
EUROmediSAFE INVENTORY

Inventory of available data sources in all 28 EU Member States for potential use when evaluating the long-term risks for children associated with in-utero exposure

Maria Gkori and Joan Morris on behalf of the EUROmediSAFE consortium

Authors Affiliation: Queen Mary University of London

Prepared for the European Medicines Agency

July 2018 (Version 2)



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1 INTRODUCTION

The EUROMediSAFE Inventory consists of available data sources in all 28 European Union (EU) Member States for potential use when evaluating the long-term risks for children (ages 0-18 years). The listed data sources on health, neurodevelopmental and educational outcomes contain individual patient data with individual identifiers or unique identifying numbers enabling linkage with other databases. Where possible data sources have been identified as to whether they are population-based or not and whether linkage with other databases is allowed.

In addition to the Inventory this review also updates the information in the “Systematic overview of data sources for drug safety in pregnancy research - Consultancy EMA/2010/29/CN” (Chartlon & de Vries, 2012). Additional information has been added to the two tables “An overview of pregnancy registries” and “A summary of the data sources identified to evaluate the safety of medicine use during pregnancy”. For ease of reference we have retained the titles, numbering, format and order of the original tables.

A final part of this work was to report on the regulations governing the use of social media in the 28 EU Member States.

2 EUROMEDISAFE INVENTORY

2.1 METHODS

The EUROMediSAFE Inventory has drawn on the EncePP database of data sources, PROTECT, EMA’s “Systematic overview of data sources for drug safety in pregnancy research”, data sources known to EUROMediCAT/EUROLINKCAT, and a survey of 28 European countries through PRAC (which received responses from 24 of the EU Member States partners). Additional databases of data sources were consulted including the EMIF catalogue, MOCHA database, Health Data Navigator (by EuroREACH), Registry of Registries (RoR)-PARENT and Birthcohorts.net. Independent internet searches covered official/governmental websites, national health system web links, university research departments and independent research networks where available. Further searches by content or relevant terminology (using recurrent terms among data sources e.g. patient/disease register, medical birth register, childhood cancer register etc.) associated with health and neurodevelopmental outcomes were also carried out for any EU Member States where information could not be located through the above methods.

In the event we were unable to locate possible data sources independently or confirm relevant details about a specific data source, we attempted to contact all individuals or main contacts as they appeared in the questionnaire responses by the Member States partners. We made three contact attempts at maximum within a period of three months upon commencing the electronic correspondence for data collection. Each enquiry e-mail included a Questionnaire for data sources, a relevant Member-State-specific completed response questionnaire as received by the EMA partners (as guidance) and the EUROMediSAFE Information Leaflet.

2.2 STRUCTURE OF THE EUROMEDISAFE INVENTORY

Figure 2.1 shows the structure of the EUROMediSAFE Inventory. The main information is stored for each of the 28 EU Member States in a separate excel file with a file name of the format: [COUNTRY].xlsx. The excel file is arranged in six sheets (tabs) to include information of the data content, reference documents and contact details of the available datasets (see Table 2.1). Details on available birth cohorts per EU Member State are also included. More detailed information (for example a list of the coding dictionary or a list of the variables included in the database) are accessed by clicking on the embedded links in the spreadsheet or by searching in the relevant country specific folders: \DATA LINKS BY COUNTRY\[COUNTRY]\CODING DICTIONARY or \DATA LINKS BY COUNTRY\[COUNTRY]\VARIABLES. Additional information including user guides, application forms

and annual reports is also available by following the embedded links or searching the folder: **\SOURCE\[COUNTRY]**. In addition, a spreadsheet EU.xlsx provides information on networks/cohorts/registers that span more than one European country and may include non-European countries.

FIGURE 2.1 THE STRUCTURE OF THE EUROMEDISAFE INVENTORY

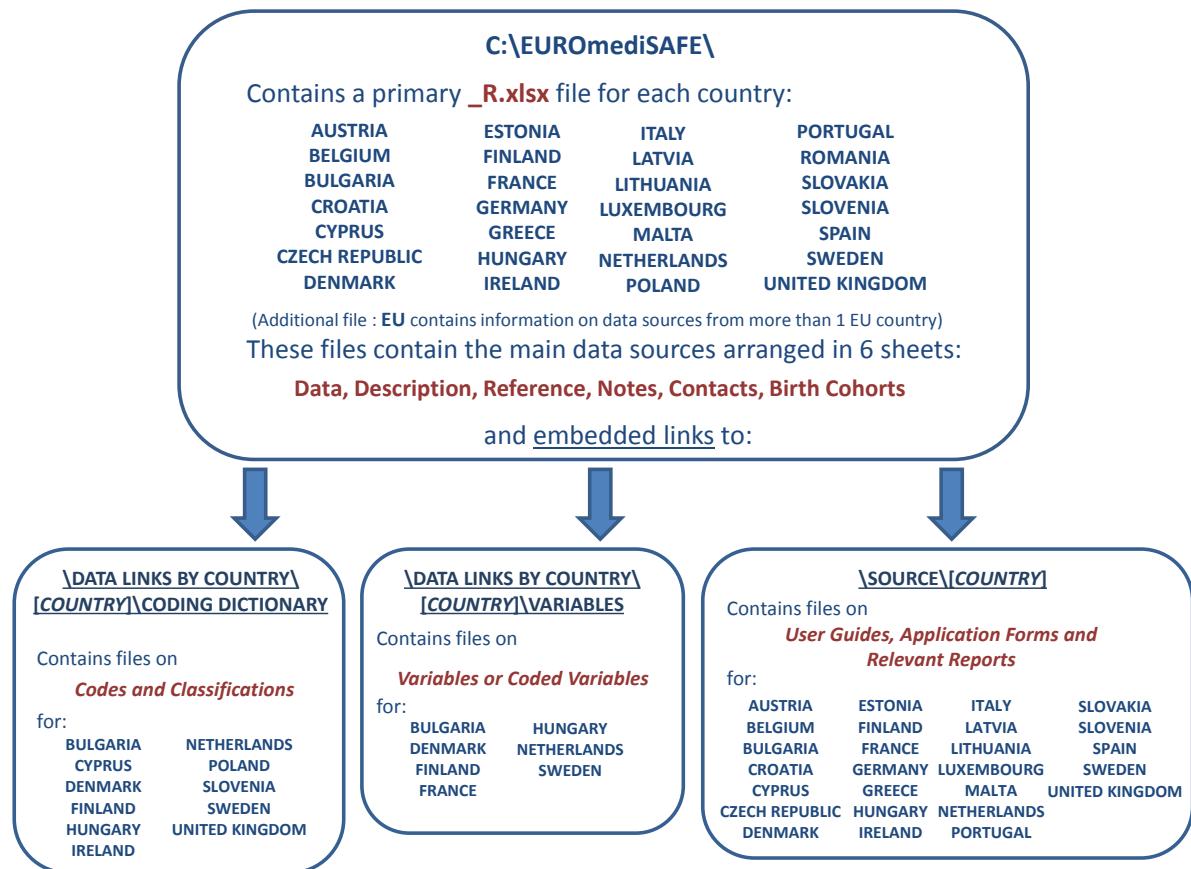


TABLE 2.1 SHEETS INCLUDED IN THE FILES : [COUNTRY].XLSX

SHEETS (TABS)	CONTENT
1. DATA	Main information on the data source, registers, links, data type, linkage, availability, permissions, costs
2. DESCRIPTION	Comprehensive information on coverage, size, completeness, variable lists, list of codes (coding dictionary), data entry professional and system
3. REFERENCE	User guides, application forms, publications using the data, collaboration and ownership information, links/URL, including register URL
4. NOTES	Further information as and when applicable per register
5. CONTACT	Name of contact, including telephone, email, address
6. BIRTH COHORTS	Name of cohort, main link and/or cohort URL, coverage, size, contact

2.3 INSTALLING THE INVENTORY

The EUROMediSAFE Inventory is located in the zipped file:

EUROMediSAFE.zip

In order to install the EUROMediSAFE Inventory, please follow these steps:

Locate the C:

Create New Folder and label “EUROMediSAFE”

Unzip EUROMediSAFE.zip into the folder C:\ EUROMediSAFE [†]

[†] The Inventory will not function correctly if you copy it into any other folder than C:\ EUROMediSAFE

2.4 SUMMARY OF THE EUROMEDISAFE INVENTORY

The EUROMediSAFE Inventory consists of registers, databases, biobanks and research cohorts across the 28 EU Member States. For ease of reference we have labelled all entries as ‘REGISTERS’ across the Inventory files and we will refer to them as such in this section. We have provided entries for each one of 28 EU Member States on population, health, healthcare, neurodevelopmental and educational outcomes as available. The EUROMediSAFE Inventory includes 511 different registers; 213 of them population based (Table 2.2). The median year of starting data collection is 1990, with 12% only stating data collection in 2010. Fifty-two percent (267/511) had some evidence that linkage with other data sets was possible (Table 2.3). This may be an underestimate as for many registers it was not possible to determine if linkage was possible. In terms of total size, the median size for a register is 250,000 individuals. For those registers where size per year is also available, the median number of individuals per year is 18,000. The median sizes for those registers for which linkage is possible are 370,000 and 18,000 respectively. Please note that the registers included in the EUROMediSAFE Inventory do allow for the investigation of long-term outcomes in children, but the sizes given above generally include the whole population and are not restricted to only children aged 0-18 years.

TABLE 2.2 EUROMEDISAFE INVENTORY: DATA SOURCES ACCORDING TO FIRST YEAR OF DATA COLLECTION AND WHETHER POPULATION BASED

First year of data collection	Total number of Registers	Population-based Registers
Before 1980	72	21
1980 - 1990	40	19
1980 - 1999	124	71
2000 - 2009	119	46
2010 - 2017	51	14
Missing	105	42
Total	511	213

TABLE 2.3 EUROMEDISAFE INVENTORY: DATA SOURCES ACCORDING TO WHETHER LINKAGE IS POSSIBLE

Country	Linkage			Total
	Yes	No	Unknown	
Austria	4	0	7	11
Belgium	7	2	12	21
Bulgaria	2	0	9	11
Croatia	7	3	5	15
Cyprus	5	1	0	6
Czech Republic	7	2	5	14
Denmark	29	0	1	30
Estonia	2	0	5	7
Finland	24	3	1	28
France	23	5	9	37
Germany	4	3	13	20
Greece	0	0	7	7
Hungary	1	0	13	14
Ireland	6	0	15	21
Italy	21	0	8	29
Latvia	9	0	4	13
Lithuania	1	0	7	8
Luxembourg	0	0	7	7
Malta	9	0	4	13
Netherlands	13	1	18	32
Poland	3	0	5	8
Portugal	1	1	9	11
Romania	0	0	9	9
Slovakia	0	0	12	12
Slovenia	1	0	10	11
Spain	10	7	6	23
Sweden	41	0	1	42
United Kingdom	37	2	12	51
Total	267	30	214	511

The Inventory also includes (for completeness) information on birth cohorts. As details for all these cohorts are readily available (for example at Birthcohorts.net) we have provided basic descriptive and contact information on the 57 larger cohorts ($n \geq 1000$) for each individual EU Member State (Table 2.4).

A separate spreadsheet on 53 networks/cohorts or registers/databases that span more than one European country and may include non-European countries is also included following a similar format to the birth cohort sheets. It includes data content, countries, start year, size, coverage, linkage and contact details.

TABLE 2.4 EUROMEDISAFE INVENTORY: BIRTH COHORTS ACCORDING TO COUNTRY AND SIZE

COUNTRY	Number of Cohorts	Total Size
Belgium	1	1196
Czech Republic	1	7577
Denmark	7	219787
Finland	4	32926
France	6	153112
Germany	6	16880
Greece	1	1590
Ireland	2	3259
Italy	3	11170
Lithuania	1	4405
Netherlands	9	36615
Poland	1	1800
Portugal	2	1645
Slovakia	1	1134
Spain	2	1000
Sweden	3	22411
UK	7	63456
Total	57	579963

2.5 FUTURE OF THE EUROMEDISAFE INVENTORY

In order for the full use of the Inventory to be achieved this Inventory should be transferred into a database. At present there is available a STATA data file (STATA 14 on request from J Morris), which can be used to simply obtain summary statistics and create tables as seen above.

3 UPDATE OF “SYSTEMATIC OVERVIEW OF DATA SOURCES FOR DRUG SAFETY IN PREGNANCY RESEARCH”

3.1 PREGNANCY EXPOSURE REGISTRIES

Pregnancy exposure registries were updated by referring to the FDA website where a number of international product specific and USA based disease registries are listed (<https://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm251314.htm>). A list of these and other pregnancy registries as they emerged in the literature review is provided in Table 3.1.

TABLE 3.1 PREGNANCY REGISTRIES WITH CONTACT DETAILS (IDENTIFIED AT 1 DECEMBER 2017)

Registry	Drug / Disease	Date range	Number of pregnancies reported	Mean number of exposures per year	Further information
Disease specific					
UK Epilepsy and Pregnancy Register	Epilepsy All anticonvulsants	1996 – is ongoing	7,120 by April 2009	~565	http://www.epilepsyandpregnancy.co.uk/
Irish Epilepsy and Pregnancy Register	Epilepsy All anticonvulsants	2001 – 2007 2007 – formally joined with the UK Epilepsy and Pregnancy Register			http://www.epilepsypregnancyregister.ie/about%20the%20register.html
Australian Epilepsy Pregnancy Register	All anticonvulsants	1999 – is ongoing	1,436 by 2009	~150	http://www.neuroscience.org.au/apr/
North American Antiepileptic Drug Pregnancy Registry	Epilepsy All anticonvulsants	1997 – is ongoing	8,500 by April 2012	~550	http://www2.massgeneral.org/aed/
Antiretroviral Pregnancy Register	HIV/AIDS All antiretrovirals	1989 – is ongoing	16,142 by July 2011 14,198 with outcome data	~717 ~630	http://www.apregistry.com/
Transplantation Pregnancy Registry International	Renal transplant Nulojix (belatacept)	Is ongoing			http://www.ntpr.giftoflifeinstitute.org/
National Transplantation Pregnancy Registry	Including: Mycophenolate (Myfortic and Cellcept) Belatacept (Nulojix)	1991 – is ongoing	>3,300	~165	http://www.tju.edu/NTPR/

The UK Transplant Pregnancy Registry		Mar 1997 – is ongoing			
Adenovirus vaccine Pregnancy Registry		Dec 2011 – is ongoing			adenovirus@incresearch.com
Cancer and Childbirth Pregnancy Registry	Multiple drugs	Is ongoing			www.cancerandpregnancy.com
Antiepileptic Drug Pregnancy Registry	Epilepsy Including: Pregabalin	1997 – is ongoing	10,200		http://www.aedpregnancyregistry.org
Antiretroviral Pregnancy Registry	HIV/AIDS Multiple drugs	Is ongoing			http://www.apregistry.com/
Benlysta Pregnancy Registry (GSK)	Systemic Lupus Erythematosus (SLE)	Nov 2011 - is ongoing	500 by 2022		http://pregnancyregistry.gsk.com/belimumab.html
Mother Pregnancy Registry	Breast cancer (Herceptin, Kadcyla, Perjeta)	Is ongoing			http://theMotherpregnancyregistry.com/
Product specific					
EURAP – European and International registry of antiepileptic drugs in pregnancy	All anticonvulsants	1999 – is ongoing	17,454 by June 2012	~1300	http://www.eurapinternational.org/
National Pregnancy Registry for Antidepressants	Multiple antidepressants	Is ongoing			https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/
National Pregnancy Registry for Atypical Antipsychotics	Abilify (aripiprazole) Clozaril (clozapine) Geodon (ziprasidone) Invega (paliperidone) Risperdal (risperidone)	Nov 2008 – is ongoing			http://www.womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/ http://clinicaltrials.gov/ct2/show/NCT01246765?term=pregnancy+registry&rank=14

	Seroquel (quetiapine) Zyprexa (olanzapine) Saphris (asenapine) Latuda (lurasidone)				
National Pregnancy Registry for Psychostimulants	ADD/ADHD Multiple psychostimulants	Is ongoing			https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/othermedications/
Laronidase	Mucopolysaccharidosis I Hurler's Syndrome Scheie's Syndrome Hurler-Scheie Syndrome	April 2003 – is ongoing	>1000 by Dec 2011	~120	https://www.lsdregistry.net/mpsiregistry/
Benlysta Pregnancy Registry	Systemic lupus erythematosus (SLE)	Nov 2011 – is ongoing			http://pregnancyregistry.gsk.com/benlysta.html
Exenatide Pregnancy Registry	Type 2 Diabetes	Dec 2007 – is ongoing			http://www.exenatidepregnancyregistry.com/ http://clinicaltrials.gov/ct2/show/NCT00579150
Cymbalta Pregnancy Registry	Major Depressive Disorder Generalized Anxiety Disorder Diabetic Peripheral Neuropathic Pain Fibromyalgia	July 2009 – is ongoing			http://www.cymbaltapregnancyregistry.com/ http://clinicaltrials.gov/ct2/show/study/NCT01074151 https://lillypregnancyregistry.com/
Fabry Registry	Fabry Disease Agalsidase beta	Is ongoing			https://www.lsdregistry.net/fabryregistry/
The Gilenya Pregnancy Registry	Multiple sclerosis Fingolimod	Oct 2011 – is ongoing			http://clinicaltrials.gov/ct2/show/NCT01285479
The Herceptin Pregnancy Registry	Breast cancer Trastuzumab	Dec 2008 – is ongoing			http://www.herceptinpregnancyregistry.com/ http://clinicaltrials.gov/ct2/show/NCT00833963
The Pregnancy Registry	Type 2 Diabetes	Is ongoing			http://www.merckpregnancyregistries.com/januvi

for JANUVIA and JANUMET					a.html
UCB Keppra Pregnancy Registry	Epilepsy Levetiracetam (Keppra)	Dec 2004 – is still ongoing			http://www.kindle.com/LS_Pregnancy_Registries.php http://clinicaltrials.gov/ct2/show/NCT00345475
Merck Pregnancy Registry Program – Maxalt	Migraine headaches Maxalt (rizatriptan)				http://www.merckpregnancyregistries.com/maxalt.html
Pompe Disease Registry	Myozyme (alglucosidase alfa)	Sept 2004			https://www.lsregistry.net/pomperegistry/
Neoral Pregnancy Registry for Psoriasis and Rheumatoid Arthritis					https://www.inspire.com/groups/talk-psoriasis/discussion/neoral-pregnancy-registry-for-women-with-psoriasis-psoriatic-arthritis-2/
Nplate (romiplostim) Pregnancy Exposure Registry	Thrombocytopenic Purpura				http://www.amgenpregnancy.com/en-us/patient/the-program.aspx
Nuvigil Pregnancy Registry	Excessive sleepiness associated with obstructive sleep apnea, hypopnea syndrome, narcolepsy, shift work sleep disorder	Is ongoing			http://www.nuvigilpregnancyregistry.com/
Amgen's Pregnancy Surveillance Program	Available for all of Amgen's medications	Is ongoing			http://www.amgenpregnancy.com/en-us/patient/pregnancy-exposure-registries/pregnancy-exposure-registries-for-other-amgen-products.aspx
PROMACTA Pregnancy Registry	Thrombocytopenia	Mar 2010 – is ongoing			http://clinicaltrials.gov/ct2/show/NCT01064336
Provigil Pregnancy Registry	Excessive sleepiness associated with	Is ongoing			http://provigilpregnancyregistry.com/

	obstructive sleep apnea, hypopnea syndrome, narcolepsy, shift work sleep disorder				
Ribavirin Pregnancy Registry	Hepatitis C	2003 – is ongoing	391 by Feb 2011	~50	http://www.ribavirinpregnancyregistry.com/
Savella Pregnancy Registry	Fibromyalgia	Nov 2009 – is ongoing			http://www.savellapregnancyregistry.com/
Singular Merck Pregnancy Registry	Asthma Singular (montelukast)				http://www.merckpregnancyregistries.com/singulair.html
VIBATIV Pregnancy Registry	Antibacterial skin infection	Nov 2009 – is ongoing			http://www.vibativ.com/SafetyInPregnancy.aspx http://clinicaltrials.gov/ct2/show/NCT01130324
The ellaOne Pregnancy Registry	Emergency contraception				http://www.hra-pregnancy-registry.com/en/
ALLERGAN Global Safety Database	Multiple prescribed products	Is ongoing			https://www.allergan.com/products/drug-safety
ACROSTUDY Pregnancy Database	Acromegaly (pegvisomant)	2004 – is ongoing	>2,000		https://medicaloutcomes.pfizer.com/acrostudy
Amgen's Pregnancy Surveillance Program	Osteoporosis	Is ongoing			http://www.amgenpregnancy.com/en-us/patient/home.aspx ; 1-800-772-6436
Global Lomitapide Pregnancy Exposure Registry	Homozygous Familial Hypercholesterolemia	Is ongoing			http://www.JUXTAPID.com
LETRADA Pregnancy Exposure Registry	Multiple Sclerosis (Alemtuzumab)	Is ongoing			pregnancyregistries@increasearch.com
Mycophenolate Pregnancy Registry	Cellcept Myfortic	Is ongoing			https://www.mycophenolaterems.com/PregnancyRegistry.aspx

Vaccine specific					
Merck Gardasil Pregnancy Registry	Human papillomavirus	Is ongoing			http://www.merckpregnancyregistries.com/gardasil.html
Menactra vaccine Pregnancy Registry	Meningococcal vaccine	Is ongoing			http://www.sanofipasteurpregnancyregistry.com/?fa=menactra
ADACEL vaccine Pregnancy Registry	Booster immunization for the prevention of tetanus, diphtheria, and pertussis	Is ongoing			http://www.sanofipasteurpregnancyregistry.com/?fa=adacel
The pregnancy registry for Varicella Zoster Virus containing vaccines	VARIVAX PROQUAD ZOSTAVAX	1995 – is ongoing 2006 – is ongoing 2006 – is ongoing			http://www.merckpregnancyregistries.com/varivax.html
Cervarix Pregnancy Registry	Cervarix TM Human Papillomavirus Bivalent (Types 16 and 18) Vaccine	Is ongoing			http://pregnancyregistry.gsk.com/Cervarix.html
Twinrix Pregnancy Registry	Twinrix [®] Hepatitis A & Hepatitis B (Recombinant) Vaccine	Is ongoing			http://pregnancyregistry.gsk.com/twinrix.html
Boostrix Pregnancy Registry	Boostrix [®] Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed	Is ongoing			http://pregnancyregistry.gsk.com/boostrix.html
Varilrix Pregnancy Registry	Varicella Vaccine	Is ongoing			http://pregnancyregistry.gsk.com/Varilrix.html
Priorix Pregnancy Registry	Measles, mumps and rubella vaccine	Is ongoing			http://pregnancyregistry.gsk.com/Priorix.html
Fluorix Pregnancy Registry	Influenza virus vaccine	Is ongoing			http://pregnancyregistry.gsk.com/fluarix.html

Flulaval Pregnancy Registry	Influenza virus vaccine	Is ongoing			http://pregnancyregistry.gsk.com/flulaval.html
Varivax Pregnancy Registry	Prevention of chickenpox	1995 – is ongoing			
Menveo® Pregnancy Registry (GlaxoSmithKline)	Meningitis Vaccine	Sep 2014 - is ongoing	100 by Feb 2019		http://pregnancyregistry.gsk.com/menveo.html
Bexsero Pregnancy Registry	Bexsero (Meningococcal Group B Vaccine)	Is ongoing			BexseroPregnancyRegistry.SM@ppdi.com
Closed registries					
Acyclovir Pregnancy Registry	Herpes Simplex	01/06/1984 Stopped enrolment in 30/04/1999	597	~40	http://pregnancyregistry.gsk.com/acyclovir.html
Amevive Pregnancy Registry	Chronic plaque psoriasis Ameviv	March 2004 – March 2012			http://clinicaltrials.gov/ct2/show/NCT00342862
Avonex Pregnancy Registry	Rheumatoid arthritis Ankylosing spondylitis Psoriatic arthritis Psoriasis Relapsing multiple sclerosis	February 2004 – September 2011			http://clinicaltrials.gov/ct2/show/NCT00168714
Betaseron Pregnancy Registry	Relapsing forms of multiple sclerosis	Stopped enrolment 31/07/2011			http://www.betaseronpregnancyregistry.com/index.html
Bupropion Pregnancy Registry	Depression	31/09/1997 Stopped enrolment 01/11/2007	1,597	~150	http://pregnancyregistry.gsk.com/documents/bup_report_final_2008.pdf
Fluoxetine Pregnancy	Depression	01/07/1989 –	796	~120	Closed

Registry	Fluoxetine	Closed 09/04/1999			
Lamotrigine Pregnancy Registry	Lamotrigine regardless of indication	31/09/1992 – Stopped enrolment 03/06/2009	3,416 2,444 with known outcomes	~200 ~150	http://pregnancyregistry.gsk.com/lamotrigine.html
Raptiva Pregnancy Registry	Chronic moderate to severe plaque psoriasis	Jan 2005 – Sept 2009			http://clinicaltrials.gov/ct2/show/NCT00097240
Rebif Pregnancy Registry	Multiple Sclerosis	Dec 2002 – Feb 2008	34	~7	http://clinicaltrials.gov/ct2/show/NCT00338741
Sumatriptan and Naratriptan Pregnancy Registry	Migraine Sumatriptan and Naratriptan	01/01/1996 Stopped enrolment 31/01/2012	809 sumatriptan 92 naratriptan	~50 ~ 6	http://pregnancyregistry.gsk.com/sumatriptan.html
Valacyclovir Pregnancy Registry		01/01/1995 Stopped enrolment 30/04/1999	22	~5	http://pregnancyregistry.gsk.com/acyclovir.html
TYSABRI® Pregnancy Exposure Registry	Multiple Sclerosis (MS) or Crohn's Disease (CD) (natalizumab)	Jan 2007 – 2012	376		https://clinicaltrials.gov/ct2/show/NCT00472992
EXPECT Xolair Pregnancy Registry	Asthma	Closed			http://www.xolairpregnancyregistry.com/
Other					
* OTIS – Autoimmune Disease in Pregnancy study [OTIS = Organization of Teratology Information Specialists]	Tocilizumab Leflunomide Etanercept Adalimumab Abatacept *Rheumatoid Arthritis Psoriatic Arthritis	Is ongoing *Enrolled *Completed			http://www.otispregnancy.org/ http://mothertobaby.org/pregnancy-studies/

	Ankylosing Spondylitis Psoriasis				
OTIS* Vaccines and Medications in Pregnancy Surveillance Study	Asthma Multiple drugs *Influenza (Afluria Vaccine)	Is ongoing *Enrolled *Completed			http://mothertobaby.org/pregnancy-studies/
MotherToBaby Pregnancy Studies conducted by the Organization of Teratology Information Specialists (OTIS*) – Evolocumab Pregnancy Exposure Registry	Repatha (evolocumab)				http://mothertobaby.org/ongoing-study/repatha/ 1-877-311-8972 (toll-free)
Motherisk Pregnancy Registry Program	Including: Lamisil Meridia (Sibutamine) Singulair (Montelukast)				http://www.motherisk.org/women/currentStudies.jsp
Hepatitis B Vaccine in Pregnancy Motherisk Program	Twinrix Engerix-B Recombivax HB Comvax				http://www.motherisk.org/women/index.jsp

*OTIS = Organization of Teratology Information Specialists

3.2 LITERATURE REVIEW

A review of the literature was conducted to update “The summary of data sources identified to evaluate the safety of medicine use during pregnancy” by identifying papers (excluding conference abstracts) reporting on the safety of medicine use during pregnancy that had used a data source which had systematic data collection. In PubMed, papers were identified based on the following search terms: ((‘Pregnancy’[Mesh] OR ‘Congenital Abnormalities’[Mesh] OR ‘Teratogens’[Mesh]) AND (‘Product Surveillance, Postmarketing’[Mesh])). In Embase, papers were identified based on the following search terms: ((‘Pregnancy’ OR ‘Pregnancy outcome’ OR ‘Pregnancy termination’ OR ‘Congenital disorder’ OR ‘Congenital malformation’ OR ‘Birth defects’ OR ‘Teratogenic agent’ OR ‘Teratogenicity’) AND (‘Postmarketing surveillance’ OR ‘Drug surveillance program’)). The searches were restricted to papers reporting on studies in Humans. All papers were restricted to those published in English between 1 December 2011 and 30 November 2017.

3.3 RESULTS

The literature searches identified 140 articles through PubMed and a further 374 articles via Embase. Of these articles 381 were excluded following review of the title and abstract and a further 58 were excluded following review of the full text (Figure 3.1).

FIGURE 3.1 IDENTIFICATION OF ARTICLES IN THE LITERATURE

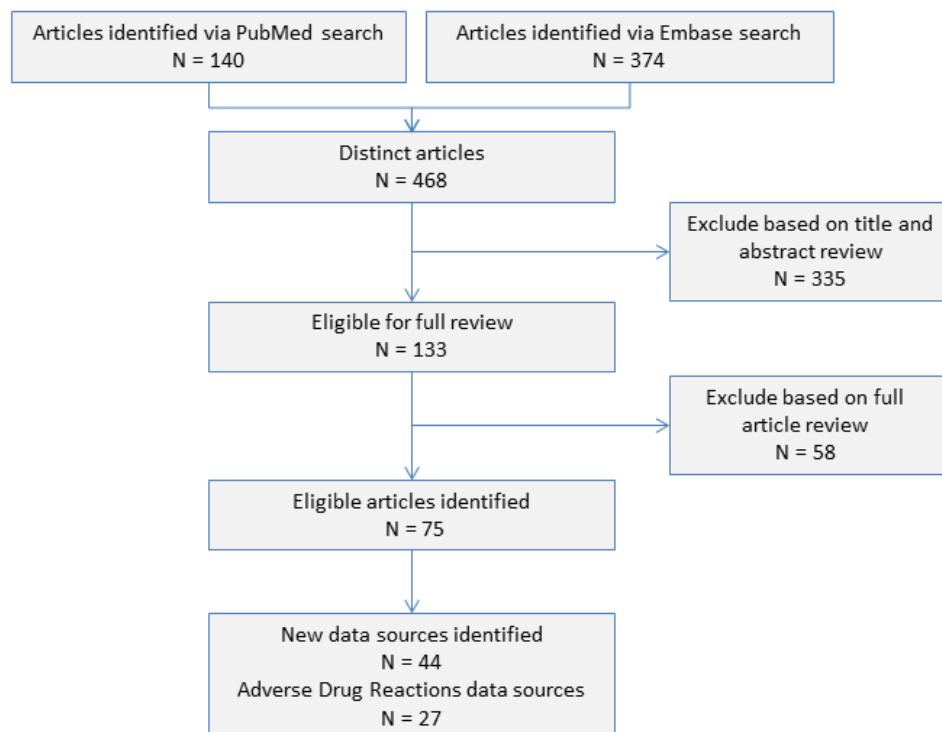


Table 3.2 summarises the rationale for excluding the papers identified. A total of 75 articles were included. Overall the studies reported on used data from 44 new different data sources (Table 3.3). These new data sources are inclusive of 27 Adverse Drug Reaction databases which we added as a further category and have labelled as such. Adverse drug reaction databases (or ADR surveillance systems) capture the types of

pregnancy outcomes of interest, as the surveillance data includes reporting on live births, still births, spontaneous losses and elective terminations.

Table 3.3 provides an overview of each of the 44 new data sources identified. Where the papers identified via the literature search did not have sufficient information to complete all the fields in the table, further internet and literature searches were performed. Please note we have marked the fields where information has not been confirmed.

TABLE 3.2 SUMMARY OF THE RATIONALE FOR ARTICLES EXCLUDED

Reason for exclusion	Number of articles excluded
Pregnancy exposure registries	13
Teratology information centres	8
Field studies with one-off manual data collection	35
Meta-analyses	3
Spontaneous/case reports	4
Environmental or occupational exposures	0
Alcohol or illicit drug use exposures	0
Overview of teratogenicity in general or pregnancy exposure registries	5
Comments or letters to the editor	14
Review papers	53 [†]
Other (e.g. product surveillance in general - not specifically pregnancy, reviews of medical conditions during pregnancy)	188 [†]

† These categories are large but they mainly come from the Embase search where the search strategy is not as refined as in PubMed and this results in a large number of unrelated publications being identified

3.4 DATA SOURCES IDENTIFIED TO EVALUATE THE SAFETY OF MEDICINE USE DURING PREGNANCY

TABLE 3.3 DATA SOURCES IDENTIFIED TO EVALUATE THE SAFETY OF MEDICINE USE DURING PREGNANCY

Key: Dark text = variables captured by the data source; light text = variables that are not available; highlighted text = unconfirmed information.

Name of data source	Time period of data collection	Population covered	Source of exposure information	Types of pregnancy outcome captured	Source of outcome information	Additional risk information (all capture maternal age)
Population-based record linkage surveillance systems						
Swedish Medical Birth Register(1-4)	Medical Birth Register since 1973, including drug use since July 1994 Prescribed drug register since 2005 The information can be linked with that in other Swedish health care registers and population registers	Country Sweden Population-based – Yes ~98% of all deliveries (mandatory reporting) Sample size ~110,000 births per year	Maternal self-reporting at first antenatal interview and copies of antenatal care records are reviewed Prescribed drug register of filled prescriptions since 2005	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	Identified from the Register of Birth Defects and the Patient Register – data recorded by a paediatrician Opportunity for medical record review – Yes	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status (link to population register) • Maternal diagnoses • Co-prescribing • Folic acid - if reported • Over-the-counter medicines - if reported • Reproductive history
Norwegian Medical Birth Register(5, 6)	Medical Birth Registry of Norway since 1967, including drug use since 1998 Norwegian Prescription database since	Country Norway Population-based – Yes Compulsory reporting of all births and late abortions from 12 weeks gestation	Recorded during antenatal visits to GP, midwife and obstetrician. Potential to use prescribed drug register of filled prescriptions since	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations - from 12 weeks gestation 	Recorded by physicians and midwives Opportunity for medical record review – Yes	<ul style="list-style-type: none"> • Smoking status – since 1998 • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid - Since 1998

	2004	Sample size ~60,000 births per year	2004			<ul style="list-style-type: none"> • Over-the-counter medicines <ul style="list-style-type: none"> - if the GP is aware • Reproductive history
Finnish linked national health registers(7, 8)	<p>Medical Birth Register since 1987</p> <p>Register on induced abortions since 1977</p> <p>Register of reimbursement drugs since 1994.</p> <p>The Hospital Discharge Register - inpatient diagnoses from 1969</p> <p>- outpatient diagnoses in public specialized care since 1998</p> <p>-outpatient primary care 2011-</p>	<p>Country Finland</p> <p>Population-based – Yes Compulsory reporting of all deliveries and elective terminations</p> <p>Sample size ~58,000 deliveries and ~ 10,500 elective terminations per year</p>	<p>Information on reimbursed purchases of prescription medicines from the Register of Reimbursement Drugs – coverage close to 100%</p>	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations • Spontaneous losses treated in hospital inpatient care since 1969, hospital outpatient care since 1998 and primary care from 2011 	<p>Identified from the register of congenital malformations – data recorded by hospital personnel.</p> <p>Opportunity for medical record review – Yes</p>	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index – from 2004 • Socioeconomic status • Maternal diagnoses - chronic • Co-prescribing • Folic acid – high dose only • Over-the-counter medicines • Reproductive history
Icelandic Medical Birth Register(9)	<p>Medical Birth Register since 1982</p> <p>The Icelandic Medicines Registry since 2003</p>	<p>Country Iceland</p> <p>Population-based – Yes at least ~99% of all deliveries</p> <p>Sample size ~4000-5000 births per</p>	<p>Maternal self-reporting at first antenatal interview and copies of antenatal care records are reviewed</p> <p>Prescribed drug register of filled</p>	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	<p>Identified from the Medical Birth Register and the Patient Register – data recorded by a physician</p> <p>Opportunity for medical record review – Possibly</p>	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines - as free text if reported

		year	prescriptions since 2003			• Reproductive history
Danish National Patient Registry(10-12)	Danish National Patient Registry since 1996 Prescription data from 1995 but only available since 2003	Country Denmark Population-based – Yes Compulsory reporting of all births Sample size ~50,000 deliveries per year	Filled prescription data from the Registry of Medicinal Product Statistics since 2003 Previously would have been self-reported via maternal interview	• Live births • Stillbirths • Spontaneous losses • Elective terminations	Routinely recorded inpatient and outpatient data recorded by paediatrician Opportunity for medical record review - Yes	• Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses - hospital diagnoses only • Co-prescribing • Folic acid – high dose only • Over-the-counter medicines • Reproductive history
Nordic Health Registers(9, 13, 14)	Combines the data sources registers listed above	Country Norway, Sweden, Denmark, Iceland, Finland Population-based – Yes Sample size ~X,XXX,000 deliveries per year	Combines the 5 data sources listed above	Combines the 5 data sources listed above	Combines the 5 data sources listed above	Combines the 5 data sources listed above
The North Jutland Pharmaco-Epidemiological Prescription Database with linked registries(15)	Prescription database since 1991 Danish National Patient Registry since 1996	Country Denmark Population-based – Yes County of North Jutland - compulsory reporting of all births Sample size ~6,000 deliveries a year	Dispensed prescription data used to secure reimbursement from the Health Service to the pharmacies	• Live births • Stillbirths • Spontaneous losses • Elective terminations	County hospital Discharge Register – discharge diagnoses recorded by paediatrician Opportunity for medical record review - Yes	• Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses - hospital diagnoses only • Co-prescribing • Folic acid – high dose only • Over-the-counter medicines • Reproductive history
Saskatchewan	Hospital data from	Country	Dispensed	• Live births	Identified from the	• Smoking status

population registries	1970 Prescription data from 1975	Canada Population-based – Yes Covers >90% of the Canadian province Sample size ~11,400 deliveries per year	prescriptions on the Outpatient Prescription Drug Database	<ul style="list-style-type: none"> • Stillbirths • Spontaneous losses • Elective terminations 	Hospital Services Database – data recorded electronically by physician Opportunity for medical record review – Yes	<ul style="list-style-type: none"> • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history
Taiwan National Health Insurance Research Dataset linked to the Birth Certificate Registry(16)	Since 1996	Country Taiwan Population-based – Yes ~98% of the Taiwan population Sample size ~200,000 births per year	Dispensed prescription data recorded in the National Health Insurance Research Dataset	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	Identified from medical claims recorded in the National Health Insurance Research Dataset Opportunity for medical record review – No	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status - maternal education only • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history
Western Australia population-based Data Linkage System(17, 18)	Since 2002 Birth defect registry since 1980	Country Australia Population-based – Yes All pregnancies in Western Australia Sample size ~ 40,000 pregnancies a year	Dispensed prescriptions. Covers those issued in community and private hospitals and from 2004 public hospitals that are subsidised ~80% of all prescriptions	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations <p>Looking into linking elective terminations with the birth defect registry</p>	Notifications received from paediatricians, obstetricians, cytogenetics, ultrasound, genetic counselling departments to the Birth Defects Registry of western Australia.	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history
Region Emilia-	Since 2000	Country	Reimbursed	<ul style="list-style-type: none"> • Live births 	Hospital assistance at	<ul style="list-style-type: none"> • Smoking status

Romagna (RER) Database(19)		<p>Italy</p> <p>Population-based – Yes ~99% of pregnancies in Region Emilia-Romagna</p> <p>Sample size ~ 33,000 pregnancies a year</p>	<p>prescription data (~70% of medicines can be reimbursed)</p>	<ul style="list-style-type: none"> • Stillbirths • Spontaneous losses • Elective terminations 	<p>birth records, hospital discharge records and links to Congenital anomaly register</p> <p>Opportunity for medical record review – No</p>	<ul style="list-style-type: none"> • Alcohol consumption • Body mass index – from 2011 • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid – when prescribed • Over-the-counter medicines • Reproductive history
Tuscany	Since 2003 Since 2004 also prescriptions from secondary care are available.	<p>Country Italy</p> <p>Population-based – Yes 100% of pregnancies in the Tuscany region</p> <p>Sample size >30,000 pregnancies a year</p>	<p>Reimbursed prescription data (~70% of medicines can be reimbursed)</p>	<ul style="list-style-type: none"> • Live births • Stillbirths <p>The following records</p> <ul style="list-style-type: none"> • Spontaneous losses • Elective terminations <p>may be retrieved by means of record linkage with hospital discharge records and may be incomplete</p>	<p>Hospital assistance at birth records, hospital discharge records and links to Congenital anomaly register</p> <p>Opportunity for medical record review – No</p>	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status - maternal education level • Maternal diagnoses • Co-prescribing • Folic acid – when prescribed • Over-the-counter medicines • Reproductive history
IADB.nl prescription database(20, 21)	Since 1994	<p>Country The Netherlands</p> <p>Population-based – Yes</p> <p>Sample size ~600,000 patients, including a mother–infant subset of approximately 40,000 children and their mothers, living in the</p>	<p>Prescription records of community pharmacies</p>	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	<p>Hospital assistance at birth records, hospital discharge records and links to Congenital anomaly register</p> <p>Opportunity for medical record review – Yes/No</p>	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid – when prescribed • Over-the-counter medicines • Reproductive history <p>Over-the-counter medication</p>

		northern part of the Netherlands				and medication dispensed during hospitalization were not recorded in the database.
Military Health System (MHS) healthcare data(22)	Since MHS service users may enroll in the military's single-payer healthcare program, TRICARE. Once enrolled in TRICARE, all beneficiaries are registered in the Defense Eligibility Enrollment Reporting System (DEERS).	Country United States Population-based – Yes Sample size ~4,700,000 enrolments Between January 2005 and December 2013, data exist for over 4.7 million women of reproductive age who were eligible to receive care in the MHS.	Prescription data via pharmacy records	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	<p>Reported by a health service provider</p> <p>Opportunity for medical record review –Yes</p>	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid – when prescribed • Over-the-counter medicines • Reproductive history <p>Mother–child data are extracted on a quarterly basis from the MDR and loaded into a relational database. Indexed data is used to identify pregnancies within the Pharmacovigilance Defense Application System (PVDAS).</p>

Healthcare databases

Medical record databases

Clinical Practice Research Datalink (CPRD)(23-26) Formerly the General Practice Research Database (GPRD)(27-32)	Since 1987	Country United Kingdom Population-based – Yes ~8% sample of the UK population Sample size ~80,000 pregnancies per year	Prescriptions issued by GPs and recorded in medical records	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	<p>Diagnoses recorded in medical records by GPs</p> <p>Opportunity for medical record review – Yes</p>	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid – when prescribed • Over-the-counter medicines • Reproductive history
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The Health Improvement Network (THIN)(33-35)	Since 2003	<p>Country United Kingdom</p> <p>Population based – Yes ~6% sample of the UK population</p> <p>Sample size ~60,000 pregnancies per year</p>	Prescriptions issued by GPs and recorded in medical records	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	<p>Diagnoses recorded in medical records by GPs</p> <p>Opportunity for medical record review - Yes</p>	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid – when prescribed • Over-the-counter medicines • Reproductive history
Secure Anonymised Information Linkage Databank (SAIL)(36)	<p>General practice data since 1992</p> <p>Hospital admissions from 2004</p>	<p>Country Wales</p> <p>Population based – Yes</p> <p>Sample size ~44,000 pregnancies per year</p>	Prescriptions issued by a GP	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	<p>Diagnoses recorded by a GP or paediatrician</p> <p>Opportunity for medical record review - Yes</p>	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid – high dose only • Over-the-counter medicines • Reproductive history
Care Register for Social Welfare and Health Care (HILMO)(37)	Since 2008	<p>Country Finland</p> <p>Population based – Yes/No</p> <p>Sample size >6,000,000 outpatient visits per year</p>	Prescriptions issued by xx	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	<p>Diagnoses recorded by health service providers (hospitals, health centres and home-nursing service providers)</p> <p>Opportunity for medical record review - Yes</p>	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid – when prescribed • Over-the-counter medicines • Reproductive history
Administrative claims databases						
Tennessee	Since 1985	Country	Pharmacy claims	<ul style="list-style-type: none"> • Live births 	Identified from	<ul style="list-style-type: none"> • Smoking status

Medicaid(38-40)		<p>United States</p> <p>Population-based – No - generally low income adults</p> <p>Sample size ~36,000 deliveries per year</p>	<p>data for dispensed prescriptions</p>	<ul style="list-style-type: none"> • Stillbirths • Spontaneous losses • Elective terminations 	<p>Medicaid inpatient, emergency department physician visit, hospital, discharge diagnoses records</p> <p>Also link to birth and foetal death certificates</p> <p>Opportunity for medical record review - Yes</p>	<ul style="list-style-type: none"> • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses - chronic • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history
Kaiser Permanente(41-44) This encompasses many sites and each is somewhat unique. Data on Kaiser Permanente Northern California is given as an example	Since ~1995	<p>Country United States</p> <p>Population-based – No Under-represents those at the extremes of household income</p> <p>Sample size ~30-35,000 deliveries per year</p>	<p>Pharmacy data for dispensed prescriptions</p>	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	<p>Medical claims records</p> <p>Opportunity for medical record review - Yes</p>	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status - maternal education only • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history - parity
Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP)	2001-2008 for all sites, 2001-2013 for some sites	<p>Country United States</p> <p>Population-based – Yes However, there is considerable overlap with Kaiser Permanente and Tennessee Medicaid</p>	<p>Pharmacy data for dispensed prescriptions</p>	<ul style="list-style-type: none"> • Live births <p>At some sites in some years:</p> <ul style="list-style-type: none"> • Stillbirths • Spontaneous losses • Elective terminations 	<p>Electronic medical records, insurance claims data, birth certificate data</p> <p>Opportunity for medical record review - Yes</p>	<ul style="list-style-type: none"> • Smoking status†‡ • Alcohol consumption • Body mass index • Socioeconomic status – education level† • Maternal diagnoses • Co-prescribing • Folic acid – when prescribed • Over-the-counter medicines • Reproductive history

		<p>Sample size ~150,000 deliveries per year</p>				<ul style="list-style-type: none"> • Opportunity to link to automated laboratory data (varies by site) • Race/ethnicity† <p>† From the EMR for some sites and linking to birth certificate data for other sites</p> <p>‡Available for ~60%</p>
United Healthcare(45-47)	Since 1990	<p>Country United States</p> <p>Population-based – No ~2% of US population. 90% are employer groups, some individuals from Medicaid population</p> <p>Sample size ~32,000 deliveries per year. ~ 75% of infants remain in the health plan</p>	Electronically recorded dispensed prescription data	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	<p>Medical claims records from inpatient, hospital, outpatient, emergency department, surgery centre and physician's office</p> <p>Opportunity for medical record review - Yes</p>	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history
Régie de l'assurance maladie du Québec (RAMQ)(48, 49)	<p>Since 1980 – recipients of social welfare</p> <p>Since 1997 – workers and their families not covered under private drug insurance</p>	<p>Country Canada</p> <p>Population-based – No Drug information for only recipients of social welfare and those who do not have private healthcare</p> <p>Sample size ~20,000 pregnancies per</p>	Dispensed prescription data	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	<p>Diagnoses recorded in the administrative databases of RAMQ and MED-ECHO</p> <p>Opportunity for medical record review - No</p>	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history

		year				
Clalit Data Warehouse(50, 51)	Since 1998	<p>Country Israel</p> <p>Population based - No Members of the Southern district of Clalit Health Services - ~70% of women 15-49 years</p> <p>Sample size ~9,500 births per year</p>	Dispensed prescription data	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	<p>Medical diagnoses during hospitalisation drawn directly from hospital records</p> <p>Opportunity for medical record review - Yes</p>	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid - some • Over-the-counter medicines • Reproductive history
Evaluation chez la Femme des Enceinte MEDicaments et de leurs RISques (EFEMERIS Database)(52, 53)	Since 1 July 2004	<p>Country France</p> <p>Population based - No Pregnant women in the Haute-Garonne department registered under general state coverage (~80% of the population)</p> <p>Sample size ~13,500 pregnancies per year</p>	Dispensed prescription data recorded to be sent to the French Health Insurance System Caisse Primaire d'Assurance Maladie (CPAM)	<ul style="list-style-type: none"> • Live births • Stillbirths[†] • Spontaneous losses[†] • Elective terminations and therapeutic abortions <p>[†] Available but not fully reliable</p>	<p>Live births: recorded by physician during compulsory medical examinations at 8 days, 9 months and 2 years</p> <p>Prenatal diagnoses: resulting in a termination are recorded by the antenatal diagnostic centre</p> <p>Stillbirths and spontaneous losses: recorded from both CPAM and Programme de medicalisation des Systemes d'Information (PSMI)</p>	<ul style="list-style-type: none"> • Smoking status[†] • Alcohol consumption[†] • Body mass index • Socioeconomic status[‡] • Maternal diagnoses • Co-prescribing – during pregnancy & 3 months before • Folic acid – when prescribed • Over-the-counter medicines • Reproductive history <p>[†] Available but not fully reliable</p> <p>[‡] maternal occupation for live births</p>

					medical record review - Yes for elective terminations and pregnancy losses recorded by PMSI.	
Truven Health MarketScan® Commercial Claims and Encounters (Commercial)(54)	Since	Country United states Population based – Yes Sample size Annually, approximately 30 million individuals are represented in these databases (MarketScan® & Medicare Supplemental).	These Commercial and Medicare Supplemental databases comprise inpatient and outpatient medical and outpatient prescription drug claims for employees, dependents, and retirees with employer-sponsored primary or Medicare supplemental insurance	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	Recorded by health professionals. Opportunity for medical record review –Yes/ No	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history <p>Included for medications was pregnancy, which is listed under use in specific populations.</p>

Medicare Supplemental and Coordination of Benefits (Medicare Supplemental)(54)	Since	Country United States Population based – Yes Sample size Annually, approximately 30 million individuals are represented in these databases (MarketScan® & Medicare Supplemental).	These Commercial and Medicare Supplemental databases comprise inpatient and outpatient medical and outpatient prescription drug claims for employees, dependents, and retirees with employer-sponsored primary or Medicare supplemental insurance.	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	Recorded by health professionals. Opportunity for medical record review –Yes/ No	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history <p>Included for medications was pregnancy, which is listed under use in specific populations.</p>
Medicaid Analytic eXtract (MAX)(55)	Since States provide Medicaid claims to the Centers for Medicare and Medicaid Services (CMS) through the Medicaid Statistical Information System (MSIS), and Medicaid Analytic eXtract (MAX) data are extracted from the MSIS to	Country United States Population based – Yes/No Sample size To date > 0,000 xxx per year	Reporting via	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	Recorded by XXX Opportunity for medical record review –Yes/ No	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history <p>MAX data are available through CMS conditional on data use agreements and fees</p>

	support research and policy analysis					
Adverse drug reaction databases						
EudraVigilance (EV) (56-59)	<p>Since 2001</p> <p>A system for monitoring the safety of medicines.</p> <p>The European database of suspected adverse drug reaction reports drreports.eu is a publicly accessible portal designed to search and view EudraVigilance data on suspected adverse reactions for</p>	<p>Country</p> <p>European Economic Area (EEA)</p> <p>Russia & former Soviet Republics</p> <p>Middle East</p> <p>Asia</p> <p>North America</p> <p>Central America & Caribbean</p> <p>South America</p> <p>Africa</p> <p>Australia & Oceania</p> <p>For medicinal products authorised in the EEA, adverse drug reaction reports are collected from both within and outside the EEA.</p>	<p>Electronic reporting of suspected adverse reactions related to medicines and the effective analysis of data.</p>	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	<p>Recorded by healthcare professionals</p> <p>Data collected in EudraVigilance Clinical Trials module:</p> <p>Suspected unexpected serious adverse reactions (SUSARs) reported by sponsors of interventional clinical trials;</p> <p>EudraVigilance Post-authorisation module:</p> <p>Suspected serious and non-serious side effects from:</p>	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history <p>EV is not accessible to the general public, and therefore the European Medicines Agency (EMA) must be approached to grant data access.</p>

	authorised medicinal products in the EEA.	<p>Population based – Yes</p> <p>Sample size In 2016, 1,238,178 reports related to suspected adverse reactions were collected and managed in EudraVigilance, 339,544 of which originate from the EEA.</p> <p>EV now holds 10.8 million reports referring to 6.7 million cases. The post-authorisation module (EVPM) contained 9,928,217 ADR reports (6,367,422 cases) and the clinical trial module (EVCTM) 960,171 reports (336,313 cases) (Annual Report, 2016).</p>			<p>Healthcare professionals' and patients' spontaneous reporting;</p> <p>Post-authorisation studies (non-interventional);</p> <p>Worldwide scientific literature (spontaneous, non-interventional);</p> <p>Opportunity for medical record review – No</p>	
Spanish Pharmacovigilance System (60)	Since 1982 Spanish System of Pharmacovigilance of Medicines for Human Use [Servicio Español de Farmacovigilancia en humanos (SEFV-H)] whose national	<p>Country Spain</p> <p>Population based – Yes/No (213 per million population)</p> <p>Sample size ~10,000 notifications per year (FEDRA)</p>	Reporting via	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	<p>Recorded by a xxx</p> <p>Opportunity for medical record review – Yes/ No</p>	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history

	registry was launched in late 1991. FEDRA [Farmacovigilancia Española, Datos de Reacciones Adversas (Spanish pharmacovigilance database on adverse reactions)]					
Portuguese pharmacovigilance system (PPS) database(61)	Since	Country Portugal Population based – Yes/No Sample size To date > xxx per year	Reporting via an official paper form and an online form with a set of questions aimed at describing adverse events, suspected drugs, concomitant drugs, patient details and reporter details	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	Recorded by healthcare professionals, namely physicians, pharmacists and nurses, who are legally required to report adverse events. Patients or consumers are allowed to report adverse events to the PPS since July 2012.	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history
Eli Lilly and Company(62)	Established 1876 A world-wide safety database of all adverse events reported to Lilly relative to	Country United States Population based – Yes/No Sample size 1,912,300 enrolments (2018; Research Volume	Spontaneous reporting and follow-up questionnaire	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations • Congenital anomalies 	Recorded by healthcare provider/patient	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines

	treatment with products marketed by Lilly since 1983.	available via Thomson Reuters)				<ul style="list-style-type: none"> Reproductive history <p>This database consists of all spontaneous adverse events—regardless of severity—reported in patients treated with olanzapine (including data from published literature and regulatory agency reports), and serious adverse event reports from clinical trials and post-marketing studies. Additionally, the database contains reports of olanzapine use during pregnancy and/or breastfeeding, even if no adverse outcome was reported.</p>
Food and Drug Administration's Adverse Events Reporting System (Medwatch Program)(63)	Since 1993 It was set up by the FDA in June 1993 to improve the postmarketing surveillance of drugs on the U.S. market by encouraging health care professionals to voluntarily report adverse events to the FDA or to the manufacturer	Country United States Population based – Yes/No Sample size To date > 55,000,000 reports	Reporting via the downloadable copy of the Medwatch 3500 FDA Form or directly online	<ul style="list-style-type: none"> Live births Stillbirths Spontaneous losses Elective terminations Congenital anomalies 	Recorded by a physician, dentist, pharmacist, and any person who knows of or suspects an association between a drug and a specific adverse effect Opportunity for medical record review –Yes/ No	<ul style="list-style-type: none"> Smoking status Alcohol consumption Body mass index Socioeconomic status Maternal diagnoses Co-prescribing Folic acid Over-the-counter medicines Reproductive history

	The database is a rich resource for pharmacovigilance that includes more than 55 million adverse event reports.					
World Health Organization (WHO) Systematic surveillance for adverse events following immunization (AEFI) (64, 65)	Since Active and passive AEFI surveillance systems for pregnant women and their offspring in WHO member countries	Country International; countries from WHO regions Population based - Yes Sample size To date > xxx per year	[Survey]	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	<p>Reporting via National Pharmacovigilance Center (NPC) representatives</p> <p>Opportunity for medical record review – Yes/No</p>	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history <p>National passive AEFI surveillance do not specifically capture pregnancy status on the reporting forms consistently</p>
Janssen Research & Development, LLC Global Medical Safety (GMS) database (66)	Since A database of post marketing reports	Country United States Population based - Yes Sample size To date > xxx per year	Reporting via	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations • Congenital anomalies 	<p>Recorded by a xx</p> <p>Opportunity for medical record review – Yes/No</p>	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history

Vaccine Adverse Event Report System (VAERS) (65, 67-77)	Since	Country United States Population based - Yes Sample size To date > xxx per year	Reporting via	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	Recorded by a xx Opportunity for medical record review – Yes/No	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history
Food and Drug Administration Adverse Event (AE) Reporting System (FAERS)(78-82) United States Food and Drug Administration Adverse Event Reporting System (FDA-AERS)(83)	Since	Country United States Population based - Yes Sample size To date > xxx per year	Reporting via	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	Recorded by a xx Opportunity for medical record review – Yes/No	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history
French Pharmacovigilance Database(84-86)	Since The French pharmacovigilance system consists of a network of 31 regional centres (RPVC) and is based on a spontaneous surveillance system in which reports of	Country France Population based - Yes Sample size To date > xxx per year	Patient completed form	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	Reporting assistance by a medical practitioner Opportunity for medical record review – Yes	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history

	'serious' and/or 'unlabelled' adverse events (AEs) are mandatory for all HCPs.					
Italian National Pharmacovigilance Network(87)	<p>Since An electronic spontaneous reporting database that collects reports of all suspected ADRs from the Italian National territory</p>	<p>Country Italy</p> <p>Population based - Yes</p> <p>Sample size To date > xxx per year</p>	Reporting via	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	<p>Recorded by a xx</p> <p>Opportunity for medical record review – Yes/No</p>	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history
VigiBase®, the World Health Organization (WHO) Global Individual Case Safety Report (ICSR) database(88)	Since	<p>Country Global (established in Sweden)</p> <p>Population based - Yes</p> <p>Sample size To date > xxx per year</p>	Reporting via	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	<p>Recorded by a xx</p> <p>Opportunity for medical record review – Yes/No</p>	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history
Pharmacovigilance Programme of India (PvPI)(89-91)	Since 2005	<p>Country India</p> <p>Population based – Yes/No</p> <p>Sample size</p>	Reporting via	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	<p>Recorded by a xx</p> <p>Opportunity for medical record review – Yes/No</p>	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines

						<ul style="list-style-type: none"> • Reproductive history
Taiwan passive surveillance system for adverse event following immunization (AEFI) (92) Taiwan Centers for Disease Control (TCDC) and Taiwan Food and Drug Administration	Since	Country Taiwan Population based – Yes/No Sample size To date > xxx per year	Reporting via	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	Recorded by a xx Opportunity for medical record review – Yes/No	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history
China Guangdong Provincial Center of ADR Monitoring and Database(93)	Since	Country China Population based – Yes Sample size To date > xxx per year	Reporting via	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	Recorded by a xx Opportunity for medical record review – Yes/No	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history
Rufiji Health and Demographic Surveillance System (HDSS)(94)	Since	Country Tanzania Population based - Yes Sample size ~97,000 enrolments The prevalence of women delivering in health facilities in the study area is 74%.	Reporting via routine HDSS quarterly surveys	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	Recorded by health facilities centres which have Reproductive and Child Health (RCH) clinic services Opportunity for medical record review – Yes/No	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history

		All recorded in the database including social and health characteristics. Data from all 13 health facilities within DSS catchment area are also routinely being collected.				
Cuban pharmacosurveillance system(95)	Since	Country Cuba Population based - Yes Sample size To date > xxx per year	Reporting via	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	Recorded by a xx Opportunity for medical record review – Yes/No	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history
Turkish Pharmacovigilance Center (TUFAM) (96) Turkish Adverse Drug Reaction Monitoring and Evaluation Center (TADMER)	Since	Country Turkey Population based - Yes Sample size To date > xxx per year	Reporting via	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	Recorded by a xx Opportunity for medical record review – Yes/No	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history
Italian Pharmacovigilance Adverse Event (AE) Spontaneous Reporting System [Rete Nazionale Farmacovigilanza]	Since	Country Italy Population based - Yes Sample size To date > xxx per year	Reporting via	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	Recorded by a xx Opportunity for medical record review – Yes/No	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid

(RNF)(81, 97)	Italian Medicines Agency (AIFA), Italian regions, local health units, hospitals, Institute of Research and Care and drug industries					<ul style="list-style-type: none"> Over-the-counter medicines Reproductive history
Base Nationale de Pharmacovigilance (BNPV)(81)	Since French SRS (2000–2010)	Country France Population based - Yes Sample size To date > xxx per year	Reporting via	<ul style="list-style-type: none"> Live births Stillbirths Spontaneous losses Elective terminations 	Recorded by a xx Opportunity for medical record review – Yes/No	<ul style="list-style-type: none"> Smoking status Alcohol consumption Body mass index Socioeconomic status Maternal diagnoses Co-prescribing Folic acid Over-the-counter medicines Reproductive history
Federal Institute for Drugs and Medical Devices (German name, BfArM)(81)	Since German SRS (2005–2010)	Country Germany Population based - Yes Sample size To date > xxx per year	Reporting via	<ul style="list-style-type: none"> Live births Stillbirths Spontaneous losses Elective terminations 	Recorded by a xx Opportunity for medical record review – Yes/No	<ul style="list-style-type: none"> Smoking status Alcohol consumption Body mass index Socioeconomic status Maternal diagnoses Co-prescribing Folic acid Over-the-counter medicines Reproductive history
Israel drug surveillance program (98)	Since	Country Israel Population based - Yes Sample size	Reporting via	<ul style="list-style-type: none"> Live births Stillbirths Spontaneous losses Elective terminations 	Recorded by a xx Opportunity for medical record review – Yes/No	<ul style="list-style-type: none"> Smoking status Alcohol consumption Body mass index Socioeconomic status Maternal diagnoses Co-prescribing

		To date > xxx per year				<ul style="list-style-type: none"> • Folic acid • Over-the-counter medicines • Reproductive history
Japanese Adverse Drug Event Report database(99, 100)	Since	<p>Country Japan</p> <p>Population based - Yes</p> <p>Sample size To date > xxx per year</p>	Reporting via	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	<p>Recorded by a xx</p> <p>Opportunity for medical record review – Yes/No</p>	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history
Thai Vigibase(101) Health Product Vigilance Center (HPVC) under the Thai Food and Drug Administration	Since	<p>Country Thailand</p> <p>Population based - Yes</p> <p>Sample size To date > xxx per year</p>	Reporting via health product surveillance systems and programmes	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	<p>Recorded by a xx</p> <p>Opportunity for medical record review – Yes/No</p>	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history
Pharmaceuticals and Medical Devices Agency Japan(102)	Since	<p>Country Japan</p> <p>Population based - Yes</p> <p>Sample size To date > xxx per year</p>	Reporting via	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	<p>Recorded by a xx</p> <p>Opportunity for medical record review – Yes/No</p>	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history

National Center for Pharmacovigilance (NCF), as a part of the Medicines and Medical Devices Agency of Serbia(103, 104)	Since	Country Serbia Population based - Yes Sample size To date > xxx per year	Reporting via	• Live births • Stillbirths • Spontaneous losses • Elective terminations	Recorded by a xx Opportunity for medical record review – Yes/No	• Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history
Swiss national ADR database(105)	Since	Country Switzerland Population based - Yes Sample size To date > xxx per year	Reporting via	• Live births • Stillbirths • Spontaneous losses • Elective terminations	Recorded by a xx Opportunity for medical record review – Yes/No	• Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history
Purpose built surveillance systems						
Slone Epidemiology Unit Birth Defects Study(106, 107)	Since 1976	Country United States and previously Canada Population based - Yes Sample size To date >40,000 women have been interviewed	Self-reporting via maternal telephone questionnaire (face to face interview up until 1998)	• Live births • Stillbirths • Spontaneous losses • Elective terminations	Recorded by a paediatrician Opportunity for medical record review - Yes, with mothers' permission	• Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history

						Opportunity to add additional interview questions relevant to a particular study.
National Birth Defects Prevention Study(108-110)	Since 1997	Country United States Population based - Yes Sample size ~10% of annual US birth cohort	Self-reporting of exposure by maternal assisted telephone interview between 6 weeks and 2 years after the expected date of delivery	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations The capture of stillbirths and elective terminations varies by state Controls are live births only	Medical record extraction Opportunity for medical record review - Yes	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history Opportunity to add additional interview questions relevant to a particular study
The Latin-American Collaborative Study of Congenital Malformations (ECLAMC)(111, 112)	Since 1967	Country 9 countries in South America Population based - Yes Sample size ~150 - 200,000 births per year	Self-reported by the mother and collected by a trained paediatrician during the puerperium	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	Identified from registered malformations diagnosed at birth Opportunity for medical record review - No	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history Collects data on 50 possible risk factors
Spanish Collaborative Study of Congenital Malformations	Since 1976	Country Spain	Maternal interviews with paediatricians within the first 3 days	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses 	Diagnosed by paediatricians within the first 3 days of life.	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index

(ECEMC)(113, 114)		<p>Population based - Yes</p> <p>Sample size ~87,000 births per year ~1,100-1,300 case-control pairs per year</p>	following delivery.	<ul style="list-style-type: none"> Elective terminations 	<p>Opportunity for medical record review - No</p>	<ul style="list-style-type: none"> Socioeconomic status Maternal diagnoses Co-prescribing Folic acid Over-the-counter medicines Reproductive history <p>>300 data points of information collected.</p>
Hungarian Case-control of Congenital Abnormalities Study(115-117)	1980-1996 Appears to be no longer recruiting - Emailed Professor Czeizel but did not get a response	<p>Country Hungary</p> <p>Population based - Yes</p> <p>Sample size In 1996 ~22,843 cases and 38,151 controls</p>	Review of antenatal log book and medical records recorded by obstetrician, additional data requested by maternal questionnaire	<ul style="list-style-type: none"> Live births Stillbirths Spontaneous losses Elective termination - following a prenatal malformation diagnosis 	<p>Cases reported by a physician or paediatrician during first 3 months after birth or termination.</p> <p>Opportunity for medical record review - Yes, discharge summaries</p>	<ul style="list-style-type: none"> Smoking status Alcohol consumption Body mass index Socioeconomic status - employment status only Maternal diagnoses Co-prescribing Folic acid Over-the-counter medicines Reproductive history
European Concerted Action on Congenital Anomalies and Twins (EUROCAT)(118-121)	Since 1979	<p>Country 20 European countries</p> <p>Population based - Yes</p> <p>Sample size ~1.7 million births per year</p>	<p>Varies by register – hospital records, GP records, pharmacy records, maternal interview</p> <p>Not all registers capture drug exposure data</p>	<ul style="list-style-type: none"> Live births Stillbirths Elective terminations 	<p>Multiple sources, paediatric units, neonatal units. See Registry Profiles available at: http://www.euromedicat.eu/content/Partners-Registry-Descriptions.pdf</p> <p>Opportunity for medical record review - varies by registry</p>	<ul style="list-style-type: none"> Body mass index Socioeconomic status Co-morbidities Co-prescribing Folic acid Over-the-counter medicines Reproductive history <p>All vary by register</p>

EUROmediCAT central database(122-126)	Since 1995 - it was set up in 2011	Country 18 European countries Population based – Yes. Some countries have national registries and others cover a specific region. Sample size ~650,000 births per year	All EUROmediCAT registries record medication exposures in pregnancy. Varies by register – maternal records, child health records, pharmacy records, maternal interview. Some registries can link CA data to local prescription databases See Registry Profiles available at: http://www.euromediat.eu/content/Partners-Registry-Descriptions.pdf	<ul style="list-style-type: none"> • Live births • Stillbirths • Elective terminations 	Multiple sources, paediatric/ neonatal/ geneticists etc. See Registry Profiles available at: http://www.euromediat.eu/content/Partners-Registry-Descriptions.pdf Opportunity for medical record review - varies by registry	<ul style="list-style-type: none"> • Body mass index • Socioeconomic status • Co-morbidities • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history <p>• All vary by register</p>
Alberta Congenital Anomalies Surveillance System(127)	Since 1966	Country Alberta province of Canada Population based – Yes. Sample size ~55,000 births per year	Dispensed prescription medications for outpatients	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations carried out for fetal anomalies 	Health providers report congenital anomalies diagnosed by 1 year of age (since 1980, up to 6 years pre 1980). Opportunity for medical record review - Yes	<ul style="list-style-type: none"> • Smoking status* • Alcohol consumption* • Body mass index* • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid – when prescribed • Over-the-counter medicines • Reproductive history <p>* collected but largely missing</p>
pREGnant (pregnancy drug registry)	Started 2014	Country The Netherlands Population based – No –	Web-based questionnaires filled out by the mother (3 times during pregnancy)	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	Web-based questionnaires filled out by the mother (3 times during pregnancy)	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Illicit drug intake • Body mass index

		<p>self enrolment</p> <p>Sample size 1 October 2017: 3,113 pregnancies enrolled (825 reached data completion)</p>	<p>pregnancy and 3 times postpartum).</p> <p>Additional data (if desired) upon request (GP records, pharmacy records, Perinatal Registry).</p>	<p>Child's health until 1 year of age (hospitalizations, malformations etc.).</p> <p>Effects of medicines during lactation period</p>	<p>and 3 times postpartum).</p> <p>Opportunity for medical record review - Yes</p> <p>Additional data (if desired) upon request (GP records, pharmacy records, Perinatal Registry).</p>	<ul style="list-style-type: none"> • Educational level • Co-morbidities (incl. relevant disease parameters like epileptic insults) • Concomitant medicinal drug use • Folic acid • Over-the-counter medicines • Reproductive history • ART
EURAP (International Registry of Antiepileptic Drugs and Pregnancy)(128)	Since 1999	<p>Country 42 countries worldwide</p> <p>Population-based – No – self enrolment</p> <p>Sample size End of 2015: ~21,800 pregnancies enrolled</p>	<p>Different sources, dependent of the country.</p> <p>Either through health care provider or pregnant woman</p>	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations <p>Child's health until 1 year of age (hospitalizations, malformations etc.).</p>	<p>Different sources, dependent of the country.</p> <p>Either through health care provider or pregnant woman</p> <p>Opportunity for medical record review - Yes</p>	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Educational level • Co-morbidities (incl. relevant disease parameters like epileptic insults) • Concomitant medicinal drug use • Folic acid • Over-the-counter medicines • Reproductive history • ART
The UK and Ireland Epilepsy and Pregnancy Register(27, 129)	Since 1996	<p>Country United Kingdom and Ireland</p> <p>Population-based – No – self enrolment</p> <p>Sample size End of 2014: >8,000 completed registrations</p>	<p>Either through health care provider or pregnant woman</p>	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	<p>Either through health care provider or pregnant woman</p> <p>Opportunity for medical record review - Yes</p>	<ul style="list-style-type: none"> • Maternal age • Family history of MCM • Folic acid • Parity • Epilepsy seizure type • Co-prescribing 3m before pregnancy

The North American Antiepileptic Drug Pregnancy Registry	Since 1997	Country United States and Canada Population-based – No – self enrolment Sample size >10,200 enrolments	Either through health care provider or pregnant woman Also have a control group with no AED exposure	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	Either through health care provider or pregnant woman Opportunity for medical record review - Yes	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Educational level • Co-morbidities (including diabetes) • Folic acid
'bumps' website (online patient information and reporting facility) www.medicinesinpregnancy.org	Launched April 2014	Country Global Population based – No – self enrolment Sample size 186 pregnancy records/ registrations (1 April 2016)	Women create and update their own password protected online record throughout pregnancy Information collected about a live born child's health at 6 months and then yearly	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses (SA, IUD) • Elective terminations • GA at delivery • Birth weight • Congenital malformations • Neonatal complications • Genetic diagnoses 	Self-reporting by women Follow up of child to teens	<ul style="list-style-type: none"> • Maternal age • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Co-morbidities • Pregnancy complications • Co-prescribing • Folic acid • Over-the-counter medicines • Vaccination in pregnancy • Reproductive history • Family history • Long term child health, development and growth <p>For specific prospective studies it is possible to request specific additional data collection</p>
Dutch Teratology Information Service, part of the Netherlands Pharmacovigilance Centre Lareb(130, 131)	Since The Dutch Teratology Information Service (TIS) of the Netherlands	Country The Netherlands Population based – Yes/No Sample size	Questionnaires were sent during the pregnancy to the health care providers and a second one 6 weeks after the estimated date of	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations • Congenital anomalies 	Recorded by a health provider Opportunity for medical record review – Yes/No	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing

	<p>Pharmacovigilance Center Lareb is a center of expertise in the field of teratology and has a consultation service for health care providers (HCPs) on drug exposure during pregnancy and lactation.</p> <p>During the 2009 H1N1 influenza pandemic, the Dutch TIS recruited vaccinated pregnant women through health care providers.</p>	<p>A cohort of 925 (2009)</p> <p>birth.</p>				<ul style="list-style-type: none"> • Folic acid • Over-the-counter medicines • Reproductive history <p>A cohort of 295 vaccinated pregnant women was prospectively enrolled and evaluated in assessing the adjuvanted A/H1N1 (2009) influenza vaccine safety during pregnancy.</p>
<p>Teratogen Information System Program at the University of Washington (TERIS)(132)</p>	<p>Since Provides current information on the teratogenic effects of drugs and environmental agents. Agent summaries derived from thorough literature reviews rate reproductive</p>	<p>Country United States</p> <p>Population based – Yes/No</p> <p>Sample size >3500 agents</p>	<p>Reporting via</p>	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations • Congenital anomalies 	<p>Recorded by a xx</p> <p>Opportunity for medical record review – Yes/No</p>	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history <p>Information also included:</p>

	risk and explain data used to determine the rating.					magnitude of teratogenic risk, quality and quantity of the data, summary of teratology studies, key references. Retrieval of agent summaries can be done using domestic, international, generic, and proprietary names.
German Embryotox Pharmacovigilance Centre and database(133-135) Berlin Institute for Clinical Teratology and Drug Risk Assessment in Pregnancy	Since	Country Germany Population based – Yes/No Sample size >xxx births per year	Reporting via	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations 	Recorded by a xx Opportunity for medical record review – Yes/No	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history
Vaccine Safety Datalink (VSD) (136-141)	Since A collaboration between the Centers for Disease Control and Prevention's Immunization Safety Office and several large integrated healthcare systems in the USA, is one such system. The VSD	Country United States Population based – Yes Sample size >100,000 births per year	Reporting via	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations • Congenital anomalies 	Recorded by a xx Opportunity for medical record review – Yes/No	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history

	includes data on approximately 2.5 million reproductive age women and over 100,000 live births annually.					
World Health Organization Pregnancy Registry(142)	Since 2009 A prospective observational cohort study that enrolls pregnant women at their first antenatal visit to a selected health facility.	Country Africa, Asia, Latin America Population based – Yes/No Sample size >XXX births per year	Published and unpublished examination records of newborns, where women have been followed during pregnancy and newborns have undergone a physical assessment at or immediately after birth, including drug exposure data.	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations • Congenital anomalies 	<p>Recorded by a health provider or community nurse</p> <p>To obtain a more accurate medical and drug exposure history, early enrolment is desirable.</p> <p>Opportunity for medical record review – Unknown</p>	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history <p>In collaboration with the Making Pregnancy Safer Programme of WHO, the Global Malaria Programme and the HIV Programme.</p>
World Health Organization Central registry for epidemiological surveillance of drug safety in pregnancy	Since	Country Global Population based – Yes/No Sample size >XXX births per year	Reporting via	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations • Congenital anomalies 	<p>Recorded by a xx</p> <p>Opportunity for medical record review – Yes/No</p>	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history <p>The pooled data will only be</p>

						accessible to WHO, and the WHO will undertake periodic analysis of the data collected within the framework of signal detection.
Roche Global Safety database(143, 144)	Since	Country Global (established in Switzerland) Population based – Yes/No Sample size >XXX births per year	Reporting via	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations • Congenital anomalies 	Recorded by a xx Opportunity for medical record review – Yes/No	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history
European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC)(145)	Since	Country 13 European countries Population based – Yes/No Sample size >XXX births per year	Reporting via	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations • Congenital anomalies 	Recorded by a xx Opportunity for medical record review – Yes/No	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history
Hawai'i Pregnancy Risk Assessment Monitoring System (PRAMS)(146)	Since	Country Hawaii Population based – Yes/No Sample size	Reporting via	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations • Congenital anomalies 	Recorded by a xx Opportunity for medical record review – Yes/No	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid

		>XXX births per year				<ul style="list-style-type: none"> Over-the-counter medicines Reproductive history

Teratology Information Services

European Network of Teratology Information Services (ENTIS)	Varies by country	Country 31 centres within and outside Europe (Including Argentina and Brazil) Population based – No – self enrolment Sample size	Telephone interview with mother or healthcare provider	<ul style="list-style-type: none"> Live births Stillbirths Spontaneous losses Elective terminations 	Mother self-report – the mother is contacted shortly after the expected date of delivery	<ul style="list-style-type: none"> Smoking status Alcohol consumption Body mass index Socioeconomic status Co-morbidities Co-prescribing Folic acid Over-the-counter medicines Reproductive history <p>For specific prospective studies it is possible to request specific additional data collection</p>
Organization of Teratology Information Services/Specialists (OTIS)	Since 1990	Country Largely North America and Canada Population based – No – self enrolment Sample size	Telephone interview with mother or healthcare provider	<ul style="list-style-type: none"> Live births Stillbirths Spontaneous losses Elective terminations 	Mother self-report – the mother is contacted shortly after the expected date of delivery	<ul style="list-style-type: none"> Smoking status Alcohol consumption Body mass index Socioeconomic status Co-morbidities Co-prescribing Folic acid Over-the-counter medicines Reproductive history <p>For specific prospective studies it is possible to request specific additional data collection</p>

UK Teratology Information Service (UKTIS.org) pregnancy registry / database	Since 1983	Country UK Population based – No – spontaneous reporting /enrolment Sample size	Telephone interview and questionnaire follow-up through healthcare provider	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses (SA, IUD) • Elective terminations • GA at delivery • Birth weight • Congenital malformations • Neonatal complications • Genetic diagnoses 	Health care professional enquiry or report; follow up via questionnaire to healthcare professional shortly after the expected date of delivery Voluntary reporting by HCPs of longer term outcomes	<ul style="list-style-type: none"> • Maternal age • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Co-morbidities • Pregnancy complications • Co-prescribing • Folic acid • Over-the-counter medicines • Vaccination in pregnancy • Reproductive history • Family history <p>For specific prospective studies it is possible to request specific additional data collection</p>
California Teratogen Information Service (CTIS) (147)	Established 1983 Developed in 2007, the “CTIS Womb to Classroom Screening Program for the Detection of Agents with Adverse Effects on Neuropsychological Development” is the first program designed to identify agents not yet known to be of	Country United States (California) Population based – <input type="checkbox"/> Yes/No Sample size To date > 0,000 xxx per year	One to three additional telephone interviews during pregnancy to update exposure information and pregnancy events, a postpartum telephone interview, and, ideally, an appointment in which a dysmorphological examination is conducted.	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations (*birth outcomes captured, explicit list not found) 	Recorded by physicians Opportunity for medical record review <input type="checkbox"/> Yes/ No	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history

	concern.					
Terappel program (148)	Established 1984 by the Lyon pharmacovigilance centre, which was later made available to 18 other centres. Prospective cohort including about 30000 pregnant women exposed to medicines with known outcomes.	Country France Population based – Yes/No Sample size ~30,000 enrolments	Standardised questions at initial telephone contact and structured questionnaires after birth on drug-exposed pregnancies.	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations • Preterm birth • GA at delivery • Birth weight • Congenital malformations • Neonatal complications • Genetic diagnoses • Maternal complications 	Enrolment via participants' health providers and recorded at 8 days, 9 months and 24 months Opportunity for medical record review –Yes	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history <p>Demographic characteristics and medical history captured; BMI/ SES not directly mentioned.</p>
Paris Teratology Information Service (Centre de Référence sur les Agents Tératogènes) database(85, 148)	Since	Country France Population based – Yes/No Sample size To date > xxx per year	Standardised questions at initial telephone contact and structured questionnaires after birth on drug-exposed pregnancies.	<ul style="list-style-type: none"> • Live births • Stillbirths • Spontaneous losses • Elective terminations • Preterm birth • GA at delivery • Birth weight • Congenital malformations • Neonatal complications • Genetic diagnoses • Maternal complications 	Enrolment via participants' health providers. Opportunity for medical record review –Yes	<ul style="list-style-type: none"> • Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history <p>Demographic characteristics and medical history captured; BMI/ SES not directly mentioned.</p>

4 REGULATIONS GOVERNING THE USE OF SOCIAL MEDIA IN THE EU

There are currently no regulations governing the use of social media in the EU. The most popular method of recruiting patients is by promoting a study's Facebook page or website through paid text and image-based advertisements displayed on the news feed or side panel. Paid advertisements can be customized towards the interests, demographics, and location of the target population.

The EU General Data Protection Regulation (GDPR) will come into force on 25 May 2018. It will have implications for the collection and processing of all personal data and all researchers will need to comply with these new regulations.

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