# Evolving strategies for generating evidence on medication safety in pregnancy

Marianne Cunnington, GSK Epidemiology and on behalf of the ConcePTION consortium

# Disclaimer

- The speaker is an employee of GlaxoSmithKline (GSK) and holds stock in GSK
- The speaker is a member of the ConcePTION consortium and speaking on behalf of the broader consortium with content developed and approved by the ConcePTION Managing Board

The research leading to these results has received support from the EU/EFPIA Innovative Medicines Initiative [2] Joint Undertaking ConcePTION grant n° 821520

# Overview:

- Background: information gap
- Traditional approaches and their limitations
- Leveraging developments in real world evidence generation to fill the gap
  - Example of IMI ConcePTION

The research leading to these results has received support from the EU/EFPIA Innovative Medicines Initiative [2] Joint Undertaking ConcePTION grant n° 821520

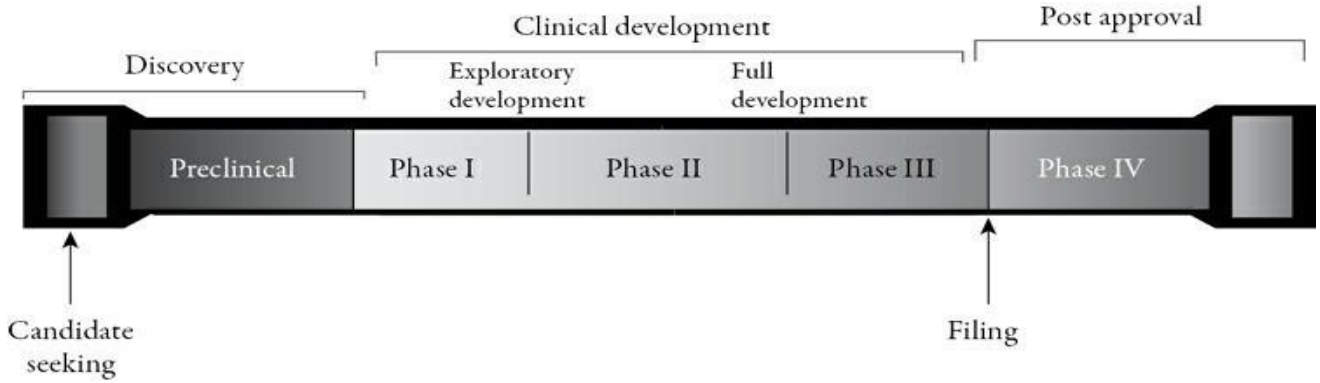
# The need for information on medication safety in pregnancy

- Globally 200 million women get pregnant each year, 5 million in EU
- Many women have chronic illness requiring continued medication use or become ill during pregnancy
- Medication use in pregnancy is high estimated at 57-97%* of pregnancies across European countries
- **But** the majority of newly approved medicines are of unknown teratogenic potential
  - 2011 EMA review found 94.6% products reviewed had restricted use in pregnancy and 71% had no information on use in pregnancy

Mosley JF 2nd, Smith LL, Dezan MD. *PharmPract (Granada)*. 2015;13(2):605. Arguello B,. Assessing the information in the Summaries of Product Characteristics for the use of medicines in pregnancy and lactation. Br J Clin Pharmacol. 2015;79(3):537–544. doi:10.1111/bcp.12515

The research leading to these results has received support from the EU/EFPIA Innovative Medicines Initiative [2] Joint Undertaking ConcePTION grant n° 821520

# Challenges in understanding medication safety in pregnancy




**Reproductive toxicology in animals**

**Reproductive safety in human**

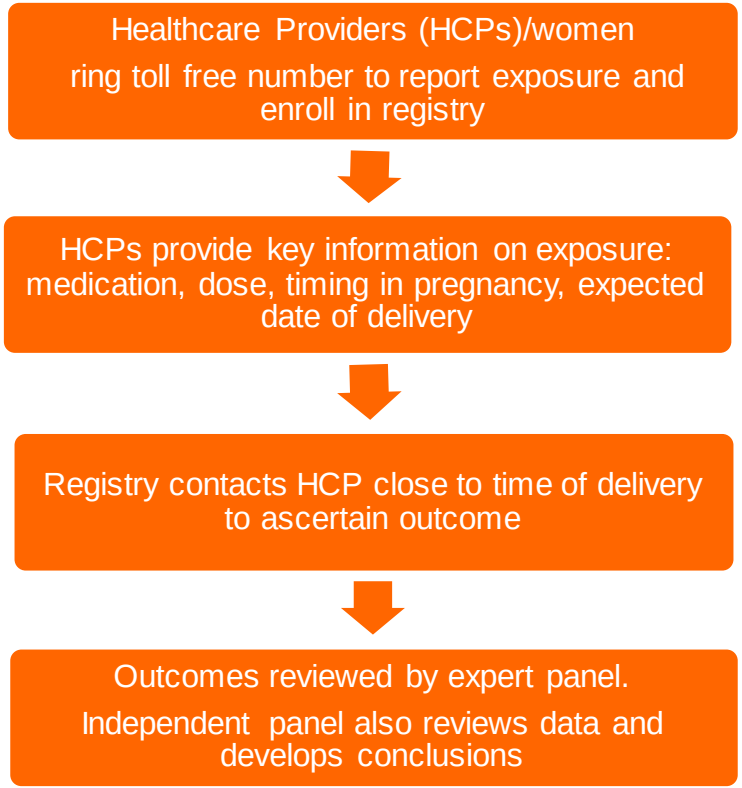
- Usually no pregnant wome actively included
- Follow-up of pregnancies occurs during trial

**Postmarketing:**
**Routine and additional Pharmacovigilance**
Routine pharmacovigilance
Epidemiology studies including:
**Pregnancy registries**
Prospective cohorts
Retrospective cohorts (routine health data)
Case control
Systematic reviews/meta analyses



The research leading to these results has received support from the EU/EFPIA Innovative Medicines Initiative [2] Joint Undertaki
ConcePTION grant nº 821520
https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-s5-r3-guideline

# Pregnancy registries approaches have evolved




**Methodological improvements over time:**

Internal comparator groups:
Unexposed
Exposed to other medications

Consent for medical record release

Collection of birth outcomes beyond malformations, including longer term follow up after birth

**But challenges remain:**

Voluntary enrolment linked to:

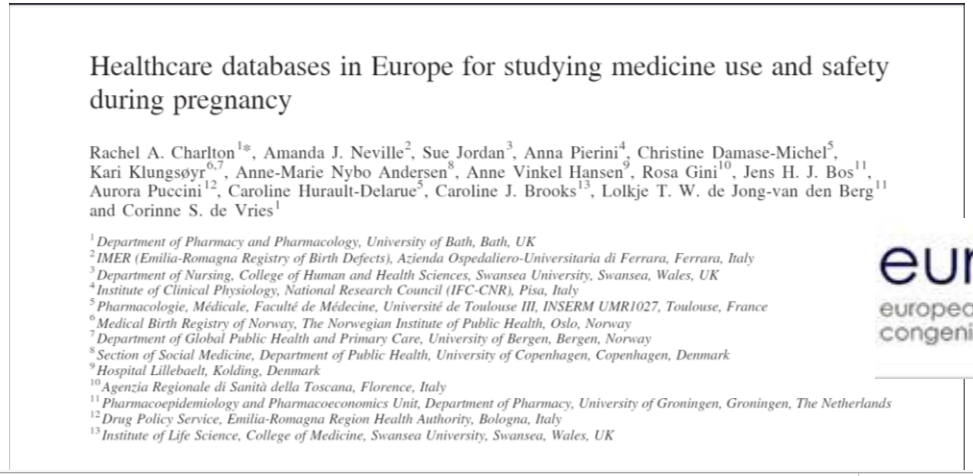
- Selection bias
- Low enrolment
- High loss to follow up
- Limited power to detect all but signal for major teratogenicity

# Variable experience from GSK sponsored pregnancy registries

| Drug registry<br><br>*(loss to FU)* | Date | Comparator | No. MBD | Total 1st trimester exposures | % MBD | 95% CI |
|---|---|---|---|---|---|---|
| **Antiretroviral**[1]<br>*(9.4%)* | 1/1/1989-1/31/2019 | Internal, other antiretrovirals | 271 | 9854 | 2.8% | 2.4-3.1% |
| **Lamotrigine**[1,2]<br>*(28.5%)* | 9/1/1992 – 3/31/2010 | None | 35 | 1558 | 2.2% | 1.6-3.1% |
| **Sumatriptan**[2]<br>*(23.8%)* | 1/1/1996-9/19/2012 | None | 20 | 478 | 4.2% | 2.6 -6.5% |
| **Bupropion**[2]<br>*(35.8%)* | 9/1/1997-3/31/2008 | None | 24 | 675 | 3.6% | 2.3-5.3% |
| ***Menveo***<br>*(0)* | 9/30/2014-present | None | 0 | 0 | 0 | 0 |

[1]Lamotrigine and Antiretroviral exclude chromosomal defects; [2] Registry is closed: data from final report

# Potential to leverage existing healthcare and surveillance datasources

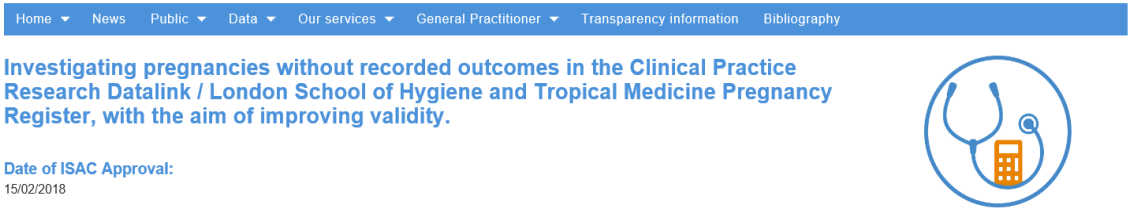


Healthcare databases in Europe for studying medicine use and safety during pregnancy

Rachel A. Charlton[1]*, Amanda J. Neville[2], Sue Jordan[3], Anna Pierini[4], Christine Damase-Michel[5], Kari Klungsøyr[6,7], Anne-Marie Nybo Andersen[8], Anne Vinkel Hansen[9], Rosa Gini[10], Jens H. J. Bos[11], Aurora Puccini[12], Caroline Hurault-Delarue[5], Caroline J. Brooks[13], Lolkje T. W. de Jong-van den Berg[11] and Corinne S. de Vries[1]

[1] Department of Pharmacy and Pharmacology, University of Bath, Bath, UK
[2] IMER (Emilia-Romagna Registry of Birth Defects), Azienda Ospedaliero-Universitaria di Ferrara, Ferrara, Italy
[3] Department of Nursing, College of Human and Health Sciences, Swansea University, Swansea, Wales, UK
[4] Institute of Clinical Physiology, National Research Council (IFC-CNR), Pisa, Italy
[5] Pharmacologie, Médicale, Faculté de Médecine, Université de Toulouse III, INSERM UMR1027, Toulouse, France
[6] Medical Birth Registry of Norway, The Norwegian Institute of Public Health, Oslo, Norway
[7] Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
[8] Section of Social Medicine, Department of Public Health, University of Copenhagen, Copenhagen, Denmark
[9] Hospital Lillebaelt, Kolding, Denmark
[10] Agenzia Regionale di Sanità della Toscana, Florence, Italy
[11] Pharmacoepidemiology and Pharmacoeconomics Unit, Department of Pharmacy, University of Groningen, Groningen, The Netherlands
[12] Drug Policy Service, Emilia-Romagna Region Health Authority, Bologna, Italy
[13] Institute of Life Science, College of Medicine, Swansea University, Swansea, Wales, UK

eurocat
european surveillance of congenital anomalies



Home | News | Public | Data | Our services | General Practitioner | Transparency information | Bibliography

**Investigating pregnancies without recorded outcomes in the Clinical Practice Research Datalink / London School of Hygiene and Tropical Medicine Pregnancy Register, with the aim of improving validity.**

**Date of ISAC Approval:**
15/02/2018

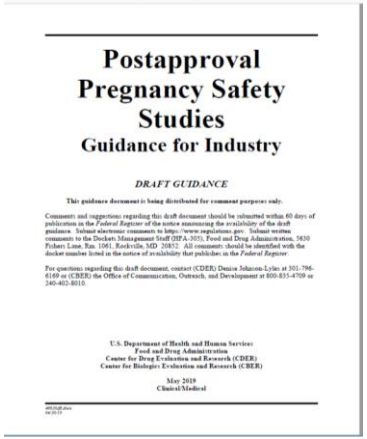
## Key strengths

- Large populations
- Objectively captured medication exposure
- Multiple exposures and outcomes exposures
- Potential for longer term follow up
- Internal comparators
- Information on confounders

## Some limitations

- Time lag
- % mother and babies linked
- Prescription medication only
- No outcome adjudication
- Completeness of some confounders e.g. smoking

# Different regulatory perspectives



Postapproval
Pregnancy Safety
Studies
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2019
Clinical/Medical

**Pregnancy registries remain an important tool for safety data collection in the postmarketing setting because of the prospective design and the ability to collect detailed patient level data**. However, because of the recurring challenges of achieving sufficient enrollment, **pregnancy registries generally are not sufficient by themselves to assess the safety of products during pregnancy;** therefore, other study methods capable of appropriately assessing the occurrence of specific major congenital malformations (MCMs) (e.g., birth defects and congenital anomalies) and other pregnancy outcomes are needed. In addition, **use of complementary approaches may help address the limitations inherent to a specific study design and provide greater confidence in the conclusions.**

HMA

EUROPEAN MEDICINES AGENCY

EMA/813036/2019 DRAFT FOR PUBLIC CONSULTATION
4 December 2019

Guideline on good pharmacovigilance practices (GVP)
Product- or Population-Specific Considerations III: Pregnant and breastfeeding women

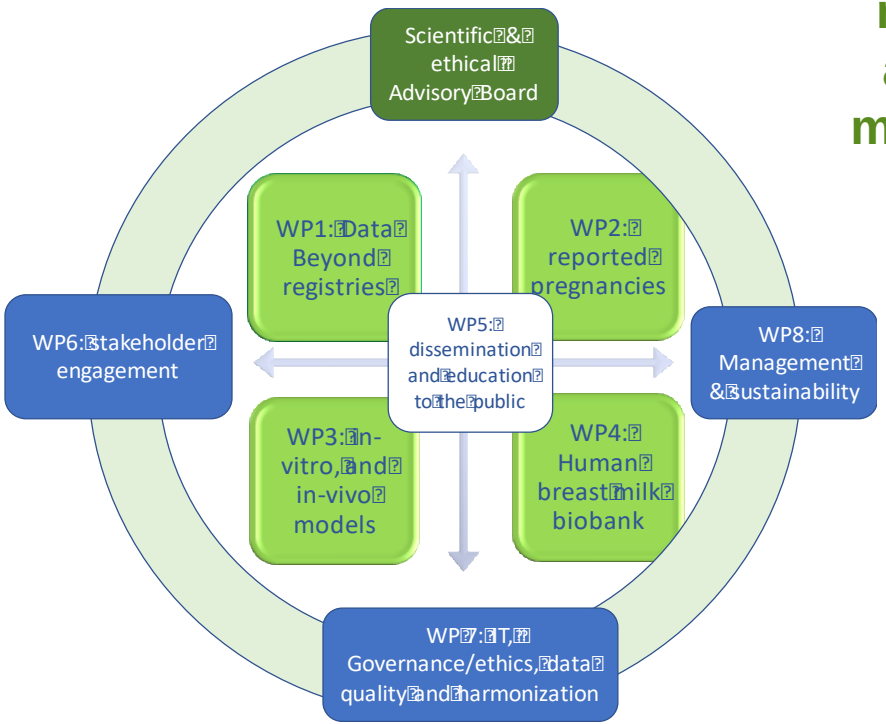
| | |
|---|---|
| Draft finalised by the Agency in collaboration with Member States | 19 November 2019 |
| Draft agreed by the EU Network Pharmacovigilance Oversight Group (EU-POG) | 29 November 2019 |
| Draft adopted by Executive Director | 4 December 2019 |
| Release for public consultation | 11 December 2019 |
| End of consultation (deadline for comments) | 28 February 2020 |
| Anticipated date for coming into effect after finalisation | Q4 2020/Q1 2021 |

Comments should be provided using this template. The completed comments form should be sent to

**Preferably and if feasible, epidemiological studies should be carried out using existing data sources (i.e. secondary data use)** and be designed in such a way as to minimise bias and confounding (see P.III.B.4.2.3.). Given the usually limited exposure to medicines in pregnancy and the low incidence of causally related adverse outcomes (see P.III.A.1.3.), it is usually necessary to include participants from more than one country in order to achieve adequate power.

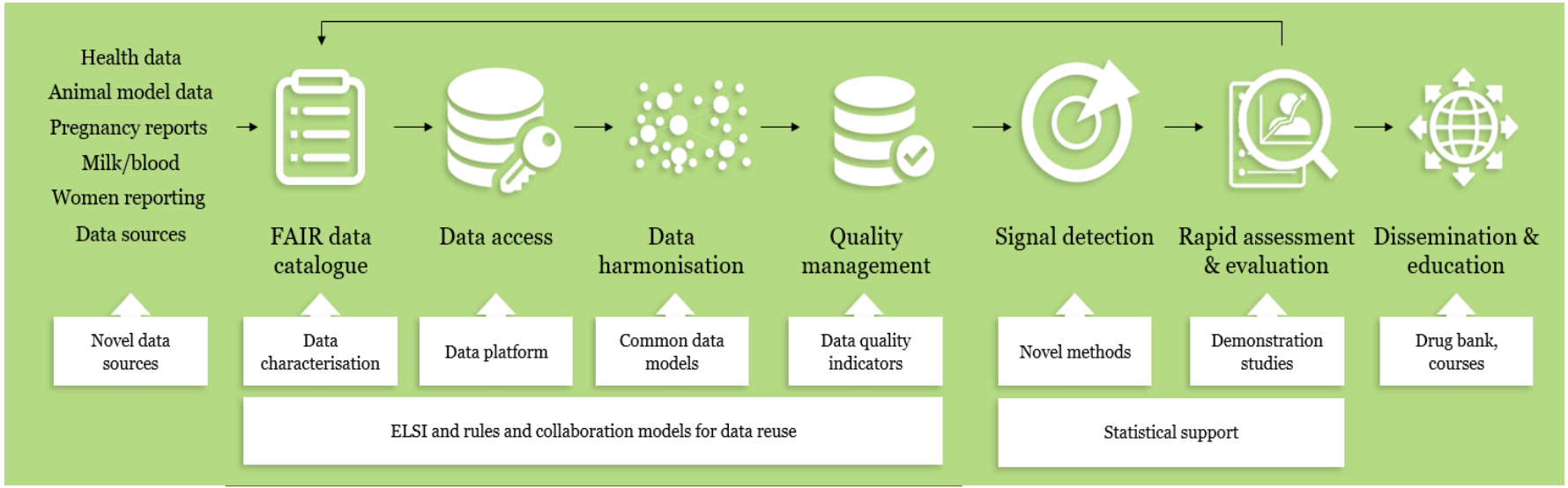
# IMI ConcePTION project:

Building and testing a pan-European ecosystem for **generating, monitoring, and providing robust and rapid real world evidence on medication safety in pregnancy and breastfeeding**




The research leading to these results has received support from the EU/EFPIA Innovative Medicines Initiative [2] Joint Undertaking ConcePTION grant n° 821520

# ConcePTION conceptual model




The research leading to these results has received support from the EU/EFPIA Innovative Medicines Initiative [2] Joint Undertaking ConcePTION grant n° 821520

# ConcePTION data catalogue

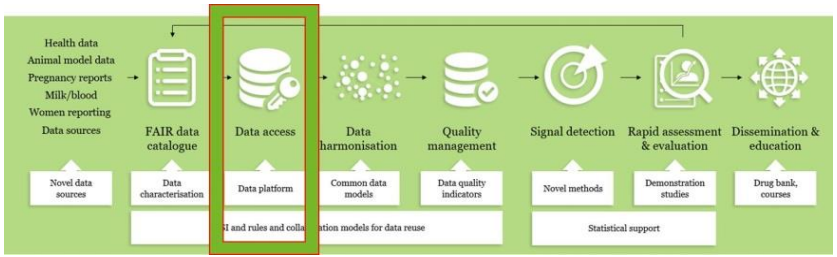

- **FAIR**: Findable Accessible Interoperable Re-usable (EU rules)

- **Catalogue features**
  - Meta-data (descriptors) of organization and datasource
  - Storage of documentation (dictionary/governance/ETL scripts)
  - Negotation service to contact data access providers for participation
  - Querying option of data quality indicators

The research leading to these results has received support from the EU/EFPIA Innovative Medicines Initiative [2] Joint Undertaking ConcePTION grant n° 821520

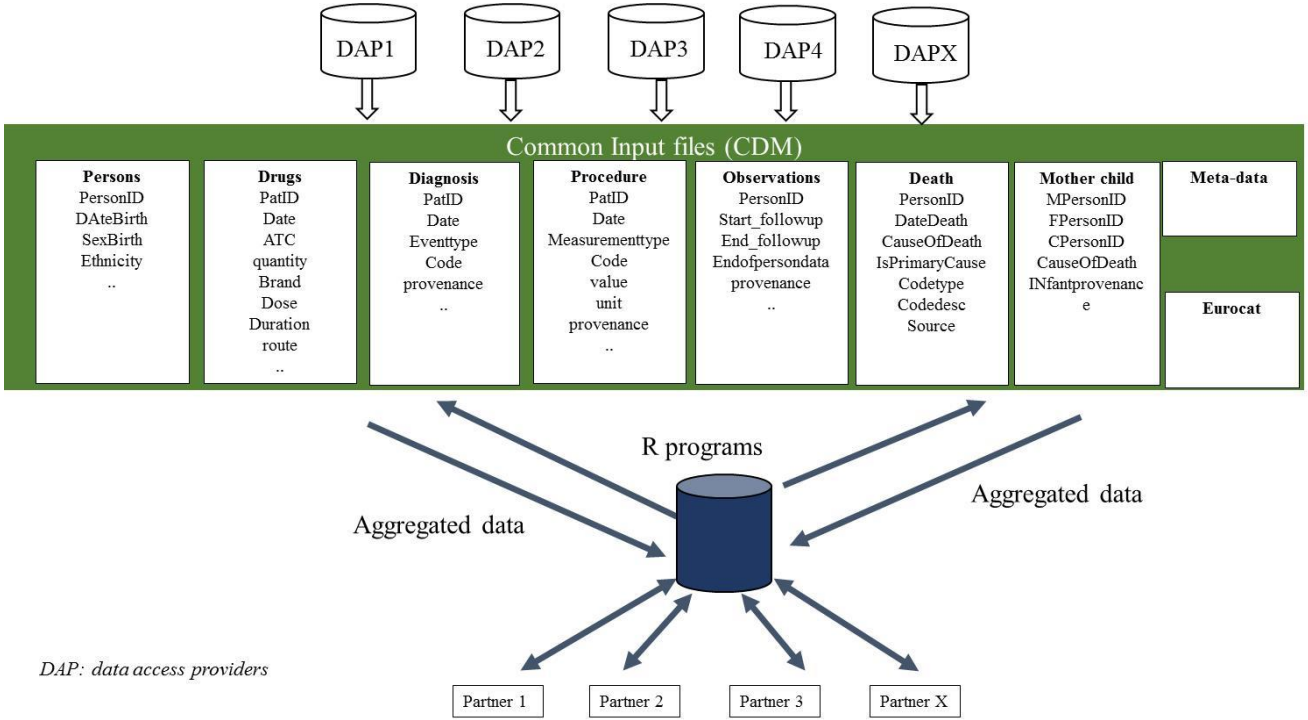
# ConcePTION data access

Organizations with access to relevant data sources (DAP) are being asked to participate




| Country | Area | Source pop. Size (million) | Total Births captured per year (thousands) | Type of data sources * |
|---|---|---|---|---|
| **Population based data sources** | | | | |
| Italy | Tuscany | 3.7 | 25 | Record linkage of regional/national health services data and registries |
| | Caserta | 0.9 | 6 | Record linkage of health services data |
| | Emilia Romagna | 4.4 | 35 | Record linkage of regional/national health services data and registries |
| Norway | Entire country | 5.4 | 60 | Record linkage of health insurance data and registries |
| Netherlands | Sample | 4.4 | 15 | Record linkage of health insurance data and registries |
| Denmark | Entire country | 5.6 | 60 | Record linkage of health insurance data and registries |
| UK | Scotland | 5 | 50 | Record linkage of medical records and registries |
| | Wales | 3.7 | 33 | Record linkage of medical records and registries |
| Spain | Catalunya | 5.8 | 40 | Record linkage of health insurance GP data and registries |
| | Valencian Region | 5 | 50 | Record linkage of health insurance and registries |
| Finland | Entire country | 1.9 | 60 | Record linkage of health insurance data and registries |
| France | Entire country | 66 | 700 | Health insurance, hospital data |
| | Haute Garonne | 1.4 | 10 | Cohort & linkage to health insurance data |
| Germany | sample | 16 | 100 | Health insurance data |
| Multiple countries | EUROmediCAT | Approx. 75 million | 750 000 | Congenital anomaly registries in EUROCAT surveillance |

# ConcePTION data & analytics harmonization

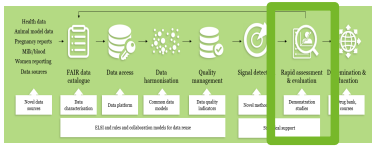




Low level CDM
Syntactic harmonization

Generation of variables (semantic harmonization) & results

The research leading to these results has received support from the EU/EFPIA Innovative Medicines Initiative [2] Joint Undertaking ConcePTION grant n° 821520

# Optimizing methods and demonstrating scientific robustness of ConcePTION approach



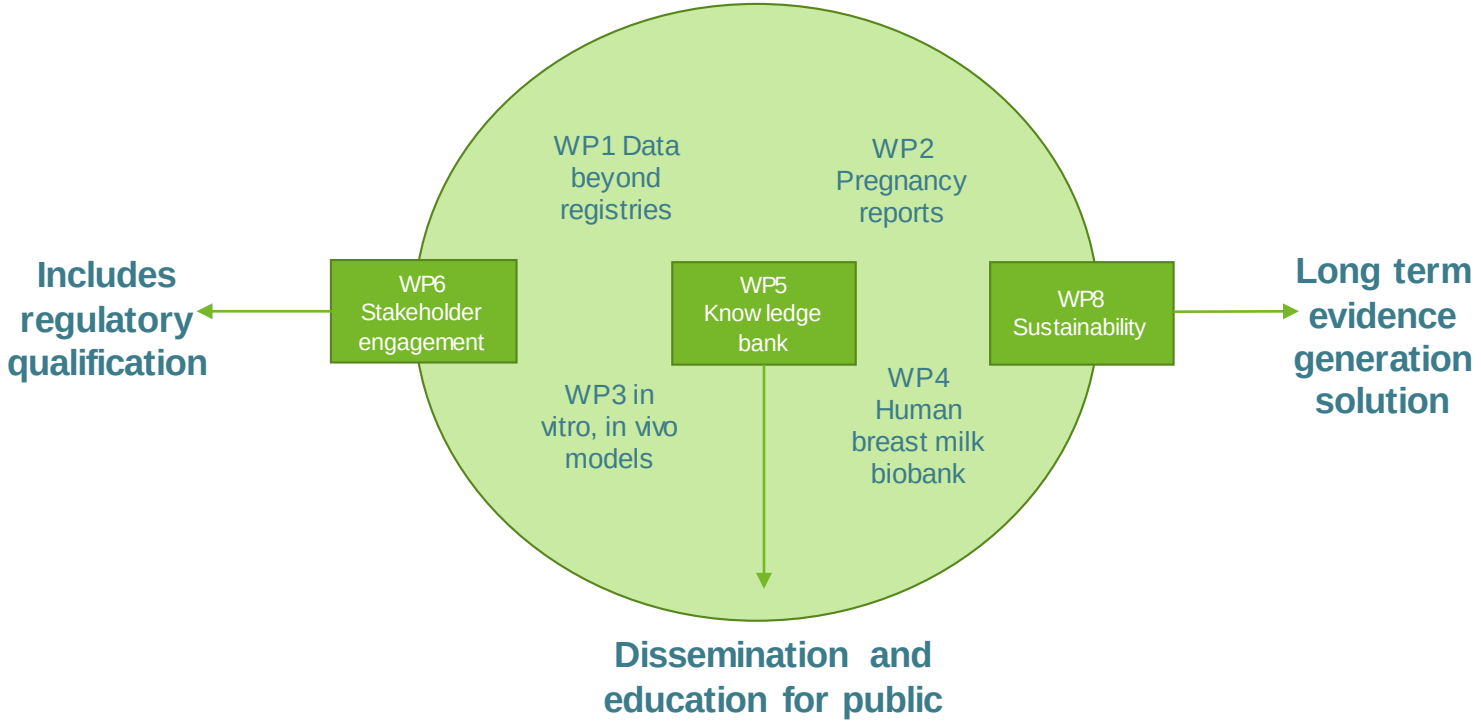
## PHARMACOEPIDEMIOLOGY DEMONSTRATION STUDIES

- For each area: Drug utilization, Disease impact and Medication Safety

| Therapeutic Area in Pregnancy | Methodology to be addressed |
|---|---|
| **Neuropathic pain** | Methods for controlling **confounding by indication** |
| **Mental Health Disorders (Psychotropics)** | Effect of time varying confounding factors on **long-term childhood outcomes** |
| **Multiple sclerosis and Systemic lupus erythematosus** | Novel statistics/Bayesian techniques to handle **small sample sizes/**rare disease |
| **Migraine** | Studying **intermittent medication exposures** for episodic manifestations during pregnancy |
| **Breast cancer** | **Accurate identification** of an incident case. |

The research leading to these results has received support from the EU/EFPIA Innovative Medicines Initiative [2] Joint Undertaking ConcePTION grant n° 821520

# Sustainable evidence generation to inform and empower choices of pregnant women




The research leading to these results has received support from the EU/EFPIA Innovative Medicines Initiative [2] Joint Undertaking ConcePTION grant n° 821520

# With thanks to ConcePTION?

- Management team:
  - Michael Steel, Miriam Sturkenboom, Pieter Stolk, Marie Teil
- Managing Board (WP leads):
  - Amanda Neville, Anja Geldof, Laura Yates, David Lewis, Isabelle Huys, Michele Bouisset-Leonard, Mats Hansson, Marie Teil, Stephanie Tcherny-Lessenot, Agnes Kant, Dipak Kalra, Christine Allan, Miriam Sturkenboom, Marianne Cunnington, Pieter Stolk, Ida Niklson, Hildrun Sundseth
    Participants:
  - > 200 persons from 88 organizations including the European Medicines Agency, drug manufacturers, academia, small medium enterprises, public health organizations, women's health and teratology networks

The research leading to these results has received support from the EU/EFPIA Innovative Medicines Initiative [2] Joint Undertaking ConcePTION grant n° 821520