

# Pharmacovigilance of pregnancy exposures to medicinal products focusing on the risk of orofacial clefts

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Basel, 12.12.2019

.....  
Prof. Dr. Primo Schar, Dekan

*“Two there are who are never satisfied  
The lover of the world  
And the lover of knowledge”*

*Rumi -Persian poet*

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## Summary of the project

**Background:** It is important to obtain robust scientific information on possible safety concerns related to the use of drugs during pregnancy in post-approval settings. Since pregnant women are actively excluded from trials in the clinical development of most products, at the time of the drug entry in the market meaningful human data on the effects of that drug during pregnancy are rarely available. There are approximately 5 million pregnancies in the EU each year, and about 1 in every 10 women of childbearing age is pregnant each year. Insufficient information for management of maternal disease during pregnancy can have teratogenic impact on fetus.

**Aim and objectives:** This reach comprises three studies, in the first study; the goal was to evaluate the maternal use of medicines and the associated risks of cleft lip and/or palate in fetus and to link this to the accuracy and currency of safety information available in prescribing information. The second area of research was aimed at identifying and exploring social and digital media to understand patients' experiences regarding medicine use during pregnancy. Last, but not least, I contributed to the development of an enhanced pharmacovigilance programme for analysing drug exposure during pregnancy and outcomes in neonate.

**Method:** Firstly, I identified medication-induced risk factors for oral clefts with safety signal detection and safety signal evaluation techniques. Then I assessed the completeness of the safety information for pregnancy exposures in the Summary of Product Characteristics and the Patient Information in the UK and the US.

In second study, the content of posts concerning pregnancy and use of medicines in online pregnancy forums was analysed using artificial intelligence in the form of natural language processing and machine learning algorithms.

Third, the PRIM (PRegnancy outcomes Intensive Monitoring) system was developed as an enhanced pharmacovigilance data collection method. This was used to improve the quality and content of prospective case reports using sets of targeted checklists, structured follow-up, a rigorous process of data entry and data quality control, and programmed aggregate analysis.

**Results:** For 12 antiepileptic drugs studied there was a statistical disproportionality in individual case safety reports indicative of an increased risk of cleft lip and/or palate.

There are inconsistencies between the UK and US safety labels, despite the same evidence being available for assessment.

The second study showed that in social media forums many pregnant women with MS shared profound uncertainties and specific concerns about taking medicines during the reproductive period. There was evidence of concealment of information with health care professionals; however, the same evidence was shared with a peer group.

The PRIM method of enhanced pharmacovigilance has yielded substantially more information on the safety of fingolimod exposure during pregnancy than has been achieved via the regulatory authority-mandated pregnancy registry.

**Conclusion:** Use of medicines during pregnancy is an important topic for public health. There is a significant need to provide inclusive, unbiased, up to- date information to prescribers and women of childbearing age concerning the use of medicines in pregnancy and postpartum during breastfeeding. Information must be provided in a timely manner by a trusted source and patients should have access to health care professionals with the relevant expertise and knowledge. It is important that the full anonymised data set, along with evidence-based conclusions are made publicly available to inform decision-making.

## List of Abbreviations

Adverse event	AE
Cleft lip and/or palate	CL/P
European Medicines Agency	EMA
European Union	EU
Follow-up	FU
Food and Drug Administration (US)	FDA
Health care professional	HCP
Individual case safety report	ICSR
Innovative Medicine Initiative	IMI
Marketing authorization holder	MAH
Medicines and Healthcare products Regulatory Agency	MHRA
Multiple sclerosis	MS
Patient information leaflet	PIL
Pharmacovigilance	PV
Pharmacovigilance Risk Assessment Committee	PRAC
Summary of product characteristics	SmPC
United States	US
Web-Recognizing Adverse Drug Reactions	WEB-RADR
World Health Organization	WHO

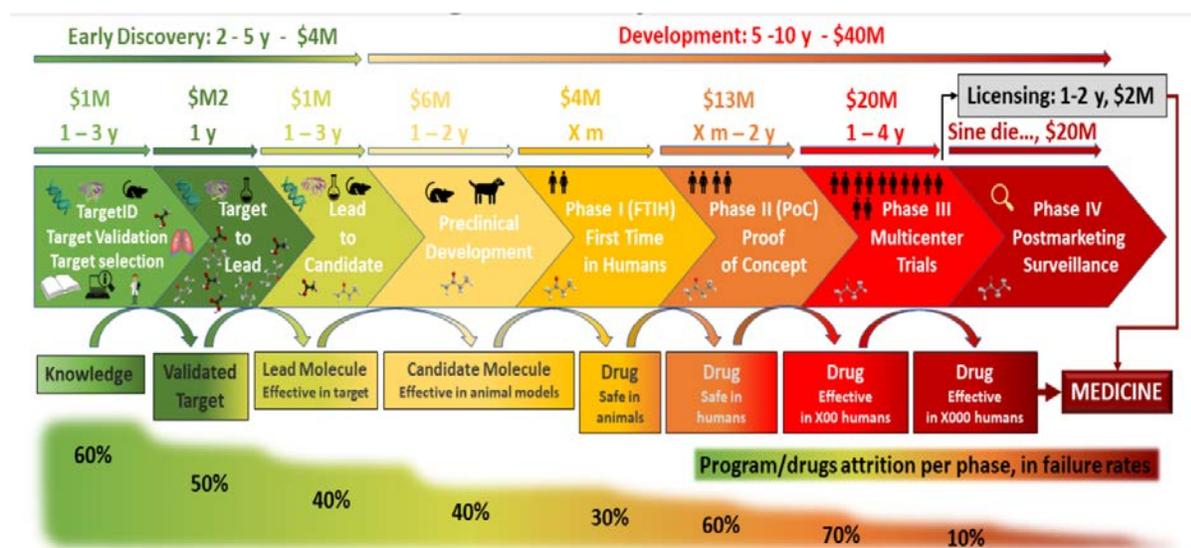
# 1. Introduction

## 1.1 Medicinal product development

Development of human medicinal products follows a highly regulated process prior to marketing authorisation. Controlled clinical trials are conducted in a rigorous and organized way in order to generate substantive medical data in support of a marketing authorization application. This involves systematic data collection and analysis of efficacy safety and quality of the medicine (see Figure 1). Although the controlled clinical trials are considered as standard for providing efficacy and safety data, the available data for safety from these trials have known limitations such as:

- Limited study sample size compared to real world patient population
- Limited exposure time
- Exclusion of high-risk patients such as:
  - Patients with organ impairment (e.g. hepatic dysfunction, renal dysfunction)
  - Paediatric and geriatric patients, and
  - Pregnant and breastfeeding women

Therefore, to overcome these limitations it is necessary that the marketing authorization holder (MAH) for a medicine and the health authorities continue monitor the safety of a medicine after approval and throughout the post-marketing or Phase IV period.



**Figure 1. Drug Discovery and Development process**

Source available at <https://doctortarget.com/machine-learning-applied-drug-discovery/> Internet Accessed Oct 2019

## 1.2 Definition of Pharmacovigilance by the World Health Organization

Pharmacovigilance (PV) is defined by the WHO as “...*the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. The aims of PV are to enhance patient care and patient safety in relation to the use of medicines; and to support public health programmes by providing reliable, balanced information for the effective assessment of the risk-benefit profile of medicines...*” (1). The WHO originally established its Programme for International Drug Monitoring in response to the thalidomide disaster detected in 1961.

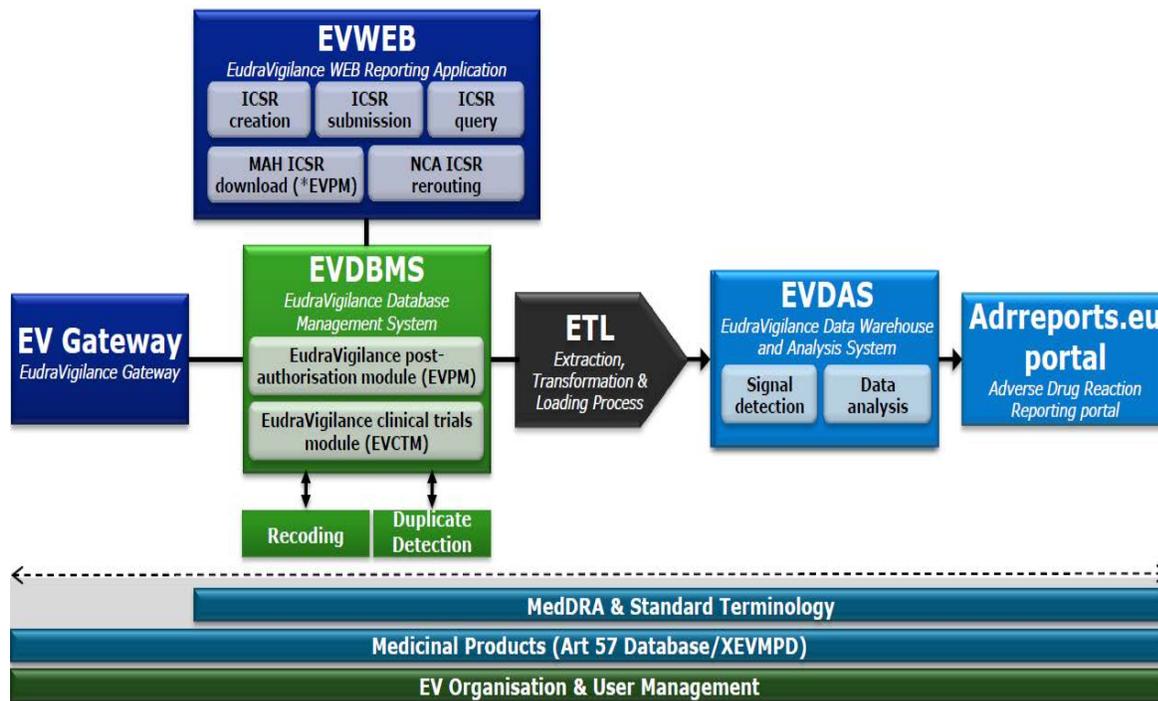
Pharmacovigilance begins during phase I clinical trials and translational studies; PV continues after the drug is authorised for marketing. Due to the different limitations of clinical trials, the complete safety profile of a drug cannot be fully assessed before marketing. Post-approval adverse reactions represent a major public health problem; causing or contributing to up to 5% of hospital admissions, around 28% of emergency visits, and approximately 5% of hospital deaths; the associated costs amount to an estimated seventy-five billion US dollars annually (2,3). Thus, MAHs, national bodies and government agencies such as the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and international organizations such as the World Health Organization (WHO) have expanded their pharmacovigilance activities in various ways. For example, in the U.S., post-marketing surveillance of medicines occurs actively via Phase IV studies and passively with voluntary and mandatory reporting through to the FDA’s Adverse Event Reporting System (FAERS), e.g. using MedWatch forms, and the Institute of Safe Medication Practices Medication Error Reporting System (MERP) (4,5). The MedWatch program allows the public including patients and HCPs to report adverse events that they suspect are related to medical treatment. Reporting by the public is voluntary via a mobile app or webpage, whereas reporting of suspected adverse reactions is mandatory for manufacturers (3).

In the European Economic Area, the EudraVigilance is a system implemented for managing and analysing information on suspected adverse reactions to medicines that have been authorised or are being studied in clinical trials . The EMA is responsible for operating the system. This PV system is described extensively the EMA PV system manual (6) and it covers the organisational structure, responsibilities, procedures,

processes, appropriate resource management, compliance management and record management (7). (See Figure 2)

In the past, most PV activities at pharmaceutical companies were focused on the handling of adverse event case reports also called individual case safety reports (ICSRs).

Currently the main PV activities are focused on systematic data collection, collation, analysis, expedited and aggregate reporting of adverse events, signal detection, signal management, and risk management planning and mitigation. Bearing in mind that generally all PV activities and systems including handling of ICSRs and timely reporting of these cases to the regulatory authorities are highly regulated (8). There are several guidelines published to ensure standardisation, reporting compliance and quality including but not limited to the Good Pharmacovigilance Practice (9), the EMA PV system manual (6) and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E2B R3 guideline for uniform format of exchanging and transmission of ICSRs (10).



**Figure 2. Post-marketing reporting system- Eudravigilance system overview**

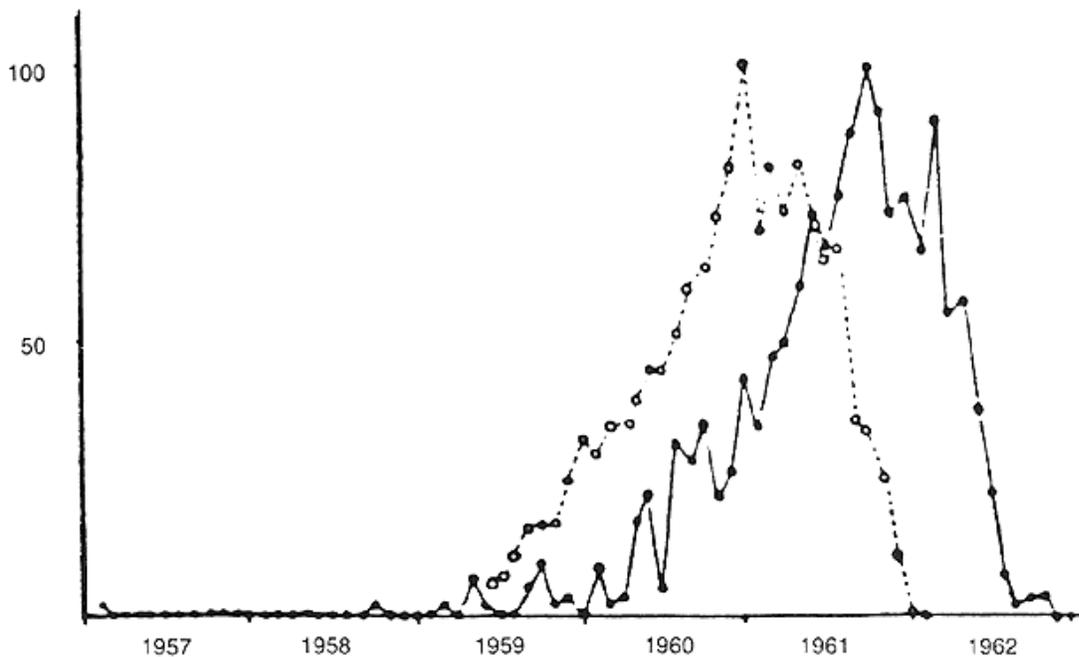
Source available at: <https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance/eudravigilance-system-overview>  
Internet accessed on 4.Nov.2019.

### 1.3 History - What we know about Thalidomide today?

***“The further you can look back, the longer you can look forward”***

Winston Churchill, Royal College of Physicians, 1944

The well-documented tragedy of birth defects that occurred after *in utero* exposure to thalidomide in the late 1950s and early 1960s. It affected tens of thousands of children, many of whom were born with severe birth defects (11) (See Figure 3).



**Figure 3. The relationship between the sales of thalidomide (broken line) and the number of malformations of thalidomide (solid line)**

Source: Lenz W: Discussion in Symposium on Embryopathic Activity of Drugs. Robson JM, Sullivan FM, Smith RL(eds): Eur J Obstet Gynecol Reprod Biol 16:365, 1984.

The thalidomide disaster completely changed the way medicinal products were tested and authorised, particularly in respect of their safety profiles. After the thalidomide scandal, regulatory agencies and their advisory scientific bodies focused on the importance of rigorous and relevant testing of pharmaceutical medicines, biologicals and vaccines prior to marketing authorisation (12). Later on, many studies were conducted to

understand different aspects of thalidomide-induced teratogenicity and three main topics were discussed.

### ***“Poetry is what is lost in translation”***

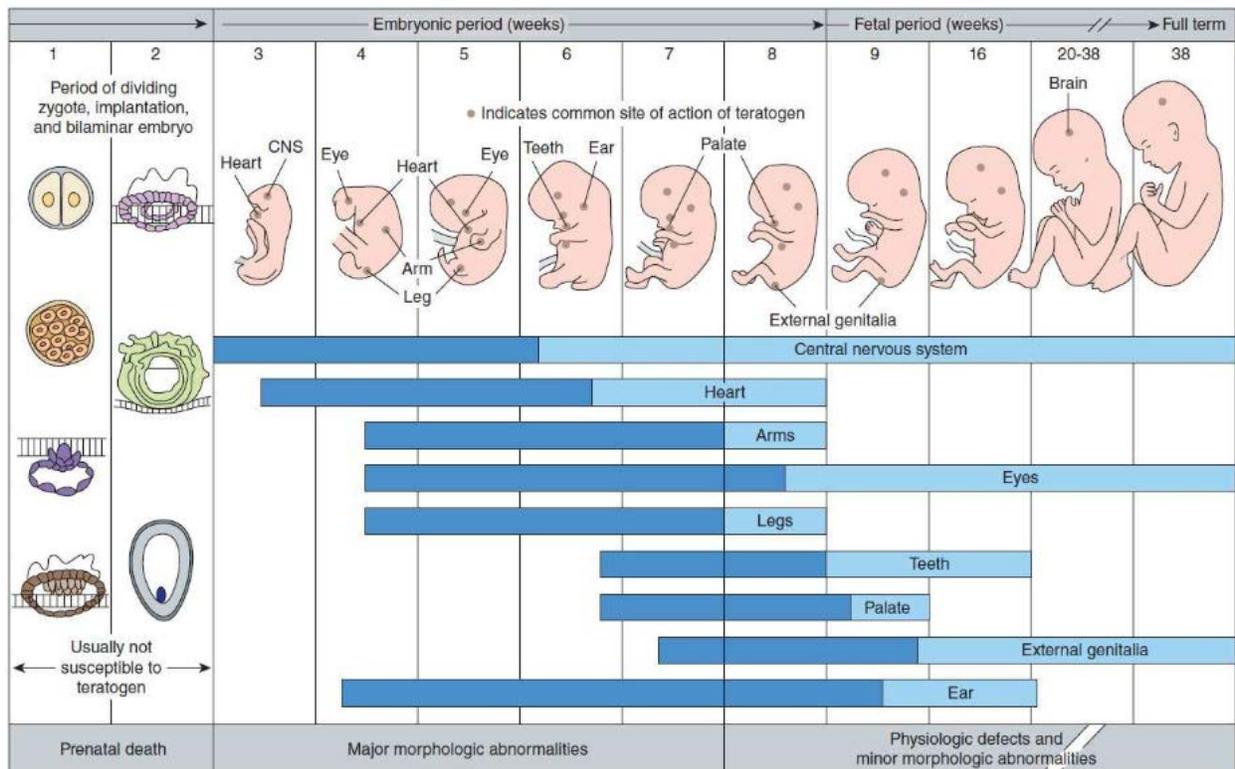
Robert Frost (1847-1963)

The initial studies showed the different sensitivity between species of animal models related to drug exposure. Data for thalidomide showed that rat experiments had not produced malformations comparable to those which were evident in humans. As a result, developmental toxicity testing for pharmaceuticals was extended, such that manufacturers were obliged to conduct reproductive toxicology testing in at least two species, one of which was not a rodent. In 1966, the FDA laid the foundation for the development of the segment I (fertility and general reproduction), II (teratogenicity), and III (perinatal) testing protocols. The aim was to address potential developmental and reproductive toxicities of pharmaceuticals. Prior to the development of these three segments of the testing protocols, toxicology testing was more hypothesis-driven rather than the systematic bioassay testing strategy that is in place today. Even today, it is known that the results provided from animal models do not always translate faithfully to humans, in valproate, as there is no qualified animal model for autism (13) and it is impossible to model ‘low IQ’, as far as I am aware.

Secondary key findings from further studies on thalidomide exposures emphasized the importance of the timing of exposure of the mother and the embryo in relationship to the period of organogenesis. As most organs and systems develop during the first trimester, exposure to any potentially teratogenic agent at that time carries the highest risk of major congenital malformation as an outcome. For individual organ systems, the periods of risk are quite specific (see Figure 4).

Thalidomide causes embryopathy in a relatively brief, time-sensitive window, which extends approximately between day 20 and day 36 after fertilization (around 34–50 days after last menstrual period) (14). It is recognized that central nervous system development continues into the second and third trimesters, therefore effects on fetal growth and development may occur as a result of exposure in these later phases of pregnancy (15). Exposure in late stage of pregnancy and near-term carries the greatest risk related to functional neonatal health and development, such as neonatal toxicity following maternal

use of opioid analgesics or maternal neonatal withdrawal effects following maternal use of selective serotonin reuptake inhibitors (15). Pregnancy exposure to benzodiazepines in third trimester resulted in infants born either with the floppy infant syndrome, or neonatal withdrawal symptoms (16).



**Figure 4. Stages of human embryo-fetal development**

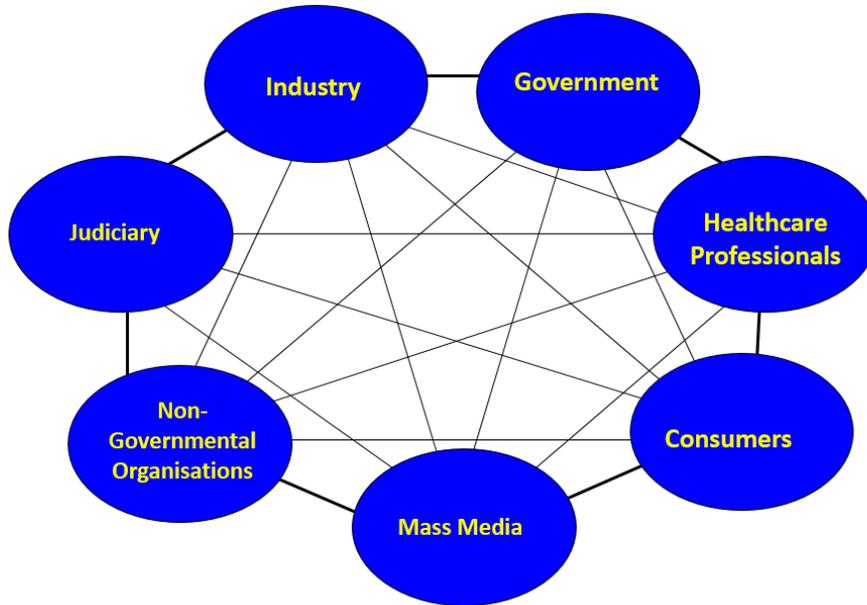
Source: available at <https://basicmedicalkey.com/special-aspects-of-perinatal-pediatric-pharmacology/> Internet accessed Oct. 2019.

Last but not the least, the mechanism of action of thalidomide is directly related to the pattern of congenital anomalies observed; in 1998, FDA approved thalidomide use for the treatment of Behçet's disease, Hansen's disease, and multiple myeloma. As an anti-angiogenic drug, thalidomide inhibits tumor hyper-vascularity, thereby inhibiting tumour growth, and metastasis (14). These properties of thalidomide, which confer significant toxicity to the human embryo have been clearly demonstrated to be specifically valuable in the treatment of multiple myeloma (14). Prescription and use of thalidomide is carefully monitored using the System for Thalidomide Education and Prescribing Safety\_program (17) which enforces the monitoring of patients to ensure they are not pregnant while receiving treatment. However, despite the very best efforts of pregnancy prevention

programmes and the provision of additional risk minimization measures the diversion of supply has occurred into South America, leading tragically to a new generation of thalidomide-exposed babies which occurred predominantly in Brazil (14). Thalidomide is used to treat complications of Hansen's disease in Brazil, as it is endemic in this area. Unfortunately, the product is given to patients who share the medicine with others, many of whom do not possess or understand the prescribing information (which is often written in English). A substantial cohort of patients are not informed of the dangers of taking thalidomide in pregnancy, hence a second cohort of children have been born with similar major congenital malformations to the phocomelia and amelia seen in children exposed to thalidomide in utero between 1957 and 1962 (14).

It is important to understand the mechanism of action of teratogens, as malformations may occur across structurally-related pharmaceuticals within a particular class of medicines. In addition, more effort is required for global and national PV systems to coordinate their efforts concerning pregnancy prevention programmes, as well as to put a strong emphasis on the provision of effective risk communication via simple, direct pathways. For example, a visual warnings being placed not only on the outer packaging and on patient information leaflets, but also imprinted over each blister cell of a medicine. Pictograms, which can be understood without reference to extensive text, could be applied globally in case pack inserts are not translated, or are not required or provided with the medicine.

Based on animal models (both *in vitro* and *in vivo*) there is still no completely reliable method , to predict and much less to prevent potential teratogenic effects of medicines. Therefore, there is a huge importance applied to the careful collection, collation, investigation medical evaluation of data concerning human pregnancy exposures as soon as marketing occurs. A systematic approach to data management and signal detection can provide more comprehensive data in this field, and thereby yield important safety information for communication to patients, healthcare professionals, carers, regulatory authorities, manufacturers and indeed all stakeholders in public health. (See Figure 5)



**Figure 5. Risk communication in Pharmacovigilance**

#### 1.4 Pregnancy and maternal disease control

In the European Union (EU) more than 5 million women become pregnant each year (18). Evidence suggests that almost 75% of women take at least one medication during pregnancy (19). Besides the short-term use of prescription-only medicines (e.g. for severe nausea or urinary tract infection) during pregnancy, use of over-the-counter products (e.g. for headache, coughs and colds) there is also a need for the treatment of chronic illnesses (e.g. epilepsy, multiple sclerosis, inflammatory bowel disease) during pregnancy (18). Nowadays, with the trend of women becoming pregnant later in life and with the increasing occurrence of certain chronic diseases such as obesity, diabetes, epilepsy, hypertensive heart disease, multiple sclerosis and systemic lupus erythematosus, more pregnant women require medication for treatment of pre-existing conditions throughout pregnancy. Uncontrolled disease during pregnancy can lead to irreversible harm to the mother and the embryo or foetus. Globally, almost 44% (90% uncertainty interval [UI] 42–48) of pregnancies are unplanned (20), which could result in potential unintended exposure to medicinal products in pregnancy when a woman may not be aware she is pregnant.

Since the thalidomide tragedy over half-a-century ago, the potential teratogenic effects of medicines have been a cause of distress in pregnant women and have provided a challenge to prescribers. Incomplete information may affect the willingness of physicians to prescribe medicinal products and patients may be reluctant to take prescriptions to the pharmacy. Even if the prescription is dispensed and accepted by the patient there may be limited adherence to the prescribed dose of medicine (15).

Pregnancy is a specific phase of life that requires special care in every aspect particularly from a therapeutic point of view. Prescribers are generally taught to select the safest, most effective medicinal product available, and assess the benefit–risk at an individual patient level before providing a prescription. The concern of the mother cannot be dealt with in isolation, rather the prescriber must consider the mother and child as a “maternal placental-fetal triad”. A maternal placental-fetal triad together with pharmacokinetic and pharmacodynamic information should be considered for all therapeutic interventions in pregnancy including active treatment, maintenance therapy and prophylaxis (21). The majority of medicines and/or their metabolites can cross the placenta, and the pharmacokinetics of many human medicinal products are altered during pregnancy, potentially affecting efficacy and safety. Despite this at the time of authorisation little information is usually known about an individual drug and its effects on the human embryo or fetus (15). Therefore, the maternal benefit–risk assessment might be very different from the benefit-risk assessment for non-pregnant women or men.

The primary target of therapeutic treatment in pregnancy is the mother; the fetus is essentially an unwanted secondary recipient. Exceptionally in a few disease areas, such as in the treatment of HIV infection, the fetus is the target (22). Any adverse effects of treatment may be sustained throughout pregnancy and even into the early life of the neonate, with long-lasting pharmacodynamics (e.g. B cell depletion in newborn exposed to immunosuppressant *in utero*), and the possibility of drug exposure via breast milk. In exceptional cases the adverse effects on the fetus may be of very long latency (e.g. neurodevelopmental delay with sodium valproate which evident several years after exposure (23)) and vaginal cancer with diethylstilbestrol (DES) (24). The daughters of women who used DES while pregnant—commonly called DES daughters—have about 40 times the risk of developing clear cell adenocarcinoma of the lower genital tract than

unexposed women (25). Research has shown that the risk of developing this disease remains elevated as women age into their 40s (24,25).

Risks to the foetus, however, need to be assessed against the benefits of treatment for the mother from the perspective of necessary maternal disease management and good health. In the UK, it has been reported that underlying maternal conditions are more likely to cause maternal deaths than direct pregnancy complications (26). It is incumbent upon the prescribing physician to assess the secondary effects of the disease on the embryo or fetus, and weigh the benefits and risks of the medicinal treatments that may be indicated. Equally, it is important that information is provided to the patient, so that an informed decision can be made.

Many chronic conditions are treatable, and adverse outcomes can often be prevented by providing the necessary care and carefully selected medical treatment. A meta-analysis of adverse perinatal outcomes in women with asthma showed that poor asthma control during pregnancy increases the risk of preeclampsia, predisposes the neonate to low birthweight and is associated with prematurity (27). Similarly, it is well recognized that babies born to women with pre-pregnancy diabetes are at a significant increased risk (by two to three fold) of giving birth to a child with congenital malformations. These risks are reduced in diabetic women who achieve good glycaemic control before conception and during the entire pregnancy (28,29). However, often there are insufficient data available for fully informed decision-making. As few as 5% of available medicines have been sufficiently tested, monitored with well-informed, accurate and up-to-date labelling concerning administration of the product to pregnant or breastfeeding women. On average, it takes almost 27 years to determine an appropriate label that accurately communicates the teratogenic risk of medicine (30).

During clinical development of most drugs and biological products, pregnant women are actively excluded from trials, and pregnancy prevention measures are routinely specified in study protocols, along with routine pregnancy testing where applicable. If pregnancy does occur during a trial, the patient is classified as a protocol violator, and according to standard procedure must discontinue study medication and will be monitored for outcome of pregnancy, if carried to term. For example, a study reported 66 human pregnancies during the clinical development program of fingolimod in multiple sclerosis. Of these 66

pregnancies, there were 24 elective terminations, 28 live births, 9 spontaneous abortions and 4 ongoing pregnancies and one unknown outcome (31). Hence, the number is small to allow any conclusive interpretation. Consequently, at least initially, safety information provided to prescribers and patients at the time of authorization is based on nonclinical reproductive toxicology studies. It is recognized that even major congenital malformations, such as those that occurred with thalidomide, do not invariably appear in all animal species (12), nor do they always translate from animals to the clinic. The overwhelming majority of the evidence of the teratogenic potential of medicines is gained via post-marketing monitoring (32).

The WHO recommends exclusive breastfeeding for infants up to six months of age for optimal growth, health and development (33). Yet there is almost no evidence-based information with little or no adequate well-controlled studies in humans to characterize safety of medicines exposure via human breast milk.

This is particularly true of information related to lactation, and secretion of active pharmaceutical ingredients and metabolites into breast milk, where the rodent model which is in common use is generally considered to be suboptimal (34). With lack of scientific information, women may be advised not to breastfeed if they are taking prescription medicines, or a mother may decide to forgo postpartum treatment of her disease in favour of breastfeeding her baby. However, Safety of medicine during breastfeeding is out of scope of this PhD research and future research is required in this field. (Please refer to Direction of Future Research section of this thesis).

There is an important need for safety information on the outcomes of exposure to medicinal products during human pregnancy and when breastfeeding.

The availability of more detailed, consolidated, medically-evaluated and trustworthy information related to safety of medicines used in pregnant and breastfeeding women could help the HCP and mother in making evidence-based decisions leading to an improvement in outcomes for both the mother and the baby.

## 1.5 Cleft lip and/or palate

### 1.5.1 Epidemiology

Cleft lip and/or palate (CL/P) are congenital malformations that occur in the embryonic and early fetal stages (35). Cleft lip or palate affects one in about every 700 newborns globally (36,37). Patients with this deformity require short-term and long-term care as well as medical and often surgical follow-up from practitioners in multiple specialties. Patients may need multiple surgical interventions from infancy to adulthood, in order to obtain an optimal outcome relative to speech, occlusion, facial appearance, and personal self-esteem. When taken together these interventions represent a great burden to the health care and social support systems in terms of cost and effort. There is also a potentially significant impact on the mental well-being of the patient, which may require counselling and further medical interventions including medical treatment.

### 1.5.2 Embryology and developmental physiology of cleft lip and palate

Cleft lip when it occurs is established in the first 6–8 weeks of pregnancy. It is usually considered to be caused by failure of the fusion of the maxillary and median nasal processes. It may also be caused by incomplete mesodermal in-growth into these processes, with subsequent breakdown of epithelium (35). A palatal cleft results from the failure of fusion of the palatal shelves of the maxillary processes (which normally occurs between 8th to 12th weeks of pregnancy). These shelves are initially separated by the tongue, which descends by the eighth week of pregnancy, allowing the shelves to fuse (35).

### 1.5.3 Classification of cleft lip and palate

Several methods of classification have evolved. The most accurate classifications are based on the system recommended by Kernahan & Stark, which describe the various forms of cleft lip and palate as follows (38):

- Unilateral, bilateral or median;
- Complete or incomplete (involving soft palate)

Based on the aetiology of this congenital anomaly, CL/P can be classified as syndromic and non-syndromic. Non-syndromic cleft lip with or without palate is the most frequent craniofacial malformation. Single nucleotide polymorphisms within nineteen loci (each

representing a genetic variant) have been associated with non-syndromic CL/P in genome-wide association studies of European individuals (39). Around 70% of CL/P cases are non-syndromic (36). There are also more subtle variants of the morphology of the lips and face in unaffected individuals due to the more common genetic variants.

#### 1.5.4 Aetiology cleft lip and palate

The precise aetiology of CL/P is unknown but it has been hypothesized that it may be due to a combination of genetic and exogenous factors such as maternal smoking and alcohol consumption, *in utero* exposure to certain chemical and medicines (40).

Association of folate, vitamin B6 and zinc deficiency during gestation and CL/P have been reported in animal and human studies. Folate deficiencies in early pregnancy are reported with an increased risk of CL/P (38). Other genetic factors that may affect the presence of orofacial clefts include the maternal ability to maintain red blood cell zinc concentrations and myo-inositol (a hexahydrocyclohexane sugar alcohol) concentrations (41).

Maternal ability to maintain adequate levels of Vitamins B6 and B12 and fetal ability to utilize these nutrients have also reported as a factor in the development of oral clefts (41,42). When these nutrients are not metabolized properly, errors in DNA synthesis and transcription may occur (42). Recent publications have focused on a possible genetic link, for example non-syndromic cleft Lip and palate polymorphisms affect normal lip morphology (39).

One proven cause of CL/P is the maternal use of certain medicinal products. Clear causal associations have been established between drug treatments including anticonvulsants, such as valproic acid, phenytoin and phenobarbital, and the vasoactive drug isotretinoin and an increased risk of CL/P (38,43–45). Even though these medicines have been identified as important causes of CL/P, only limited attempts have been made to evaluate the possible associations between exposure to a broad range of medicinal products during pregnancy and the occurrence of CL/P in the offspring. Moreover, the mechanisms and pathways conferring teratogenic effects are uncertain at the present time; this requires further research. It is suggestive that maybe the teratogenic effect is because of alteration in vitamin K metabolism, folate deficiency to a reactive toxic intermediate (epoxide), apoptosis and hypoxia-reoxygenation damage (46).

## 2. Background - Data collection and analysis of pregnancy exposure to medicines

### 2.1 Pre-Clinical reproductive toxicity

As mentioned above, one of the regulatory requirements for authorisation of a medicinal product is successful completion of a range of animal toxicology studies, including reproductive toxicology. In some cases, the data generated from tests in animal models can provide a means to predict teratogenic effects in the clinic. However, many times, the results from reproductive toxicology studies may not translate into human risk because of significant variations in teratogenic response among species (47). In addition, animal toxicology studies are designed so that at least one dose tested will provoke an adverse toxic response. The results at those dose levels may not be predictive of those effects that might be observed at the intended therapeutic doses used in humans (48).

### 2.2 Post-marketing surveillance method

Health authorities such as the FDA in the US and the EMA in the EU often require the marketing authorization holder to conduct pregnancy safety studies as a condition of authorisation or after approval in the post-marketing phase (49). The ultimate goals are to further characterize risk of reproductive toxicity in human pregnancy and provide more information for prescriber and patients in the product's label. Where a teratogenic risk is identified there may also be an obligation imposed on the MAH to communicate, inform, educate and to establish and maintain a pregnancy prevention programme. There are a number of surveillance methods including spontaneous reporting, solicited reporting, pregnancy (or product) exposure registries (50) and population-based surveillance studies such as using claim medical records and insurance claims (32).

#### 2.2.1 Pregnancy exposure registry

Pregnancy registries are, in most instances, either product-specific or focused on a class of medicines. Registries have for decades been considered to be the preferred method to collect safety information on human exposure to medicines during pregnancy because they are designed to collect data prospectively on drug exposures during pregnancy. Often a pregnancy registry is required as a condition at the time of a new drug approval

especially when there is a safety concern or when there is a need to collect data on the use of the product in pregnancy based on the following circumstances (47):

- Prior knowledge of the product suggests a safety concern based on the pharmacology or a class effect;
- A teratogenic risk has been detected from animal studies or clinical trials data;
- The product will of necessity be used during pregnancy where the potential benefits are likely to outweigh the risks (e.g. vaccines);
- The product is likely to be used in women of childbearing potential (e.g. multiple sclerosis)
- The product is primarily indicated for use in men, but is known to have adverse effects on the fetus (e.g. anti androgenic agents (51))

A pregnancy exposure registry is an observational prospective pharmacoepidemiological study to monitor the outcomes of pregnancies during which the mother or father was exposed to certain medicinal products. Participants are a cohort of women receiving a biopharmaceutical product(s) of interest as part of their routine clinical care and who are predominantly enrolled voluntarily during gestation, before outcomes are known. Pregnant women are followed until the end of pregnancy or longer to systematically collect information on specific pregnancy outcomes and compare to a scientifically valid reference population(s) (47). Some registries also permit intake of retrospective reports of pregnancies and outcomes, but it is well documented that there is a bias towards reporting of adverse outcomes when retrospective reporting occurs (52).

The overall purpose of pregnancy registries is to provide human data on the safety of medicines during pregnancy (53). In many pregnancy registries, the primary objective is to assess the risk of major congenital malformations in the offspring of women exposed to the exposed drug immediately before conception or at any time during pregnancy. Ultimately, the aim is to determine whether the risk of a clinically important malformation in the neonate is higher or lower than expected in the unexposed population. Hence, this approach requires a careful study design, statistical analysis plan and well-written protocol to enable the research questions to be answered and objectives addressed.

### **Advantages of pregnancy registry:**

1. While approximately 50% of women reported taking at least one medication during pregnancy (54), the use of individual drugs for specific conditions (e.g. treatment of chronic diseases) is uncommon. By enrolling an exposure group of women who took the medication(s) of interest, pregnancy registries can efficiently collect data on effects of rare exposures during pregnancy.
2. Pregnancy registries usually have a longitudinal study design to observe women during different stages of pregnancy. Often prospective pregnant mothers are considered for enrollment; before any prenatal tests have been performed and before information about the pregnancy outcome is known. This allows the estimation of absolute risks of pregnancy outcome and ascertainment of the exposure window. Moreover, by performing several follow-ups with pregnant women detailed information can be obtained on exposure time in relation to gestational age, dose, frequency of medication use, as well as other variables. Thus, well-designed prospective registries can reduce exposure misclassification, recall bias, and confounding.
3. Pregnancy registries can potentially collect data on variety of pregnancy outcomes (e.g. stillbirth, live birth, etc.) and infant outcomes including long-term data on infant health and development. It is recognised that long-term follow-up for adverse outcomes (e.g. neurodevelopmental delay) requires significant effort and investment (23).
4. As part of the design of a protocol governing a registry, it could be required that each new born is examined by a physician to collect additional clinical data related to the outcome of interest.
5. A pregnancy registry can be designed to compare the risk of outcomes among different groups including, monotherapies, polytherapy or population with no treatment. This information is useful to both women and treating physician for making informed decisions about whether to treat a condition during pregnancy and assess the alternate therapeutic strategies to use (47).

## Limitations of Pregnancy Registries

Unfortunately, many pregnancy registries fail to provide answers, or simply fail to operate as planned for a variety of reasons. The pregnancy registry approach has a number of limitations:

1. While registries are an efficient way to assess rare exposures, low numbers of case reports do not provide the required statistical power to detect rare pregnancy outcomes.
2. Most pregnancy registries report the overall risk of major congenital malformation rather than a specific type of malformation. Pregnancy registries usually do not have sufficient sample size and/or power to evaluate increased risks for specific defects unless the relative risks are quite large or the cohort of exposed patients and adverse outcomes is disproportionately large. However, many drugs associated with adverse effects in pregnancy result in only small increases in rare outcomes (e.g. risk of CL/P reported for ondansetron (55)). Therefore, specific patterns of malformation maybe missed for the less potent teratogens.
3. Identification of a comparator group (controls) may not always be feasible. The control group should ideally be closely matched to the exposed group so that both groups have the same baseline risk for adverse pregnancy outcomes. Matching cases and controls is particularly difficult for global registries that recruit exposed women from different countries with different backgrounds.
4. Patient recruitment and retention are usually challenging. Moreover, due to voluntary participation in pregnancy registries the participants represent a small proportion of all women who have been exposed to a particular drug. For these reasons, the characteristics and experience of women who participate (e.g. more health conscious, higher socioeconomic status) in a registry may differ from those of non-participants, and these characteristics may modify the effect of the drug (e.g. a balanced diet in those patients who better understand nutrition and can afford a wider range of nutritious foodstuffs).
5. Another important limitation of pregnancy registries is the length of time required to enroll sufficient numbers of exposed women to generate meaningful results (47).This timeframe maybe due to infrequent exposure in the general population

or methods and extent of recruitment efforts by the registry. Most registries run for many years before publishing any results, and even in these circumstances the results may never attain statistical significance. This extended period of evaluation before reaching conclusions can affect public health (47).

6. Due to the long duration of registries, they are viewed as costly.
7. Data from one pregnancy registry in a single country or region may not be sufficient to support a change in medical practice. However, if multi-national registries are implemented to address this challenge another limitation surfaces in that the registry owner must first ensure homogeneity of design and operation of the registry across different medical cultures operating within different healthcare systems. The data owners must also agree beforehand how best to review pooled data from different centres in order to conduct meaningful analyses and to ensure that there is consistency of medical evaluations.

### 2.2.2 Spontaneous case reports

Collection of spontaneous reports of suspected adverse reactions is a legal requirement of all marketing authorization holders of medicinal products. Information on all pregnancy cases associated with exposure to a medicinal product (including exposure in the work environment such as at a manufacturing site for the active pharmaceutical ingredient (API) for which the marketing authorization holder has a pharmacovigilance responsibility is collected. (56,57).

Good pharmacovigilance practice comprises comprehensive data collection on adverse pregnancy outcome to identify safety signal and develop a case series for analysis (50,58). Sources of pharmacovigilance data include spontaneous reports submitted to the MAH, competent authorities (including Swissmedic, the EMA and FDA) from consumers, healthcare professionals, including literature, at least some of which will result from clinical studies. ICSRs are most common source of reports of adverse pregnancy outcomes particularly if the pregnancy outcome is rare.

The quality of ICSR and precise details of information reported (e.g. start date of medication(s), and the date of the last menstrual period) are critical for the evaluation of any potential causal association between the product and adverse outcomes. On some occasions, the competent authorities and some MAHs have considered a series of ICSRs

to be adequate and appropriate data sources for establishing a causal association between exposure and a specific congenital anomaly, such as for isotretinoin (59) or trastuzumab with serious adverse event such as oligohydramnios (60).

**Advantages of spontaneous reporting systems:**

1. Well-documented ICSRs can be used to identify safety signals specifically in rare pregnancy outcomes. When supplemented by appropriate follow-up these ICSRs may be used to characterise the nature of the adverse outcomes and for the identification of potential risk factors (e.g. exposure in the first trimester).
2. Receipt of spontaneous reports is relatively higher when compared with enrolment into registries (61), but it is recognized that significant under reporting occurs in spontaneous reporting systems. (refer to 1 limitation below)
3. Because of 1 and 2, spontaneous reporting systems represent the best source to generate hypotheses for safety signal detection and, depending upon the quality of the data, ICSRs may contribute to the medical and scientific evaluation for the detection of teratogenic effects.
4. To maintain drug safety surveillance for a long time, spontaneous reports are a cost-effective source (62). This is particularly important where long-latency adverse reactions are suspected, or where data must be collected over a prolonged period in order to establish a meaningful sample size for analysis.

**Limitations of spontaneous reporting systems:**

1. Under-reporting is one of the major drawbacks of spontaneous reporting systems (63), HCP and consumers can voluntarily report suspected adverse reactions, however, for a variety of reasons they do not necessarily report all cases of potential reaction to the correct recipients. Deficiencies in post-authorisation reporting of suspected adverse reactions are well documented (64–69). Professor Bill Inman commented on the ‘seven deadly sins’ which in his view contributed to under-reporting in the UK (64). Inman’s hypothesis was that the following were the main reasons for the under-reporting of adverse drug reactions (ADRs):
  - Ignorance ('I am unsure how to report an ADR')
  - Diffidence ('I may appear foolish about reporting a suspected ADR')
  - Fear ('I may expose myself to legal liability by reporting an ADR')

- Lethargy ('I am too busy to report ADRs')
- Guilt ('I am reluctant to admit I may have caused harm')
- Ambition ('I would rather collect cases and publish them')
- Complacency ('only safe drugs are marketed')

Some of the above are speculative, and despite a grain of truth behind each, Belton et al (68) could only confirm that item 4 in the list above (lethargy) made a significant contribution to inhibit ADR reporting in the UK. Nevertheless, it was clear that there is significant under-reporting

2. Spontaneous report data are collected passively relying on healthcare professionals and patients to recognise suspected adverse reactions, collect and collate relevant information and submit reports in the required format, hence the information received is often insufficient or incomplete.
3. The majority of patients are lost to follow-up (FU), at least for reports submitted to the pharmaceutical industry. The MAH is obliged to follow-up with reporter to obtain clinically relevant information however around 60% of these FU attempts fail (62).
4. Reporting biases exist which tend to devalue the calculation of frequencies and limit the use of statistical comparisons. Examples of reporting biases are:
  - Tendency to report fatal, life-threatening or serious more than non-serious (70),
  - Temporality – Weber effect suggests peak reporting in first 3-5 years of marketing (70),
  - Stimulated reporting – where a publication or media publicity may generate many further examples (71),
  - For pregnancies there is a tendency to report adverse or abnormal outcomes, thus there is under-reporting of full-term, normal deliveries of healthy infants (72).

### 2.2.3 Pharmacoepidemiological studies

Considering the limitations of pregnancy registries and spontaneous reports, regulatory agencies such as the EMA and FDA may mandate complimentary studies that can help to address these limitations. Ultimately the goal is to provide more information for better characterization of the risk of reproductive toxicity (73). These are usually retrospective

in design and are considered 'secondary use of data' (50) since these data were primarily collected for a purpose other than monitoring the safety of a specific drug such as (73):

- Use of electronic data source (e.g. health insurance claims and electronic health records)
- National registries and population-based surveillance
- Population-based case control studies

Evaluation of these approaches are out of scope for this PhD thesis.

### 2.3 A critique of current approaches to data collection, collation and analysis

In summary, there are many limitations in the data available for the assessment of pregnancy exposures and outcomes:

- Animal models are sometimes poorly predictive of the teratogenic risk in humans.
- Product-specific pregnancy registries can take a long time to set-up and establish good recruitment but often there is low enrolment and studies remain incomplete versus recruitment targets. This in turn means that study results are non-informative and such programmes are costly if they yield no useful data.
- There are no standard end-to-end processes for the capture and collation of spontaneous case reports of pregnancy exposures and outcomes, and methods of analysis vary.
- Critical variables for generating evidence-based safety information in pregnancy spontaneous case reports are often missing (e.g. precise dates of exposure to medicines and pregnancy outcomes).

Thus, this field is inherently difficult to study, and it suffers from a lack of systematically gathered data and efficient or preferably harmonised methodological approaches. Therefore, often there is a knowledge gap between stakeholders' requirements for current, evidence-based safety information and the actual volume of relevant, timely and adequate information for assessing the safety of medicines use during pregnancy.

There is a need for an efficient, sustainable and high quality system that collects, and supports the generation and provision of scientific and unbiased information for prescribers and patients.

The overall objective of this research is to assess new and improved tools and methods to generate more valuable, reliable (better quality) data and thus to support a timely

communication of information to HCPs, pregnant women and the general public, indeed all stakeholders in public health.

### 3. Objectives of this Research

- To identify drug-induced risk factors for CL/P using safety signal detection and safety signal evaluation techniques in safety databases such as the FDA FAERS system and/or the MHRA Sentinel database
- To investigate potential big data sources such as the multiplicity of social and digital media webpages. This research would require the development of novel machine learning techniques for potential adverse drug reactions manifesting as adverse outcomes of pregnancy. This would be supported by human curation to assess the content of discussion threads concerning the use of medicines during pregnancy
- To develop an enhanced pharmacovigilance method for pregnancy outcome monitoring using post-marketing spontaneous reports

#### 3.1 Safety Signal Detection and Signal Management

##### **Risk of Cleft Lip and/or Palate Associated With Antiepileptic Drugs: Postmarketing Safety Signal Detection and Evaluation of Information Presented to Prescribers and Patients (74)**

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DOI: 10.1177/2168479018761638. – [Chapter 4 of this thesis])

Generally, health authorities have implemented pharmacovigilance databases such as FDA FAERS in the US (4), Eudravigilance in the EU (7), and Vigibase® in the WHO's global monitoring centre in Uppsala, Sweden (75). These large relational databases contain millions of adverse event reports as suspected adverse reactions of medicines are being entered and stored. The first two named systems can be accessed publicly (58). Each of these systems includes a small proportion of pregnancy exposure and outcome reports. The primary purpose of establishing and maintaining such large datasets is for the detection of safety signals associated with human medicinal products. The Council for International Organizations of Medical Sciences (CIOMS) defined a safety signal as:

“Information that arises from one or multiple sources (including observations and experiments), which suggest a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action” (76).

Safety signal detection and management comprises a series of related, planned processes and activities including (77):

- Signal detection: Identification of safety signal via statistical algorithms
- Signal characterisation to identify temporal association, onset time, severity, outcome, possible treatment, etc.
- Medical impact assessment, according to the primary indication of the product (i.e. the disease under treatment, seriousness of the adverse reaction, frequency of occurrence of the adverse reaction, etc)
- Signal validation: prioritization and resulting of introducing risk management plan and/or labeling change (78,79). Therefore, signal detection leads to hypothesis generation and assessment of causal association between the drug and event. Generally this method has proven a useful tool in facilitating the timely detection of adverse drug events (80–82).

To date, only a very few studies have used spontaneous case reporting datasets to identify statistical signals of possible teratogenic risks of medication exposures during pregnancy (83,84). Hence [ in Chapter 4, (74)] we performed safety signal detection and evaluation to identify all antiepileptic medicines with ICSRs reported an association with cleft lip and/or palate in two large safety data bases; FDA FAERS in the US and the MHRA Sentinel database in the UK.

Epilepsy is one of the most common chronic diseases that require continuous drug treatment during pregnancy. Epilepsy affects more than 1 million women of childbearing potential in the USA (74). Over the past two decades, several anticonvulsant drugs have been authorized indications beyond epilepsy, including the treatment of psychiatric diseases, generalized anxiety disorder, migraine prophylaxis, and management of neuropathic pain. In the USA, the prescription rate of AEDs has been reported at >4 million per year for women of between 14-55 years old (74).

Second, we evaluated the completeness of safety information in the regulatory authority -approved prescribing information in the two countries. Our aim was to highlight the potential for optimizing maternal epilepsy management by the provision of important and current information on pregnancy exposures and outcomes to prescribers and patients.

### 3. 2 Pharmacovigilance and Social Media

#### **Social Media Surveillance of Multiple Sclerosis Medications Used During Pregnancy and Breastfeeding: Content Analysis (85)**

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In recent years, social media sources such as Twitter, Facebook and patient fora are providing a huge volume of information related to health, medicinal products and other forms of treatment (86).

Social networks continuously increases the number of users globally (e.g., as of 11th July 2014, Twitter has over 645,750,000 users and grows by an estimated 135,000 users every day, generating 9100 tweets per second) (3).

The Pew Research Center survey has confirmed that of the 74% of adults who use the internet, around 80% have looked online for information about health topics such as a specific disease or treatment. This translates to 59% of all adults. In addition, 34% of internet users, or 25% of adults, have read someone else's commentary or experience about health or medical issues on an online news group, website, or blog (87,88). Moreover, 11% of caregivers and 6% of patients share experiences and post questions online (3). Individual posts in social media about treatment outcomes provide early access to reported adverse drug reaction that could be useful due its large volume (89).

The PV systems mainly rely on voluntary reports from consumers and HCPs, which is known to have the limitation of under-reporting. This shortcoming must be weighed against the evidence that users of social media tend to share their views openly with others facing similar concerns, which makes social networks unique and robust sources of information which is not invariably shared with HCPs and others in the chain of care.

The ability to process large volumes of data automatically, using artificial intelligence such as natural language processing (NLP) and machine learning algorithms, has opened new opportunities for PV (3,90).

In this field, Web-Recognizing Adverse Drug Reactions (WEB-RADR) was a groundbreaking EU Innovative Medicines Innovation (IMI) project. WEB-RADR was an initiative to recommend policies, frameworks, tools and methodologies to use social media to further proactive pharmacovigilance and protection of public health (91). After just over three years' research the WEB-RADR consortium recommended that social media channels may provide useful information related to pharmacovigilance in specific niche areas such as exposure during pregnancy and abuse/misuse of medicines (92). This project provided the stimulus for further research related to one niche area identified by WEB-RADR as 'data rich' (93). It was identified that using Twitter as the source, posts relating to pregnancy exposures with identifiable medicines occurred at least twelve times more frequently than was expected based on spontaneous sources (93). Equally relevant was the fact that Twitter users could be followed for an average of 2.8 years, i.e. expectant mothers could be observed from first exposure to a medicinal product to term, and then for a period beyond, if required. The two elements suggested that further exploration of social media posts should be conducted to evaluate a potentially valuable source of data, particularly in patients with chronic diseases affecting mobility. The latter is important as it has been reported that the use of social media and of the internet in general is higher amongst patients with neurological diseases (e.g. Parkinson's disease, multiple sclerosis) which limit movement (93).

I decided to conduct further research in multiple sclerosis (MS), as it is a chronic disease of the central nervous system with a higher prevalence in females than males, with a ratio of approximately 3:1 (94,95). Female MS patients are predominantly of childbearing potential with the average age of disease onset being 29.2 years (94). Thus, I selected this patient population, as there was a significant likelihood of their being active in social media. Also there seemed to be a realistic prospect of the opportunity to gain insights into patients' real-life experiences with medicinal products during pregnancy, as well as their comprehension of the benefits and risks associated with medical treatments of MS.

We utilized machine learning algorithms developed by WEB-RADR on pregnancy forums to analyze the content of posts concerning pregnancy and use of medicines for treatment of MS [ In Chapter 5- (85)]. We used this innovative method to engage with pregnant women through identifying and exploring novel sources such as social and digital media

to understand more about patients' information needs, issues with medication and potential solutions regarding exposure to medicines during pregnancy.

### 3.3 Enhanced Pharmacovigilance – PRegnancy outcome Intensive Monitoring (PRIM)

#### **An alternative to product-specific pregnancy registries? PRIM; PRegnancy outcomes Intensive Monitoring**

Yvonne Geissbuehler and Bitia Rezaallah, Alan Moore

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[Chapter 6 of this thesis].

Considering the document shortcomings of registries the anticipated recruitment of participants to registries are often not attained within the proposed timelines. Recruitment that is slower than forecast typifies the most common failing of pregnancy registries. It is important to obtain robust scientific information in a timely manner on missing data which may reveal potential safety concerns related to the use of drugs during pregnancy in the post-approval setting. In this study [Chapter 6] we established and described an enhanced pharmacovigilance or PRIM (PRegnancy outcomes Intensive Monitoring) process. The PRIM process builds on the knowledge from that initiated for fingolimod (Gilenya®) and was designed to characterize further the pregnancy outcome including risk of major congenital malformation in exposed infants. There are some parallels of the PRIM system to national and international teratology systems (e.g. UKTIS, ENITS(96)) but the PRIM system is, as far as I am aware unique in the pharmaceutical industry. In my view, it is important that high-quality data be obtained as early as possible in the post-authorisation period in order to provide more complete information to patient and prescribers.

Fingolimod is a sphingosine 1-phosphate receptor antagonist which is classified as is an immunomodulating agent. It was authorised for the treatment of relapsing remitting MS. During preclinical safety testing in <sup>35</sup>rodents fingolimod was shown to cause teratogenic effects (persistent truncus arteriosus and ventricular septal defect) in one species, namely rats. Furthermore, the sphingosine 1-phosphate receptor that is

mechanistic pathway for the teratogenic effects exists. Fingolimod did not cause effects on sperm morphology or male fertility in animals, nor did exposure to the drug elicit any known genotoxic effect. The potential exposure of a female partner via seminal fluid has been estimated to be several thousand fold lower than the doses at which teratogenicity has been observed in rats (97), hence concern is very low following fingolimod treatment of men with MS.

Advice and warnings are provided to prescribers at multiple points within the FDA Label for before initiation of fingolimod treatment, women of childbearing potential should be counselled regarding the potential for serious risk to the foetus and the need for effective contraception during treatment with fingolimod. Since it takes approximately two months to eliminate fingolimod from the body on stopping treatment, the potential risk to the foetus may persist and contraception should be continued during that period (97).

## 4. Publication I

### **Risk of cleft lip and/or palate associated with antiepileptic drugs: Post-marketing safety signal detection and evaluation of information presented to prescribers and patients**

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The format of this publication is adjusted to the thesis format.

#### **Abstract**

**Background:** The aim was to analyze safety data associated with the maternal use of antiepileptic drugs (AED) in pregnancy and to assess the risk of cleft lip and/or palate (CL/P) as an outcome in the neonate. A parallel objective was to assess the completeness of the safety information concerning pregnancy exposures in the Summary of Product Characteristics (SmPCs) and the Patient Information (PI) in the USA and the UK. **Methods:** We analyzed individual case safety reports (ICSRs) of CL/P associated with AEDs in the FDA Adverse Event Reporting System (FAERS). For the AEDs with signals ( $EB05 \geq 2$ ), we reviewed Drug Analysis Prints (DAPs) for CL/P cases in the UK MHRA. We performed descriptive analyses of relevant SmPCs and PIs in the UK and the USA using a checklist of recommendations collected from the literature.

**Results:** In total 817 CL/P reports were identified for twelve AEDs in FAERS. Ten out of twelve AEDs were associated with 156 CL/P cases in the MHRA Sentinel. Safety information concerning pregnancy was found to be more comprehensive in UK SmPCs than in the US equivalents.

**Conclusions:** There is statistical disproportionality in ICSRs indicative of an increased risk of CL/P with twelve AEDs studied. More studies are required to explore the association between *in utero* exposure to AEDs and the risk of CL/P. There are inconsistencies between the UK and US safety labels. CL/P associated with AEDs is an important topic and requires providing inclusive, unbiased, up-to-date information to prescribers and women of childbearing age.

**KEY WORDS** — Antiepileptic drugs; cleft lip and palate; safety signal detection; labelling; prescribing information; patient information leaflets; pregnancy outcomes

## Background

Cleft lip and palate are congenital malformations that occur in the embryonic and early fetal stages. These malformations represent the most common congenital deformities of the head and neck.<sup>1</sup> CL/P affects one in about every 700 newborns worldwide.<sup>2</sup> Patients with this deformity require short-term and long-term care as well as medical, and often surgical, follow-up from practitioners in multiple specialties.<sup>3</sup> The aetiology of CL/P is unknown but it has been hypothesized that it may be due to a combination of genetic and exogenous factors.<sup>3</sup> One well-documented cause is the maternal use of certain medicinal products such as anticonvulsants. Causal associations have been established between antiepileptic drugs including valproic acid, phenytoin, phenobarbital, carbamazepine and topiramate and an increased risk of CL/P.<sup>4,5</sup>

Epilepsy is one of the most common diseases that require continuous drug treatment during pregnancy.<sup>6</sup> Epilepsy affects more than one million women of childbearing potential in the USA.<sup>6</sup> Over the past two decades, the number of AEDs available on the market has increased. Several AEDs have indications for use which extend beyond epilepsy, including the treatment of psychiatric diseases, generalized anxiety disorder, migraine prophylaxis, and management of neuropathic pain.<sup>7</sup> In the USA the prescription rate of AEDs has been reported at >4 million per annum for women of childbearing potential (14 to 55 years).<sup>8</sup>

Pregnant women are usually excluded from clinical trials due to ethical concerns. As a direct result, when a medicine is authorised for marketing the safety information on the use of the product in human pregnancy is very limited, as the outcomes of exposures are very limited in number or entirely absent. Thus, safety information provided to prescribers and patients at the time of authorization is based at least initially, on non-clinical reproductive toxicology studies. It is recognized that even significant fetal malformations, such as those that occurred with thalidomide, do not invariably appear in all animal species<sup>9</sup>, nor do they always translate from animals to humans. Knowledge of the teratogenic potential of medicines is gained via post-marketing monitoring of accidental exposures to medicines at various time points during gestation. This form of surveillance is essential for the early detection of medication-induced fetal adverse effects.<sup>10</sup> As a result, safety data related to the teratogenicity of AEDs in the literature tends to be

equivocal because of different methodological approaches. Generally any studies conducted are not sufficiently powered to provide statistically-based conclusions.<sup>4</sup> Consequently prescribers and patients with epilepsy face challenges when considering the best treatment option due to the lack of comprehensive safety information.

In this study, our initial aim was to identify AEDs with individual case safety reports that were associated with CL/P in two large, post-marketing safety databases maintained by regulatory authorities. Secondly, we evaluated the completeness of safety information in approved prescribing information in two countries. Our aim was to highlight the potential for optimizing maternal epilepsy management by the provision of important, and wherever possible, current information on pregnancy exposures and outcomes to prescribers and patients. It is our view that the presentation of consistent, clear and current evidence to prescribers and patients will help to inform decisions about the management of epilepsy during pregnancy. Over time, we are hopeful that this will help to maintain a positive benefit-risk assessment by avoiding harms to the fetus.

## Methods

We conducted this study according to the process in Figure 1.

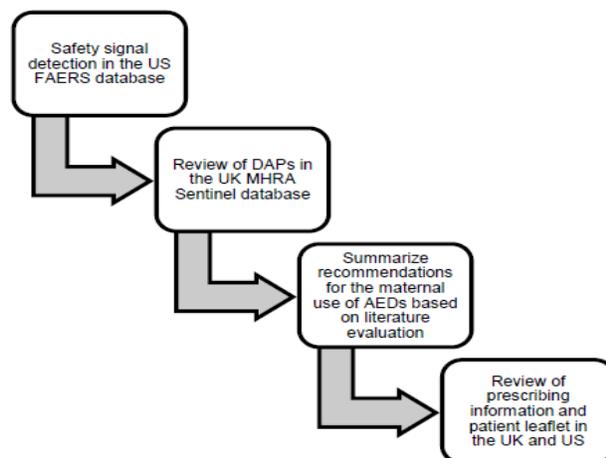


Figure 1. Process for safety signal detection and assessment of the prescribing information for anticonvulsants used in pregnancy and evaluation of the risk of cleft lip and/or palate

## Selection of terms in the Medical Dictionary for Regulatory Activities (MedDRA)

We extracted the following preferred terms (PTs) from MedDRA version 19.0: cleft lip, cleft palate, cleft lip and palate.

### **Safety signal detection using the FDA FAERS database**

The FAERS database includes post-marketing adverse events reported to FDA. FAERS receive reports from two principal sources comprising pharmaceutical companies and health care providers and consumers who can submit adverse event reports to the FDA's MedWatch programme.<sup>11</sup>

Empirical evidence was produced by conducting a cumulative search in March 2016 in the public release version of the FAERS database<sup>11</sup> using Empirica Signal software (Oracle, version 7.3, Novartis Pharma AG). A disproportionality analysis was computed in a data mining run using the Multi-Gamma Poisson Shrinker.<sup>11</sup> Initially, the information was aggregated into a 2 x 2 table. The ratio of observed to expected counts of individual drug-event combinations was calculated across all of the drugs and events reported in the database.<sup>12</sup> The computations produced values for the empirical Bayes geometric mean (EBGM) and the 90% confidence interval (CI) from 5% to 95%, EB05 and EB95, respectively. Extraction of data was performed using the Anatomical Therapeutic Chemical (ATC) level three codes for anticonvulsant drugs combined with selected PTs from MedDRA. Only ICSRs where the AEDs were causally suspected (S) were included for the period of the research (from product launch to 1Q2016). The disproportionality threshold of  $EB05 \geq 2$  was applied for this extract of ICSRs associated with AEDs. In the literature  $EB05 \geq 2$  is considered to be an observation of disproportional reporting (ODR)<sup>12</sup> and it indicates that the observed drug-event combination occurs in the dataset twice as frequently as expected. These values suggest a statistical association between the drug and event. Further investigations were conducted to determine any causal association, including verifying CL/P reports in the MHRA dataset and a review of the literature.

### **Review of Drug Analysis Prints (DAPs) in MHRA Sentinel database**

Based on the AEDs identified with observations of disproportional reporting in the US-based FAERS database, we conducted a manual review of DAPs to identify the number of CL/P reports in MHRA Sentinel.<sup>13</sup> DAPs contain cumulative counts of all suspected adverse reactions reported to the MHRA via the UK Yellow Card Scheme. The MHRA

collects information on suspected Adverse Drug Reactions (ADR) via this scheme. The yellow card system was set-up in 1964 and from its inception has received reports of suspected ADRs directly from health care professionals and, more recently, from patients. Healthcare professionals have been advised to report ADRs to the Yellow Card Scheme even if there is only a suspicion on an association i.e. no facts or evidence is required to prove that a medicine may have caused the reaction. It is a statutory requirement that pharmaceutical companies report suspected ADRs to the MHRA, whereas reporting by healthcare professionals and members of the public is voluntary. It is widely recognised that not all ADRs are reported.<sup>13</sup>

Data were extracted from the publicly available MHRA web resources known as Drug Analysis Prints<sup>14</sup>. A record was kept for each AED of the number of ICSRs for the selected adverse event terms, total number of reports of CL/P, and the total number of ICSRs in the MedDRA System Organ Class of congenital disorders. It is important to note that all ICSRs for each event of interest were reported only when the drug was prescribed as a single ingredient and not as a component of combination therapy.<sup>14</sup>

### **Descriptive analysis of prescribing information**

We reviewed the literature in PubMed (from 2000 to 2016) using relevant keywords and phrases such as maternal epilepsy, epilepsy during pregnancy, management of women with epilepsy. The manufacturer's recommendations provided concerning the maternal use of AEDs from literature were evaluated using an eight-item checklist to assess the content of the UK SmPC and US PI.<sup>6-8,15</sup> The results of this analysis are shown in Table 1. A binary scoring system was adopted, based on the "presence = 1" or "absence = 0" of each item in the checklist. The percentage of the total available information was calculated for each approved item of labelling. Figure 3 provides the results of this evaluation.

A single reviewer analysed the content of relevant sections of each reference safety information documents. The evaluation was inclusive of safety information provided in the indication, use in pregnancy, warnings and precautions, drug-drug interactions, and contraindications sections of the texts. In addition to the binary scoring system, specific information concerning the risk of CL/P was assessed in the pregnancy section of each reference text. The results of this assessment are presented in the discussion. The same

reviewer, using the same checklist, then assessed the text of each patient information leaflet (PIL or pack insert) for both UK and the US. No scoring was applied in to the PILs. Information gaps were identified and they are described in the next section.

For the ten AEDs reference information was obtained from the USA prescribing information and patient information leaflet (PIL) were obtained from the Drugs@FDA database.<sup>16</sup> The UK was used as a reference source for the European Union because English is the common language with the US, thus obviating any requirement for translation. Approved SmPCs and PILs were extracted from the UK electronic Medicines Compendium (eMC).<sup>17</sup> Information on both of these websites is regularly updated, and the eMC provides the full document history with changes recorded by date. We reviewed the most recent label in both websites for each product irrespective of the manufacturer. The last search for this information was performed in March 2016. This article does not contain any studies with human or animal subjects performed by any of the authors.

**Table 1. Management of epilepsy during pregnancy**

<b>Precautionary approaches for the use of AEDs in epileptic women of childbearing potential</b>
Dose adjustment especially before gestation and later on during pregnancy with lowest effective dosage for effective seizure control. <sup>8,15</sup>
Serum drug concentration monitoring during entire pregnancy. Plasma concentrations of AEDs tend to decrease from the first to the third quarter of pregnancy. <sup>8,15</sup>
Use of effective contraceptives for women of childbearing potential because of drug-drug interactions with AEDs and hormonal contraceptives. <sup>8,15</sup>
Because of the risk of folate antagonism with certain AEDs, prescribing folic acid prior to and during pregnancy is suggested in order to avoid major congenital malformation in the fetus (e.g. neural tube defects) <sup>8,15</sup>
Administration of vitamin K1 to the newborn and to mother during delivery helps to avoid bleeding disorders <sup>8,15</sup>
Polytherapy should be avoided, as far as is possible in pregnant females. If polytherapy is required the teratogenic risk depends on the combination of medicines that is prescribed. Several studies have suggested avoiding polytherapy with valproic acid in particular to reduce the risk of MCM <sup>7,8,15</sup> .
Equally it is important that prescribers consult patients to ensure pregnancy is planned in order to minimize the risks <sup>8</sup> .
It is also considered good practice to avoid the sudden discontinuation of anticonvulsant therapy in case of pregnancy <sup>8</sup> .

## Results

### Disproportionality analysis scores from FAERS

The results of the disproportionality analyses are presented in Figure 2 alongside the counts of ICSRs. Twelve AEDs were statistically associated with the occurrence of CL/P in this database. Topiramate followed by phenobarbital, primidone, lamotrigine and carbamazepine had higher EBGM values than valproic acid, which has a well-documented association with causing congenital anomalies. Whilst mephenytoin had the highest EBGM score of 49.7 (90% CI, EB05-EB95; 4.4 – 137.2) this was for only four ICSRs. It is recognised that the disproportionality statistic tends to be unreliable when calculated for low numbers of reports.<sup>18</sup> In contrast there were three medicinal products, namely topiramate, lamotrigine and valproic acid were associated with >100 ICSRs and a relatively high EBGM (>6).

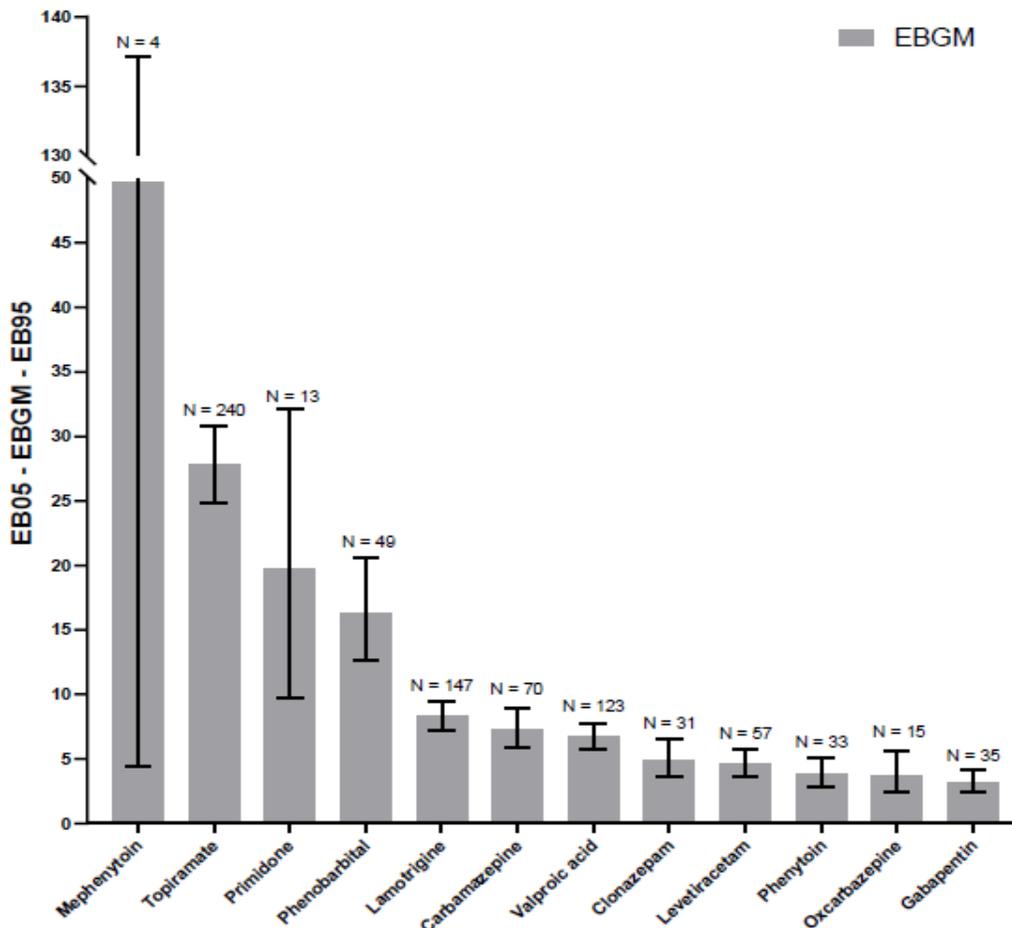


Figure 2. Antiepileptic medicines associated with risk of cleft lip and/or palate in the FAERS database with EB05≥2

## Drug Analysis Prints for AEDs from MHRA

Ten of the twelve AEDs identified in FAERS were reported in the MHRA DAPs with 156 case reports of drug-associated CL/P. There were no ICSRs including CL/P for oxcarbazepine and mephenytoin in Sentinel. Mephenytoin was excluded from further research because there were no reports of CL/P recorded in Sentinel and the because of the limitation previously described for the disproportionality statistic generated from FAERS.

Valproate, phenytoin, phenobarbital and primidone had the highest number of ICSRs describing CL/P. We recorded the total number of ICSRs in the Congenital Disorders System Organ Class in MedDRA to show the overall teratogenic profile of each drug; valproic acid followed by carbamazepine and lamotrigine has the highest number of reports of congenital anomalies. Table 2 shows CL/P reports on Sentinel.

**Table 2. The number of case reports for cleft lip and/or palate associated with antiepileptic medicines reported to the MHRA in the UK**

<b>Suspected Drug</b>	<b>Congenital Disorder System Organ Class</b>	<b>Cleft Lip Reports</b>	<b>Cleft Palate Reports</b>	<b>Cleft Lip and Palate Reports</b>	<b>Total Number of cleft lip and/or palate Reports</b>
Valproic acid	920	3	32	1	38
Carbamazepine	263	3	10	0	13
Lamotrigine	181	0	2	2	4
Phenytoin	128	13	19	0	32
Topiramate	121	1	2	4	7
Levetiracetam	76	0	0	1	1
Primidone	74	6	21	0	27
Phenobarbital	58	11	17	1	29
Gabapentin	27	2	2	0	4
Clonazepam	19	0	1	0	1

## Evaluation of prescribing information for AEDs

Figure 3 shows summary of the completeness of the information presented within the prescribing information between UK and the US.

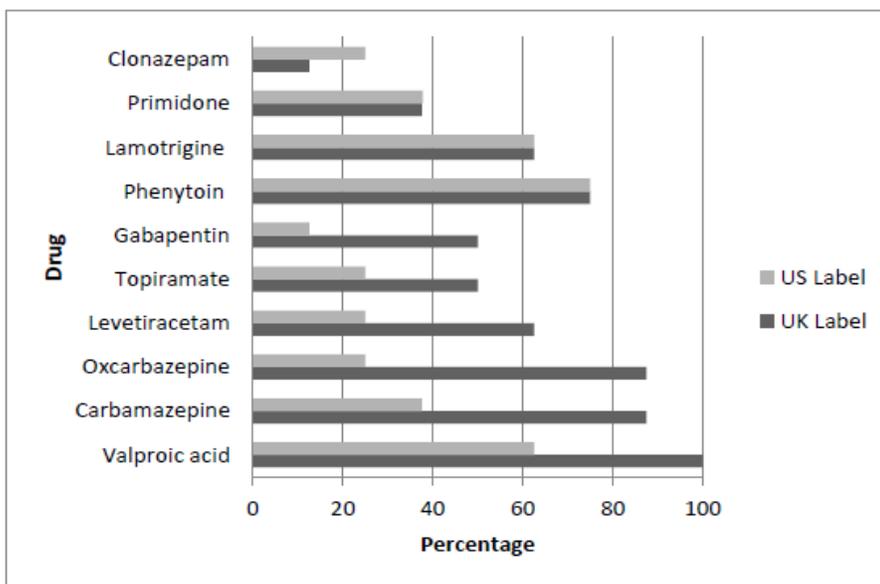


Figure 3. Summary of the completeness of the information presented within the prescribing information between UK and the US.

Phenobarbital was excluded from further analysis because there was no PI in the Drug@FDA website at the time of this research.

In general, the UK SmPCs that were evaluated included more information on safety in pregnancy than the US prescribing information. Notably the safety information content for valproate was more inclusive in the UK<sup>19</sup> than in the US.<sup>20</sup> It is unclear why for carbamazepine, which has a well-documented safety profile, the information appears to be incomplete in the US PI.<sup>21,22</sup> The FDA has begun to address the potential gaps in labelling by the introduction of the ANDA guidance which obliges generic manufacturers to align labelling for new generics with the approved label for the reference listed drug (RLD).<sup>23</sup> As recently as July 2016 the FDA provided further guidance to applicants, in order to extend the recommendations to include scenarios where the RLD has been withdrawn.<sup>24</sup> In the light of the guidance provided by the European Commission<sup>25</sup> on the content of SmPCs it is also difficult to comprehend the gaps in the information content of the UK SmPC for clonazepam.<sup>26,27</sup>

The risk of CL/P is described in the approved labelling for valproate, topiramate, carbamazepine and phenytoin in both the UK and the USA<sup>19-22, 28-31</sup>. Broadly, the

statements reviewed were consistent with literature.<sup>4,5</sup> However, there were some notable differences in the recommendations provided in the UK and US for certain products. Illustrative examples of these discrepancies are provided below.

### **Topiramate**

The UK SmPC<sup>30</sup> includes a statement which reads: “*Contraindicated in pregnancy and in women of childbearing potential if a highly effective method of contraception is not used for use in migraine prophylaxis.*” In the US this guidance was not present in the prescribing information despite migraine being an approved indication.<sup>31</sup>

### **Phenytoin**

The US PIL for phenytoin<sup>28</sup> includes a warning concerning the management of epilepsy in pregnancy: “... *If you take [phenytoin] during pregnancy, your baby is at risk for serious birth defects...*” and “... *If you take [phenytoin] during pregnancy, your baby is also at risk for bleeding problems right after birth...*”<sup>28</sup>. This information is not present on the UK PIL for phenytoin.

### **Carbamazepine**

Studies have shown that in utero exposure to AEDs, especially polytherapy including valproate increases the risk of congenital malformation up to three-fold.<sup>8</sup> The SmPC for carbamazepine in the UK<sup>21</sup> advises that “...the risk of MCM to [carbamazepine] as polytherapy may be higher in poly-therapy combinations that include valproate”. A second recommendation states: “...*In order to prevent bleeding disorders in the offspring, it has also been recommended that vitamin K<sub>1</sub>, be given to the mother during the last weeks of pregnancy as well as to the neonate.*” Neither of these two important recommendations are present in the US PI.<sup>22</sup>

### **Primidone**

According to the literature, primidone is teratogenic<sup>5</sup> and maternal exposure to primidone is associated with an increased risk of cleft palate and congenital heart diseases.<sup>32</sup> There is evidence that maternal exposure to primidone may increase the risk of major congenital malformations, and the product can delay the development of the fetus.<sup>5,32</sup> Again, there are essential differences between the UK and US labelling. On the primidone UK label<sup>33</sup> it is stated that “...*[primidone] is suspected to have caused serious birth defects, congenital abnormalities including cleft palate...*” and also “...*treatment with folic acid*

*although controversial, should be considered.*". But on the primidone US label<sup>34</sup> only the class risk of ADEs after exposure is specified following this statement "...*The effects of [primidone] in human pregnancy and nursing infants are unknown.*". Again with primidone the UK PIL<sup>35</sup> recommends that women with epilepsy should use an effective contraceptive method, due increased risks to the fetus and reduced folic acid levels in maternal blood. In contrast a US PIL for primidone<sup>34</sup> did not provide any of the information for patients as specified immediately above.

Information about the impact of AEDs on hormonal contraception, use of effective contraceptive methods, and the importance of planning pregnancy is not always provided to patients, despite the impact of pregnancy on epilepsy and seizure control and the potential teratogenic effects of AEDs on the fetus.<sup>36</sup> According to the literature approximately 75% women with epilepsy of childbearing age were prescribed a category D or X (according to FDA's Pregnancy and Lactation Labelling Rule) AED and were not on contraception, despite the risk of having a baby with a congenital anomaly.<sup>36</sup> Additionally, among the 26% of this population prescribed a contraceptive, 53% were using a product with potential drug-drug interaction with AEDs, which could of course reduce the efficacy of the contraceptive.<sup>36</sup>

### **Lamotrigine**

According to the literature, lamotrigine is associated with drug-drug interactions with estrogen-containing oral contraceptives.<sup>37</sup> Lamotrigine also has folate antagonist properties which, it has been hypothesized, may induce major malformations in the fetus after in utero exposure.<sup>38</sup> It was determined that the safety information about exposure to lamotrigine during pregnancy differs between the US and the UK. The US-approved label includes the statement "...*there are no adequate and well-controlled studies in pregnant women...*".<sup>39</sup> In contrast, the text within the lamotrigine UK SmPC<sup>40</sup> includes detailed information: "... *A large amount of data on pregnant women exposed to [lamotrigine] monotherapy during the first trimester of pregnancy (more than 8700) do not suggest a substantial increase in the risk for major congenital malformations, including oral clefts*" In addition there is a recommendation for pregnant women to supplement their normal intake of folic acid. In the UK PIL for lamotrigine<sup>41</sup> there is reference to a potential risk of birth defects, including CL/P when used in the first trimester. Information is provided

concerning the impact of pregnancy on the effectiveness of lamotrigine, and there is a recommendation concerning the intake of extra folic acid before and during pregnancy. On the US equivalent<sup>39</sup> these recommendations are not present and the following text is present: “*It is not known if [lamotrigine] will harm your unborn baby.*”

Findings in the literature for human maternal exposure to lamotrigine monotherapy and the risk of MCM and CL/P vary between different pregnancy registries.<sup>42</sup> In 2012, a systematic review of the major pharmacoepidemiological studies, including registries, was performed.<sup>42</sup> The range of risk of major malformations in general following in utero exposure to lamotrigine was from 2.0% to 5.6% and the risk of CL/P ranged from 0.1% to 0.4%.<sup>37,38,42–46</sup> New data from the UK and Ireland epilepsy and pregnancy registry were released in 2014.<sup>43</sup> Analyses of these data revealed that among 2,089 first trimester exposures to lamotrigine monotherapy there were 49 instances of MCM, with 2 (0.1%) reports of CL/P.<sup>43</sup>

### **Levetiracetam**

Results of the non-clinical studies for levetiracetam are consistent with the safety information presented from the animal studies that are reported in the US and UK labelling including “...*increased incidences of minor fetal skeletal abnormalities*”.<sup>47,48</sup> However, planning pregnancy is recommended in the UK SmPC<sup>48</sup>, as well as avoidance of polytherapy and avoiding sudden discontinuation of the drug. None of these three pieces of information are present in the US PI.<sup>47</sup> A systematic review of the safety of levetiracetam in pregnancy revealed a MCM rate of 2.2%.<sup>49</sup> Among 1,213 monotherapy exposures to levetiracetam from different pregnancy registries, twenty-seven outcomes with MCM were reported (95% CI of 1.53-3.22) with a single case of CL/P.

There are a very few human studies of the safety of levetiracetam during pregnancy. Consequently our view is that the safety warnings about the maternal use of levetiracetam in both the UK and FDA labels are incomplete for both prescribers and patients.<sup>47,48,50</sup>

### **Gabapentin**

In the UK SmPC<sup>51</sup> it is recommended to use an effective method of contraception, to avoid polytherapy, to plan pregnancy and to avoid the sudden discontinuation of the drug. In contrast these recommendations do not appear in the US PI.<sup>51,52</sup> A systematic review of the safety of gabapentin in pregnancy revealed a rate of 1.7% MCM (five ICSRs) with

no reports of CL/P among 294 congenital anomalies.<sup>53</sup> The sample size of these studies was insufficient to draw firm conclusions about teratogenic effects and specifically concerning the risk of CL/P.<sup>53–55</sup> Despite the evident gaps in the data the UK PIL for gabapentin<sup>56</sup> included a reference to planning pregnancy and recommended the use of an effective contraceptive method as the risk to the fetus was unknown. This information was not present in the US PIL.<sup>52</sup>

### **Oxcarbazepine**

A systemic literature review of the safety of oxcarbazepine in pregnancy reported a rate of 2.0 % MCM (eight case reports) among 414 exposed fetuses.<sup>57</sup> The same study revealed a 3.3% rate of congenital anomaly from the European registry of antiepileptic drugs and pregnancy. According to this study the prevalence of congenital anomaly including CL/P was not higher than background rate.<sup>57</sup> The information is accurately reflected in both the UK and US labels.<sup>58,59</sup>

In the UK SmPC for oxcarbazepine recommendations for management of a maternal epilepsy include recommendations for drug dose adjustments, monotherapy, use of folic acid prophylaxis during the pregnancy, avoidance of sudden discontinuation of the drug and the risk of bleeding disorder for mother and neonate during delivery and the use of prophylactic vitamin K1.<sup>58</sup> These six pieces of information or specific recommendations are not provided in the US PI.<sup>59</sup>

### **Clonazepam**

Clonazepam is a benzodiazepine which is indicated for treatment of epilepsy, panic attacks and anxiety.<sup>60</sup> There are of course substantial published data related to the teratogenic effects of benzodiazepine in general and increase risk of MCM including CL/P.<sup>61</sup> However limited data was available in literature about specific risk of CL/P and clonazepam.<sup>60</sup>

The US PI<sup>27</sup> for clonazepam includes the statement that: *"...a similar pattern of malformations (cleft palate, open eyelid, fused sternbrae and limb defects) was observed in a low, non-dose-related incidence in exposed litters from all dosage groups..."*. This document also recommends: *"....Because use of these drugs is rarely a matter of urgency in the treatment of panic disorder, their use during the first trimester should almost always be avoided."* In addition, general recommendations and concerns

about the use of AEDs is present. Panic disorder is not an approved indication for clonazepam in the UK.<sup>26</sup> Compelling data about the risk of CL/P were published in 2005.<sup>62</sup>

### **Valproate**

In February 2016 there was a publication informing stakeholders about the high teratogenic potential of valproate, with the implementation of additional risk minimisation methods and a requirement for the communication of this information.<sup>63</sup> The MHRA introduced four types of resources to communicate the safety risk to women of childbearing potential, including a booklet for health care professionals, a consultation checklist, as well as a medication guide, and a card to be given to patients. This, in our view, constitutes an optimization of the risk minimization measures for the prescriber and patient. We consider it essential to provide this information and advice prior to conception, ideally with follow-up via postpartum education. The introduction of these measures followed the initiation of a referral procedure across the European Union (according to Article 31 of Directive 2001/83/EC). This led to the full evaluation of safety data related to pregnancy exposures, and a regulatory decision to strengthen warnings on the use of valproate-containing medicines in women and girls.<sup>64</sup> The safety review was first initiated by French national competent authority, ANSM (Agence Nationale de Sécurité du Médicament et des Produits de Santé or French Agency for the Safety of Health Products), following an analysis of malformations linked to the drug.<sup>65</sup> The European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) plans to hold its first public hearing to discuss the safety of the use of valproate during pregnancy commencing on 26 September 2017.<sup>66</sup> Patients residing in the European Union have been invited to speak about their experiences with valproate during this PRAC-initiated public safety review. The hearing is part of a broader plan to determine the adequacy of current warnings, precautions, and prescribing restrictions concerning adverse outcomes in babies born to women who take valproate during pregnancy.<sup>65</sup>

### **Discussion**

In this research, we set out to identify all AEDs that were statistically associated with the risk of CL/P in the MHRA UK Sentinel and US FAERS post-marketing adverse event reporting databases. Relatively high numbers of CL/P safety case reports were present in both databases for valproic acid, phenytoin, phenobarbital, primidone, carbamazepine,

topiramate and lamotrigine. We also conducted a descriptive study based on a structured qualitative assessment of the product labelling in the UK and US. This was performed to understand the completeness and currency of the information provided. Even where data are available concerning real world use, such as from spontaneous reports, disease or drug registries, and pharmacoepidemiological studies there are still inconsistencies in the information provided via the approved prescribing information. Further to this, it is notable that there are important differences in the information content presented prescribers in the UK and US.

The safety profile of human medicinal products during gestation can only be evaluated in the post-marketing period due to practical and ethical limitations in the development phase. Effective post-marketing surveillance systems are essential to enable the capture, collation and evaluation of information on pregnancy exposures and outcomes. There is need to improve the communication of the safety profiles of medicines used in pregnancy. A potential solution to enhance the existing system would be to encourage prescribers and patients to report exposures to a central authority via transfer of electronic health records, with appropriate data security measures. By centralizing the repository for these data, followed by expert scientific evaluation, detailed and consistent information about the exposures and outcomes of human medicines taken during pregnancy could be provided to stakeholders.

Although it is recognized that there are existing disease registries for epilepsy, and pregnancy registries for AEDs, there is still a need to improve the structure and conduct of post-marketing surveillance in this domain. Ideally, centers for data collection and collation should work in tandem. It would be possible to broaden existing networks to improve and extend the evidence base for the provision of information about pregnancy exposures and outcomes. This would take time, effort and careful planning to optimize the effort and harmonize data collection.

## **Conclusion**

Improving the communication of safety information to stakeholders should be considered by sharing verified data, by constructing globally consistent, clear and appropriate recommendations in a timely, transparent, unbiased and evidence-based manner.

## Limitations

The primary limitation of spontaneous reporting schemes such as the UK Yellow Card system and the FDA MedWatch scheme is the significant level of under-reporting. ADR reporting rates may be influenced by the seriousness of reactions, by the ease of recognition of the ADR, by the extent of use of a particular drug, and by the level of publicity about the medicinal product. Spontaneous reporting systems cannot be used to determine incidence of a particular ADR as denominator data are not available and causality cannot always be established.

During our literature review we concluded that pregnancy registries usually report the overall risk of congenital anomalies rather than a specific type of malformation such as CL/P therefore we discussed congenital malformations in general to describe the teratogenic potential of a particular drug. Another limitation of reviewing data from different registries is the heterogeneity of their designs and the variety of patient populations included, which makes it difficult to draw firm scientific conclusions.

The relevant regulatory authorities approved all of the prescribing information available to us, therefore we did not assess the compliance of the information content. However, we did assess the completeness of the safety information provided in the approved prescribing information and pack inserts against the evidence in the literature.

Because the FDA's Pregnancy and Lactation Labelling Rule (PLLR) applies only in the US, we did not consider the assigned PLLR categories in this study; only the content of the text was evaluated.

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## 5. Publication II

### **Social Media Surveillance of Multiple Sclerosis Medications Used During Pregnancy and Breastfeeding: Content Analysis**

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The format of this publication is adjusted to the thesis format.

#### **Abstract**

**Background:** Multiple Sclerosis (MS) is a chronic neurological disease occurring mostly in women of childbearing age. Pregnant women with MS are usually excluded from clinical trials; as users of the Internet, however, they are actively engaged in threads and forums on social media. Social media provides the potential to explore real-world patient experiences and concerns about the use of medicinal products during pregnancy and breastfeeding.

**Objective:** To analyze the content of posts concerning pregnancy and use of medicines in online forums; thus, to gain a thorough understanding of patients' experiences with MS medication.

**Methods:** Using the names of medicinal products as search terms we collected posts from twenty-one publicly available pregnancy forums, which were accessed, between March 2015 and March 2018. After the identification of relevant posts, we analyzed the content of each post using a content analysis technique, and categorized the main topics that users discussed most frequently.

**Results:** We identified six main topics in seventy social media posts. These topics were: (1) Expressing personal experiences with MS medication use during the reproductive period (55 out of 70, 80%); (2) Seeking and sharing advice about the use of medicines (52 out 70, 74.28%); (3) Progression of MS during and after pregnancy (35 out of 70, 50%); (4) Discussing concerns about MS medications during the reproductive period (35 out of 70, 50%); (5) Querying the possibility of breastfeeding while taking MS medications

(30 out of 70, 42.85%); (6) Commenting on communications with physician(s) (26 out of 70, 37.14%).

**Conclusions:** Overall, many pregnant women or women considering pregnancy shared profound uncertainties and specific concerns about taking medicines during the reproductive period. There is a significant need to provide advice and guidance to MS patients concerning the use of medicines in pregnancy and postpartum, as well as during breastfeeding. Advice must be tailored to the circumstances of each patient and, of course, to the individual medicine. Information must be provided by a trusted source with relevant expertise, and made publicly available.

**Key words:** Social media vigilance, multiple sclerosis medications, pregnancy, postpartum, breastfeeding, text mining

## Introduction

Multiple Sclerosis (MS) is a chronic disease of the central nervous system [1]. It is more prevalent in females than males, with a ratio of approximately 3 to 1 [2]. Female MS patients are predominantly of childbearing potential with the average age of disease onset being 29.2 years [1]. The prevalence of MS is more common further from the Equator, this can be explained due to vitamin D deficiency rather than only genetics.[3] Pregnancy is not contraindicated in MS but remains a concern among female patients for a variety of reasons [2]. Pregnancy appears to have a protective effect in MS such that pregnant women suffer a reduced number of MS relapses, especially during the third trimester (reduction of around 70%). Thereafter, relapse rates tend to increase in the first three months postpartum [4,5]. However, this protective effect of pregnancy and the risk of postpartum relapse are both related to each patient's MS history and current disease activity [6].

Pregnant women are usually excluded from clinical trials due to ethical issues [7]; thus, safety information about human drug exposure during pregnancy is very limited at the time a marketing authorization is granted [8]. Pregnancy registries have been developed to address this gap in the safety profile of newly authorized medicines. Despite the evident advantages, such registries often suffer from low enrolment, resulting in delayed findings, selection bias, heterogeneity in data collection methods, and high costs [9]. As a result prescribing information and patient information leaflets, contain limited safety information for pregnant and breastfeeding patients [8]. Despite the evident need, to the best of our knowledge there are no globally accepted guidelines by regulatory agencies for the medical management of MS during pregnancy and breastfeeding.

The rapid expansion of the Internet and the availability of various social media platforms in recent years has increased the frequency with which patients use the Internet [10]. In the US, 90% of adults use the Internet regularly, and 72% have searched for health information online [11]. Pregnant women in particular often access the Internet to seek health information [12]. A cohort of pregnant women has been identified in Twitter using text mining and machine learning [13]. The availability of data for this cohort of pregnant women in social media provides an opportunity to explore and gain further insights into patient experiences related to MS medications. Therefore, by increasing HCPs'

awareness of patient concerns, carers can better advise patients during clinical visits. The objective of this study was to analyze data qualitatively and describe the content of posts in online pregnancy forums in order to understand better patient experiences resulting from the use of MS medications during pregnancy, postpartum and breastfeeding.

## Methods

### Data Acquisition and Classification

We obtained data from publicly available online pregnancy forums. An existing digital monitoring platform called MedWatcher Social was utilized; this system has been described elsewhere [10,13,14]. MedWatcher Social comprises the natural language processing component that acquires public data from the Internet, apply classification algorithms, and extract adverse event-related posts. The aggregated frequency of product-event pairs identified by MedWatcher was concordant with data from the public FDA Adverse Event Reporting System by System Organ Class (SOC) [9].

The classifier was designed to automatically collect, classify, and analyze social media discussions and threads pertaining to medical products [10,13,14]. The system collected online forum posts both retrospectively and prospectively, via authorized third-party data vendors, using the names of medicinal products as search terms. After data ingestion, a naïve Bayes classifier scored and filtered each post according to its relevance. Using statistical machine learning and a training set of over 360,000 hand-labeled social media posts, the classifier was trained to recognize:

- Descriptions of adverse drug reactions,
- Medication errors,
- Product quality issues, and
- Other patient experiences with medical products

The classifier was also used to exclude 'noise' (e.g., non-valid product posts and spam). After filtering the data, natural language processors were applied to recognize and extract product and symptom terms through tokenization and proprietary taxonomies. References to products were standardized and consolidated, and vernacular descriptions of medical concepts were translated into the best matched term within the Medical Dictionary for Regulatory Activities (MedDRA) terminology [15]. For this analysis, we identified and extracted a dataset from the system comprising posts acquired from twenty-

one publicly accessible pregnancy social media forums listed in Table 1, published between March 2015 and March 2018. The forum data were acquired using third-party data from vendors (Socialgist and Datasift) and thus was dependent on availability from those vendors. Data were not randomly sampled; rather, we selected any forums that were both available from Socialgist or Datasift and were dedicated to discussions around pregnancy or breastfeeding. The classifier used for the analysis was trained only on English language data, so we only used English language posts for this analysis.

Additionally we identified a list of products authorized for the treatment of MS, and filtered the data accordingly. The products were alemtuzumab, teriflunomide, interferon beta-1a, interferon beta-1b, glatiramer acetate, daclizumab, dimethyl fumarate, fingolimod, and natalizumab. Posts mentioning either the active substance or brand name of each medicinal product were collected as shown in Multimedia Appendix 1.

**Table 1. Lists of publicly available pregnancy forums**

List of pregnancy online forums

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Babiesbase.com

Babycenter.com

Babycenter.com.au

Babycentre.co.uk

Cafemom.com

Dcurbanmom.com

Fertility.org

Magrossesse.com

Mumsnet.com

Whattoexpect.com

Swissmomforum.ch

Baby-cafe.cz

Babycenter.ca

Babycenter.in

Circleofmoms.com

Essentialbaby.com.au

Justmommies.com

Netmums.com

Thebump.com

Fertilethoughts.com

## **Content Analysis**

After automated classification, reports were manually divided into two groups: discussions related to pregnancy or breastfeeding, and posts containing no thread relevant to pregnancy or lactation. In this study, we focused only on posts where an individual wrote about an experience related to a current or previous pregnancy, or breastfeeding related to medicinal treatment of MS medication, or a complication of MS or treatment of this disease.

A human expert reviewed the posts to characterize the experiences described in each post. First, we collected any medical information that a user shared in a post, such as time since their diagnosis of MS, planned or unplanned pregnancy, gestational age, outcome of pregnancy (or multiple pregnancies), number of pregnancies, current or previous pregnancy, concomitant medication(s), and John Cunningham (JC) virus serology results. Second, for the questions and/or concerns written in posts, we applied the content analysis method [16,17]. The aim was to use this categorization to identify common themes (threads) and to assess their frequency. To start with, we used open coding for obtaining the sense of the content. The coding team was composed of a physician (BR), a pharmacovigilance expert (DL), a statistician (AZ) and a machine-learning expert (CP). We created a codebook based on features that individual users shared (e.g. what were their concerns and what action was taken with the medication(s), etc.). Subsequently the initial codes formed higher order headings of main topics. The entire data set was reviewed and posts were assigned to each topic. In addition, we quantified the content by measuring the frequency of each topic, which we cautiously proposed may stand as a proxy for significance [17].

The unit of analysis was the number of posts. It should be noted that in each individual post, the author might have provided comments on more than one main topic.

## **Ethic Statement**

All human subject data used in this analysis were publicly available and have been presented in a de-identified format; in no case was any personally identifiable information (PII) reviewed. In fact, the classifier was set-up to de-identify individual posts by removing

any text relating to PII. We did not contact any individual on social media for follow-up as felt that this posed unacceptable ethical and potential data privacy concerns. Thus, all of the posts were evaluated without knowledge of the identity of the patients involved.

## Results

### Data Processing Results

Our initial dataset comprised 376,691 posts that had been shared publicly on the pregnancy forums during the four-year period of observation. This dataset was reduced to 168 (0.04% of total) posts relevant to pregnancy or breastfeeding and MS after filtering for posts mentioning the specified products. Finally, 16 posts containing spam-like language, non-English text, or non-valid mentions of the product were automatically identified as irrelevant and were filtered out, leaving 152 posts for analysis as shown in Table 2.

**Table 2. Result of data processing**

<b>Number of posts extract from database via automation</b>	<b>Pre-Spam Removal</b>	<b>Post-Spam Removal</b>
Posts mentioning any product	376,691	359,306
Posts mentioning multiple sclerosis products	168	152
<b>Manual selection of unique posts where previous or current pregnancy was mentioned</b>	152	70

Among the 152 posts, 70 unique posts discussed a current or previous pregnancy or breastfeeding experiences related to MS medications. The remaining 82 posts were non-informative concerning pregnancy or breastfeeding. As a result, we focused on the 70 posts that provided pertinent and substantive information. Table 3 provides illustrative examples of medically relevant information shared by the post authors. We could not identify the gender of individual users in each post, but based on the content, and the way that the text related personal sentiments and explanations, we assumed that it was predominantly pregnant women who authored the content.

**Table 3. Medically relevant information shared by MS patients on the online post**

Information shared in posts	Number of posts (%)	Illustrative text extracted from post
Gestational age	22 (31.42%)	"I am 30 weeks pregnant"
First trimester <sup>a</sup>	8 (11.42%)	
Second trimester	7 (10%)	
Third trimester	7 (10%)	
Time diagnosed for MS	21 (30.00%)	"I got diagnosed in 2009'..."
Unplanned pregnancy	22 (31.42%)	"...found out I was pregnant at 8 weeks and immediately stopped Gilenya..."
Planned Pregnancy	8 (11.42%)	"...stopped the medication in July to get pregnant..."
Outcome in Newborns	18 (25.71%)	"My daughter is [a] healthy one year old..."
Previous pregnancy	10 (14.28%)	"It's my second baby..."
First pregnancy	7 (10.00%)	"It's my first pregnancy..."
Concomitant medication	5 (7.14%)	..."Taking Methadone and Percocet as well'..."
JC virus result	3 (4.28%)	"...I am JC positive..."

A first trimester (1-12 weeks), second trimester (13-28 weeks), third trimester (29-40 weeks) according definition available in the US Department of Health and Human Services at <https://www.womenshealth.gov/pregnancy/youre-pregnant-now-what/stages-pregnancy>

Patients indicated that their newborn children were healthy, with no reports of congenital anomalies, in 18 of 70 posts (25.71%). MS patients shared in 22 (31.42%) posts their gestational age, and in 21 (30%) posts the year of the first diagnosis of MS were mentioned.

## Content Analysis Results

Upon detailed review of the content of each post, we identified six main topics, which are presented in Tables 4 and 5. Patients used the pregnancy forums as an outlet for:

- (1) Describing in detail personal experiences with medicines, including changes in therapy, stopping medication, taking medication during pregnancy and breastfeeding;
- (2) Sharing and seeking information about MS medication in pregnancy and postpartum;
- (3) Reporting MS progression (disease status) in this period;
- (4) Expressing uncertainty or fears related to MS medication;
- (5) Discussing or commenting on breastfeeding and MS medication;
- (6) Sharing details or comments on communications with HCPs involved in the care of the pregnant mother or offspring.

**Table 4. Main topics posted by individuals on social media related to MS, pregnancy and breastfeeding**

Topic	N <sup>b</sup> (%)
<b>1. Discussion about personal experiences with MS medication in reproductive period</b>	<b>56 (80%)</b>
Switched, switching, or will change medication during pregnancy or breastfeeding	28 (40%)
Stopped, stopping, or will stop medication during pregnancy or breastfeeding	26 (37.14%)
Took, taking, or will take medication during pregnancy or breastfeeding	22 (31.42%)
<b>2. Reporting MS Diseases Status during and after pregnancy</b>	<b>35 (50%)</b>
Reported no relapse and healthy pregnancy	16 (22.85%)
Reported relapse during pregnancy	15 (21.42%)
Reported relapse postpartum	12 (17.14%)
<b>3. Seeking and Giving advice</b>	<b>52 (74.28%)</b>
Seeking advice about MS, pregnancy and postpartum	36 (51.42%)
Giving advice about MS, pregnancy and postpartum	16 (22.85%)

<b>4. Communication with the HCP</b>	<b>26 (37.14%)</b>
Good communication and patient express trust in the HCP	8 (11.42%)
Poor communication	18 (25.71%)
<b>5. Discussion related to breastfeeding and MS medication</b>	<b>30 (42.85%)</b>
<b>6. Express uncertainty and fear about MS medication in reproductive period</b>	<b>35 (50%)</b>

<sup>b</sup> Percentages are calculated using N=70 total individual posts about pregnancy and breastfeeding. The unit used was topic posted. One post may contain several pieces of information or an individual might have written about more than one pregnancy experiences.

**Table 5. Illustrative example of posts related to each main topic and subtopic**

<b>Topic</b>	<b>Subtopic</b>	<b>Illustrative text extracted from individual posts</b>
<b>Sharing experiences on MS medications</b>	Stopping medication	<i>"...I don't plan on taking anything [during] this pregnancy either."</i>
	Switching treatment	<i>"...I took Copaxone throughout my pregnancy and breastfeeding and then started Tecfidera..."</i>
	Taking medication	<i>"...I took Copaxone throughout my pregnancy and breastfeeding under the direction of my neuro [sic]...."</i>
<b>MS Diseases Status</b>	No relapse	<i>"...I had no issues with my MS during my pregnancy..."</i>
	Relapse in pregnancy	<i>"...I have very active MS had 2 relapse in 29 weeks journey. Have been on copaxone [sic] throughout and short steroids course twice..."</i>
	Postpartum relapse	<i>"...I didn't start flaring up until my son was over 6 months old. I've been in [sic] Tysabri since...!"</i>
<b>Seeking and Giving advice</b>	Seeking advice	<i>"...I am 8 weeks pregnant and was taking my gilenya [sic] during those 8 weeks meaning the baby will be exposed to it for 2 additional months Has anyone dealt with a pregnancy like this? The doctors have such limited information."</i>
	Giving advice	<i>"...MS patients are advised [sic] to come off their meds when trying for a baby. my understanding is that Copaxone and the interferons are perfectly ok to take until a positive pregnancy test. I'm a little bitter because I got the same advice and suffered a disabling relapse as a result. Copaxone especially is probably fine to take even during pregnancy (though now that I have finally found luck, I have chosen to stay off during pregnancy and restart after birth and yes I will be breastfeeding). Good luck."</i>
<b>Breastfeeding</b>		<i>"...My neuro [sic] recommended a 3-day steroid infusion treatment. I had to pump and dump [sic] the whole time and for 24 hours following the last infusion..."</i>
<b>Express uncertainty or concern(s)</b>		<i>"...I just found out I am unexpectedly pregnant and conceived while in gilenya [sic]. Everything everyone has been telling us has made us to start thinking about terminating the pregnancy, which I really badly do not want to do. But if this child is any kind of danger I don't want to risk that. I just want</i>

		<i>someone to tell me it will be okay. I just don't know if that's realistic..."</i>
<b>Communication with HCPs</b>	Good communication	<i>"...I have been on Tysabri! I talked to neuro [sic] and she completely calmed my nerves! She just had me stop all meds for now then we'll switch to Copaxone after birth..."</i>
	Bad communication	<i>"...My neurologist never mentioned anything, and said I can just start taking Gilenya after I give birth. She said attacks are more common after birth but didn't suggest anything to prevent them..."</i>

## Discussion

In this study, we performed text mining and characterization of posts acquired from pregnancy-related online forums where patients discussed MS medications. The aim of this study was to gain a better understanding of information sought by, or provided to, pregnant and breastfeeding MS patients who are active on social media. Our data shows that the main topics of concern were switching, stopping or taking medication during and after pregnancy; there was clear evidence of information seeking related to the risk of MS relapse during pregnancy or postpartum; and finally, questions were raised about breastfeeding while on medication. The most frequently observed content (approximately 80% of all relevant posts) was personal experiences with MS medications. Individuals shared their reasons for personal decisions regarding treatment, described how they felt after changes in therapy: switched, started, or stopped medication, whether this was due to a HCP's recommendation or due to the patient's personal beliefs.

Patients used online forums to seek information from, and provide advice to, others (the latter occurred in 52 out of 70 (74.28%) of posts). In 36 (51.42%) posts individuals asked their peers about decisions and outcomes: or about experiences when taking a specific medication, or queried the safety profile of certain medications, asked about the risk of MS relapses, and enquired about when to restart medical treatment postpartum. Our findings concur with the hypothesis that maternal medicine use is one of the four topics pregnant women care about most [18]. We had hoped that all of the topics would have been openly discussed with HCPs, but this was not invariably the case. In a number of posts, the patient expressed concerns that they had received medical advice from a HCP, and either actively disagreed or least significantly doubted what they had been told. For example:

*"...I went to the infusion center for my first Tysabri treatment, the nurse said my neurologist requested a pregnancy test to rule it out before we got started. Long story short, it came back positive! My treatment was canceled. Here I am 3 years later, and pregnant with our third baby. Coincidentally, I missed my last two months of treatment (I only get it once a month) so it should be well out of my system and there shouldn't be any issues..."*

In comparison to our results, a Swedish study found that, when speaking with their midwives, most pregnant women (70%) did not discuss information that they had retrieved online despite perceiving this information to be reliable [19]. Interestingly more than half of the study subjects searched online for topics first raised by a midwife [19]. We were not in a position to explore the reason why patients went online and searched for information about their medicines; however, a web-based survey among women who used the Internet to seek pregnancy information showed that 48.6 % of respondents were not satisfied with the information provided by their respective HCPs. The majority of these respondents (46.5%) stated that they primarily turned to the Internet because they did not have time during appointments to discuss their concerns [20]. Moreover, pregnant women used the Internet because the information given to them by their HCPs was neither clear nor sufficient [20].

In the breastfeeding category, 30 out of 70 (42.85%) posts described refusal or delay in commencing medical MS treatment for the sake of breastfeeding, or described foregoing breastfeeding to restart treatment, or requested evidence of which medication might be safer to take whilst breastfeeding, and others commented on discarding breast-milk which was suspected to contain medication whilst receiving treatment (so-called 'pump and dump') [21]. Several individuals shared confusion about the risks and benefits of breastfeeding and expressed anxiety about the dilemma of caring for their own health whilst not doing any harm to the baby.

There is very limited information about the safety of MS medication during breastfeeding. The *in vivo* model for drug exposure to breast milk is suboptimal and human milk biobanks suffer from a paucity of human breast milk samples [22]. This is paradoxical, particularly when one considers the posts concerning the 'pump and dump' phenomenon. A small adjustment in behavior, based on medical advice or guidance from a midwife, could yield a range of useful samples for retention and assay within existing biobanks. In addition, it is known that pregnancy registries often have low enrollment rates [23]. In our study, just

two posts (2.85%) mentioned contacting pregnancy registries. One possible solution to increase the enrollment rate of pregnancy registries and human milk biobank centres could be improving the communication to pregnant MS patients about participation both at the point of care and in online forums. A simple scripted explanation about the existence of registries, the purpose of their research, and the impact that they can have on the MS population might yield better recruitment for altruistic reasons. Encouraging individuals to participate in the available biobanks with all exhibiting a *“pump and save rather than pump and dump”* philosophy after treatment could yield valuable evidence to aid decision-making.

Another important finding was the rate of unplanned pregnancies with 22 out of 70 (31.42%) posts describing such events, and only eight posts (11.42%) describing planned pregnancies. Nonetheless, in some patient information leaflets for MS medicines, both contraception and careful planning of pregnancy is clearly recommended [24]. A Danish study surveyed 590 MS patients about family planning and reported that 42% of female and 74% of male partners did not know if their MS medication was teratogenic or not. This study also reported that 10% of pregnancies during MS treatment were unplanned; 49% of these pregnancies were terminated [25].

Generally, there are gaps in current methods for collecting and analyzing data pertaining to the safety of medicines during pregnancy and lactation [26,27]. The safety of medicinal products administered during pregnancy and lactation is a complex topic that needs coordinated communication across many disciplines to obtain, analyze and present information in a harmonized approach. Harmonized methods and metrics among different pregnancy specialties should be developed to allow better analysis of outcomes and endpoints [26]. In this regard, we are aware of an Innovative Medicine Initiative (IMI) project called ‘Continuum of Evidence from Pregnancy Exposures, Reproductive Toxicology and Breastfeeding to Improve Outcomes Now’ (ConcePTION) [28]. The IMI ConcePTION project is a collaboration between public-private partners and the pharmaceutical industry in order to address this problem. The aim of ConcePTION is *“Building an ecosystem for better monitoring and communicating safety of medicines use in pregnancy and breastfeeding: validated and regulatory endorsed workflows for fast, optimized evidence generation”* [28]. Participants in this project and the authors of this

paper believe that there is an important societal obligation to reduce uncertainty about the effects of medicines used during pregnancy and breastfeeding.

Furthermore, even when safety data are available, it is often not effectively communicated to patients and HCPs. On September 26, 2017, the Pharmacovigilance Risk Assessment Committee (PRAC) and the European Medicine Agency (EMA) held its first public hearing about safety concerns with the use of medications containing sodium valproate during pregnancy [29]. Patients and carers participated in the public hearing and both mothers and affected children expressed concern about the lack of effective risk minimization communication for safety of valproate during pregnancy, despite the drug having been authorized for >50 years [30]. After the public hearing, the PRAC and the EMA provided new measures for comprehensive risk minimization, including;

- A pregnancy prevention programme;
- Visual warning about the risk in pregnancy on the box (outer packaging);
- A patient reminder card attached to outer package for pharmacists to discuss with patients each time the medicine is dispensed;
- Updated educational materials for patients and HCPs [29]

In the valproate pregnancy prevention programme, HCPs are instructed to assess patients' potential for becoming pregnant by evaluating their individual circumstances and then assist their patients in making informed decisions. HCPs are responsible for informing their patients about the use of effective contraception methods throughout valproate treatment and to review such treatment annually. Interestingly, as an adjunct to all of these measures, a new risk acknowledgement form has been designed and implemented for patients and their HCPs to document that sufficient advice has been provided and understood [29]. Such comprehensive guidelines and the risk minimization methods adopted for valproate could serve as an example for improving and strengthening the warnings for MS medication in pregnancy.

In 2009, the EMA published guidance for assessing medicinal product risks on human reproduction and lactation [31]. In the US, the Food and Drug Administration (FDA) issued the Pregnancy and Lactation Labeling Rule (PLLR) for industry. This document provides a detailed framework for clearly communicating information to prescribers to aid improved decision making [21,32]. It is worth noting a study that reviewed medication risks during pregnancy for 172 drugs approved by FDA between 2000 and 2010. Among these, in

97.7% of drugs teratogenic risk in human pregnancy was “undetermined” and amount of data for 73.3% of these drug was described as “none” [33]. For 468 drugs approved by FDA between 1980 and 2000, the average time required for a drug’s risk category to be changed from “undetermined” to a more precise risk was estimated to be 27 years [33]. A web-based survey reported that patient leaflets were not comprehensive enough to answer pregnant women’s questions and did not facilitate decision-making [20]. In addition, inconsistencies have been found between the safety information concerning use during pregnancy provided in the US prescribing information and the UK summary of product characteristics for the same medical product [8].

Evidently, there is a need to improve regulatory policy and guidance by involving not only health authorities, but also HCPs, patients and other stakeholders including the national Teratology Information Services. Two recommendations we suggest are to conduct active post-marketing surveillance and to provide globally harmonized evidence-based information for the prescriber, patients and carers in a timely manner. Inevitably, with the Internet and the wide variety of social media available, information is rapidly disseminated and patients have access to, and appear to trust non-traditional sources of medical information. We anticipate that in future it will not be permissible to take three decades to vary existing labelling once sufficient evidence has been generated to provide useful information to patients and prescribers.

## **Conclusion**

Social media can provide insight into patients’ real life experiences with medical products during pregnancy as well as their struggle in comprehending the benefits and risks that this poses. Our study showed that MS patients expressed uncertainty and concerns around reproductive health; however, social media could be utilized as a platform to engage and encourage patients to enroll in pregnancy registries and to donate samples to milk biobank research centers. The adoption of these simple methods would support the generation of essential missing safety data, and would support the communication of risk minimization strategies to pregnant patients and women of childbearing potential [34]. The role of HCPs involved in supporting pregnant patients, or during early child development, should not be underestimated. HCPs could provide comprehensive information for MS patients throughout different stages of pregnancy and postpartum, as

well as during breastfeeding. Additionally, improving safety data collection and analysis as well as implementing efficient policies in regards to practical guidelines for MS populations of childbearing age would prove advantageous. Future guidelines should address the impact of MS on pregnancy and the effect of pregnancy on MS, the risks of the occurrence of birth defects, recommendations concerning the most effective contraceptive methods, and planning pregnancy as far as possible, in order to allow optimal wash-out time of medication, disease control during and after pregnancy, approved medication to use in reproductive periods and lactation guidelines following the treatment [2,35]. Further research is needed to explore the effectiveness of risk minimization methods and to improve communication among HCPs and patients to the extent that it enables and informs shared decision-making.

### **Limitations of the Study**

Social media surveillance for medical product insight poses multiple challenges which has been addressed in literature [10,11,13]. In summary, there are technical, regulatory, privacy and ethical considerations that need to be addressed when leveraging social media for this purpose [11]. In this study, the classifier was specifically selected to conduct research focusing on the exposure to MS medicines, not the effects of MS disease on the outcomes of pregnancy. In addition, these searches were only performed in pregnancy forums where posts related to MS medications were published. Hence, we recommend that further research to be conducted in both MS and other disease-specific forums including 'multiple sclerosis' term.

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### **Conflict of Interests**

B. Rezaallah is an employee of Novartis. D. Lewis is an employee of Novartis and holds shares in Novartis and GlaxoSmithKline. C. Pierce was an employee of Booz Allen Hamilton when this research was conducted. B.-I. Berg and H.-F. Zeilhofer have no conflicts of interest.

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## Abbreviations

Multiple sclerosis	MS
Healthcare professional	HCP
System Organ Class	SOC
Medical Dictionary for Regulatory Activities	MedDRA
John Cunningham	JC
Personally identifiable information	PII
Innovative Medicine Initiative	IMI
Continuum of Evidence from Pregnancy Exposures, Reproductive Toxicology and Breastfeeding to Improve Outcomes Now	ConcePTION
Pharmacovigilance Risk Assessment Committee	PRAC
European Medicine Agency	EMA
Food and Drug Administration	FDA
Pregnancy and Lactation Labeling Rule	PLLR

## E -Table:

### Search terms used to filter multiple sclerosis product-relevant data

<b>Product</b>	<b>Synonyms</b>
alemtuzumab	alemtuzumab, Lemtrada™
teriflunomide	teriflunomide, Aubagio™
interferon beta-1a	interferon beta-1a, Avonex™, Plegridy™, Rebif™
interferon beta-1b	interferon beta-1b, Betaferon™, Betaseron™, Feron™, Extavia™, Compesk™
glatiramer acetate	glatiramer acetate, Copaxone™, Glatopa™
daclizumab	Daclizumab
dimethyl fumarate	dimethyl fumarate, Tecfidera™
fingolimod	fingolimod, Gilenya™
natalizumab	natalizumab, Tysabri™

## 6. Publication III

### **An alternative to product-specific pregnancy registries?**

#### **PRIM; PRegnancy outcomes Intensive Monitoring**

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<sup>1</sup>Authorship: YG and BR are co-first authors (listed alphabetical) – As both of them have equally contributed.

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The format of this publication is adjusted to the thesis format.

#### **Abstract**

Patient safety during pregnancy is an important concern. This article presents a method of using an industry post-marketing database to access prospective pregnancy cases. This method, termed 'PRegnancy outcomes Intensive Monitoring' (PRIM) was developed for fingolimod (Gilenya TM), a treatment option for multiple sclerosis (MS), due to slow enrollment in the company pregnancy registry. The aim of PRIM was to enhance the process of pregnancy data collection and improve data quality, and in turn particular to enable estimation of the proportion of major congenital malformation and other pregnancy outcomes. To do this, the spontaneous reports of fingolimod maternal exposure or in the eight weeks immediately before the last menstrual period reported to the safety database but not enrolled in the pregnancy registry were identified. Follow up checklists were sent at four time points: initial pregnancy report, end of pregnancy, and infant follow-up at 3 and 12 months of age. These focused on core data required for derivation of programmed analyses. From 01 Mar 2014 to 28 Feb 2018, a total of 831 prospective maternal exposures with 843 infants were reported, with fetal outcomes reported in 459 (54.4%) of those infants. This enabled the calculation of proportions of pregnancy cases with the main pregnancy outcomes and of fetal cases with malformation. The number of reported

pregnancies was significantly higher in PRIM than in the registry, showing that structured use of pharmacovigilance data could enable speedier assessment of risks of maternal drug exposure.

## **Keywords**

Pregnancy outcome; Intensive monitoring; Targeted follow-up; Pharmacovigilance; Multiple sclerosis; Maternal exposure

## **1 Introduction**

### **1.1 Background**

Pregnant women are usually excluded from clinical trials for ethical reasons. Therefore, at the time of marketing authorization safety data of medical products in pregnant women are usually limited to animal data (1). Post-marketing surveillance methods such as pregnancy registries are sometimes required by health authorities in order to characterize the outcomes of the use of medicines in human pregnancy (2). Collection of spontaneous reports is a legal requirement of all marketing authorisation holders; information on all cases of pregnancy associated with exposure to a medicinal product for which the marketing authorization holder (MAH) has a pharmacovigilance responsibility is collected and processed in order to provide data of the required quality for assessment (3,4). Pregnancy registries have been considered as the preferred method to collect safety information on human exposure to authorised medicines during pregnancy. Registries have well-documented advantages such as providing structured studies, supported by customized databases. But they also have important limitations including difficulties in enrolling patients and poor follow-up rates, which in turn results in high costs and delays or even complete failure to obtain meaningful results regarding the outcomes of the use of medicines in pregnancy (2,5,6). Delays in providing such information has an impact on public health. A good example is valproate which was first approved in 1978 (7). The Pharmacovigilance Risk Assessment Committee (PRAC) held a public hearing to discuss this product in January 2015 in order to further inform stakeholders about the impact of its use during pregnancy. As a result, the European Medicines Agency (EMA) and National Competent Authorities across Europe have informed healthcare professionals and patients of the high risks of valproate concerning congenital malformations and

neurodevelopmental delay in the infant. A series of new pregnancy prevention and risk minimization measures were established (8). A systematic review of pregnancy registries for 34 products showed a median registry enrollment of 36 pregnancies compared with a median of 450 spontaneous reports of pregnancy exposure received by manufacturers contemporaneously (9). The same study reported that for products rarely used in pregnancy, the worldwide spontaneous reporting rate was much higher than the registry enrollment rate (9). However, despite the fact that receipt of spontaneous reports is high compared with enrollment into registries, spontaneous report data are collected passively relying on healthcare professionals and patients to submit reports, so the information received is often insufficiently complete or not of the required quality and consistency for data aggregation and programmatic analysis.

In addition to these issues, there is insufficient harmonization of terminologies, methods of assessment, and standardization of data elements with respect to safety interventions in pregnancy. Innovative solutions are required to provide enhanced safety data collection and pharmacovigilance (10).

## **1.2 Multiple sclerosis and fingolimod**

MS is an immune-mediated inflammatory disorder of the central nervous system (11) The gender ratio is different depending on the subtype of MS; relapsing remitting multiple sclerosis (RRMS) has a female-to-male ratio of 2-3:1 (12). The average age of onset of MS is 29.2 years indicating that many MS patients are women of childbearing age when diagnosed with the disease (13). Fingolimod (Gilenya™) is indicated as a disease-modifying therapy for the treatment of patients with relapsing type of MS. In animal models, it was shown that fingolimod (5.0 mg/kg orally) and its metabolites cross the placental barrier in pregnant rabbits to a limited extent (14). Fingolimod was found to have a teratogenic effect in rats including persistent truncus arteriosus and ventricular septal defect (14). Before initiation of treatment with Gilenya in women of childbearing potential, a negative pregnancy test result needs to be available and counselling should be provided regarding the potential for serious risk to the foetus and the need for effective contraception during treatment with Gilenya (14).

In response to the need for prospective follow-up data in human pregnancy, the Gilenya Pregnancy Registry (referred to as the Registry) was established, with the first patient first

contact on 15 Oct 2011 (EU PAS register number: ENCEPP/SDPP/2569) (15). The purpose of the Registry was to collect more safety data on the risk of reproductive toxicity of fingolimod exposure during or shortly before pregnancy. However, due to slow enrollment in the Registry (15), the routine pharmacovigilance (PV) process was accessed to collect more data on spontaneous reports of pregnancy exposed to fingolimod received in the company safety database. However, it was recognized that not all registry variables would be available from spontaneous reports, therefore PRIM was designed in order to focus on the most important data to support medical assessment (namely core data on the mother, on the pregnancy outcome, and on the fetal and infant outcomes) needed to quantify the risks of reproductive toxicity.

The objective of PRIM was to establish an enhanced pharmacovigilance method by improving collection, quality, and processing of prospective data from spontaneously reported pregnancies reported to the global safety database, to enable computer programmed estimation of the proportion of infants/fetuses with major congenital malformation and of other pregnancy outcomes such as stillbirth and termination of pregnancy.

## **2 Methods**

### **2.1 PRIM description**

The PRIM (PRegnancy outcomes Intensive Monitoring) was defined as enhanced pharmacovigilance data collection and processing via sets of targeted checklists, structured follow-up, rigorous process of data entry and data quality control, and programmed aggregate analysis. This enhancement was initiated on 01 March 2014 for fingolimod to access data from pregnancies prospectively reported to the MAH safety database in patients who were not enrolled in the Registry. To reduce bias in these estimates, the process focused on prospectively-reported pregnancies.

Differences between PRIM and routine PV for pregnancy case follow-up are summarised in Table 1. PRIM was established as an end-to-end process including determining crucial outcomes of interest, definition of terms, data collection and follow-up, data processing and analysis. Table 2 shows each step of PRIM methodology.

**Table 1 The PRIM (PRegnancy outcomes Intensive Monitoring) and routine pharmacovigilance procedure for pregnancy cases**

<b>PRIM</b>	<b>Routine pregnancy pharmacovigilance procedure</b>
Data collection points: Baseline, EDD <sup>a</sup> +1 month, EDD+ 3months and EDD+12 months	Data collection points: Baseline, EDD+1 month; EDD+3 months, EDD+ 12 months
Four follow-up (FU) attempts at each data collection point before a patient would be considered lost to follow-up	Three FU attempts at outcome of pregnancy (no information received after sending EDD+12 months follow-up) before a patient would be considered lost to follow-up
For specific Patient Oriented Programs (POP) with continuous interactions with patients, Novartis or External service provider collects the necessary FU information (when allowable by local regulations and program design) by contacting the reporter through all possible means (i.e. phone, e-mail, letter, fax etc.)	Data collections from POP would be as per routine process i.e. spontaneous reporting
Automated check of overdue FUs by central site which contacts Novartis local affiliates directly with long overdue FU (>30 days)	Check of overdue FUs by Novartis local affiliates only
Data collection and follow-up on normal infants not just those reporting adverse events (AEs)/ malformations	Data are usually reported only on adverse pregnancy or fetal outcomes
Adjudication of cases of malformation and categorization of major, minor, or other by an external expert panel	No adjudication of cases of major malformation

Enhanced data quality control and data correction focusing only on crucial data needed for programmed statistical data aggregation	Data quality and control as per the routine pharmacovigilance process
Programmed data extraction and aggregate analysis detailed in a Statistical Analysis Plan	Manual intervention needed to produce outputs

<sup>a)</sup> EDD: Estimated delivery date

**Table 2 The PRIM end-to end process steps**

<b>Sequential step</b>	<b>Details</b>
Regulatory / Scientific objectives	Determine the specific objectives on reproductive toxicity to be addressed to regulatory authorities and/or scientific bodies (e.g. prevalence of major malformation, or pregnancy outcomes such as stillbirth etc.)
Summary data tables / Core statistics	Determine the content of all required data summary tables.
Core data selection	Selection of raw and derived data needed for required data tables.
Core data definition	Define each core data element for consistency
Database structure	Define data fields for core data elements needed to create analysis datasets <sup>a</sup> . Define any necessary customization of the safety database <sup>b</sup>
Data source	Define the set of cases in the safety database for inclusion in PRIM
Targeted data collection forms	Define type, format, layout, content of the targeted follow up checklist. Ensure that the checklist can collect all fields needed to create analysis datasets and that the format encourages complete and accurate data.
Data collection	Define initial and follow-up data collection process including the method of distribution and receipt of completed data collection tool. Define case adjudication process
Data entry and quality control	Define clear rules for data transfer from the completed data collection checklist to the safety database  Determine and apply data quality control tools
Data analysis	Perform programmed data extraction and aggregate analysis via programmed algorithms according to statistical analysis plan with no manual interventions

<sup>a)</sup> Programming of data retrieved for fingolimod was in SAS™ software <sup>b)</sup> Novartis uses the Argus Safety™ spontaneous report safety database

## **2.2 Regulatory / Scientific objectives**

Following the EMA recommendations (EMEA/CHMP/313666/2005) (4), pregnancy outcomes were defined in two groups of primary and secondary outcome as described below. Importantly, in the PRIM full data on pregnancies with a normal outcome were also collected to ensure an overall denominator for estimation of the prevalence of major malformations.

The primary pregnancy outcome of interest was the occurrence of major congenital malformations in the offspring. In addition, pregnancy outcomes such as live birth, spontaneous abortion, stillbirth, elective termination, and ectopic pregnancy were collected. Prevalence of such outcomes was calculated.

The following adverse pregnancy outcomes were also collected:

Minor malformation; which are anomalies with no serious medical or cosmetic consequence to the child

Data on infant adverse events such as infections and developmental milestones at three months and one year of age were collected.

## **2.3 Summary data tables / Core Statistics**

Descriptive and quantitative analysis of the data were conducted, supplemented by medical analysis of individual cases. The number of reports with specific pregnancy outcomes (for example, major congenital malformations, minor congenital malformations, spontaneous abortions, stillbirths, elective terminations), was presented. Reporting proportions of outcomes were calculated. Prevalence estimates of major malformation in live births and in live births, stillbirths, and termination of pregnancy due to fetal anomaly (TOPFA) were calculated with exact 95% confidence interval (CI). Format and content of summary tables of core statistics were designed to address core regulatory / scientific research statements, specifically: case disposition, case demography, timing of exposure, pregnancy outcome, estimated prevalence of major malformation. All analyses was performed using SAS<sup>TM</sup> version 9.2.

## **2.4 Core Data selection**

Core data were selected carefully based on what was needed for derivation of core statistics for tabulation to answer regulatory objectives. The list was adjusted to find a balance between reporting requirements and feasibility considering the structure of the

safety database and the likelihood of obtaining high-quality data. The more important core data are outlined in Table 3. Such lists for other products, might differ depending on alternative research objectives and data sources like claims databases, electronic medical records and registries. Guidance documents from regulatory authorities (e.g., EMA and FDA) should also be considered.

**Table 3- Core data**

<b>Case identification</b>	<b>Product exposure</b>	<b>Pregnancy and fetal outcome</b>	<b>Infant follow up (3 and 12 months)</b>	<b>Maternal risk factors</b>
Mother case identifier	Product name(s)	Pregnancy status: known pending unknown (lost to follow up)	Outcome specific for product/ disease	Pre eclampsia, Eclampsia Gestational diabetes
Baby case identifier	Product start date	Pregnancy outcome: Live birth Still Birth Termination (e.g. spontaneous abortion)	Sign of developmental delay	Chronic disease: Hypertension Diabetes Epilepsy Infections Thyroid disease Autoimmune disease
Case receipt data	Product stop date	Number of fetuses	Infections	Smoking Alcohol use Use of Recreational drugs
Demographic data	Exposure during washout period of drug (Pre-LMP)	Mode of delivery (vaginal, C-section, etc.)	Malformation not detected at birth	Concomitant medication

Date of LMP <sup>a</sup> or EDD	Trimester exposure (1st, 2nd , 3rd)	Newborn demographics	Obstetric history
Date of delivery / end of pregnancy			
Pre-natal test(s) result(s)	Dose and Route	Congenital malformation Major or minor	Family history of birth defect and degree of relationship

<sup>a)</sup> LMP: Last menstrual period, EDD: Estimated date of delivery

## 2.5 Core data definition

Definition of terms for the core data elements was established to ensure consistency across and within pregnancy datasets.

### 2.5.1 Prospective case definition

In PRIM, only prospective pregnancies were considered for analysis and follow-up. Different definitions of a prospective pregnancy case are suggested by the EMA, FDA, and other bodies. For PRIM, the EMA definition from GVP Module VI; of a prospective pregnancy case was used, (4) because this is also the standard in the Argus safety database. Table 4 shows the definition used in PRIM and the variation used in the Novartis pregnancy registry (16).

**Table 4 Prospective case definition from different sources**

Timing and results of prenatal testing	PRIM (based on EMA definition)	Gilenya pregnancy registry (based on FDA definition)
Pregnancy outcome has not occurred and prenatal tests have not been performed at the time of reporting or enrollment (entry) <sup>a</sup>	Prospective	Prospective
Prenatal testing was performed at the time of entry, result of congenital malformation have not been received by provider/patient/Novartis or results were normal	Prospective	Retrospective
Prenatal test results were available and were known to be abnormal at the time of entry	Retrospective <sup>b</sup>	Retrospective

a) 'Entry' is considered the date of initial report received by Novartis for PRIM cases, and entry is considered date of enrollment/signed informed consent for the registry.

### 2.5.2 Pregnancy periods for analysis

The following basic periods can be defined:

- Peri-LMP: within 8 weeks prior to LMP
- First Trimester: from LMP to 12 weeks ( $\geq 0$  days to  $< 84$  days) of gestation
- Second Trimester: from 12 weeks to 26 weeks ( $\geq 84$  days to  $< 182$  days) of gestation
- Third Trimester: from 26 weeks ( $\geq 182$  days) of gestation until end of pregnancy

The eight-week peri- LMP timeframe was set specific to fingolimod to cover the wash-out period of medicine considering the four-week half-life of product.

Exposure to the product of interest in any of these four periods could be derived from the date of LMP and drug start/stop dates (if complete), targeted questions asking about exposure in each period, but may also be logically determined from narrative text.

### 2.5.3 Categories fetal exposure for analysis

Information on occurrence of exposure in one or more of these four pregnancy periods can be combined if considered more informative. For fingolimod the following categories were used when describing fetal exposure:

- Only peri-LMP; exposure was reported only in the peri-LMP period
- At least first trimester; exposure was reported in the first trimester but possibly also in other categories
- Only after the first trimester; exposure was reported only after the end of the first trimester
- Exact timing of exposure in pregnancy is unknown

### 2.6 Database structure

All core data elements needed to create analysis datasets must be mapped to a defined data field of the safety database. This allowed efficient automated data extraction via programming with no manual intervention. Where needed, available fields in the existing safety database structure were customized to capture those elements.

### 2.7 Data sources

Cases reported to the Argus database that were selected for PRIM were those reported from spontaneous post-marketing report sources, post-marketing observational studies and patient support programmes, and reports from the Novartis clinical trials programme. Crucially, PRIM included only pregnancy cases with a documented exposure to fingolimod during pregnancy; these cases were associated with the Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) 'maternal exposure during pregnancy'.

**Exclusion Criteria:** The following cases were excluded from the PRIM dataset:

- Retrospective reports of pregnancy
- Reports of male partners taking fingolimod
- Reports in which the woman discontinued fingolimod before the 8 weeks washout timeframe (> 8 weeks prior to LMP)
- Reports included in the Registry; these were excluded to avoid case report duplication (fingolimod-specific)

- Reports reported before 01-Mar-2014 (fingolimod-specific) – start of PRIM.

## **2.8 Data collection**

### **2.8.1 Follow up checklist**

The follow-up checklist used for fingolimod on collection of the required core data. Information was to be collected from reporters at four time points as summarized in Table 5. Each time point was set based on pharmacovigilance requirements as well as time points requested by health authorities specifically for fingolimod (e.g., to collect data on infections and the achievement of developmental milestones within the first year of life of the offspring) but the timings could be adjusted to any product and its potential or identified risks. The checklists were sent for the mother and the offspring separately, aiming to collect the maternal, fetal, and neonatal data.

**Table 5 Case follow-up**

<b>Follow-up number</b>	<b>Checklist name</b>	<b>Type of information collected</b>	<b>Timing</b>	<b>Attempts cycle (in case of no response)</b>
FU 1	Baseline	Baseline characteristics and demographics of the mother	As soon as possible after initial pregnancy report, or at initial report if possible	At least 4 attempts, at a minimum of 1 week and maximum of 1 month apart, unless EDD <sup>a</sup> is reached (in such case merge FUs 1 and 2)
FU 2	Pregnancy Outcome	Information related to the end of pregnancy, delivery, and neonate	Between EDD and EDD+30 days	At least 4 attempts, at a minimum of 1 week and maximum of 1 month
FU 3	Infant health status at 3months	Information related to infant health status and development	EDD + 3 months	At least 4 attempts, at a minimum of 1 week and maximum of 1 month
FU 4	Infant health status at 12 months	Information related to infant health status and development	EDD + 12 months	At least 4 attempts, at a minimum of 1 week and maximum of 1 month

<sup>a)</sup> EDD: estimated delivery date

To enhance completeness of data, four attempts were made to collect data from the reporter. After the initial checklist was sent, reports with incomplete or missing data received follow-up attempts from the Novartis local affiliates on a monthly cycle. Reports were considered lost to follow-up 30 days after the fourth documented unsuccessful attempts to collect follow-up information or in case the reporter refused further contact. Automated checks for overdue FUs were performed and listings of any overdue FUs were generated centrally; requests for action were distributed to county affiliates in order to

complete the information gathering process. Reports of live births were considered complete when data regarding the pregnancy outcome (primary outcome) and the infant outcomes at one-year of age were received. Where the reported outcome was not a live birth, only the pregnancy outcome FU checklist was sent.

### **2.8.2 Adjudication process**

Adjudication of individual cases of reported congenital abnormality or developmental delay was performed by an independent external panel of three experts. Two teratologists were responsible for adjudication of individual cases. The third independent expert (Neurologist) was contacted in case of different opinions by the two adjudicators. This panel was selected from a list of available experts in the field of teratology and reproductive toxicology and with no affiliation to Novartis. Adjudicators evaluated the data to determine whether the malformation was major or minor using the European Surveillance of Congenital Anomalies (EUROCAT) definitions. Major malformations are defined as any structural defects with recognized surgical, medical, or cosmetic importance (17). If the report had insufficient information for adjudication it was classified as “congenital anomaly not otherwise specified (NOS)”.

### **2.10 Data entry in the safety database**

Data collected through the targeted checklists were entered into the company safety database. Infant/fetus and maternal AEs were coded using MedDRA [version 20.1], mapping verbatim terms to the MedDRA hierarchy. Where multiple abnormalities were reported in the neonate all AEs were recorded in order to ensure completeness of content for the medical evaluation. Only the most significant malformation was counted in the prevalence estimation.

## 2.11 Data Quality

Quality control of data entered to the company safety database was performed according to the standard operational procedures for pharmacovigilance. Additional checks focusing on core data elements were performed in order to improve data quality and support programmatic data summarisation. As a result extra guidelines were imposed, and additional training was provided for the designated case processing team.

## 3 Results

Analysis of cumulative fingolimod pregnancy outcome data from 01 March 2014 to 28 February 2018 extracted from the global safety database for individual case safety reports (ICSRs) defined for PRIM are presented in this section to illustrate the PRIM concept. The focus is on the method rather than illustration of the safety profile of the product.

### 3.1 Case disposition and exposure during pregnancy

Overall, 831 prospectively reported pregnancy cases and 843 infants/fetuses (12 sets of twins) met the definition for the PRIM process. The follow-up status of these ICSRs is presented in Table 6.

**Table 6 Case disposition**

Case distribution	Cases
Total prospective pregnancy cases	831
Total infant cases	843
• Pregnancy - outcome known	459 (54.4%)
• Pregnancy - outcome pending	136 (16.1%)
• Lost to follow-up <sup>a</sup>	248 (29.4%)

<sup>a</sup>) Birth-type not known. Permission or contact information for report was not provided or all attempts to obtain outcome information per PRIM guidelines were exhausted

The 16.1% of pending reports mainly comprise pregnancies not yet having an outcome at data cut-off. A summary of fetal exposure to fingolimod is provided in Table 7. Timing of exposure was reported for 826 (98.0%) of the 843 fetuses. In 17 fetuses, exact timing

of exposure during pregnancy was unknown although exposure to fingolimod was known to have occurred during the pregnancy. In pregnancies with a known birth-type outcome, timing of exposure was reported for 455 (99.1%) of the 459 fetuses.

**Table 7 Fetal exposure to fingolimod**

Timing of exposure in pregnancy	All Cases N = 843 n (%)	Cases with Known Pregnancy Outcome N = 459 n (%)
Peri-LMP only <sup>a</sup>	46 (5.5)	32 (7.0)
At least first trimester <sup>b</sup>	779 (92.4)	423 (92.2)
Only after first trimester <sup>c</sup>	1 (0.1)	0
Exact timing in pregnancy unknown	17 (2.0)	4 (0.9)
Other categories	0	0

<sup>a</sup>) Exposure was reported only in the peri-LMP period (within 8 weeks prior to LMP)

<sup>b</sup>) Exposure was reported in the first trimester but possibly also in other categories

<sup>c</sup>) Exposure was reported only after the end of the first trimester

### 3.2 Demographic data

A summary of baseline demographic characteristics is presented in Table 8. Patients had a mean age of 31 years. They were primarily Caucasian but ethnicity and pre-pregnancy body mass index (BMI) were under-reported.

**Table 8 Maternal demographics for all maternal cases**

<b>Demographic variable</b>	<b>Mother cases</b>
Category Statistic	<b>N = 831<sup>a</sup> (%)</b>
<hr/>	
<b>Age at LMP<sup>b</sup> (years)</b>	
n (%)	588 (70.8)
Mean (SD)	31 (5.6)
Median (min, max)	31 (17, 47)
<b>Ethnicity</b>	
n (%)	294 (35.4)
Caucasian	226 (76.9)
Black	19 (6.5)
Asian	10 (3.4)
Hispanic	10 (3.4)
Oriental	2 (0.7)
Other	25 (8.5)
Unknown	2 (0.7)
<b>Region</b>	
n (%)	831 (100)
Europe	369 (44.4)
Canada/US	274 (33.0)
Japan	18 (2.2)
Other	170 (20.5)
<b>Pre-pregnancy BMI (kg/m<sup>2</sup>)<sup>c</sup></b>	
n (%)	331 (39.8)
Mean (SD)	26.1 (6.05)

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n = number of cases with non-missing data.

<sup>a)</sup> All cases with demographic information are included, including all outcomes and lost to follow-up cases.

<b>Demographic variable</b>	<b>Mother cases</b>
Category Statistic	<b>N = 831<sup>a</sup> (%)</b>

<sup>b)</sup> Age as reported or calculated based on date of birth and LMP; if LMP is not available, age was based on date of birth and manufacturer's receipt date.

<sup>c)</sup> BMI may correspond to the time of reporting, which may be in the early stages of pregnancy. BMI is calculated using the following formulas, based on reported units of measurement: (Weight (lbs.)/(Height (in) × Height (in)) × 703) or (Weight (kg)/(Height (cm) × Height (cm)) × 10 000).

### 3.3 Pregnancy outcomes

Birth type and fetal outcome for 459 infants/fetuses from pregnancies with known outcome are summarized in Table 9. Results are shown overall but also by pregnancy period and the number of cases of malformation could be described for each main outcome type. There were no stillbirths or ectopic pregnancies reported.

**Table 9 Summary of pregnancy outcomes by timing of exposure to fingolimod; infants/fetuses with known birth type**

<b>Birth type</b>	<b>Peri-LMP only<sup>a</sup></b>	<b>At least first<sup>b</sup> trimester</b>	<b>Only after first trimester</b>	<b>Exact timing in pregnancy unknown<sup>c</sup></b>	<b>Overall n (%)</b>
<b>All pregnancies with known birth type</b>	<b>32 (100)</b>	<b>423 (100)</b>	<b>0</b>	<b>4 (100)</b>	<b>459 (100)</b>
Without reported congenital malformations	31 (96.9)	409 (96.7)	0	4 (100)	444 (96.7)
Congenital malformations	1 (3.1)	14 (3.3)	0	0	15 (3.3)
Major	1 (3.1)	7 (1.7)	0	0	8 (1.7)

Minor	0	3 (0.7)	0	0	3 (0.7)
Unspecified <sup>d</sup>	0	4 (0.9)	0	0	4 (0.9)

**Ectopic pregnancy**                    **0**        **0**            **0**            **0**            **0**

**Spontaneous abortion<sup>e</sup>**            **3 (9.4)**    **61 (14.4)**    **0**            **0**            **64**  
**(13.9)**

**Elective termination**                **3 (9.4)**    **74 (17.5)**    **0**            **0**            **77**  
**(16.8)**

Without reported congenital malformations	2 (66.7)	72 (97.3)	0	0	74 (96.1)
Congenital malformations	1 (33.3)	2 (2.7)	0	0	3 (3.9)
Major	1 (33.3)	1 (1.4)	0	0	2 (2.6)
Minor	0	0	0	0	0
Unspecified <sup>d</sup>	0	1 (1.4)	0	0	1 (1.3)

**Stillbirth**                                **0**        **0**            **0**            **0**            **0**

Without reported congenital malformations	0	0	0	0	0
Congenital malformations	0	0	0	0	0
Major	0	0	0	0	0
Minor	0	0	0	0	0
Unspecified <sup>d</sup>	0	0	0	0	0

<b>Live birth</b>	<b>26</b>	<b>288 (68.1)</b>	<b>0</b>	<b>4 (100)</b>	<b>318</b>
	<b>(81.3)</b>				<b>(69.3)</b>

Without reported congenital malformations	26 (100)	276 (95.8)	0	4 (100)	306 (96.2)
Congenital malformations	0	12 (4.2)	0	0	12 (3.8)
Major	0	6 (2.1)	0	0	6 (1.9)
Minor	0	3 (1.0)	0	0	3 (0.9)
Unspecified <sup>d</sup>	0	3 (1.0)	0	0	3 (0.9)

<b>Live births, stillbirths, and TOPFA</b>	<b>27</b>	<b>290 (68.6)</b>	<b>0</b>	<b>4 (100)</b>	<b>321</b>
	<b>(84.4)</b>				<b>(69.9)</b>

Without reported congenital malformations	26 (96.3)	276 (95.2)	0	4 (100)	306 (95.3)
Congenital malformations	1 (3.7)	14 (4.8)	0	0	15 (4.7)
Major <sup>f</sup>	1 (3.7)	7 (2.4)	0	0	8 (2.5)
Minor	0	3 (1.0)	0	0	3 (0.9)
Unspecified <sup>d</sup>	0	4 (1.4)	0	0	4 (1.2)

<sup>a)</sup> Exposure was reported only in the peri-LMP period

<sup>b)</sup> Exposure was reported in the first trimester but possibly also in other categories

<sup>c)</sup> Exposure was reported only after the end of the first trimester

<sup>d)</sup> Unspecified malformations = congenital anomaly NOS

<sup>e)</sup> Spontaneous abortion includes fetal outcome cases of Fetal death /intrauterine death and blighted ovum

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<sup>7)</sup> 1. Congenital cardiac septal defect, 2. Fallot's tetralogy and congenital pulmonary valve atresia, 3. Oesophageal atresia and atrial septal defect, 4. Congenital ureteric anomaly and congenital hydronephrosis, 5. Cryptorchism, 6. Corpus callosum agenesis, 7. Trisomy 21, 8. Embryo overt spina bifida and banana-shaped skull.

### **3.4 Prevalence of major congenital malformations**

The estimated prevalence of major congenital anomalies (including chromosomal anomalies or genetic disorders), adjudicated according to EUROCAT definitions, could be calculated; 1.89 % (95% CI 0.70, 4.06) in live birth, and 2.49% (95 % CI 1.08, 4.85) in live births, stillbirths, and TOPFA.

### **3.5 Individual case safety reports of infant adverse events**

The programmed algorithms identified groups of neonates for individual case assessment. AEs were reported in 15 of the 310 infants without reported congenital malformations. Overall, the AEs reported were heterogeneous with no evidence of a safety signal of infant AEs in the first year of life. The infant AE "small for dates" or "small for gestational age" was reported in one full term birth and three preterm births. One infant was reported to have motor developmental delay and one had an unspecified developmental delay; both infants were born prematurely.

## **Discussion**

A systematic review confirmed the well-documented challenges of operating pregnancy registries and thus emphasised the need for complementary or alternative methods (5). Because post-marketing data are the main data source for safety of medicines in pregnancy, better post-marketing surveillance methods can enhance the assessment of pregnancy exposures and thereby yield meaningful information on outcomes and adverse or risks in a shorter time-frame than traditional registries.

PRIM showed that information can be collected faster and from a larger patient population than a registry and with a better quality than that of conventional spontaneous reports. In order to conduct an informed medical assessment, good quality ICSRs are required containing important data elements as described in Table 3. PRIM enhanced data collection by establishing targeted checklists focused on data completeness and data quality of the core data needed for reporting essential statistics to regulatory and other scientific bodies. Mother's age at LMP was available for 70% of the ICSRs, but by comparison BMI for only 39.8%, and ethnicity for 35%. Remarkably the timing of exposure

to fingolimod during pregnancy was reported for 98.0% of the 843 fetuses, increasing to 99.1% of the 459 fetuses from pregnancies with a known birth-type outcome.

In our example, the pregnancy outcome was known for 54.4% of cases, 16.1% pending outcome and 30% of all ICSRs were lost to follow-up as such there may be selection bias for pregnancies with documented outcomes versus those that were not documented. This selection bias may be either towards the presence of adverse pregnancy outcomes or towards a particular subgroup of women who have higher healthcare seeking behavior. It is also thought that the seriousness of an adverse event contributes to whether or not it is reported, with serious events more likely to be reported than non-serious events (18). Some of the known limitations of spontaneous reports that pose considerable challenges for analysis are the lack of a denominator and gaps (null values) in essential data fields (19). However, this enhanced pharmacovigilance method ensures a denominator for the calculation of proportions (for example of spontaneous abortions among all pregnancies or of major congenital malformations in live births) by prospectively following up and collecting maximum data on all pregnancy cases regardless of their outcome. Incidence of birth types and fetal outcomes including malformation classified as major, minor and unspecified outcome could therefore be calculated and prevalence of major malformations estimated. Keeping in mind that PRIM like other non-interventional studies (e.g. registry) represents the reported population rather than exposed population.

The results obtained using PRIM (a subset of fingolimod pregnancy safety data) enabled an estimation of the prevalence of major congenital malformation for live birth (1.89% (95% CI, 0.70-4.06)) and for live birth, still births and TOPFA (2.49% (95% CI, 1.08-4.85)), that could be compared with general population data, in which the prevalence of major malformations varied between 2.0% (95% CI, 2.0-2.1) (20) and 4.5% (95% CI, 4.5-4.5) for live births(21). The range for live births, stillbirths and TOPFA was 2.6% (95% CI, 2.6-2.6) (20) to 6.9% (95% CI, 6.6-7.2) (15,20).

A study that reviewed medication risks during pregnancy for 172 drugs approved by FDA between 2000 and 2010 reported that in 97.7% of drugs the teratogenic risk in human pregnancy was “undetermined” and amount of data for 73.3% of these drug was described as “none” (22). For 468 drugs approved by FDA between 1980 and 2000, the average time required for a drug’s risk category to be changed from “undetermined” to a

more precise risk was estimated to be 27 years (22). Experiences from other MS and non-MS medicinal products have indicated that treatment-specific registries have mostly failed to deliver timely and robust information and the limited amount of evidence accrued in these registries has not been helpful in deciphering the reproductive toxicities risk associated with these products (9,23). Despite all efforts Novartis has experienced similar recruitment challenges with the Registry. The PRIM process for fingolimod included almost six times (674 prospective cases) as many prospective pregnancies (113 case) in four years as the Registry had enrolled in seven years (15).

There is a need to make better scientific use of existing PV systems to collect data and thereby facilitate the medical evaluation process. This will better inform decisions concerning the communication of outcome information following exposure to medicines during pregnancy. Thus enhanced pharmacovigilance studies such as the PRIM can support the provision of evidence-based information in timely manner which will in turn enable patients and healthcare professionals to make informed choices. This method could be complementary to or potentially an alternative to traditional pregnancy registries for any medicinal product.

To date, there is no harmonized definition of terms related to pregnancy exposure, definition of retrospective and prospective cases as well as minimum required data for identification of major malformations (10). Therefore, harmonized metrics and measure for data collection and analysis could provide efficient data collection and evaluation of the risk of reproductive toxicity. In this regard, we are aware of an Innovative Medicine Initiative (IMI) project called Continuum of Evidence from Pregnancy Exposures, Reproductive Toxicology and Breastfeeding to Improve Outcomes Now (ConcePTION) (24). The IMI ConcePTION project is public-private partnership to address this problem. The aim of ConcePTION is “Building an ecosystem for better monitoring and communicating safety of medicines use in pregnancy and breastfeeding: validated and regulatory endorsed workflows for fast, optimized evidence generation”

### **Limitation of the this approach**

Data used in PRIM were the pregnancy cases reported to the company that were primarily reports from patients and healthcare professionals or other spontaneous post-marketing sources, but also include patients from clinical trials and non-interventional studies who

did not participate in the Registry. The limitations of PRIM are consistent with the well-known limitations of voluntary post marketing report systems (e.g, under reporting, potentially more missing or incomplete information than in a study) (25–27).

Bias that may occur when outcome information is known prior to reporting was reduced by excluding retrospective cases (i.e., pregnancies reported after the pregnancy outcome is known) from PRIM. However the definition of a prospective pregnancy report may also introduce a bias and a deviation between the PRIM results and those of other data sources using other conventions. In PRIM the definition of prospective and retrospective cases specified by EMA guidance has been used but collection of sufficient data from cases should be attempted to allow alternative definitions to be constructed in parallel for sensitivity analysis. This has proved to be a difficulty in the current dataset due to the constraints of the global database structure (which is based on the ICH E2B R2 data model) (28) and will need further development. Although the prevalence estimates of congenital malformation in PRIM appear to be in line with estimates from external reference general populations, a direct comparison between PRIM and external references are hampered by differences in spontaneous reporting and registry data collection. Nevertheless the results can be put in context with a range of estimates from the general population coming from different data sources with a focus on those which use similar data collection methods as PRIM.

To reduce the potential for selection bias due to loss to follow-up (a recognized limitation of voluntary reporting systems), contact attempts via multiple contact modalities were systematically and repeatedly performed under the PRIM processes, however this needs further improvement.

Performing long-term FU (3 month and one year) has operational challenges for voluntary post marketing data. Initiation and completion of long-term follow-up is a considerable resource activity. In addition, in the targeted FU checklist some data can be collected from a primary reporter but other data (e.g. health and development status of the baby) ultimately require referral to other stakeholders (e.g. pediatrician) which in turn requires consent; currently there is no complete guideline for Industry to get information from such sources.

## Conclusion

Using enhanced pharmacovigilance of spontaneously reported data, the PRIM process applies intensive monitoring of maternal drug exposure during pregnancy, prospective collection of critical safety data, and structured programming of data to estimate prevalence of major malformations and other pregnancy outcomes. This was applied to fingolimod data but could be adapted for use with a wide range of medicinal products. Use of the large volume of pregnancy data in industry pharmacovigilance databases and the achievement of sufficient data quality can qualify PRIM as a feasible alternative to costly and often lengthy pregnancy registries.

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## 7. Discussion

### 7.1 Contribution of this thesis

There is an unmet need for evidence-based, current and accurate information on safety of drug during pregnancy. Speed of generating sufficient high-quality evidence is vital which may assist for medicine label update and informing HCP and patient. Currently data collection and analysis of human pregnancy safety is at best inefficient, at worst inadequate and incomplete, thus the prescribing guidance and pack insert are in fact non-informative. Diseases with low or very prevalence inevitably lead to low exposure numbers, particularly in pregnancy, which in turn results in a low sample size for study and evaluation. One study reported that enrollment and retention in 34 US pregnancy registries were lower relative to the manufacturer's capture of spontaneous reports for exposed pregnancies (61). The authors suggested a need for worldwide safety data collection of pregnancy exposures in order to achieve an adequate cohort of exposed pregnant women to support meaningful medical and statistical analyses; this is particularly important for products that are rarely used by pregnant women.

Examples of additional approaches that go beyond routine pharmacovigilance to capturing case reports of pregnancy exposures include (61):

1. Enhanced pharmacovigilance strategies with follow-up questionnaires directed to exposed pregnant women who do not choose to enroll in formal registries;
2. Population-based networks that capture birth defects and matched controls, and
3. Population-based studies employing mother–baby linkages in reimbursement claims or electronic medical records (61)

We established a method of enhanced pharmacovigilance by using an industry-based global post-marketing safety database to access pregnancy-specific safety data for prospective case reports. Due to slow enrollment in pregnancy registry, alternative method is required for the provision of appropriate and up-to date safety information in a timely manner for better decision-making. This method is called PRIM (PREgnancy outcome Intensive Monitoring) to increase the amount of data with which to evaluate the risk of reproductive toxicity for fingolimod (Gilenya®). The PRIM process applies intensive monitoring of maternal drug exposure during pregnancy, prospective collection of critical safety data, and structured programming of data to estimate prevalence of major

congenital malformations and other pregnancy outcomes. This was applied to fingolimod data but could be adapted for use with a wide range of medicinal products.

It is my view that this is a significant enhancement to routine pharmacovigilance because diseases such as MS require careful medical assessment of the benefits and risks of continuing medical treatment during pregnancy. This assessment should, of course be inclusive of the patient, and there should be an open discussion of the evidence and any concerns.

The main strengths and advantages of the PRIM process are that this systematic series of controls assure the achievement of good data quality thereby optimizing the value and utility of the large volume of pregnancy data in the Novartis pharmacovigilance database. This is illustrated by the implementation of the PRIM process for fingolimod. As a direct result, the PRIM dataset included a large cohort of pregnancy exposures. Almost six times as many spontaneous reports (674 prospective cases) of pregnancy exposures to fingolimod were received in four years when compared to prospective pregnancies (113 cases) enrolled into the pregnancy registry in seven years (98). On this basis the PRIM method could be complementary to, or potentially an improved alternative, to traditional pregnancy registries for any medicinal product where close monitoring of pregnancy exposures and outcomes is required.

There is a need to make better scientific use of existing PV systems to collect the best possible data on pregnancy exposures and outcomes, thereby to facilitate the medical and scientific evaluation process. Enhanced pharmacovigilance methods such as the PRIM can support the provision of evidence-based information in a timely manner that will in turn enable patients and HCPs to make informed decisions.

Another important area that was investigated in this research project was concerning the behaviors of HCPs and pregnant patients in relation to prescribing and use of medicines during pregnancy. The fast-changing and ever expanding technological landscape brings new capabilities for information provision relating to the safety of medicines and there is ever-increasing use of the internet to seek and find medical information. Patients, carers and HCPs have adopted social media platforms and forums to discuss their experiences of medication use. The IMI Web-RADR project has explored the value of online

exchanges through social media and has developed a mobile application for identifying adverse events in order to aid signal detection. The WEB-RADR project also developed a novel algorithm for adverse event recognition and text-mining in social media (91,92). This consortium agreed that general social media such as Facebook and Twitter are not recommended for broad statistical safety signal detection, however these channels may be a useful asset to PV activity in specific areas including exposure to medicines during pregnancy (92).

I adopted the WEB-RADR machine learning technique to characterize posts acquired from pregnancy-related online forums where patients discussed MS medications using WEB-RADR tools. Approximately 80% of all relevant posts were representative of personal experiences with MS medications. Individuals shared the reasons behind their personal decisions regarding treatment; some patients described how they felt after changes in therapy: other described experiences when they switched, started, or stopped medication, and whether this change in treatment was because of an HCP's recommendation or because of the patient's personal beliefs.

Data from this study showed that pregnant patients were evidently seeking information online related to the risk associated with their disease (e.g. MS relapse during pregnancy or postpartum). A cohort of patients queried the safety profile of one or more medications in pregnancy. Certain patients asked about when to restart medical treatment postpartum, and somewhat linked to this raised questions about breastfeeding whilst taking medication (85). Last, but not least, there was a significant number of social media users who provided advice to others about decisions and outcomes or based on their own personal experiences when taking a specific medication (85). It remains to be determined whether such advice is appropriate, consistent with the available evidence across a wider cohort, or if it is well-informed and up to date. There certainly appears to be some evidence that personal experiences as reported by social media users are trusted by the recipients of such anecdotal information.

Overall, the results emphasize that patients and carers are willing to share personal data in social media threads and within online fora. In my view, more effort should be made to engage pregnant mothers and their family members or carers in active medical research

targeted at informing them about the purpose of pregnancy registries and teratology information programmes. Ideally, the sponsors of clinical research programmes should set the expectation for participants that either at the end of a study, or when a registry is complete, all important safety findings, and, if possible, an overview of the overall results, should be shared with the contributors.

When a woman is pregnant or breastfeeding and she may need therapeutic treatment the decision is complex as she is taking medication “for two”. Ultimately, it is for the mother to decide for herself and her unborn baby by weighing the benefits versus the potential risks of medical treatment. In order to make an informed decision, some mothers rely on the attending physician’s advice and approved product labelling e.g. the summary of product characteristics, pack insert or patient information leaflet. Each one of these documents is based on scientific evidence. The problem is that in relation to pregnancy exposures and outcomes that evidence is often missing, very often incomplete, and sometimes unreliable as it is unknown if reproductive toxicology outcomes in animal models translate to human mothers and their offspring. A study reviewed medication risks during pregnancy for 172 drugs approved by the FDA between 2000 and 2010. Amongst these medicinal products, in 97.7% of drugs, the teratogenic risk in human pregnancy was classified as **undetermined**, and the amount of data for 73.3% of these drugs was described as **none** (30). In my view, this shows a significant lack of information to protect the public’s health. There is a need to coordinate efforts from all stakeholders (see Figure 5) to collect more data, perform formal analysis in a regular basis and to update medicine labels on current evidence.

My analysis of the risk of cleft lip and/or palate associated with anticonvulsant medicines was conducted using the evidence from two large post-marketing safety databases (99). In addition, I performed an evaluation of the completeness of safety information provided in the approved product labels for prescribers and patients in order to optimize informed decision-making. The results of the disproportionality analysis from the FAERS database showed that twelve antiepileptic drugs were statistically associated with risk of cleft lip and palate (74). The risk of cleft is described in the regulatory agency-approved labeling for valproate, topiramate, carbamazepine, and phenytoin in both the UK and the USA (74) and the information provided was consistent with the literature. It was observed that there

were important differences in the information content presented to prescribers in the UK and US such as a product being contraindicated in one location but not in the other, and precautionary measures being provided in one country but a distinct lack of the same information being available in the other. In my view, these constitute clear discrepancies, and this constitutes a significant problem for recipients of the information, in that it has the propensity to cause doubt, and perhaps even to engender a lack of trust in both the MAH and the health authority that approved the label. Other studies have reported inconsistencies in defining and reporting the foetal risk category/assessment among different drug regulatory authorities in different countries (100–102). Taken in their totality these discrepancies and inconsistencies create confusion, particularly for patients and carers who travel between the two countries. Moreover the discrepancy concerning the absolute contraindication could well affect prescribing decisions in the two countries. I believe that there is a need to improve the communication of the safety profiles of medicines used in pregnancy via standardization and inclusion of information in medicines labels and package insets. In addition, patients and HCPs should be informed more proactively and efficiently how to access, interpret and act on comprehensive information which should be harmonised and provided in its most complete and up-to-date form.

## 7.2 History repeats itself – some parallels between sodium valproate- induced birth defects and thalidomide?

Sodium valproate provides another example of a lack of a harmonised, systematic approach to inform for patients and HCPs in a timely manner about important safety concerns related to the outcomes of exposures in pregnancy. This goes far beyond the provision of comprehensive, current, evidence-based labeling information; and, in my opinion, has led to catastrophic results in the offspring of mothers treated with this drug. Sodium valproate or valproic acid has approved indications in multiple European countries various for treatment of epilepsy, bipolar disorder and migraine (103). For some patients with serious conditions, valproate may be the best or only treatment option (104). However, it has long been known that if taken during pregnancy valproate affects the unborn baby and is strongly associated with a specific pattern of congenital anomalies in around 10% of neonates (104). Maternal exposure to valproate is known to cause specific

birth defects such as spina bifida, cleft lip and palate, malformations of the limbs, heart, kidney, urinary tract and sexual organs, and neurodevelopmental delay (104). Even more significant is the more recently gathered evidence that the most significant concern associated with valproate exposure in utero is the occurrence of neurodevelopmental delay in around 40% of the offspring (104). Due to the long latency of the appearance of autism or low IQ in children these anomalies are not detectable at birth (105).

The term Fetal Valproate Syndrome was first suggested by DiLiberti *et al.* in 1984, following publication of a case series (106). This term refers to a pattern of anomalies in infants exposed to valproate. Typical facial dysmorphias were reported to include trigonocephaly, tall forehead with bifrontal narrowing, epicanthic folds, infraorbital groove, medial deficiency of eyebrows, flat nasal bridge, broad nasal root, antverted nares, shallow philtrum, long upper lip and thin vermilion borders, thick lower lip, and small downturned mouth (107). The authors also reported the occurrence of developmental disorders in children born to women who took valproate during pregnancy.

Three decades later, following a review in 2013, the EMA recommended restrictions to the use of valproate. The product information for all formulations of valproate was updated and educational materials were developed for healthcare professionals and patients. These included a guide for prescribers, a patient booklet, an acknowledgment of risk form and a letter to inform healthcare professionals. However, just a few years later the French national competent authority, ANSM (Agence Nationale de Sécurité du Médicament et des Produits de Santé, which is the French Agency for the Safety of Health Products), has suggested that these measures have not had the desired effect.

On 26 September, 2017, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) held its first public hearing to discuss the safety of the use of valproate during pregnancy (104,108). Whilst public hearings have been a part of the regulatory process outside of Europe this was a bold experiment aimed at improving transparency in public health topics relevant to safety. The hearing was planned to determine the adequacy of current warnings, precautions, and prescribing restrictions concerning adverse outcomes in babies born to women who take valproate during pregnancy. Members of the public such as patients and their mothers, as well as expert health care professionals, a

representative of industry, the mass media and journalists across the EU were invited to attend and express their view to the PRAC on the following three questions:

1. What are EU citizens' views of the risks of taking valproate during pregnancy, including its potential effects on the child?
2. What are their views on the measures currently in place to reduce the risks of using valproate during pregnancy?
3. What other measures should be taken to reduce the risks of using valproate during pregnancy?

The full recording of public hearing is available online at <https://www.youtube.com/watch?v=07LImEpwY9g&feature=youtu.be> . (109)

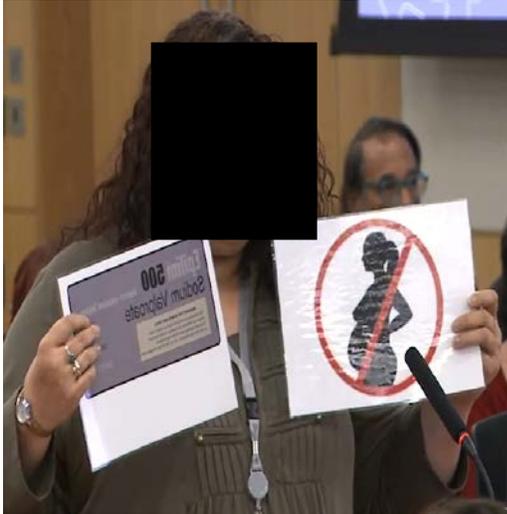
The Public Hearing provided the PRAC with a very transparent means to gather the public's views and concerns, particularly where regulatory actions were being considered in a wider public health context (110). For example, here are two patients who shared their concerns during the public hearing.

### **Epilepsy patient and mother of three valproate-affected children**

Photo taken from the EMA video recording of public hearing, YouTube record available at <https://www.youtube.com/watch?v=07LImEpwY9g&feature=youtu.be>, Accessed online Oct.2019.



- “I am a mother of three adult children affected by valproate...and we have a number of important concerns...”;
- “Many patients receive their medications in plastic bags...without any original patient leaflets or pack inserts...”;
- “Educational Materials can only be found online and are not printed or distributed sufficiently... [By the manufacturer]” (109).



### **Epilepsy patient and mother of valproate-affected child**

Photo taken from the EMA video recording of public hearing, YouTube record available at <https://www.youtube.com/watch?v=07LImEpyY9g&feature=youtu.be>, Accessed online Oct 2019.

“...In France they are developing an on-box warning (visual warning) this is what we have in the UK (right side) as you can see there is a very big difference!”(109)

In addition to the two detailed histories shared by these patients, I observed several more key messages confirming that patients (mothers, and indeed both parents) and carers require clear communication, for example (selected quotations from the evidence presented in the public hearing) (109):

- “I took ‘Epilim’ (brand name) not sodium valproate (generic name)...”  
[Interpretation: patient had not been informed and did not understand from the pack insert that the active ingredient of ‘Epilim’ is valproate; key learning: prescribing doctor or pharmacist or nurse should have explained about the active ingredient of ‘Epilim’ and warned the patient about potential adverse effects on the fetus if the patient was pregnant]
- “No educational booklets available - vital information are missing...”  
[Interpretation of statement: Educational material was not available in pharmacies/key learning: better distribution system and even digital solution is required for global access of safety information]

As a result of the public hearing, the PRAC and the EMA provided new measures for comprehensive risk minimization, including the following (111):

- A pregnancy prevention programme (PPP);
- Visual warning(s) about the risk in pregnancy in the outer packaging;
- A new risk acknowledgement form for patients;
- Updated, clear and comprehensive educational materials for patients and HCPs

In the valproate pregnancy prevention programme, HCPs are instructed to assess each patient's potential for becoming pregnant by evaluating their individual circumstances and then assist their patients in making informed decisions. HCPs are responsible for informing their patients about the use of effective contraception methods throughout the administration of valproate, and to review all such treatments at least annually. Overall, the public hearing led to better safety recommendations, tailored to meet the real needs and problems of patients, which were identified at the hearing (110). It allowed different stakeholders to listen to and learn from each other.

However, much of the discussion related more to healthcare professionals' actions and less to what the PRAC can influence. Furthermore it was mentioned that several of the issues under consideration needed to be implemented at national level, rather than by EMA. In my view, the public hearing didn't provide a complete solution to the current gap of risk mitigation and communication. There remains a significant concern about what harmonised actions, if any, should be taken at a global level concerning the risks to the embryo and fetus from valproate. Legislation differs from country to country in terms of medicines dispensation and prescribing, but all countries have an obligation to protect public health. There remains a genuine concern that children of patients treated with valproate may still suffer congenital anomalies and/or neurodevelopmental disorders, simply because of the differences in regulations when an international border is crossed. Another important issue is restrictions in the use of valproate practically in the secondary indications such as migraine and bipolar disorder (104) where clearly the risks outweigh the benefits for use in a vulnerable population.

## 8. Conclusion

Data collection, collation and analysis concerning pregnancy exposures and outcomes is disparate and fragmented. As a direct consequence the provision of timely, evidence-based, comprehensive information via product labels is lacking, or at best woefully inadequate. Whilst there have been some positive steps taken in the last decade, including risk characterization, the provision of tools for risk minimization during pregnancy, and the inauguration of pregnancy prevention programmes, much work remains to be done.

Optimization of existing pharmacovigilance systems for the collection, processing (including follow-up) and analysis of pregnancy reports such as it is presented in the PRIM programme could be a starting point for standardization and harmonization. This in turn could lead to novel methods for prompt qualitative and quantitative signal detection. As always where spontaneous prospective reporting is involved there is a clear requirement for high quality data, particularly concerning the timings of exposure to medicines, and precision when reporting the outcomes for both mother and neonate(s). When data are available, there is a need for more transparent, faster, and harmonized evaluations according to aligned medical assessment standards. Last, but not least, open source tools should be adopted for communicating information on the safety of medicines during pregnancy and breastfeeding with HCPs, patients and all other stakeholders in pharmacovigilance. Moreover, there is an imperative to ensure that there is a life-cycle process implemented for data collection, collation, processing, and evaluation to support real-time decision making concerning the benefits and risks of medicines and how to maintain optimal lines of communication of new information to stakeholders. It is also vitally important to consider providing consolidated recommendations across whole regions or continents, aiming for the widest possible outreach. Digital solutions should be considered, such as mobile applications (app) and social media platforms which support patients, carers and prescribers in order to raise awareness. I would also advocate the adoption of two-way communication between the pharmaceutical industry and patients for better exchange of safety information.

I believe that the chances of successful progress towards a better future can only be improved by dedicating resources (human, financial and technological) to a pre-competitive environment with close collaboration between all stakeholders.

It would be a very positive step for the scientific community to collaborate more closely with pregnant patients and their families, in order to establish trust and goodwill. All stakeholders including HCPs, regulators, pharmaceutical companies, Teratology Information Services (local, national or regional) and other members of the society should work together to gain mutual understanding and share data to address information needs, and provide tangible solutions.

## 9. Direction of future research

The safety of medicinal products administered during pregnancy and lactation is a complex topic. In my opinion, there are multiple areas that require further research:

- Streamlining and maximising the efficiency of data collection, from first exposure to medicine(s) to birth and beyond, particularly where there is a potential for neurodevelopmental delay. There is a clear and obvious need for more active surveillance perhaps using apps combined with wearables, or approved medical devices that collect, normalise and transmit data to a secure repository;
- Defining a set of common data fields should be established to standardise the content, providing detailed specifications for each field, such a field length, data type, units of measurement, etc.;
- Development of a common data model should be prepared in order to support the pooling of data from as many different sources as possible, from early development through to post-marketing, and perhaps even including over-the-counter medicines;
- Determining how best to use the common data model by pool data to increase statistical power and cover greater population diversity linking existing fragmented data sources such as product-specific pregnancy registries, disease registries, pharmacovigilance systems (at multiple levels within MAHs, as well as in National Competent Authorities e.g. Swissmedic, Regional Authorities e.g. EMA and in

Global Non-Governmental Organisations e.g. WHO Uppsala), and Teratology Information Units;

- Improving analytical methods used for evaluating the statistical significance of findings for example by testing the application of proven statistical methods (e.g. disproportionality analysis) to aid medical assessment;
- Using all of the above to inform decisions that impact the health of women and their children who were exposed to medicines in *utero*;
- Harmonising, at a global level, timely and appropriate communication of those decisions, and:
- Supporting those communications with reference materials that accurately reflect the evidence as well as providing educational materials covering the use of medication in pregnancy and breastfeeding.

Beyond pregnancy, information concerning the safety of medicines used during breastfeeding is largely missing. There is lack of appropriately qualified animal models to predict levels of medicinal products (active pharmaceutical ingredients and metabolites) in breast milk. Furthermore there is a very limited biobank of human breast milk donated by nursing mothers that would enable research in this field (112).

In closing my thesis I want to emphasize that there is hope! I am aware that the 5-year Innovative Medicine Initiative (IMI) project called *Continuum of Evidence from Pregnancy Exposures, Reproductive Toxicology and Breastfeeding to Improve Outcomes Now* (ConcePTION) is planning to explore these above mentioned research areas (113). The IMI ConcePTION project is a collaboration between public-private partners and the pharmaceutical industry to address this problem. The aim of ConcePTION is:

*“Building an ecosystem for better monitoring and communicating safety of medicines use in pregnancy and breastfeeding: validated and regulatory endorsed workflows for fast, optimized evidence generation”* (113).

The IMI ConcePTION provides a mechanism with the potential to address the burning platform for the development of a stronger framework and improved approaches to consolidating the evidence from case reports of exposures to medicines during pregnancy and the related outcomes. I believe that all MAHs have a moral, ethical and legal obligation to reduce the level of uncertainty affecting prescribing decisions. Improved

information will help both HCPs and pregnant mothers to make better-informed important decisions which relate to either taking potentially essential medical treatment(s) and protecting the unborn child.

Last but not the least, concerns have arisen that paternal drug exposure prior to conception may also contribute to:

- Changes in fertility (114,115);
- Adverse pregnancy outcomes (51),or
- Birth defects (116)

Further research is need regarding paternal drug exposure and risk mitigation strategies. This could be almost fully informed by first researching and communicating the results from the topics itemised above.

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## Curriculum Vitae

### **Bitu Rezaallah**

- PhD in Clinical Research
- Master of Advanced Studies in Cranio Facial Kinetic Sciences (MAS)
- Doctor of Dental Medicine (DMD)

#### **Pharmacovigilance Scientist**

- Safety signal detection and monitoring safety signals of individual case safety reports
- Clinical data analysis & evaluation of adverse event reports
- Writing periodic safety update reports (PSUR)
- Knowledge of Pharmacovigilance work stream
- Risk management plan (RMP)
- Regulatory compliance
- Regulatory requirements and drug labelling
- Causality assessment

#### **Dentist**

Performing variety of dental treatments including but not limited to:

- Restorative dentistry, Prosthodontics, Root canal therapy both anterior and posterior teeth
- Oral prophylaxis and periodontal treatment
- Treatment plan and performing full mouth rehabilitation

#### **Languages**

English: Professional, IELTS score 7

Deutsch: Intermediate B1

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