic diseases with early onset, developmental delay. Both onset and diagnosis of congenital anomalies can be delayed.

***Major anomaly:*** A life-threatening structural anomaly or one likely to cause significant impairment of health or functional capacity and which needs medical or surgical treatment. The prevalence of major abnormalities recognised at birth among live-born infants is 2%-4% in most series published.

***Minor anomaly:*** Relatively frequent structural anomaly not likely to cause any medical or cosmetic problems.

**Major congenital anomalies:**

The prevalence of major congenital anomalies among live-born infants is generally considered to be 2%-4%<sup>56</sup>. Prevalence of major congenital anomalies (including chromosomal anomalies) recorded by EUROCAT was 2.4% (2003-2007)<sup>57</sup>. All congenital anomalies will be classified and analysed according to the EUROCAT Classification (EUROCAT Subgroups of Congenital Anomalies). This includes diagnosis in the Q chapter of ICD-10 (and equivalent ICD-9 codes), but excludes a recognized list of minor anomalies, if isolated, as specified by EUROCAT. As recommended by European regulatory guidelines (GVP III)<sup>56</sup> and EUROCAT, congenital anomalies should be considered in both live and non-live births (e.g. TOPFA, stillbirths).

As recommended by these guidelines<sup>56</sup> we will use the following definitions:

$$\text{Live birth prevalence rate} = \frac{\text{Number of cases among live born infants}}{\text{Total number of live born infants}} * 1000$$

$$\text{Birth prevalence rate} = \frac{\text{Number of cases among live and stillborn infants}}{\text{Total number of (live + still) born infants}} * 1000$$

The numerator is the number of cases of the subject of interest. The denominator is the population from which the numerator came.

## Appendix VII: Covariate items across DAPs

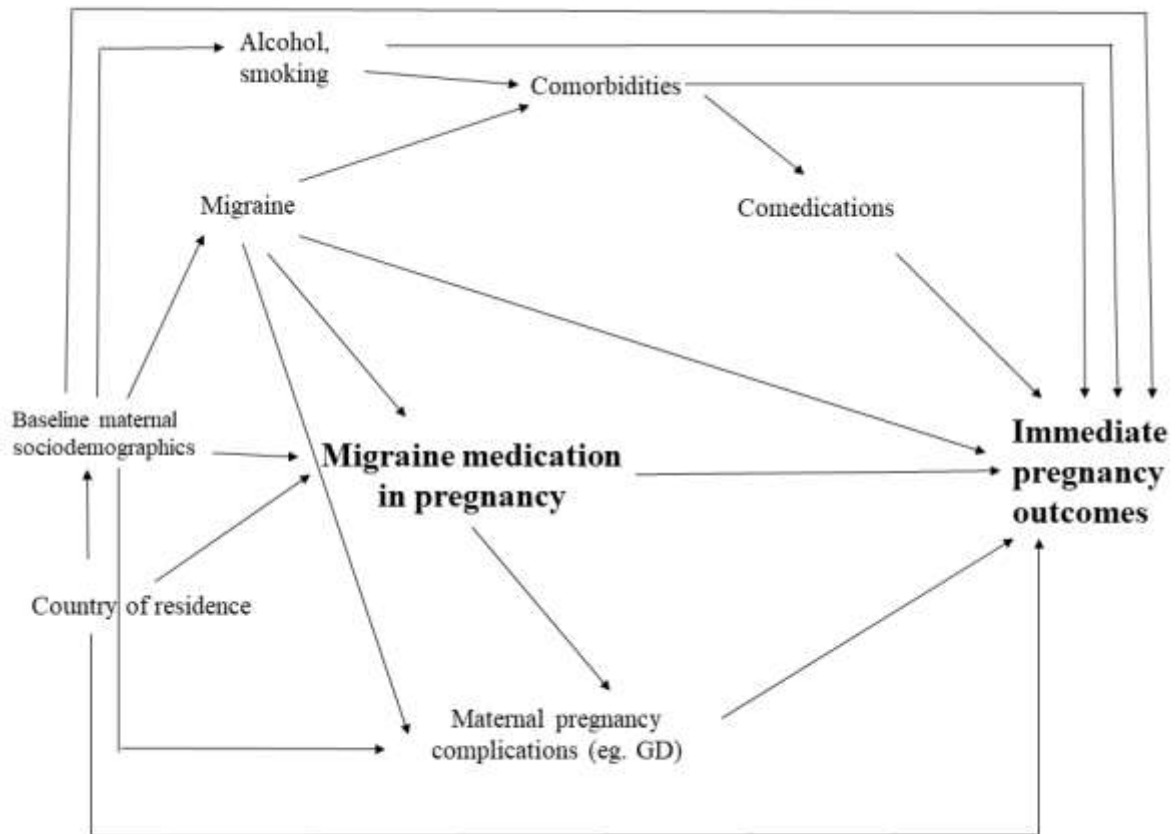
Information item	UIO	CHU T	GeP aRD	FISA BIO	UNI FE	ARS	THL	SAIL	CPRD*
<i>Pregnancy timing</i>									
Pregnancy timing	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<i>Medication exposure</i>									
<i>Source of medication information</i>									
Primary care/General practitioner prescription	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Inpatient – secondary care	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Outpatient - specialist	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Outpatient pharmacy dispensing	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Private prescriptions – private healthcare	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Details of medication</i>									
Name/ATC code of medication of interest	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Date of issued/dispensed prescription, administration or used	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Strength	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Dosage – amount taken per day	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Frequency – per day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Formulation (oral, injection, cream etc).	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
DDD dispensed	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Quantity prescribed or dispensed (tablets)	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Prescriber specialty	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Co-medications	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<i>Maternal disease/medication indication</i>									
<i>Diagnosis</i>									
Diagnosis in healthcare database e.g. ICD10	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Diagnosis in disease registry	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Type of ward where the diagnosis was given	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Intervention in healthcare database as surrogate for disease	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Healthcare admission as surrogate for disease/disease severity	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<i>Severity of disease</i>									
Health care visit pattern	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Co-morbid diagnosis/diagnoses	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Information item	UIO	CHU T	GeP aRD	FISA BIO	UNI FE	ARS	THL	SAIL	CPRD*
Co-morbidity	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<i>Maternal /Pregnancy outcomes</i>									
Spontaneous abortions	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Termination of pregnancy - elective	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Termination of pregnancy - for foetal anomaly	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Pregnancy related conditions e.g. GD, preeclampsia, hypertension, stroke	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Mode of delivery	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Maternal death	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Maternal diagnoses postpartum (e.g. stroke, infection, psychosis, death)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<i>Perinatal outcomes</i>									
Live birth: normal	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Stillbirth	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Neonatal death	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Major congenital anomalies	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Gestational age at delivery/preterm birth	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Small for gestational age/ IUGR	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Birth weight	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Head circumference	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Length at birth	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Apgar score (5, 10 minutes)	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Admission to Neonatal Intensive Care Unit	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Confounders/covariates</i>									
Folic acid – prior to/during	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Assisted conception	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Maternal age at delivery	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Maternal socioeconomic status (occupation, employment, income, education etc.)	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Smoking status – prior to/ during pregnancy	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Alcohol consumption – during pregnancy	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Substance misuse - during pregnancy	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Body mass index /	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Parity	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Information item	UIO	CHU T	GeP aRD	FISA BIO	UNI FE	ARS	THL	SAIL	CPRD*
Plurality	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Breastfeeding	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Paternal medication	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Family structure (linkage to siblings)	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

\*Information not filled in by the DAP.

## Appendix VIII: Simplified Directed Acyclic Graph (DAG)



## Appendix IX: Meta-analytic techniques for use in ConcePTION DPs

By Prof. Joan Morris, UGUL

### 1- Purpose

The purpose of this document is to suggest possible methods for use by the different demonstration projects for pooling analytic results and aggregate data from the different databases in ConcePTION.

All DPs consist of

- **Medication Utilisation and Event/Outcome Definition Study:**

The aim of the medication utilisation study is to describe the frequency / quantity of prescriptions of specified medications in the database and in particular in pregnant women within the database. The aim of the event outcome definition study is to define specific algorithms to identify outcomes / events. This is likely to involve analysing prevalence of events/outcomes over time and possibly by pre-specified subgroups of interest, in particular pregnant women. But there may be additional information on, for example, groups defined according to socio-economic status

- **Medication Safety Study:**

The aim is to assess the safety of specified medications in pregnancy. Safety will be assessed using a range of outcomes and confounders and mediators are likely to be included in analyses.

It is expected that both study types will use similar meta-analytic techniques to analyse their results when appropriate. However, many of the results from these studies are expected to be database specific and therefore meta-analytic techniques will not be required.

### 2- Use of Controls

When combining results from different data sources (especially if they are from different countries) it is highly recommended that all analyses include controls in order to reduce country specific differences. For example, when analysing birthweight in women taking a specific medication the birthweight of babies not exposed to the medication should be also analysed as it will vary by data source. The ideal measure to summarize across data sources would be the difference in birthweight compared to unexposed babies with a confidence interval for this difference – the difference could be on an arithmetic (the actual difference) or log scale (the proportional difference). Similarly, when analysing the occurrence of SGA, the ideal comparison would be the increased odds of SGA compared to unexposed pregnancies.

### 3- Considerations

Before combining results between countries, it is key that the effect estimates to be combined are logically comparable. The following questions should be considered before conducting any meta-analysis of effect estimates across countries:

- Are the outcome definitions being analysed by each country the same?
- Are the methods used to obtain exposure definitions comparable between countries?
- Do the countries have comparable drug utilisation profiles?
- Do the data sources being compared have any other underlying differences?



When extreme heterogeneity present between countries, it would not be advisable to produce a combined effect estimate as its interpretable value is low and may be misinterpreted by readers.

## Random Effects vs Fixed Effects

When conducting meta-analyses, most methods fall into one of two categories, fixed effect models or random effect models. Fixed effects models assume that the true effect being estimated in each country is the same. However, random effect models assume that the true effect being estimated varies between countries and so the estimates will also vary. The model accounts for this by assuming these estimates will follow a distribution around the true effect (usually a normal distribution). Which models are used should be decided prior to analysing the data.

## 4- Bias

When performing meta-analysis, it is recommended that the STATA programs metabias and metafunnel are run to examine potential bias in estimates. This may not be applicable in this situation when you are analysing data from different data sources rather than from published studies. So it is not essential to run these.

## 5- Effects of Covariates

The biggest challenge in this analysis is that it is not likely to be possible to fit individual models to the data in each data source, to examine the fit of the data and to adapt the models for each data source. As the data will vary between data sources this means that many may not have the same complete set of covariates. It will need to be decided if multivariate models can be fitted or whether adjusting for each covariate separately may provide sufficient information. If you have access to at least one data base the whole range of models can be fitted and then inferences can be made about the model fitting to other data sets.

## 6- Summary of Meta-Analysis Techniques and Procedures in STATA

### 1. METAN – Meta-analysis of binary or continuous data with fixed or random effects and by subgroups

metan tdeath tnodeath cdeath cnodeath  
metan tsample tmean tsd csample cmean csd,  
metan logor selogor  
metan mean semean  
metan mean lowerci upperci  
metan percent lowerci upperci (see metaprop below)

### 2. METAAN - Similar to metan, but a greater range of estimation methods and different inputs:

metaan eff SEeff,  
metaan eff effvar, varc

### 3. METAPROP– Meta-analysis of proportions with fixed or random effects and by subgroups<sup>74</sup>

(ftt Calculate the pooled estimate after Freeman-Tukey Double Arcsine Transformation)  
metaprop num denom, ftt

But this has been identified as prone to errors<sup>75</sup> so see also GLMM procedure in STATA

4. **METAREG : Meta-analysis of binary or continuous data with fixed or random effects relating value(s)** of each study to the observed relative risk or mean

metareg logrr latitude, wsse(selogrr)

metareg smd abstract duration itt, wsse(sesmd) permute (10000)

5. **MVMETA : Meta-analysis of several variables simultaneously and can include regression**<sup>76</sup>

mvmeta b V

b : set of variables all starting with b for example if looking at related factors such as diagnosis other maternal diseases : diabetes , epilepsy, other all as binary variables you would code them b1 , b2 and b3 and do a meta-analysis of the 3 beta's simultaneously.

## 7- Additional programs in STATA

6. **XTPOISSON : Analysing counts with random effects / mixed effects models**<sup>77</sup>

a. Can use small time intervals and then model risk (an event occurring within time interval) against potential confounders etc. Gives greater flexibility to use of multilevel models

b. Stsplit in STATA will create a data set of small time intervals

7. **GLST : Generalized Least Squares for trend estimation of summarized dose-response data**<sup>78,79</sup>

glst depvar dose [indepvars], se(varname) cov(n cases)

Can use to model changes in log(rr) according to dose. So could have potential when looking at SES categories for instance.

8. **MEGLM: Multilevel mixed-effects generalized linear model**

These can be used to overcome the issues in METAPROP for count data and can also be specified using MELOGIT or MEPOISSON

## 8- Meta-analysis of survival curves

The analysis of survival curves is a different situation as there will be estimated probabilities of survival for a set of different time points. These probabilities are all highly correlated and hence should not ideally be analysed without including information about these correlations.

### 1. Use of MVMETA

The survival probabilities can be combined if there are only 2 or 3 time points. You may need to use the Freeman-Tukey double arcsine transformation to stabilize the variances first.

### 2. Multivariate meta-analysis on conditional probabilities

MetaSurv in R does this:

- i. Calculate probability survival up to fixed time points conditional on survival up to that time point as the conditioning means that the estimates are not correlated
  - ii. Combine these probabilities
  - iii. Multiply these together to get overall estimate
- However, MetaSurv includes a continuity correction of 0.5, which creates bias for combining small samples sizes. SGUL are writing a program that will include a smaller continuity correction that will reduce the bias.

### 3. Bayesian multivariate meta-analysis on conditional probabilities

A Bayesian version of the method proposed by Combescure has been developed by SGUL but is currently being assessed in comparison with Frequentist variants.

## 9- Potential Issues: Mainly Small Numbers

### 1. Continuous Measures

Generally, OK particularly if analysing means as you can always estimate a mean and its se if you have at least two data points – the lack of data will usually be reflected in the variance. However, if you only have two data points and they are extremely close then the variance may be very low. You do need to examine all your data carefully.

### 2. Proportions and Odds Ratios

This can be very problematic as you may have no events and hence 0 in specific cells. Many programs either drop all data from that database or else automatically insert a 0.5 and carry on. You need to check what is happening with this. If there are several databases with this issue it may have a large effect on your overall estimates. There is a difference between medication not being prescribed in a country and hence no events with exposure for that medication in the country with no events occurring when the medication is being prescribed. The FTT transformation in METAPROP may introduce bias especially if your databases vary greatly in size.



# concePTION

## SAFETY EVIDENCE ECOSYSTEM

### Protocol Version 1.0

DP5. Studying drug exposure when disease is measured through accurate identification of an incident case: application to breast cancer in pregnancy

This study will be conducted within the ConcePTION project of the Innovative Medicines Initiative under grant agreement No 821520

<b>Title</b>	Studying drug exposure when disease is measured through accurate identification of an incident case: application to breast cancer and pregnancy
<b>Protocol version identifier</b>	1.0
<b>Date of last version of protocol</b>	09/30/2021
<b>EU PAS register number</b>	EUPAS43401
<b>Active substance</b>	Antineoplastic agents (ATC class L01) and endocrine therapy (ATC class L02).
<b>Medicinal product</b>	

<b>Research question and objectives</b>	<p>The objective is to evaluate which pharmaco-epidemiological methods are best suited to assess treatment modalities, including drug utilisation in pregnancy for malignant disease. The goal is to study drug exposure when disease is measured through accurate identification of an incident case. Therapies for pregnancy associated breast cancer (PABC) are used as motivating examples.</p> <p>We will particularly focus on improving methods for developing measurements of medication exposure in hospital settings / secondary and tertiary care. This drug utilisation study will describe patterns of medication use in PABC and in breast cancer in non-pregnant women (non-PABC). We will also assess whether time at breast cancer diagnosis and timing of medication use in pregnancy impacts maternal survival and pregnancy outcomes.</p>
<b>Countries in the study</b>	Finland, Spain (Valencian Region), UK (Wales), Germany, Scotland, and possibly other countries, all pending on results from the Data characterization (WP7).
<b>Primary Authors</b>	Dr Maarit Leinonen and Prof Mika Gissler
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## List of abbreviations

Abbrev.	Term
ATC	anatomical therapeutic chemical
BMI	Body mass index
CDM	Common Data Model
CI	Confidence intervals
DAP	Data access provider
DDD	Defined daily dose
EMA	European Medicines Agency
ETL	Extract, transform, load
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FAIR	Findable, Accessible, Interoperable, and Reusable
FISABIO	The Foundation for the Promotion of Health and Biomedical Research of Valencian Region
GA	gestational age
GePARD	The German Pharmacoepidemiological Research Database
GLST	Generalized Least Squares for trend
GVP	Guideline on good pharmacovigilance practices
ICD-O-3	International Classification of Diseases for Oncology
IUGR	Intrauterine Growth Retardation
HR	Hazard ratio
MEGLM	Multilevel mixed-effects generalized linear model
MI	Multiple imputation
MICE	Multiple imputation by chained equations
PABC	Pregnancy Associated Breast Cancer
PASS	Post-authorisation safety study
SAILS	Secure Anonymised Information Linkage
SERMS	Selective oestrogen receptor modulators
SES	Socioeconomic status
SGA	small-for-gestational age
STROBE	Strengthening the reporting of observational studies in epidemiology
TNM	TNM classification of malignant tumours
WHO	World Health Organization

## 1. Responsible parties

Responsible parties are:

Name	Role	Working institution/company
<b>Maarit Leinonen</b> <b>Mika Gissler</b> <b>Visa Martikainen</b>	PI, Protocol development lead, DAP Finland Data analysis	Finnish Institute for Health and Welfare (THL), Finland
<b>Dina Gifkins</b>	Protocol development, co-lead	Janssen
<b>WP7 representative</b>	SAP review, R Coding and analytics of SAP	UMCU
<b>Joan Morris</b>	Statistical expert, meta-analysis	St George's University of London, UK
<b>Sue Jordan, Daniel Thayer</b>	DAP Wales	University of Swansea, Wales
<b>Tania Schink</b>	DAP Germany	Leibniz Institute for Prevention Research and Epidemiology
<b>Clara Caverro-Carbonell</b> <b>Laia Barrachina-Bonet</b> <b>Laura García-Villodre</b> <b>Óscar Zurriaga</b>	DAP Spain (Valencian Region)	Rare Disease Research Unit, FISABIO: The Foundation for the Promotion of Health and Biomedical Research of Valencian Region
<b>Tom MacDonald*</b>	DAP Scotland	University of Dundee Scotland

\*protocol review lacking

## 2. Abstract

### Title

Studying drug exposure when disease is measured through accurate identification of an incident case: application to breast cancer and pregnancy

### Main authors:

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Prof Mika Gissler, Finnish Institute for Health and Welfare, Finland

### Rationale and background

Pregnancy-associated breast cancer (PABC) is usually defined as breast cancer diagnosed during pregnancy or within one year after delivery. It is a rare disease, but incidence is increasing as women are postponing childbearing. Several studies have reported poorer prognosis of PABC compared with women diagnosed with breast cancer prior to pregnancy or 1-2 years after delivery. It is uncertain to what extent this is attributed to less aggressive or delayed therapy secondary to concerns regarding foetal effects, delays in diagnosis and later stage at diagnosis due to difficulties of diagnosing PABC, or underlying immune-suppression in pregnancy, or underlying tumour characteristics. Women with history of breast cancer are recommended to wait at least two years from remission prior to conceiving. Women of childbearing age with breast cancer face unique challenges, such as reassurance that maternal outcome is not adversely affected by pregnancy and possible teratogenicity of cancer therapy exposure in-utero. Management guidelines are based on case reports, case series and small cohorts, and limited by the retrospective nature and heterogenous treatment regimens. Most studies have been hampered by low power and inability to control for tumour characteristics due to missing data.

### Research question and objectives

1. What is the incidence of PABC and non-PABC in women of reproductive age in European countries?
2. Is the pattern of cancer treatment (including surgery, radiation, chemotherapy, endocrine therapy and targeted therapy) similar in PABC and non-PABC patients?
3. What medications are used and how does the pattern of treatment change over the course of a pregnancy (e.g. prior to pregnancy, during, after pregnancy), by cancer severity, by country, and time period?
4. What is the pregnancy outcome (termination of pregnancy, live birth, stillbirth, preterm birth, small for gestational age (SGA)/ intrauterine growth retardation (IUGR), as available) and mode of delivery for women with PABC and non-PABC and does that vary by cancer severity, by country, by time period?
5. What is the 5-year relative survival for women with PABC and non-PABC when adjusted for tumour characteristics and is there a difference in survival between PABC patients diagnosed during pregnancy and those diagnosed one year postpartum?

### Study design

A multinational cohort study conducted in following countries: Finland, UK (Wales), Spain (Valencian Region), Germany, Scotland and possibly others, all pending on results from the Data characterization (WP7).

### Study population

All women free of an identifiable cancer diagnosis prior to age 15 diagnosed with breast cancer during reproductive age. Women diagnosed with breast cancer during pregnancy or within 12 months after childbirth (live births and stillbirths) will be defined as PABC. Women who have no indication within the data source of a pregnancy at diagnosis or diagnosed > 1 year after delivery will be defined as non-pregnant breast cancer (non-PABC).



#### Study period

Study period will start from the first year cancer incidence and birth outcomes are available from the data source (whichever is the latest) and will end at the most recent date of the data source where maternal death is available. Analyses will be stratified by age groups where appropriate.

#### Variables

Exposure: The exposure will be defined based on maternal record of one or more prescriptions or procedures (prescribed, dispensed, reimbursed or administered in hospital) of medications or administration of medication for breast cancer in pregnancy. Medications for breast cancer will be classified according to the Anatomical Therapeutic Chemical (ATC) classification system and the primary exposure is antineoplastic agents (ATC class L01) and endocrine therapy (ATC class L02).

Event: PABC

Maternal outcome: 5-year relative survival

Secondary outcomes: mode of delivery and the following pregnancy outcomes (termination of pregnancy, live birth, stillbirth, preterm birth, SGA/ IUGR, congenital anomalies) in women with PABC and non-PABC.

#### Study size

Assuming 25% of annual breast cancer cases occur in women of childbearing age and the ratio of PABC vs. non-PABC to be 1 to 6, to detect a 40% increased risk for death in PABC vs. non-PABC patients with 80% power and type I error rate of 0.05, we would require 2 965 breast cancer cases and a sample size of around 3.27 million women years in women of childbearing age.

#### Data analysis Milestones

An important methodological focus will be on exposure misclassification as well as co-exposure effects.

### **3. Amendments and updates**

Number	Date	Section of study protocol	Amendment or update	Reason
1	Date	Text	Text	Text
2	Date	Text	Text	Text
...	Date	Text	Text	Text

### **4. Milestones**

Milestone	Planned date
Registration in the EU PAS register	Date: 1 <sup>st</sup> October 2021
Final report of study results	Date: March 2023

## 5. Rationale and background

Malignant disease occurring during pregnancy brings particular challenges for diagnostics and treatment. Changes in the breast associated with hormonal changes in pregnancy and lactation make detection and evaluation of breast masses difficult both clinically and radiologically (Ahn 2003, Kakoulidis 2015, Expert Panel on Breast Imaging 2018). More importantly, ionizing radiation used in diagnostics and treatment may lead to death of the embryo and during organogenesis, ionizing radiation exceeding a dose of 50 mGy may cause congenital anomalies, microcephaly, intrauterine growth retardation, and severe cognitive impairment (Navrozoglou 2008, Kakoulidis 2015, MacDonald 2020). Only radiographic studies which will affect management during the course of the pregnancy should be performed and radiotherapy should be postponed after delivery (Navrozoglou 2008, Amant 2012, Cardonick 2014).

Pregnancy-associated breast cancer (PABC) is a very rare type of cancer. Most data on the prognosis of patients with PABC are based on case reports, case series and small cohorts and limited by the retrospective nature and heterogeneous treatment regimens (Zagouri 2013, Rojas 2019). Most studies have been hampered by low power and inability to control for tumour characteristics due to missing data. Also, lack of data on medications administered in hospitals is a common limitation encountered in pharmacoepidemiological studies.

Another clinical challenge is advising women who have previously been diagnosed and treated for breast cancer and who subsequently desire to become pregnant. These women should not be discouraged from future pregnancy (Rojas 2019). Many clinical guidelines have advised that premenopausal women with breast cancer diagnosis should wait two years after treatment before attempting conception. This can mean over 10 years waiting for women receiving endocrine therapy with a subsequent significant reduction in woman's ability to conceive (Navrozoglou 2008, Gerstl 2018).

### Medication safety

#### *Chemotherapy*

Chemotherapy plays a key role in improving the survival of patients with early stage breast cancer (Zagouri 2013). During pregnancy, several physiological changes alter the pharmacokinetics of many medicines, including chemotherapeutic agents. For instance, expanded plasma volume, increased renal clearance and increased activity of liver enzymes may affect free-drug levels and raise doubt about effectiveness of chemotherapy during pregnancy (Navrozoglou 2008, Amant 2012, Cardonick 2014). However, since no evidence suggests that standard treatment in PABC is less efficient than in non-PABC, the chemotherapeutic agents should be prescribed for pregnant patients as for non-pregnant breast cancer patients (Amant 2012, Zagouri 2013, Hartman 2016, Rojas 2019, MacDonald 2020).

First trimester chemotherapy is not recommended since there is substantial risk of spontaneous abortions, teratogenesis and foetal anomalies (Navrozoglou 2008, Amant 2012, Basta 2015). Exposure during the second and third trimester (after 14 weeks) has not been associated with teratogenic effects, i.e. the rate of anomalies mirrors the baseline population's risk of congenital anomalies (Hartman 2016, Rojas 2019). However, growth restriction, prematurity, intrauterine and neonatal death and haemopoietic suppression and sepsis has been reported following cytotoxic treatment in the second and third trimesters (Amant 2012, Zagouri 2012, MacDonald 2020). Chemotherapy must cease approximately three weeks prior to labour affording both the mother and the foetus the necessary period to excrete the drugs and recover from myelosuppression and, thus, avoiding postpartum infection and/or haemorrhage (Navrozoglou 2008, Amant 2012, Zagouri 2013, Cardonick 2014, Rojas 2019, MacDonald 2020). The main risks related to chemotherapeutic agents are summarized in the Table 1.

**Table 1.** The main risks to the foetus of chemotherapeutic agents

Examples of chemotherapeutic agents	The main risks to the foetus
Plant alkaloids: vincristine, vinblastine, vinorelbine	Preterm delivery, intrauterine growth restriction (IUGR) [67]. Defect in the atrial septum [68].
Anthracycline antibiotics: doxorubicin, daunorubicin, adriamycin, idarubicin, epirubicin, dactinomycin, bleomycin, mitoxantrone	Mid-trimester miscarriage, transient neonatal neutropenia, and sepsis, IUGR [69]. Transient myelosuppression [70].
Alkylating agents: cyclophosphamide, busulfan, ifosfamide, chlorambucil, carmustine, dacarbazine	Absent toes, eye abnormalities, low-set ears, and cleft palate [71]. Oesophageal atresia, abnormal inferior vena cava [72]. Pyloric stenosis, renal agenesis, and liver calcifications [73].
Antimetabolites: Methotrexate, 5-fluorouracil, aminopterin, cytarabine, mercaptopurine.	Spontaneous abortions [68, 74]. Ventriculomegaly, microcephaly, syndactyly, deficient growth and development [75–77].
Cisplatin and carboplatin	Sensorineural hearing loss, respiratory distress syndrome [10, 78].
Trastuzumab	Kidney injury [79] kidney perfusion [80]. Respiratory failure, capillary fragility, and neonatal death [33].

**Table 1.** The main risks related to chemotherapeutic agents. Figure from Basta 2015.

### *Endocrine therapy*

During pregnancy, hormonal agents such as selective oestrogen receptor modulators, SERMs can disturb the hormonal environment. Of these, tamoxifen (ATC L02BA01) and its metabolite interact with embryonic or fetal tissues, is teratogenic and may lead to severe foetal anomalies. Studies have reported a foetal malformation rate of up to 20%, including craniofacial malformations and ambiguous genitalia. Therefore, it is recommended that endocrine therapy will be delayed until after birth (Navrozoglou 2008, Amant 2012, Zagouri 2013). Oral aromatase inhibitors (ATC L02BG) are not indicated in premenopausal women (Amant 2012, Zagouri 2013). However, as the upper age limit for this investigation is 55, we expect to identify these prescriptions in non-pregnant women.

### *Targeted therapy*

Treatment with trastuzumab (L01XC03) in Her-2-positive breast cancer tumours is contraindicated during pregnancy. HER is strongly expressed in the foetal renal epithelium and exposure to trastuzumab has been associated with renal failure, reduced amniotic fluid, foetal limb anomalies, pulmonary hypoplasia and death (Amant 2012, Zagouri 2013, Rojas 2019, MacDonald 2020). The risk of oligo- and/or an-hydramnios seems to be attributed particularly to exposure after the first trimester (Zagouri 2013). Also the long-term sequelae for the foetus are unknown. HER2-targeted treatment may be discussed in special high risk situations, and if the patient conceives while taking trastuzumab, exposure is not considered an indication for termination of pregnancy (Cardonick 2014, Rojas 2019). No studies exist, yet, demonstrating safety for the use of pertuzumab (L01XC13) in pregnancy (Rojas 2019, MacDonald 2020). There are insufficient data on lapatinib (L01EH01) and bevacizumab (L01XC07) during pregnancy and their use cannot, thus, be recommended (Zagouri 2013).

This demonstration project offers solutions on how to study medication exposure in diseases where accurate diagnosis requires histopathological examination and classification and, due to course of the disease, incidence is a better indicator defining a patient than prevalence. We will focus on improving methods for developing measurements of medication exposure in hospital settings. Cancer registries often lack data on cancer therapies especially those administered at outpatient visits such as chemotherapeutic agents and radiation (Beatty 2011, Caldarella 2012, Gurney 2013, Mallin 2013).

## **6. Event: Pregnancy-associated breast cancer (PABC)**

Pregnancy has a dual effect on breast cancer risk. Full-term pregnancies in early life (below age 30) have consistently been associated with a long-term reduced risk of breast cancer while a transient increased risk immediately after the pregnancy has been observed. A study including 2.3 million Danish women and 1.6 million Norwegian women observed the reduction in breast cancer risk in pregnancies lasting 34 gestational weeks or longer (Husby 2018).

Pregnancy-associated breast cancer (PABC) is generally defined as breast cancer diagnosed during pregnancy or within one year after childbirth (Ahn 2003, Amant 2012, Hartman 2016). Although about 80 % of breast masses that develop during pregnancy and breastfeeding are benign (Ahn 2003, Amant 2012, Expert Panel 2018), up to 3.8% of all breast cancers occur in pregnant and breastfeeding women (Vinatier 2009).

PABC is a very rare type of cancer. However, given PABC occurs in 1/10 000 to 1/3000 pregnancies, it is one of the most commonly diagnosed cancer during pregnancy (Amant 2012, Expert Panel on Breast Imaging 2018). As women delay childbearing into the fourth and fifth decades, PABC is more frequently encountered by oncologists, gynecologists, and obstetricians.

### **Diagnosis**

Ultrasound has the highest, up to 100%, sensitivity for the diagnosis of PABC (Expert Panel 2018, MacDonald 2020). Therefore, breast ultrasound is considered as the first imaging modality for the evaluation of breast lumps during pregnancy and lactation (Ahn 2003, Navrozoglou 2008, Kakoulidis 2015, Expert Panel 2018). Imaging both breasts is important as the incidence of bilateral disease may be as high as 10% (Kakoulidis 2015). If the breast ultrasound is negative or there are suspicious sonographic findings, additional imaging with mammography or digital breast tomosynthesis may be indicated (Expert Panel 2018).

Knowledge of the tumor subtype and grade is crucial for the management and treatment of breast cancer. Biopsies, preferably ultrasound-guided core needle biopsy, can be safely performed for suspicious masses at any gestational age. This allows precise diagnosis and avoids surgical biopsy but pathologists should be alerted to the pregnant or lactational state of breast (Cardonick 2014 Kakoulidis 2015). Core needle biopsy also allows for evaluation of hormone receptor expression, a known predictive biomarker, by immunohistochemistry.

### **Breast cancer types**

As this demonstration project will use cancer registries as the main data source, algorithms will be based on ICD-O-3 (the latest available version), topography C50 and any ICD-O-3 morphology except those for leukemia, lymphoma and Kaposi's sarcoma i.e. morphology <9590 excluding 9140. To identify breast cancer diagnosis and/or treatment episodes from patient registry data, also ICD-10 (C50.xx) and ICD-9 (174.XX) codes can be relevant.

As in non-pregnant women, the most prevalent histological type of PABC is invasive ductal carcinoma (70-90%) followed by invasive lobular carcinoma and inflammatory carcinoma (Ahn 2003, Navrozoglou 2008, Cardonick 2014) and with all breast cancer subtypes represented (MacDonald 2020). To avoid potential effect of breast cancer screening, no precursor lesions but only malignant primary tumors (behavior = 3) of the breast according to the WHO 2012 classification will be considered (Lakhani 2012, Appendix II).

### **Breast cancer severity**

Breast cancer severity and prognosis is determined by tumour biology and stage. TNM staging system, where T stands for tumour, N for node and M for metastasis, is the most common way to evaluate the extent of

disease i.e. stage breast cancers (Sobin 2009, Appendix III). Other prognostic factors include oestrogen receptor (ER) and progesterone receptor (PR) status, human epidermal growth factor receptor 2 (HER2) status and the grade of the cancer. In order of increasing aggressiveness and worse prognosis, the subtypes are Luminal A (ER+ and/or PR+, HER2-), Luminal B (ER+ and/or PR+, HER2+) and triple negative (ER-, PR-, HER2-) breast cancer (Akinyemiju 2015). PABC is more likely to be ER and PR negative and HER2-positive compared to age-matched controls (Johansson 2019, MacDonald 2020).

Changes in breast density during pregnancy and lactation together with absence of screening at young age, contributes to delays in diagnosis, later stage at recognition and consequently poor prognosis in PABC (Ahn 2003, Kakoulidis 2015, Expert Panel on Breast Imaging 2018). Diagnostic delays up to 7 months have been documented for pregnant patients (Navrozoglou 2008, Cardonick 2014, Kakoulidis 2015). One month delay may increase the risk of nodal involvement by 0.9 % to 1.8 % while a 6-month delay increases the risk by 5.1% (Kakoulidis 2015). PABC tumours are larger and there is higher incidence of nodal involvement than in non-PABC (Ahn 2003, Amant 2012, MacDonald 2020). A Swedish study extracting medical records of 273 PABC cases and 273 age- and hospital-matched non-PABC controls found no evidence of delayed diagnosis or treatment in women with PABC following the first health care contact (Johansson 2019). However, there was an indication of longer time between symptoms to first health care contact in woman with PABC (35 days) than in controls (23 days) although the difference was not significant.

Reliable and safe staging is necessary to choose between starting with local or systemic therapy (Rojas 2019). After a definitive diagnosis, mammography (with abdominal shielding) of the unbiopsied breast is recommended to exclude contralateral disease. Because PABC is often diagnosed at an advanced stage, systemic staging is often necessary. Lungs, bone and liver are the most common metastatic sites. To exclude pulmonary metastasis, chest radiography (with abdominal shielding) can be carried out safely during pregnancy. A liver ultrasound is the preferred method to detect liver metastases. In stage I and II disease the incidence of bone metastasis is low and bone scanning or magnetic resonance imaging (MRI) can then be delayed until postpartum (Cardonick 2014, Kakoulidis 2015).

MRI is useful in staging of breast cancer in non-pregnant women and also in assessing the response to neoadjuvant therapy (Kakoulidis 2015). MRI requires gadolinium which crosses the placenta and enters fetal circulation and amniotic fluid. Gadolinium exposure is associated with foetal anomalies; therefore, routine use of MRI is not currently recommended for the evaluation and treatment of PABC (Cardonick 2014, Kakoulidis 2015, Expert Panel 2018, Rojas 2019). Furthermore, the prone positioning necessary for breast MRI may lead to prolonged pressure on the gravid uterus, disrupting uterine blood flow (Rojas 2019). In one study including 53 PABC patients, preoperative MRI had large impact on clinical management as it changed surgical management for 28 % patients. Also, MRI showed pathologically proven larger tumor size or multicentric disease and greater extent of disease than mammography or ultrasound (Myers 2017). Decision regarding use should be made on individual basis weighing risks and benefits (MacDonald 2020). Breast MRI performed with iv gadolinium is safe during lactation since less than 0.04% of the administered gadolinium will be excreted into the breast milk (Myers 2017).

Therapeutic strategies are determined by tumour biology, stage, gestational stage and the patient's wish. Cancer treatment should adhere as much as possible to treatment guidelines for non-PABC and should also be discussed in a multidisciplinary setting including obstetricians, gynaecologists, medical and surgical oncologists, pediatricians and hematologists (Amant 2012, Zagouri 2013, Basta 2015, Rojas 2019). Whether the patient already has children, her desire to continue the present pregnancy and to maintain fertility determines her choices for management of PABC (Navrozoglou 2008). A number of fertility preservation procedures such as ovarian suppression and oocyte and embryo cryopreservation exist and these should be discussed and ideally initiated before the onset of systemic therapy (Gerstl 2018). A proposed algorithm for the diagnosis and treatment of PABC is provided in Appendix IV.

## Prognosis

In Europe, the relative 5-year survival rate for breast cancer irrespective of tumour type, stage and age at diagnosis is estimated to be 81-82%, and for those with early stage disease over 90 % (Allemani 2013, Sant 2015, Simoes 2018). European estimates for 1-year and 3-year relative survival are 95% and 87%, respectively (Sant 2015). PABC is a rare disease which limits the possibilities to conduct large powered controlled studies to address the question about survival. Women diagnosed during pregnancy with stages I and IIA have similar survival rates compared to non-pregnant women (Cardonick 2014). However, PABC is two and half times more likely to be diagnosed with advanced disease than non-PABC (Amant 2012).

A meta-analysis of 30 studies found that PABC patients had a significantly higher risk of death compared with those with non-PABC, pooled hazard ratio (HR) being 1.44 (95 % CI 1.27–1.63). The same results remained when adjusted for tumor stage (tumor size, nodal status or both) pooled HR being 1.40 (1.17–1.67) (Azim 2012). The most recent meta-analysis adopted a broader definition of PABC whereby cases diagnosed during pregnancy or up to five years postpartum were included. When measured through overall survival, there was an increased risk of death for PABC patients pooled HR being 1.57 (95 % CI 1.35–1.82). When cases were limited to those diagnosed up to one year postpartum, the pooled HR was 1.97 (95 % CI 1.88–2.06) and it did not change when two years period postpartum was used (Hartman 2016). The same meta-analysis found that women who have had a previous diagnosis of breast cancer and who subsequently become pregnant have reduced risk of death compared to those who do not become pregnant following breast cancer diagnosis. The result remained when accounted for the healthy mother effect i.e. selection bias whereby women who have had earlier stage disease and favourable outcomes are more likely to conceive than those who have relapsed.

There is ongoing controversy as to whether delayed diagnosis and young age at diagnosis account for the poor prognosis of PABC or if tumour biology of PABC is more aggressive than non-PABC when matched for age and stage (Expert Panel 2018). A study including breast cancer patients mainly from Germany and Belgium in 2003–2011 did not find a significant difference in disease free survival (DFS) or overall survival (OS) between 311 PABC and those of 865 non-PABC controls matched for known prognostic factors such as stage, age, hormonal receptors and type of treatment (Amant 2013). A study from Sweden including 778 women with PABC and 1661 breast cancers in nulliparous women found that women with PABC, and particularly those diagnosed 0–12 months postpartum, had more advanced tumours, higher proportion of ER/PR negative, HER2 positive and triple negative tumours. Compared to nulliparous women, women with PABC had increased hazard ratios for mortality but when adjusted for tumour characteristics, the HRs were attenuated and nonsignificant suggesting that poorer prognosis is attributed to tumour characteristics (Johansson 2018). A retrospective chart review of 99 PABC cases and 186 non-PABC controls matched by age and year of diagnosis conducted in New York showed PABCs to be more often ER and PR negative but no difference in Her2/neu overexpression. No significant difference in disease-free or overall survival between PABC and non-PABC patients was observed. Authors concluded that PABC is not an independent negative prognostic factor when controlling for receptor status and stage (Murphy 2012).

Breast cancer arising in the postpartum period is significantly associated with poor overall survival and risk of relapse or disease progression measured through disease free survival compared to patients diagnosed during pregnancy (Azim 2012, Hartman 2016). In a study from Germany including 25 PABC patients, 5-year survival rate was 76 % and 10-year survival rate 68 %. 10-year-survival was only 50 % for patients diagnosed postpartum (Simoes 2018). Thus, the current literature suggests existence of two distinct subgroups of PABC: those diagnosed during pregnancy and those affected after delivery and it is important to specifically research these two subsets of PABC in greater detail.

There is no evidence that termination of pregnancy would improve maternal outcome i.e. provide survival benefit for PABC patients (Navrozoglou 2008, Cardonick 2010, Amant 2012, Cardonick 2014). The most significant fetal sequelae of PABC are from iatrogenic prematurity. Carrying a pregnancy to near term should be a management goal (Zagouri 2013, MacDonald 2020). The mode of delivery should be determined based on obstetrical indication i.e. vaginal delivery is preferred over caesarean section due to

shorter recovery period (Zagouri 2013, Cardonick 2014, Rojas 2019). However, relatively high rates of caesarean sections have also been reported (Simoes 2018). Induced deliveries indicated prior to the term should be limited to late preterm deliveries between 35-37 weeks for patients who complete chemotherapy by 32-33 in order to complete the treatment (Cardonick 2014).

## 7. Research question and objectives

ConcePTION is a consortium setting up a platform to generate accurate information about safety of medications in pregnancy and breastfeeding. There are overall five demonstration projects (DP) concerned with specific topics and methodological issues. The goal of this DP is to study drug exposure when disease is measured through accurate identification of an incident case. Therapies for PABC are used as motivating example. The objective of this drug utilisation study will be to describe patterns of chemotherapy, endocrine therapy and targeted therapy use before, during, and after pregnancy, during time periods available within each data source.

### The main research questions are:

1. What is the incidence of PABC and non-PABC in women of reproductive age in European countries?
2. Is the pattern of cancer treatment (including surgery, radiation, chemotherapy, endocrine therapy and targeted therapy) similar in PABC and non-PABC patients?
3. What medications are used and how does the pattern of treatment change over the course of a pregnancy (e.g. prior to pregnancy, during, after pregnancy), by cancer severity and by country?
4. What is the pregnancy outcome (terminations of pregnancy, live birth, stillbirth, preterm birth, SGA/IUGR, as available) and mode of delivery for women with PABC and non-PABC and does that vary by cancer severity and by country?
5. What is the 5-year relative survival for women with PABC and non-PABC when adjusted for tumour characteristics and is there a difference in survival between PABC patients diagnosed during pregnancy and those diagnosed on year postpartum?

## 8. Research methods

### 8.1 Study setting

Contributing countries or databases: Finland, UK (Wales), Spain (Valencian Region), Germany and Scotland (see table in Appendix I). Data availability by DAP, pending on results from the Data characterization (WP7):

DAP	Study period	Comments related to data availability
Finland	1996-2019	
Spain (Valencian Region)	2007-2019 (or latest available)	In drugs database, recommended to use since 2010
Germany	2004-2018	
UK (Wales)	1998-2019	
Scotland		protocol review lacking

### 8.2 Study design

Study design will be a cohort study. Study population is women who were free of cancer prior to age 15 (i.e. childhood cancers excluded) and diagnosed with breast cancer at reproductive. Women diagnosed with breast cancer during pregnancy or within 12 months after childbirth (live births and stillbirths included) will be defined as pregnancy-associated breast cancer (PABC). Women who have no indication within the data source of a pregnancy at diagnosis or diagnosed > 1 year after delivery will be defined as non-pregnant breast cancer (non-PABC).

Study period will start from the first year cancer incidence and birth outcomes are available from the data source (whichever is the latest) and will end to most recent date of the data source where maternal death is available.

### **8.3 Study material**

#### **Exposures**

Cancer therapies (surgery, radiation, chemotherapy, endocrine therapy and targeted therapy) will be evaluated as binary variables (treatment yes/no) overall and by trimesters. Specific analyses on medications at a substance level before, during and after pregnancy will be performed whenever possible. Medications will be classified according to the (ATC) classification system ([https://www.whocc.no/atc\\_ddd\\_index/](https://www.whocc.no/atc_ddd_index/)). Primary exposure is antineoplastic agents (ATC class L01) and endocrine therapy (ATC class L02). Full list of medications is provided in Appendix VI.

#### **Primary outcome – PABC and maternal survival**

Maternal 5-year relative survival in woman with PABC vs non-PABC patients.

#### **Secondary outcomes - pregnancy outcomes**

Mode of delivery and the following pregnancy outcomes (termination of pregnancy, live birth, stillbirth, preterm birth, small for gestational age SGA/ IUGR) in women with PABC and non-PABC.

Diagnostic codes and quality indicators from the ConcePTION data characterization will be employed. We will use the event definitions and algorithms to identify these pregnancy outcomes as agreed in the ConcePTION Consortium.

#### **Variables**

Variables that are important: maternal age at diagnosis, date of cancer diagnosis, grade TNM stage, gestational age (GA) at diagnosis, tumour morphology (histology), oestrogen receptor and progesterone receptor status, HER2/neu receptor status, tumour grade, GA age at first cycle of chemotherapy, GA at delivery, mode of delivery, pregnancy outcome, birth weight, preterm birth, congenital anomalies, and childhood development, if available.

Variables that may have an impact on pregnancy outcome, cancer risk and/or treatment choices such as country, calendar year, parity, family history, BMI, socioeconomic status, smoking, alcohol intake, substance misuse, breastfeeding, and relevant co-morbidities as available.

### **8.4 Data sources and management**

This study will utilize data from five countries with geographic spread across Europe using the ConcePTIONcommon data model (CDM). Data will remain in the country of origin, and only aggregated results will be loaded to ConcePTION platform. The following data sources have been selected (See the list of all DAP in Appendix I):

- Finland
- UK: SAIL database (Wales)
- Spain: Rare Disease Research Unit. FISABIO (Valencian Region)
- Germany: GePARD
- Scotland

#### **A description of data sources participating in this project**



### **Germany (GePaRD)**

GePaRD is based on claims data from four statutory health insurance providers in Germany and currently includes information on approximately 25 million persons who have been insured with one of the participating providers since 2004 or later. Per data year, there is information on approximately 20% of the general population and all geographical regions of Germany are represented. In addition to demographic data, GePaRD contains information on dispensations of reimbursable prescription drugs as well as outpatient (i.e., from general practitioners and specialists) and inpatient services and diagnoses. **The Leibniz Institute for Prevention Research and Epidemiology – BIPS** will be Data Access Provider for the GePaRD data. GePaRD data have been used for vaccine safety studies and pregnancy studies. GePaRD is listed under the ENCePP resources database.

### **Finland (linkage of several nationwide registries)**

Universal health insurance coverage is accessible for all citizens and permanent residents in the country. Municipalities (currently around 200) are responsible for arranging and funding health care. Health services are divided into primary health care and specialized medical care. The data that THL provides access to is the majority of healthcare registries covering the whole population of Finland (around 5.6 million inhabitants). The core data of the Drugs and Pregnancy project includes data from Medical Birth Register, Register of Congenital Malformations and Register of Induced Abortions from 1996 onwards. Drugs and Pregnancy Database also includes following registries maintained by the Kela: Special refund codes and diagnoses three months before pregnancy to three months following delivery or abortion and drug purchases and reimbursements from three months before pregnancy to three months following delivery or abortion also 1996 onwards. The core data of the Drugs and Pregnancy currently includes all pregnancies ending in delivery or induced abortion in 1996-2018 the total amount being around 1,5 million pregnancies. Additional data sources maintained or accessed by THL and mapped to ConcePTION CDM are Care Register for Health Care (HILMO), Register of Primary Health Care visits (Avohilmo), Finnish Cancer Registry and Cause of Death Registry for women diagnosed with cancer and for children up to one year of age. Data collection is mandatory by law and does not require informed consent from the recorded subjects. Data is stored on an individual level and can be linked by the personal identification number assigned to all citizens and permanent residents in Finland at birth or upon immigration.

**Spain (FISABIO) Rare Disease Research Unit of FISABIO integrates, as described in WP-7:** Prescription and dispensations dataset (GAIA), Morbidity through Hospital discharges database (CMBD), Cancer Registry (RTC), Perinatal Mortality Registry (RMPCV), Mortality Registry (RMCV), Birth Registry (MetaB) and Congenital anomaly Registry (RPAC-CV).

A set of multiple, public, population-wide electronic databases for the Valencian Region will be used. Valencian Region is the fourth most populated Spanish region, with ≈5 million inhabitants and an annual birth cohort of 48 000 newborns representing 10.7% of the Spanish population and around 1% of the European population. Together, all the included databases will provide exhaustive longitudinal information including sociodemographic and administrative data (sex, age, nationality, etc.), clinical (diagnoses, procedures, etc.), drug information (prescription, dispensation) and healthcare utilization data from hospital. It also includes a set of associated population databases and registries of significant care areas such as cancer, rare diseases, congenital anomalies, and also public health databases from the population screening programmes. All electronic health systems use the ICD-9-CM and/or the ICD-10 and its derivatives. All the information in the databases can be linked at the individual level through a single personal identification code, the health number. The databases were initiated at different moments in time, but it is recommended to use them since 2010 (due to high quality improvements) until the last year available (it could differ between databases).

### **United Kingdom: Wales (SAIL)**

The Secure Anonymised Information Linkage (SAIL) Databank sources, accesses, links and analyses prospectively collected routine health and population data, within a governed infrastructure that is safe and secure. All datasets are anonymised and encrypted by a third party, and returned to SAIL for linkage. Data are held on 5, 400,000 people, since 1998. Data are available within 3 months of events. SAIL holds linkable,

anonymised national datasets, including: Accident and emergency care from 2009, Critical care from 2016, Congenital Anomaly Register and Information Service for Wales (CARIS), In-patient and out-patient PEDW records, Maternity dataset from 2015 for additional data on childbirth, National Community Child Health Database (NCCHD, includes gestation (ultrasound), birth centiles, childbirth, infant feeding, developmental screening and vaccinations), National Pupil Database Wales (education attainment to 16), ONS births and deaths (compulsory registration), Primary care data (including all prescriptions and diagnoses) from ~75% of Welsh GP practices. **Swansea University** will be Data Access Provider for the SAIL data in this project.

## **Scotland**

The National Health Service (NHS) in the UK is a publicly-funded health service that is free at the point of care for everyone resident in the UK. Information Services Division (ISD) is a part of NHS National Services Scotland and holds national level NHS health and health-related data for over 5 million people in Scotland. The Service holds health related data which in some cases cover an individual from before birth, with the mother's antenatal records, through to that individual's death registration record. For the Data Characterisation study ISD will use the most pertinent National Dataset and registries to fill the ConcePTION CDM main columns: NRS Births, Stillbirth and Infant Deaths, Teenage pregnancy, Prescribing Information System for Scotland (PIS), Maternity Inpatient and Day Case, Scottish Birth Record, Scottish Drug Misuse Database, National Record of Scotland Deaths Data, Notification of Abortion Statistics (AAS), Outpatient data, Hospital admission, Mental Health.

Each DAP will perform the following tasks:

- 1) Obtain required ethical and legal permissions to use the data in this project
- 2) Extract and transform the individually linked data locally into ConcePTION CDM
- 2) Check and run script distributed to the DAP by the ConcePTION coordinating centre
- 3) Run standard scripts to check data quality (quality assessment of data)
- 4) Run the scripts for this specific study
- 2) Send aggregated results to the remote ConcePTION secure platform while data will remain with the DAP.

## **8.5 Study size**

Assuming 25% of annual breast cancer cases occur in women of childbearing age (15-54 years) and 3.8% of breast cancers occur in pregnant and breastfeeding woman (i.e. the ratio of PABC vs. non-PABC to be 1 to 6) and 5-year relative survival at 82%, to detect a 40% increased risk for death in PABC vs. non-PABC patients with 80% power and type I error rate of 0.05, we would require 2 965 breast cancer cases. Using the EU-27 breast cancer incidence of 90.7 per 100,000 in women aged 15-54, we will need a sample size of around 3.27 million women years in women of childbearing age. <https://sample-size.net/sample-size-survival-analysis/>

The prevalence of low birth weight in the general population is estimated to be around 5% and the prevalence of preterm birth 6 to 10 %.

## **8.6 Data analysis**

Statistical analyses will be carried out through the ConcePTION ecosystem with a common data model and common statistical analysis plan. Data will remain local, and only aggregated results or effect estimates will be submitted for pooling. Initial pilot modelling of the statistical analysis plan (SAP) will be carried out using the Finnish data. Then scripts coded in R will be circulated to all DAPs through the ConcePTION task management system.

Descriptive analysis of cancer therapies used to treat breast cancer over the course of a pregnancy (prior to, during, after pregnancy) and during pregnancy (1st, 2nd or 3rd trimester) will be provided.

Relative survival has become the “gold standard” method for estimating cancer survival in population-based data. Relative survival is the ratio of the observed probability of survival ( $S$ ) of cancer patients and the probability of survival that would have been expected ( $E$ ) if patients had had the same survival probability as in the standardized general population

$$R(t) = \frac{S(t)}{E(t)}$$

where  $R$ ,  $S$  and  $E$  are the relative, observed and expected survival probabilities, respectively, at time  $t$ . The expected survival derives from the general population mortality using life tables stratified by age, sex and calendar period (Nur 2010).

5-year relative survival analyses will be carried out using e.g. Cox proportional hazard regression and flexible parametric models to elucidate the complex associations between time-since-conception, medication exposure, breast cancer incidence and survival and to control for important confounders. Effects will be presented as relative risk estimates with CI describing the precision of the estimate (95% CI). Survival analysis is increasingly used also in perinatal epidemiology to assess time-varying risk factors for pregnancy outcomes (Ahrens 2012). Maternal survival and pregnancy outcomes will be compared according to breast cancer stage to disentangle the impact of the medication from the underlying illness (Wood 2010).

Stage at diagnosis is a very strong predictor for prognosis but data can be incomplete in the data source. Furthermore, information on stage is more often incomplete in patients with advanced tumours and poor survival. Thus, complete case analysis may restrict the dataset substantially, introduce bias and lead to incorrect conclusions (Nur 2010).

Analyses will be stratified by country and time period.

### **Handling of missing data**

Patterns of missingness will be explored and handled as appropriate (Sterne 2009, Nur 2010, Perkins 2018). If supported by ConcePTION tools and necessary variables to predict missing values are included in source data, we will perform multiple imputation by chained equations (MICE) for missing values in covariates to improve measurement of medication exposure and prognostic factors. MI will be done including exposure variables, covariates and outcome variables and estimates from imputed data sets will be combined by Rubin’s rules (Rubin 1987, Graham 2007).

Meta-analyses will be used to combine the aggregate data obtained from each DAP as appropriate. For the meta-analysis, effect estimates will be pooled using the inverse variance method for weighting i.e. weighting the country-specific log hazard ratios by the inverse of the within countries’ variances (Selmer 2016). The meta-analysis on aggregate data will allow for adjustment for country-optimized covariates (See Appendix X: Meta analytic techniques for use in ConcePTION DPs).

### **Sensitivity analyses to assess the robustness of results**

As the strongest known modifier of a woman’s breast cancer risk is her reproductive history (Husby 2018), a sensitivity analysis using only nulliparous women as a control group will be done.

Socioeconomic status (SES) has been associated with both breast cancer incidence and survival (Woods 2006, Sprague 2011, Quaglia 2013, Akinyemiju 2015). Previous studies have been unable to assess any difference in survival for women according to oestrogen receptor status with pregnancy (Hartman 2016). If supported by the available data, a sensitivity analysis adjusting for SES and sensitivity analysis according to receptor status to ascertain whether there are any differences in outcomes for those who become pregnant with endocrine-responsive tumours compared to non-responsive tumours will be done.

If it is possible to perform MICE as a primary analysis, then complete case analysis will follow as a sensitivity analysis.

## **8.7 Quality control**

The studies will be conducted in line with the ENCePP Code of Conduct for scientific independence and transparency, and the FAIR (Findable, Accessible, Interoperable, Reusable) principles of the ConcePTION.

Each DAP will be responsible for the extraction, transformation, and loading (ETL) of their original data to the ConcePTION CDM. Standardized scripts in R to run against data in the ConcePTION CDM will be written by the group of statisticians and computer scientists and delivered through the task management system. Result outputs from the scripts will be submitted to a computing platform that can be accessed remotely by DAPs and ConcePTION partners and participating DAPs using authentication. Access to each DAP's results on the platform will be limited to the data access provider, WP1 public partner statisticians, and WP7 public partner statisticians.

The data quality and characterization checks will take place in collaboration with partners. All data will remain local and only summary measures will be reviewed by DAPs in collaboration with WP7. This process will proceed iteratively in collaboration with each DAP until consensus on fitness for purpose has been reached between WP7 and the DAP, the result of this consensus process and some core results will be made available on the catalogue in a private area for inspection by investigators and DAPs. For all indicators and characterization outputs resulting in a cell count less than 5, counts will not be reported and will be replaced with "<5" programmatically (see Protection of Human Subjects, below for details on numbers 1-4, and missing data).

Level 1 data checks review the completeness and content of each data table of the ConcePTION CDM to ensure that mandatory variables contain data and conform to the formats specified by the CDM specifications (e.g., data types, variable lengths, formats, acceptable values, etc.). Level 1 data checks are to verify that ETL procedure to convert from source data to the ConcePTION CDM has been completed as expected. Formats for all values will be assessed and compared to a list of acceptable formats. Frequency tables of variables with finite allowable values will be created to identify unacceptable values. Distributions of days and months of birth to assess any rounding will be constructed.

Level 2 data checks assess the logical relationship and integrity of data values within a variable or between two or more variables within and between tables. Level 2 data checks will assess records occurring outside recorded person time (i.e. before birth, after death, or outside of recorded observation periods) and implausible combinations such as high birth weight and preterm birth.

## **8.8 Limitations of the research methods**

Coverage and validity of information on medication administered in hospitals and how well that is linkable with the cancer registry data is currently unknown. This may create observation gaps for treatment and there may be some patients classified as unexposed who are actually treated. However, the potential misclassification of treatment is assumed to be similar in PABC and non-PABC patients for which it should not affect our comparison.

Considering the optimal method of analysis i.e. MICE, it may not be possible to identify all the important covariates that are needed to predict the missingness and several rounds of data updates and calibration of the model may not be feasible in the ConcePTION setting.

All the potential data sources willing to contribute have been identified for the study. We may still have limited power to adjust for the most important prognostic factors. Also, when the exposure and outcome

are rare, there might be countries without an exposed event or DAP may prohibit disclosing the numbers which may limit the possibilities to analyse the data (see below, 9).

## 9. Protection of human subjects

This is non-interventional study based on secondary use of data. Therefore, the reporting of suspected adverse reactions as individual case safety reports is not required as per the EMA Guideline on Good Pharmacovigilance Practices. This study is not considered a PASS because it does not aim to “identify, characterize or quantify a safety hazard, confirm the safety profile of the medicinal product, nor measure the effectiveness of risk management measures.” When the data characterization is done, the marketing authority holder shall monitor the results and consider possible implications for the risk-benefit balance of the medicinal product concerned.

This study is compliant with the provisions of the ENCePP Code of Conduct, Revision 4. The protocol and governance arrangements must be reviewed and approved by a properly constituted institutional review board/independent ethics committee/research ethics board according to the national guidelines before the study start. A signed and dated statement that the approval has taken place and waiver of informed consent must be given to the principal investigator before study initiation.

DAPs may prohibit the public release of numbers 1-4 in any data category (except ‘information missing’). This applies to all documents in the public domain and communications outside secure links (e.g. emails). This not only applies to text and tables, but also to reporting that could lead to the derivation or calculation of a low number in any category, for example:

1. Where an unadjusted OR or RR is reported for a contingency table, and the denominators and numerator in the larger category are available, it is easy to calculate the missing value.
2. Where a proportion is reported in a figure or graph or table, and the total number of cases is reported either in the same report or another report or publication, the number can be calculated.
3. Where numbers in categories across Europe are low, we only have permission to say the ‘Wales contributed data’. We would breach our conditions of approval to say ‘Wales contributed cases’. \*low can only be defined with reference to the number of cases and countries.

Wales’ European projects have permission to pass low numbers (1-4) to the centre responsible for analysis, via secure links to authorised colleagues on the above conditions. These numbers are to be aggregated before reporting. <https://www.ncbi.nlm.nih.gov/books/NBK350762/>

## 10. Plans for disseminating and communicating study results

The results of this study will be published as ConcePTION report and scientific papers in peer-reviewed journals. Manuscripts will be prepared independently by the investigators and in accordance with the current guidelines of STrengthening the Reporting of OBservational studies in Epidemiology (STROBE), the ENCePP standards and EMA guidelines.

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## 12. Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1	Appendix I		Databases and third party DAPs
2	Appendix II		Main categories of malignant primary tumours of the female breast
3	Appendix III		TNM staging system for breast cancer
4	Appendix IV		Proposed algorithm for the diagnosis and treatment of PABC
5	Appendix V		Drugs used to treat event
6	Appendix VI		Procedures used to treat event
7	Appendix VII		DAPs experience on breast cancer
8	Appendix VIII		Covariate items across DAPs



### 13. Annex 2. ENCePP checklist for study protocols

*A copy of the ENCePP Checklist for Study protocols available at [http://www.encepp.eu/standards\\_and\\_guidances/checkListProtocols.shtml](http://www.encepp.eu/standards_and_guidances/checkListProtocols.shtml) completed and signed by the main author of the study protocol should be included in Annex 2.*

Doc.Ref. EMA/540136/2009

## ENCEPP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

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

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

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

**Study title: Studying drug exposure when disease is measured through accurate identification of an incident case: application to breast cancer and pregnancy**

**EU PAS Register® number:**  
**Study reference number (if applicable):**

<b>Section 1: Milestones</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection <sup>1</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.1, 8.2
1.1.2 End of data collection <sup>2</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.1, 8.2
1.1.3 Progress report(s)		<input checked="" type="checkbox"/>	<input type="checkbox"/>	
1.1.4 Interim report(s)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
1.1.5 Registration in the EU PAS Register®	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	4
1.1.6 Final report of study results.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	4

<sup>1</sup> Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

<sup>2</sup> Date from which the analytical dataset is completely available.

Comments:

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<b><u>Section 2: Research question</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
2.1 Does the formulation of the research question and objectives clearly explain:	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	5
2.1.2 The objective(s) of the study?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7
2.1.4 Which hypothesis(-es) is (are) to be tested?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7
2.1.5 If applicable, that there is no <i>a priori</i> hypothesis?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

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<b><u>Section 3: Study design</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.2
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6, 8.6
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.6
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

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<b><u>Section 4: Source and study populations</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
4.1 Is the source population described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.1
4.2.2 Age and sex	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.2
4.2.3 Country of origin	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.1
4.2.4 Disease/indication	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.2
4.2.5 Duration of follow-up	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.1, 8.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.2

Comments:

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<b><u>Section 5: Exposure definition and measurement</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6, 8.4, Appendix VIII
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6, 8.4, Appendix VIII
5.3 Is exposure categorised according to time windows?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5.6 Is (are) (an) appropriate comparator(s) identified?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.2

Comments:

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<b><u>Section 6: Outcome definition and measurement</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.3
6.2 Does the protocol describe how the outcomes are defined and measured?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.7
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

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<b><u>Section 7: Bias</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.2
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.8

Comments:

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<b><u>Section 8: Effect measure modification</u></b>	<b>Y es</b>	<b>N o</b>	<b>N / A</b>	<b>Section Number</b>
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7, 8.3, 8.6

Comments:

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<b><u>Section 9: Data sources</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6, 8.4, Appen dix VIII
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6, 8.4, Appen dix VIII
9.1.3 Covariates and other characteristics?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.4, Appen dix VIII
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.4, Appen dix VIII
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6, 8.4, Appen dix VIII
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6, 8.4, Appen dix VIII
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6, 8.3, Appen dix V- VI
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CDM docum ents
9.3.3 Covariates and other characteristics?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CDM docum ents

<b><u>Section 9: Data sources</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.4, CDM documents

Comments:

<b><u>Section 10: Analysis plan</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
10.1 Are the statistical methods and the reason for their choice described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.6
10.2 Is study size and/or statistical precision estimated?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.5
10.3 Are descriptive analyses included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.6
10.4 Are stratified analyses included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.6
10.5 Does the plan describe methods for analytic control of confounding?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.6
10.6 Does the plan describe methods for analytic control of outcome misclassification?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.6
10.7 Does the plan describe methods for handling missing data?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.6
10.8 Are relevant sensitivity analyses described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.6

Comments:

<b><u>Section 11: Data management and quality control</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.7
11.2 Are methods of quality assurance described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.7
11.3 Is there a system in place for independent review of study results?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.7

Comments:

<b><u>Section 12: Limitations</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.8
12.1.2 Information bias?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.8
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.8

<b><u>Section 12: Limitations</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.5

Comments:

<b><u>Section 13: Ethical/data protection issues</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9
13.2 Has any outcome of an ethical review procedure been addressed?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
13.3 Have data protection requirements been described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9

Comments:

<b><u>Section 14: Amendments and deviations</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
14.1 Does the protocol include a section to document amendments and deviations?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	3

Comments:

<b><u>Section 15: Plans for communication of study results</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
15.2 Are plans described for disseminating study results externally, including publication?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	10

Comments:

Name of the main author of the protocol: Maarit Leinonen

Date: 30/9/2021

Signature: 

## Appendix I: Databases and third-party DAPs

Country	Region	Data sources	DAP Name Name and Email of DAP contact person
Finland	Nationwide	Linkage of several registries	NIHW (THL) Finnish Institute for Health and Welfare, NIHW Maarit Leinonen (Maarit.leinonen@thl.fi)
Spain	Valencian Region	Linkage of several registries	FISABIO The Foundation for the Promotion of Health and Biomedical Research of Valencian Region. (Rare Disease Research Unit) Clara Caveró-Carbonell ( <a href="mailto:cavero_cla@gva.es">cavero_cla@gva.es</a> ) Laia Barrachina-Bonet ( <a href="mailto:barrachina_lai@gva.es">barrachina_lai@gva.es</a> ) Laura García- Villodre Óscar Zurriaga
Germany	17% of population	GePaRD (Claims data)	BIPS Leibniz Institute for Prevention Research and Epidemiology BIPS Tania Schink ( <a href="mailto:schink@leibniz-bips.de">schink@leibniz-bips.de</a> ) Ulrike Haug ( <a href="mailto:haug@leibniz-bips.de">haug@leibniz-bips.de</a> ) Miriam Heinig ( <a href="mailto:heinig@leibniz-bips.de">heinig@leibniz-bips.de</a> ) Katja Oppelt ( <a href="mailto:oppelt@leibniz-bips.de">oppelt@leibniz-bips.de</a> )
UK Wales	Nationwide	SAIL Databank	USWAN University of Swansea Sue Jordan ( <a href="mailto:s.e.jordan@swansea.ac.uk">s.e.jordan@swansea.ac.uk</a> ) Daniel Thayer ( <a href="mailto:d.e.thayer@swansea.ac.uk">d.e.thayer@swansea.ac.uk</a> )
UK Scotland	Nationwide		University of Dundee Scotland Tom MacDonald ( <a href="mailto:t.m.macdonald@dundee.ac.uk">t.m.macdonald@dundee.ac.uk</a> )

## **Appendix II: Main categories of malignant primary tumours of the female breast**

The World Health Organization **classification of tumors of the breast** is the most widely used pathologic classification system for tumours. Due to data availability, coding in cancer registries most likely follows the 4<sup>th</sup> edition of the WHO series published in 2012.

### **Epithelial tumors**

- microinvasive carcinoma

### **Invasive breast carcinoma**

- invasive breast carcinoma of no special type (NST)
- invasive lobular carcinoma
- tubular carcinoma
- cribriform carcinoma
- mucinous carcinoma
- carcinoma with medullary features
- carcinoma with apocrine differentiation
- carcinoma with signet-ring-cell differentiation
- invasive micropapillary carcinoma
- metaplastic carcinoma
- rare types

### **Epithelial-myoepithelial tumors**

- adenoid cystic carcinoma

### **Papillary lesions**

- intraductal papillary carcinoma
- encapsulated papillary carcinoma
- solid papillary carcinoma

### **Mesenchymal tumors**

- liposarcoma
- angiosarcoma
- rhabdomyosarcoma
- osteosarcoma
- leiomyosarcoma

### **Fibroepithelial tumors**

- phylloides tumor (malignant and pediductal stromal tumor, low grade)

### **Tumors of the nipple**

- Paget disease of the nipple

### **Clinical patterns**

- inflammatory carcinoma
- bilateral breast carcinoma



## Appendix III: TNM staging system for breast cancer

Staging is based on pathological staging (pTNM) when patient undergo surgery and/or clinical staging (cTNM). Tumour (T) describes the size of the tumour, node (N) describes whether the cancer has spread to lymph nodes and metastasis (M) describes whether the cancer has more distant metastases. Overview combining the pTNM and cTNM is provided below.

**TX** tumour cannot be assessed for size

**Tis** Carcinoma in situ (ductal carcinoma in situ, DCIS or Paget disease)

**T1** tumour is  $\leq 2$  cm further divided as

**T1mi** tumour is  $\leq 0.1$ cm

**T1a** tumour is more than 0.1 cm but  $\leq 0.5$  cm

**T1b** tumour is more than 0.5 cm but not more than 1 cm

**T1c** tumour is more than 1 cm but not more than 2 cm

**T2** tumour is more than 2 cm but  $\leq 5$  cm

**T3** tumour is bigger than 5 cm

**T4** tumour is divided into following groups:

**T4a** tumour has spread into the chest wall

**T4b** tumour has spread into the skin and the breast might be swollen

**T4c** tumour has spread to both the skin and the chest wall

**T4d** tumour is inflammatory carcinoma

**NX** lymph nodes cannot be assessed for spreading

**N0** no signs of cancer cells in lymph nodes or only isolated tumour cells (ITCs)

**N1** lymph node spreading is divided into following groups:

**N1mi** micrometastases in one or more lymph nodes

**N1a** cancer cells have spread into 1 to 3 lymph nodes and at least one is larger than 2mm

**N1b** cancer cells in the lymph nodes behind the breastbone found with a sentinel node biopsy

**N1c** cancer cells in 1 to 3 lymph nodes in the armpit and in the lymph nodes behind the breastbone

**N2**

**N2a** cancer cells in 4 to 9 the lymph nodes in the armpit, and at least one is larger than 2 mm

**N2b** cancer cells in the lymph nodes behind the breast bone and no sign of cancer in lymph nodes in the armpit

**N3** lymph node spreading is divided into following groups:

**N3a** cancer cells in  $\geq 10$  lymph nodes in the armpit of which at least one is larger than 2mm, or cancer cells in the nodes below the collarbone

**N3b** cancer cells in lymph nodes in the armpit and lymph nodes behind the breastbone

**N3c** cancer cells in lymph nodes above the collarbone

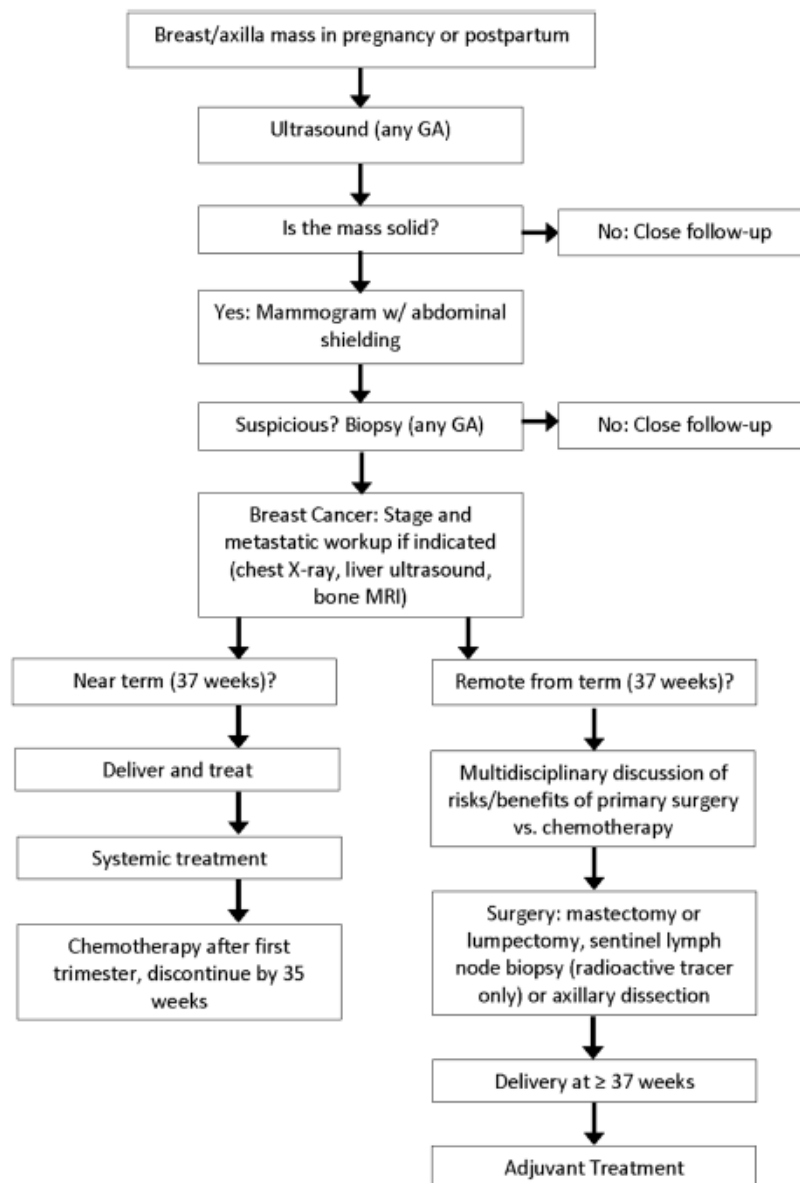
**M0** no sign of cancer spread

**Mo(i+)** no sign of the cancer on clinical examination or imaging but cancer cells present in blood, bone marrow or distant lymph nodes.

**M1** cancer has spread to another part of the body

## BREAST CANCER IN PREGNANCY

779



**FIG. 1.** Algorithm for the diagnosis and treatment of pregnancy-associated breast cancer.

Figure 1. Proposed algorithm for the diagnosis and treatment of PABC. Figure from Rojas 2019.

## Appendix V Drugs used to treat event

<b>CHEMOTHERAPY</b>	<b>ATC5</b>
Cyclophosphamide	L01AA01
Methotrexate	L01BA01
<b>Pyrimidine analogues</b>	<b>L01BC</b>
Cytarabine	L01BC01
Fluorouracil	L01BC02
Gemcitabine	L01BC05
Capecitabine	L01BC06
<b>Vinca alkaloids and analogues</b>	<b>L01CA</b>
Vinblastine	L01CA01
Vincristine	L01CA02
Vinorelbine	L01CA04
<b>Taxanes</b>	<b>L01CD</b>
Paclitaxel	L01CD01
Docetaxel	L01CD02
Paclitaxel poliglumex	L01CD03
Cabazitaxel	L01CD04
<b>Anthracyclines</b>	<b>L01DB</b>
Doxorubicin	L01DB01
Daunorubicin	L01DB02
Epirubicin	L01DB03
Aclarubicin	L01DB04
Idarubicin	L01DB06
Mitoxantrone	L01DB07
Pirarubicin	L01DB08
<b>Other cytotoxic antibiotics</b>	<b>L01DC</b>
Mitomycin	L01DC03
Ixabepilone	L01DC04
<b>Platinum agents</b>	<b>L01XA</b>
Cisplatin	L01XA01
Carboplatin	L01XA02
<b>TARGETED THERAPY</b>	
<b>Monoclonal antibodies</b>	<b>L01XC</b>
Trastuzumab	L01XC03
Bevacizumab	L01XC07
Pertuzumab	L01XC13
Ado-trastuzumab emtansine	L01XC14
Atezolizumab	L01XC32
<b>Cyclin-dependent kinase (CDK) inhibitors</b>	<b>L01EF</b>
Palbociclib	L01EF01
Ribociclib	L01EF02
Abemaciclib	L01EF03
<b>mTOR inhibitors</b>	<b>L01EG</b>
Everolimus	L01EG02
<b>Human epidermal growth factor receptor 2 (HER2) tyrosine kinase inhibitors</b>	<b>L01EH</b>
Lapatinib	L01EH01

Neratinib	L01EH02
<b>Phosphatidylinositol-3-kinase (Pi3K) inhibitors</b>	<b>L01EM</b>
Alpelisib	L01EM03
<b>Poly (ADP-ribose) polymerase (PARP) inhibitors</b>	<b>L01XK</b>
Olaparib	L01XK01
Talazoparib	L01XK04
<b>Other antineoplastic agents</b>	<b>L01XX</b>
Eribulin	L01XX41
<b>ENDOCRINE THERAPY</b>	
<b>Anti-estrogens</b>	<b>L02BA</b>
Tamoxifen	L02BA01
Toremifen	L02BA02
Fulvestrant	L02BA03
<b>Aromatase inhibitors</b>	<b>L02BG</b>
Anastrozole	L02BG03
Letrozole	L02BG04
Exemestane	L02BG06
<b>Selective estrogen receptor modulators (SERMs)</b>	<b>G03XC</b>
Raloxifene	G03XC01
Bazedoxifene	G03XC02
Lasofloxifene	G03XC03

## Appendix VI Procedures used to treat event

<b>Radiation therapy</b>	<b>ICD9</b>
Therapeutic Radiology and Nuclear Medicine	92.20 – 92.29
Stereotactic Radiosurgery	92.30 – 92.39
Intra-Operative Radiation Procedures	92.40 - 92.41
	<b>ICD10</b>
Encounter for antineoplastic radiation therapy	Z51.0
	<b>CPT</b>
Radiation treatment delivery	77401, 77402, 77407, 77412
Radiation treatment delivery (G codes)	G6003-G6014
IMRT treatment delivery	77385-77386
IMRT treatment delivery (G codes)	G6015-G6016
Port images	77417
IGRT	77387
IGRT (G codes)	G6001, G6002, G6017
CT Guidance	77014
Proton treatment delivery	77520-77525
Neutron beam treatment delivery	77422-77423
SRS treatment delivery	77371-77372
SBRT treatment delivery	77373
Hyperthermia	77600-77620
LDR Brachytherapy	77778
HDR Brachytherapy	77770-77772
Electronic Brachytherapy	0394T-0395T
IORT	77424-77425
Surface application of radiation source	77789
Infusion or installation of radioelement solution	77750
Intracavitary radiation	77761-77763
Supervision and handling	77790
	<b>OPCS</b>
Radiotherapy delivery	X65
Introduction of removable radioactive material into organ	Y35
Introduction of non-removable material into organ NOC	Y36
External beam radiotherapy	Y91
	<b>NCSP</b>
Systemic radiotherapy	WA010, WA019, WA029, WA039, WA099

Radiotherapy for primary tumour	WF001, WF002, WF003, WF004
<b>Surgery</b>	<b>ICD9</b>
Operations on the breast	85.0-85.99
Breast reconstruction	S2066-S2068
	<b>ICD10</b>
Acquired absence of breast and nipple	Z90.1x
	<b>CPT</b>
Mastectomy	19160, 19162, 19180, 19182, 19200, 19220, 19240, 19301 - 19307
Breast reconstruction	19340, 19342, 19357, 19361, 19364, 19366, 19367, 19368, 19369
	<b>OPCS</b>
Partial excision of breast	B28.2
Total excision of breast	B27.X
Breast reconstruction	B29.1, B29.3, B29.8, B30.1, B30.8, B30.9, T85.2, T86.2, T87.3, T91.1, B39.1, B39.2, B39.8, B39.9, B39.3, S48.2
	<b>NCSP</b>
Partial excision of mammary gland	HAB00, HAB10, HAB20, HAB30, HAB40, HAB99
Mastectomy	HAC10, HAC15, HAC20, HAC25, HAC30, HAC99
Reconstruction of breast	HAE00, HAE05, HAE10, HAE20, HAE99
Operations for local recurrence of breast cancer	HAF00, HAF10, HAF20, HAF99
<b>Chemotherapy Administration</b>	<b>ICD9</b>
Encounter for antineoplastic chemotherapy and immunotherapy	V58.1

Convalescence following chemotherapy	V66.2
Follow up exam following chemotherapy	V67.2
Injection of infusion of cancer chemotherapeutic substance	9925
	<b>ICD10</b>
Encounter for antineoplastic chemotherapy	Z51.1
	<b>CPT</b>
Chemotherapy administration	96400 - 96549
Drug code injections	J8000 – J9999
Chemotherapy administration other than infusion	Q0083-Q0085
Intralesional injection	11900, 11901
	<b>OPCS</b>
Procurement of chemotherapy	X70, X71
Chemotherapy delivery	X72, X73
Intravenous chemotherapy	X35.2
Continuous intravenous infusion of therapeutic substance NEC	X29.2
High cost drugs	X81-X98
	<b>NCSP</b>
Chemotherapy for local primary tumour	WP101, WB103, WB111, WB113, WB121, WB123, WB131, WB133, WB201, WB203, WB211, WB213, WB221, WB223, WB301, WB303, WB311, WB313, WB321, WB323, WB401, WB402, WB501, WB502, WB600, WB610
Chemotherapy for metastized tumour	WD105, WD115, WD125, WD135, WD205, WD215, WD225, WD305, WD315, WD325, WD405, WD415, WD505, WD515

## Appendix VII Experience of participating data sources to extract breast cancer

Datasource	Do you have any experience or expertise to share with respect to extracting this event from the data sources you have access to?	Do you have publications where this event was defined? if so can you indicate the PMID? If it is grey literature, can you indicate a link?	Can you briefly describe the algorithm(s) you have used to define this event? Please feel free to refer to the data dictionary you have shared earlier with WP7.	Can you share any additional comments with respect to this event? In particular: lessons learnt, strengths, weaknesses of the data sources you have access to identifying this event in the corresponding population	Have you conducted validation studies, or do you have any quantitative information on validity of this event or its occurrence in the population underlying the databases you have access to?
05_University_of_Dundee	Yes	22797844; 17855094; 15767381; 11297648; 11290637	22797844: Clinical Practice Research Datalink (patients' demographics, medical diagnoses, referrals to consultants and hospitals, and primary care prescriptions); 17855094: linkage between five breast cancer trials databases and the Scottish Cancer Registry (SCR) 15767381: linked database of acute	Cancer registration is reasonably robust in Scotland so we can be confident on the reliability of these data. CPRD diagnoses depend on whether or not they have been linked to hospitalization data.	We have not personally validated cancer registration data, but we believe that there is a 1% audit of this at ISD.



			hospital discharge (SMR01) records, cancer registrations, maternity (SMR02) database and death records in Scotland 11297648: Scottish Cancer Registry		
19_SIDIAP	Yes	PMID: 31819655	We use the ICD-10 C50 to identify breast cancer	Breast cancer diagnosis has been validated in SIDIAP against data from population-based cancer registries in Catalonia.	Please check the publication mentioned. Sensitivity for breast cancer was found to be of 89%.
33_THL	Yes	31199509, 22815141, 18226204, 28795403	ICD-10 codes C50 ICD-O-3 topography C50 and ICD-O-3 morphology <9590 excluding 9140 and behaviour code 3.	Registration and coding rules of multiple primaries for pairwise organs must be considered when international research projects use data from the cancer registries.	28350996, 29882462
34_USWAN	Yes	Jordan S. Knight J., Jones J. 2005 Prescription drugs: uses and effects: cytotoxics, disease control. Nursing Standard; 19(27); S1-2*	Read codes		These diagnoses are in the SAIL databases.

## Appendix VIII: Covariate items across DAPs

1=THL, 2=UK Sail, 3=FISABIO, 4=GePARD, 5=Scotland

DP5 information items considered important (x) or nice to have (red box)

Information item	1	2	3	4	5	DP 5
<i>Pregnancy timing</i>						
Pregnancy timing	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
<i>Medication exposure</i>						
<i>Source of medication information</i>						
Primary care/General practitioner	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Inpatient	if captured from cancer/patient registry	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Outpatient specialist	if captured from cancer/patient registry	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Prescription records (prescribed or dispensed)	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Private prescriptions – private healthcare	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Maternal self-report	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Details of medication</i>						
Name/ATC code of medication of interest	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Date of issued/dispensed prescription, administration or used	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
<b>Strength</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>Dosage – amount taken per day</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>Frequency – per day</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>Formulation (oral, injection, cream etc).</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>DDD dispensed</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>Quantity prescribed or dispensed (tablets)</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>Prescriber specialty</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Co-medications	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Maternal disease/medication indication</i>						
<i>Diagnosis</i>						
Diagnosis in healthcare database e.g. ICD10	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Diagnosis in disease registry	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Type of ward where the diagnosis was given	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Intervention in healthcare database as surrogate for disease	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Healthcare admission as surrogate for disease/disease severity	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Severity of disease</i>						
Health care visit pattern	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Co-morbid diagnosis/diagnoses	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Co-morbidity – Infection	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Outcomes</i>						
<i>Maternal pregnancy outcomes</i>						
Spontaneous abortions	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Termination of pregnancy – elective	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Termination of pregnancy - for fetal anomaly	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Pregnancy related conditions e.g. GD, preeclampsia, hypertension	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Mode of delivery	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Maternal death	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Maternal diagnoses postpartum (e.g. stroke, infection, psychosis, death)	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
<i>Perinatal outcomes</i>						
Live birth: normal	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Stillbirth	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Neonatal death	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Major congenital anomalies	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Gestational age at delivery/preterm birth	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Small for gestational age/ IUGR	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Birth weight	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Head circumference	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Length at birth	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Apgar score (5, 10 minutes)	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Admission to Neonatal Intensive Care Unit	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Childhood outcomes</i>						
Death - infant or childhood	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Health visitor/public health nurse records	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	2012->					
Growth in childhood	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Diagnosis in a specialist disease registry	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Healthcare diagnosis records – ADHD, ASD	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Referrals to specialists	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hospital admissions during childhood	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Childhood prescriptions	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Registered disability in child	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Academic results and school performance	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Special educational needs/educational support	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Psychometric measurements	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Confounders/covariates</i>						
Folic acid - pre-conception, first trimester, none	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Assisted conception	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Maternal age at delivery	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Maternal socioeconomic status –or	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

occupation, employment, income, education etc.						
Smoking status – prior to/ during pregnancy	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Alcohol consumption – during pregnancy	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Substance misuse services used - during pregnancy	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Body mass index	<input checked="" type="checkbox"/> 2005->	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Parity	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>