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

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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

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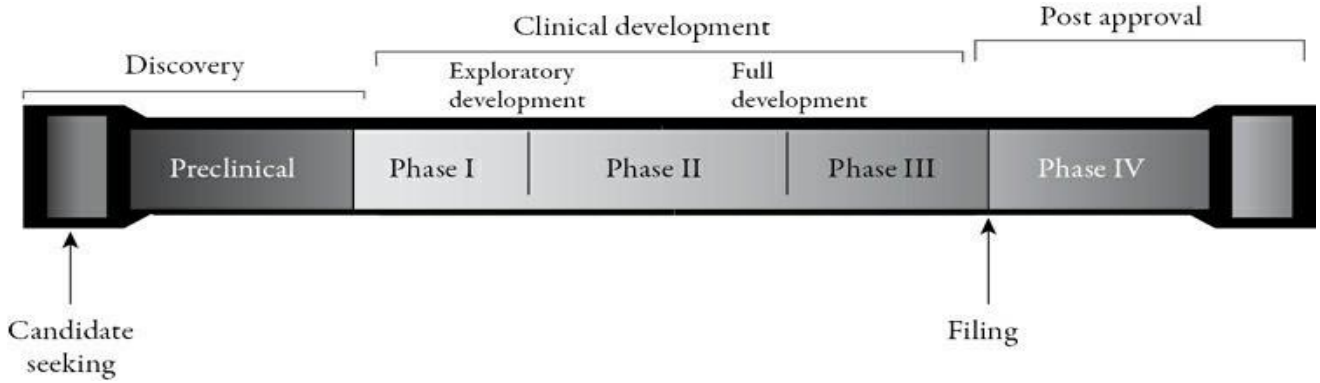
Challenges in understanding medication safety in pregnancy



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

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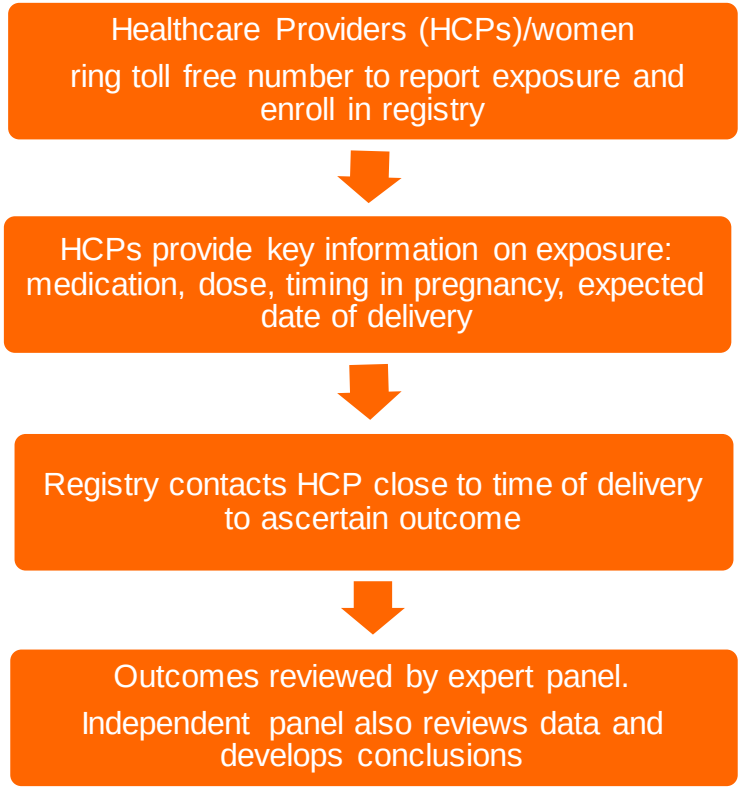
ConcePTION grant nº 821520
https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-s5-r3-guideline

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:

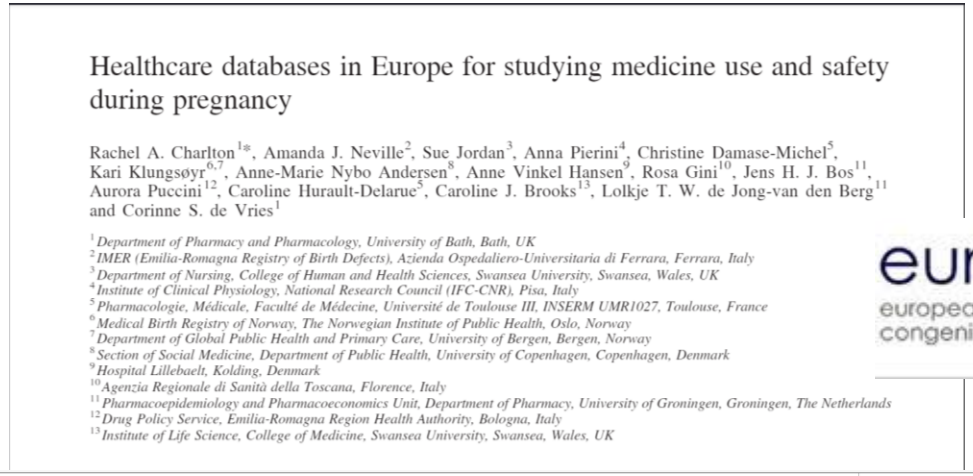
- Selection bias
- Low enrolment
- High loss to follow up
- Limited power to detect all but signal for major teratogenicity

Variable experience from GSK sponsored pregnancy registries

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

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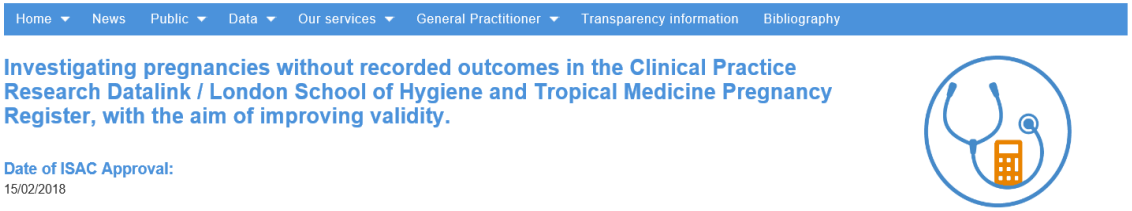
[8] Section of Social Medicine, Department of Public Health, University of Copenhagen, Copenhagen, Denmark
[9] Hospital Lillebaelt, Kolding, Denmark
[10] Agenzia Regionale di Sanità della Toscana, Florence, Italy
[11] Pharmacoepidemiology and Pharmacoeconomics Unit, Department of Pharmacy, University 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



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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

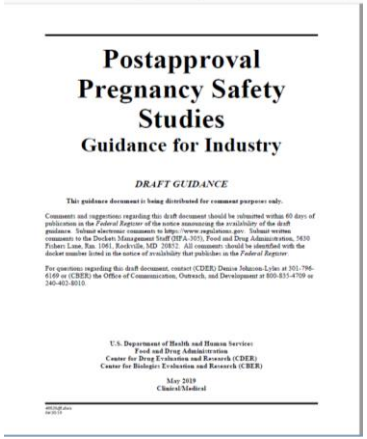
Key strengths

- 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

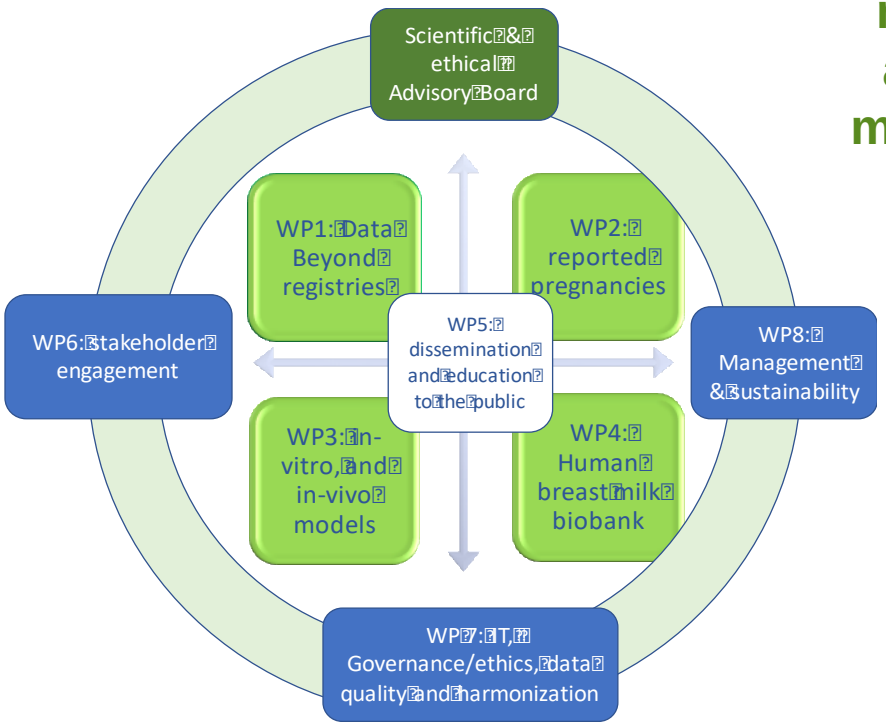
Draft finalised by the Agency in collaboration with Member States	19 November 2019
Draft agreed by the EU Network Pharmacovigilance Oversight Group (EU-POG)	29 November 2019
Draft adopted by Executive Director	4 December 2019
Release for public consultation	11 December 2019
End of consultation (deadline 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**



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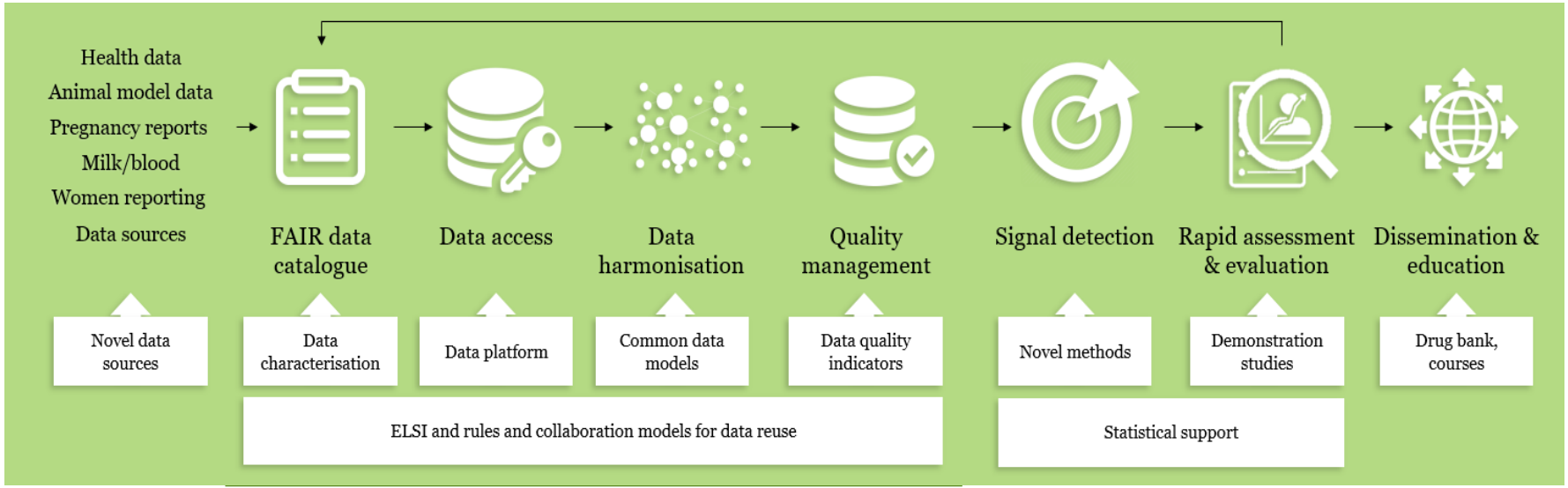
ConcePTION conceptual model



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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

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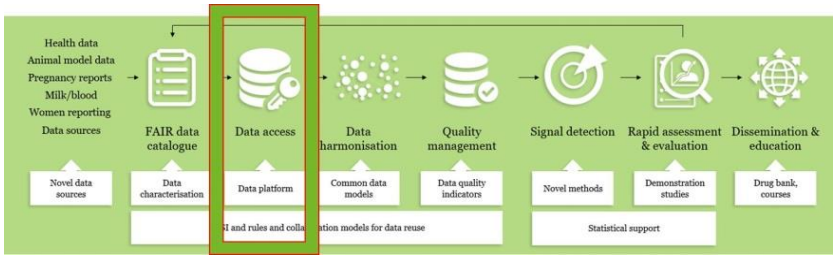
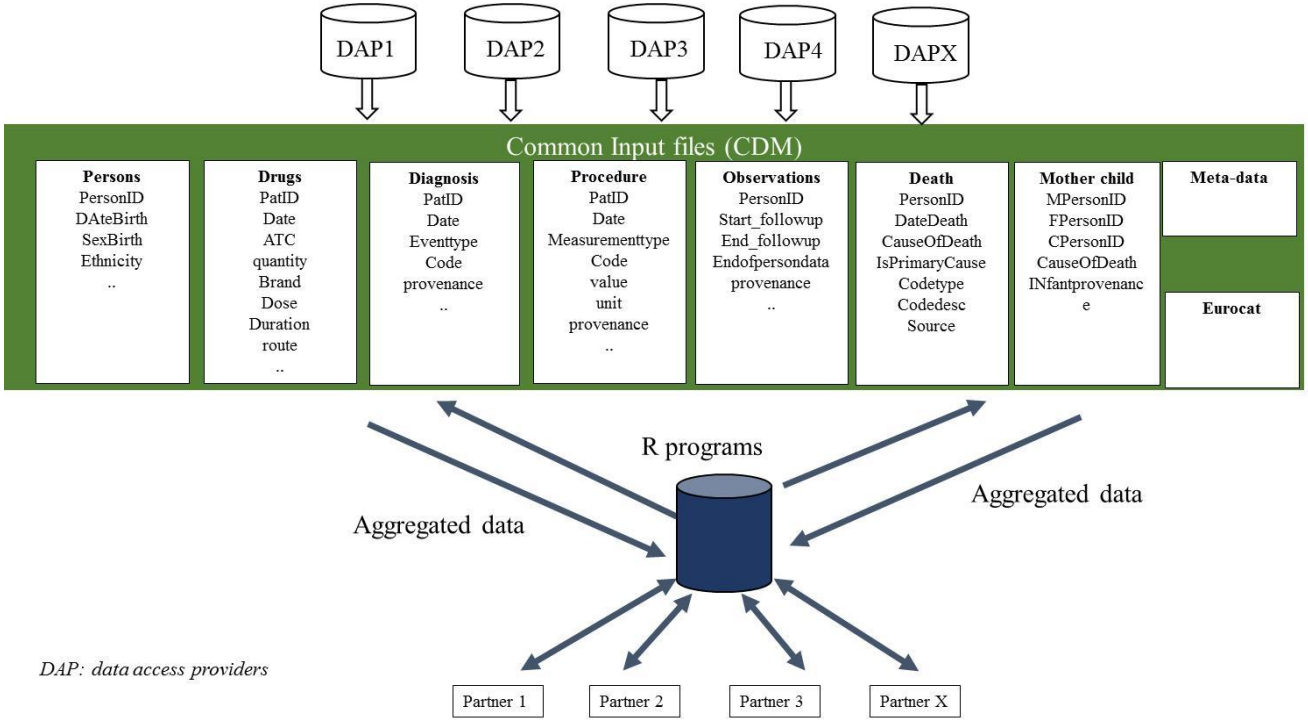
ConcePTION data access

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

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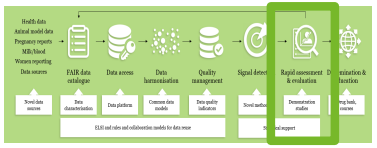
Optimizing methods and demonstrating scientific robustness of ConcePTION approach



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.

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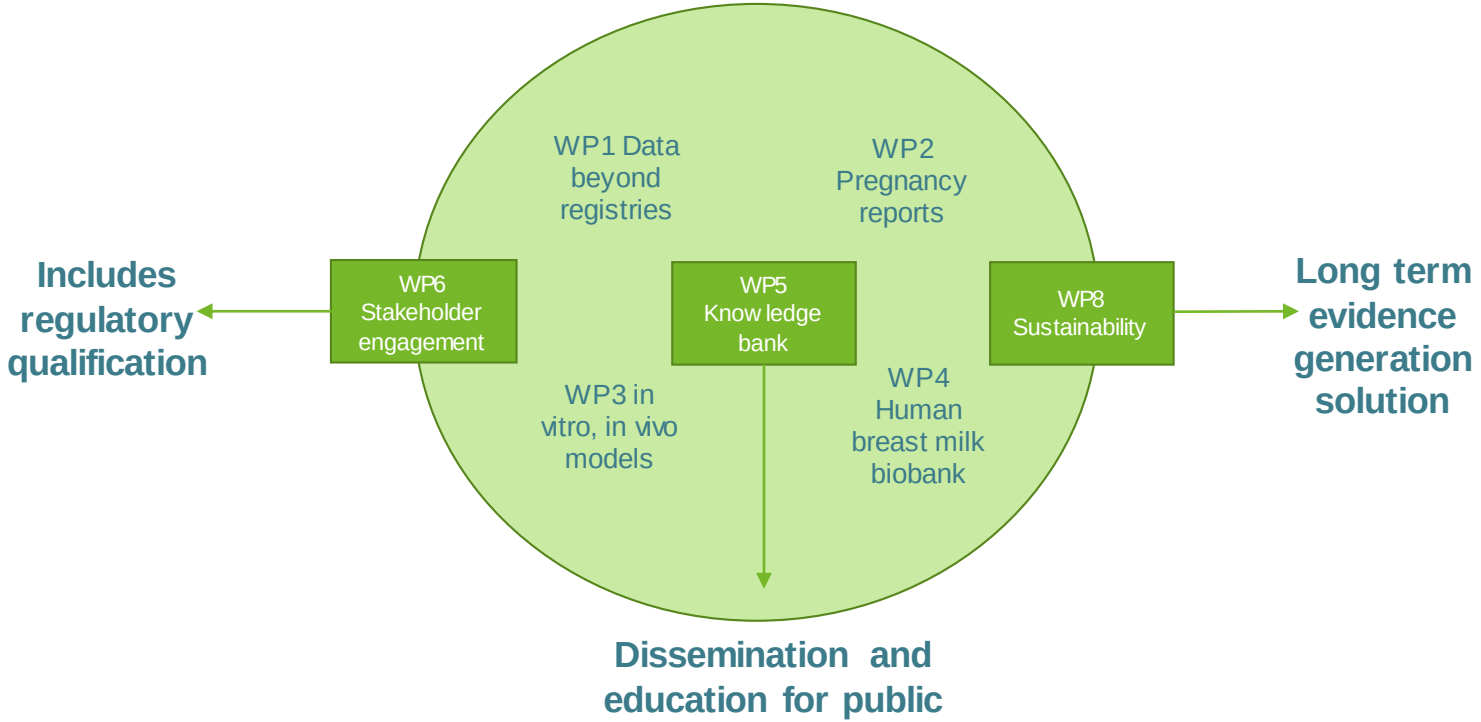
Sustainable evidence generation to inform and empower choices of pregnant women



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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

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