# *How to achieve a paradigm shift in clinical research and practice:*

## Challenges and opportunities
(60 years after thalidomide)

Helen Dolk, September 2020

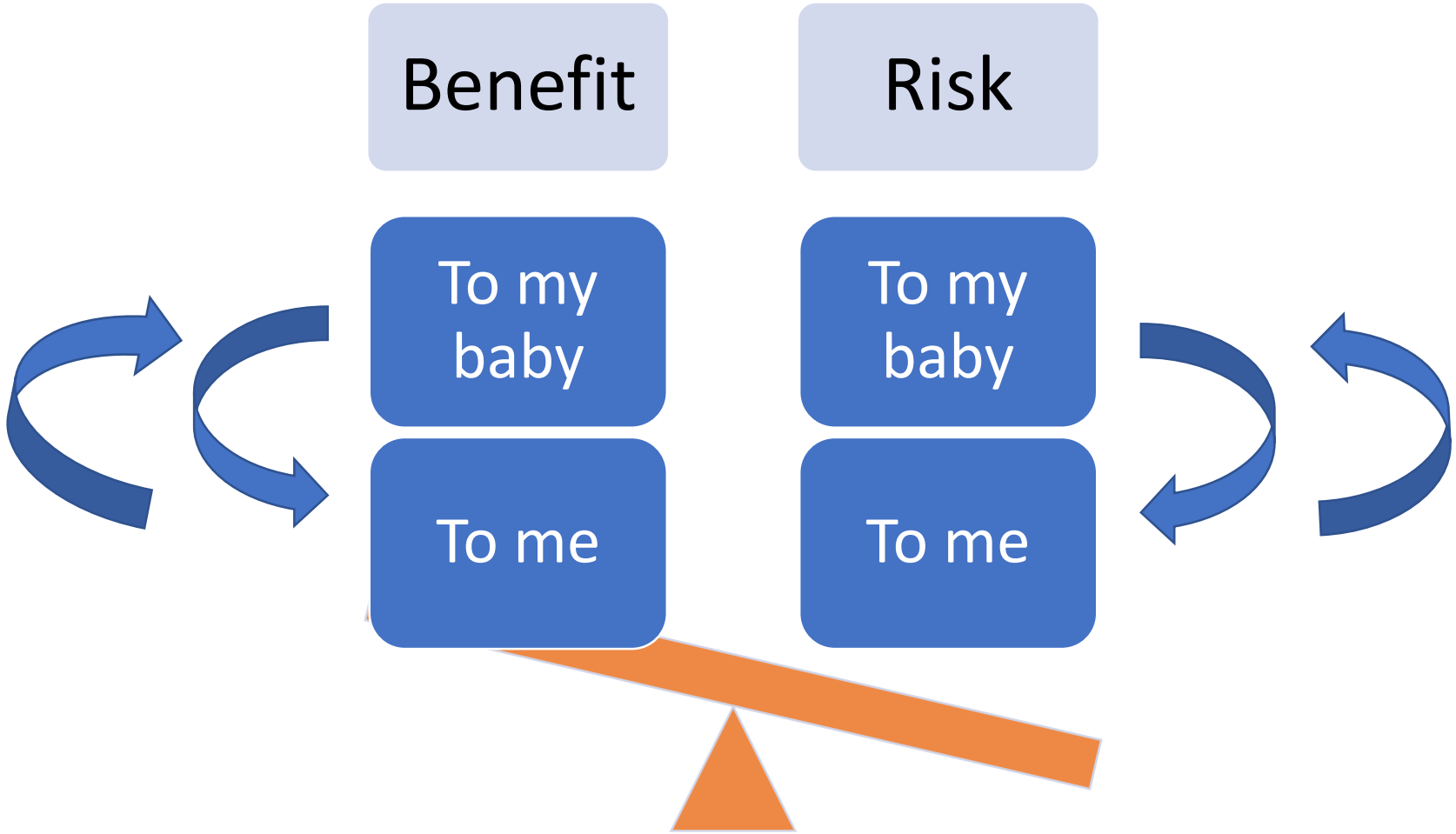
Ulster University

euromedicat

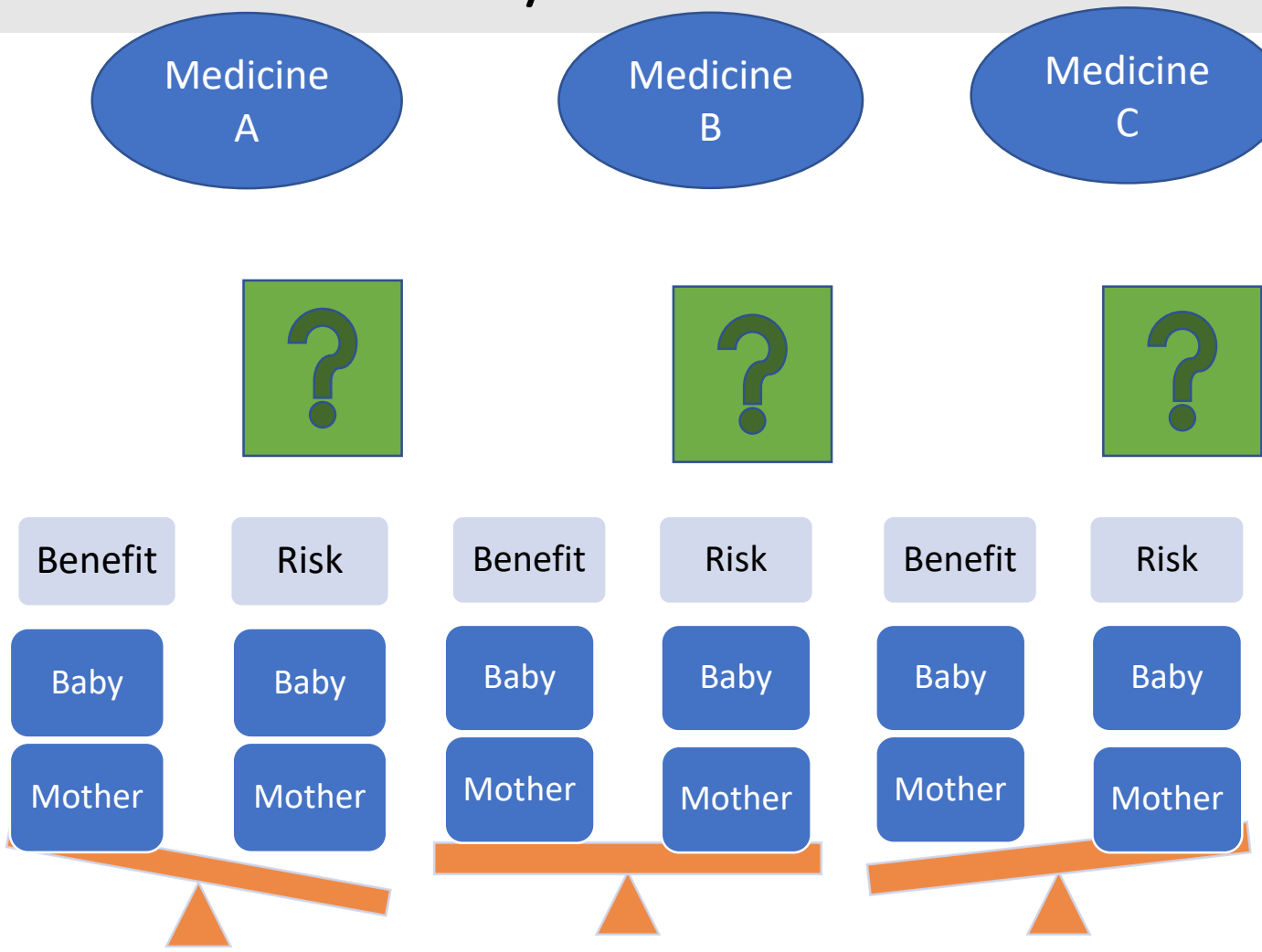
“We reviewed the safety during pregnancy of 172 drugs approved by the US Food and Drug Administration (FDA) from 2000 to 2010 …..We also reviewed safety information for 468 drugs approved by the FDA from 1980 to 2000 …..The teratogenic risk in human pregnancy was "undetermined" for 168 (97.7%) of drug treatments approved between 2000 and 2010. Furthermore, the amount of data available regarding safety in pregnancy was rated as "none" for 126 (73.3%) of these drugs. …….The mean time for a treatment initially classified as having an "undetermined" risk to be assigned a more precise risk was 27 years. The lack of information needed to assess the safety of drug treatments during human pregnancy remains a serious public health problem. A more active approach to post-marketing surveillance for teratogenic effects is necessary.”

Adam MP, Polifka JE, Friedman JM: Evolving knowledge of the teratogenicity of medications in human pregnancy. *Am J Med Genet C Semin Med Genet.* 2011;157C(3):175–82. 10.1002/ajmg.c.30313

# Benefit-risk of a medicine for a pregnant woman



# Benefit-risk of all options to treat disease/condition X



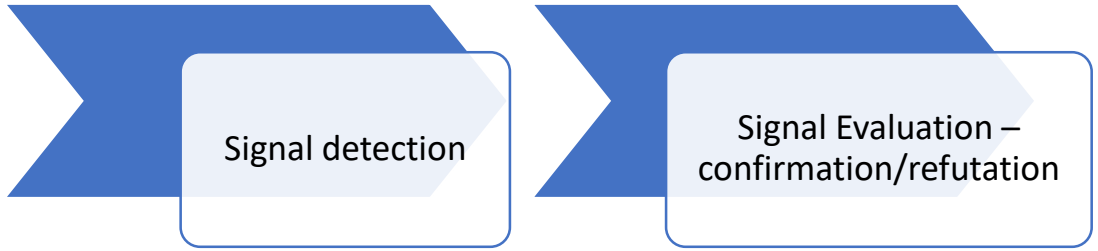
Evidence generation

Academic, clinical and Industry

Evidence dissemination and access/Risk minimization measures

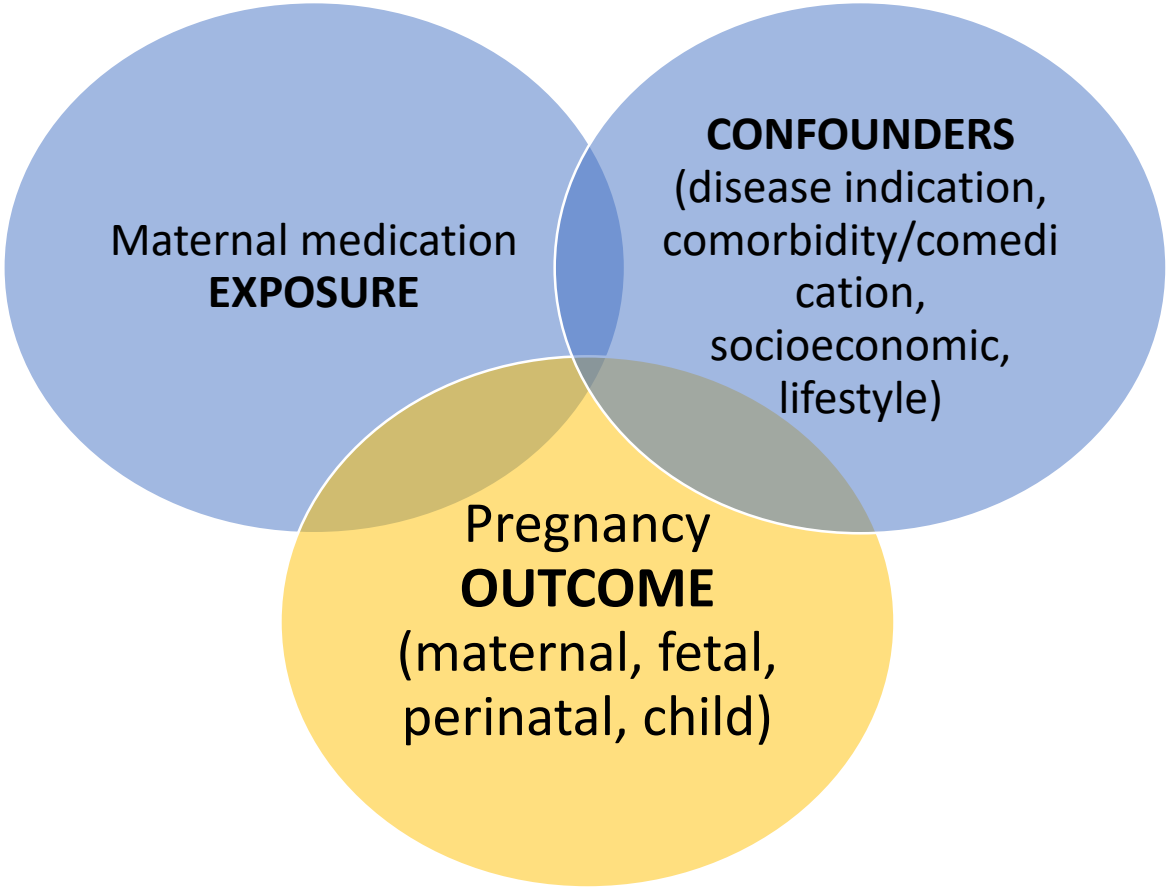
HCPs
Women

# Evidence Generation

# Evidence Generation

## Types of information




## Population size (statistical power)

e.g.

antiepileptic drug used in 1 per 1000 pregnancies

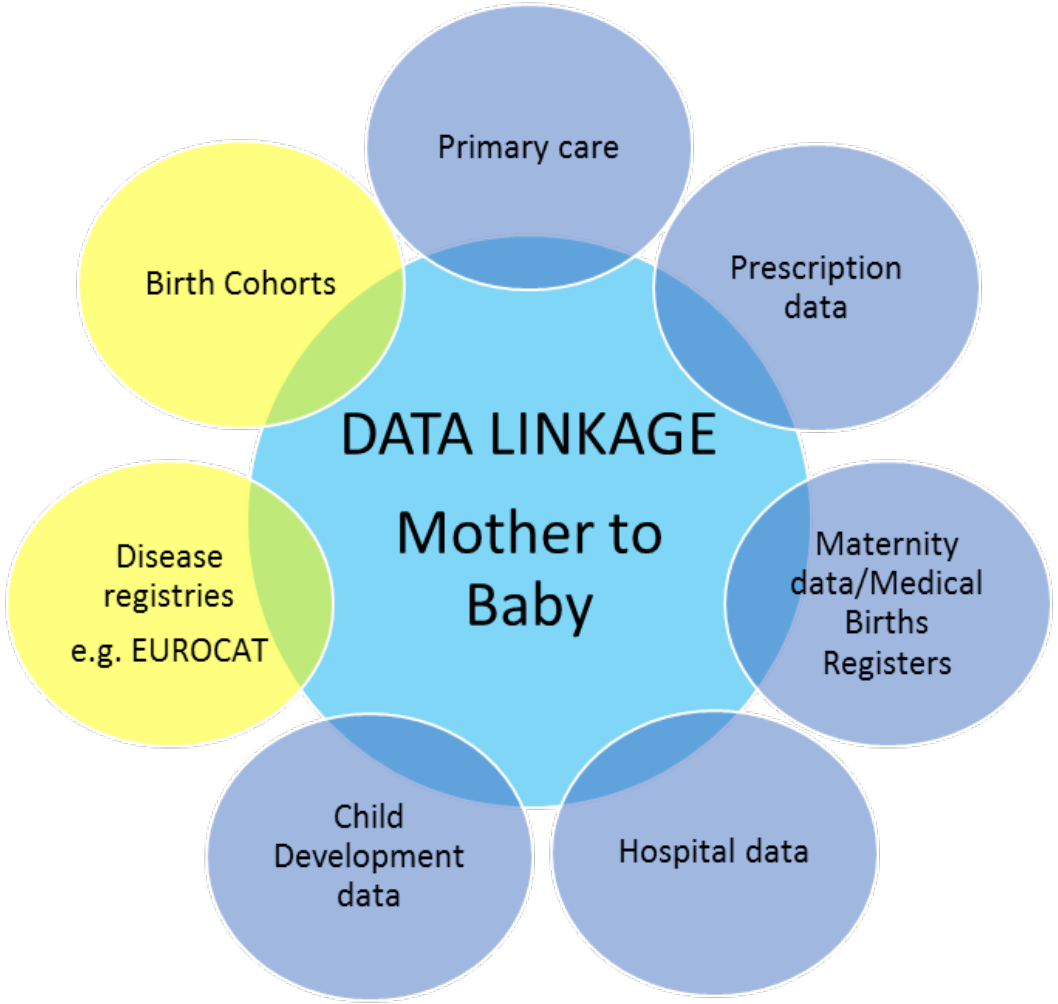
Spina bifida baseline risk (<) 1 per 1,000 pregnancies

➢5-fold risk of spina bifida = 5 per million pregnancies

- ***multinational networking***
- ***no perfect data source, multiple approaches***

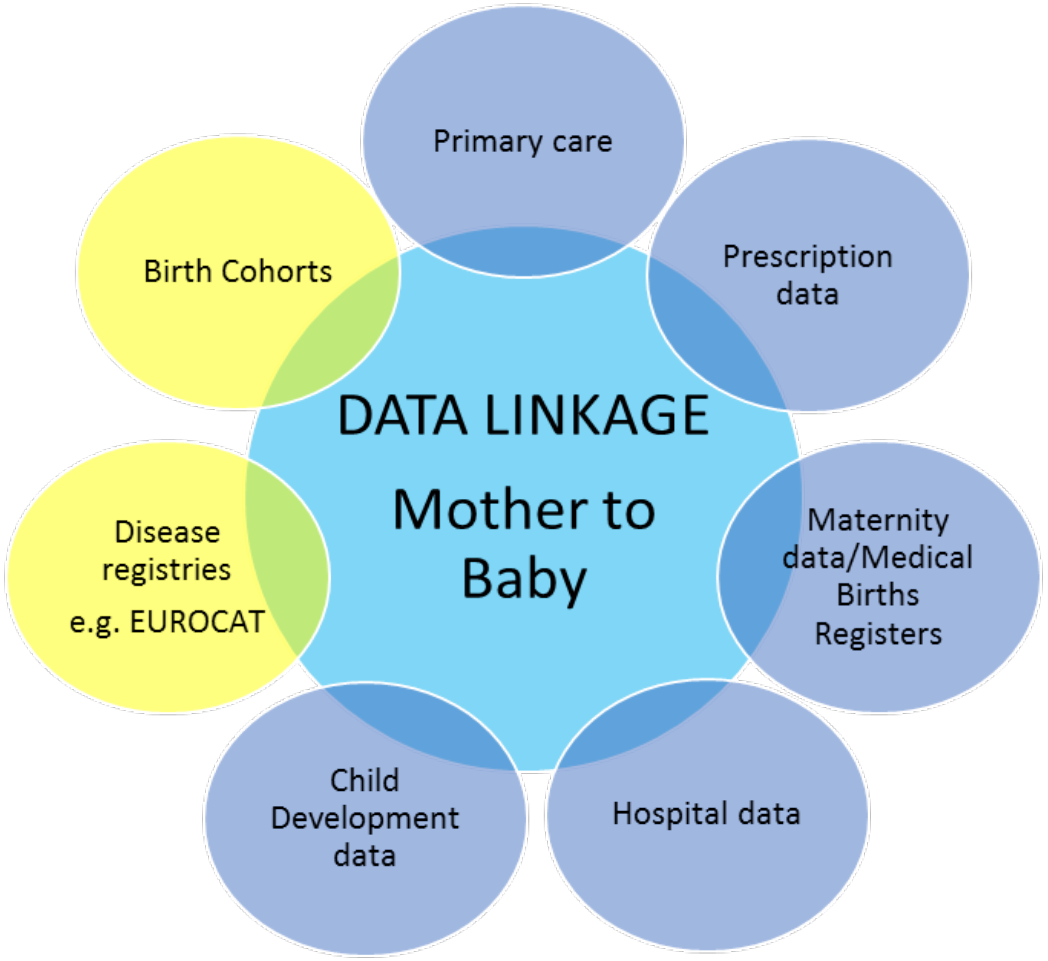
# Secondary use of Existing data ("Big data")

- Types of data source



# Secondary use of Existing data

- Types of data source




**Opportunities:**

Mother to baby linkage spine in each country

Hospital Prescriptions

Dose

# Secondary use of Existing data

- Types of data source

**Challenges:**

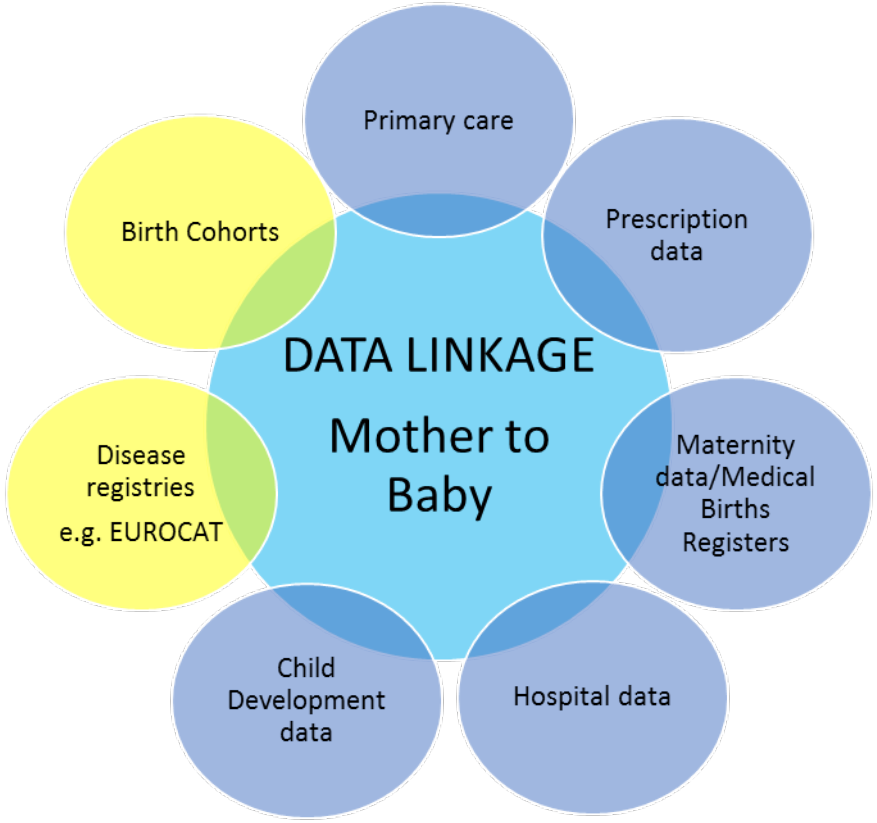
spontaneous abortions

Neurodevelopmental outcomes

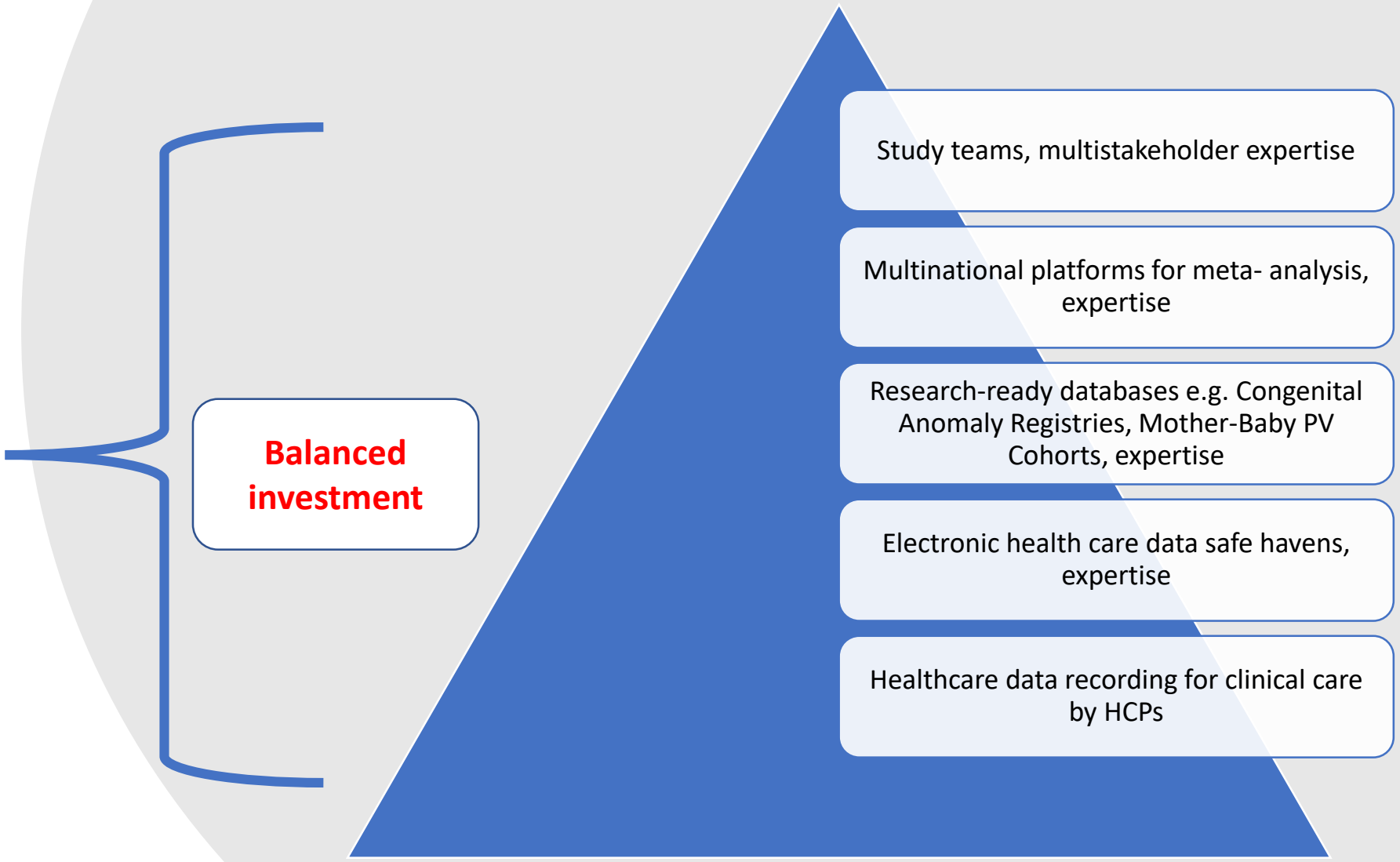
OTC drugs

Actual use/dose/timing

Exposure to outcome delay

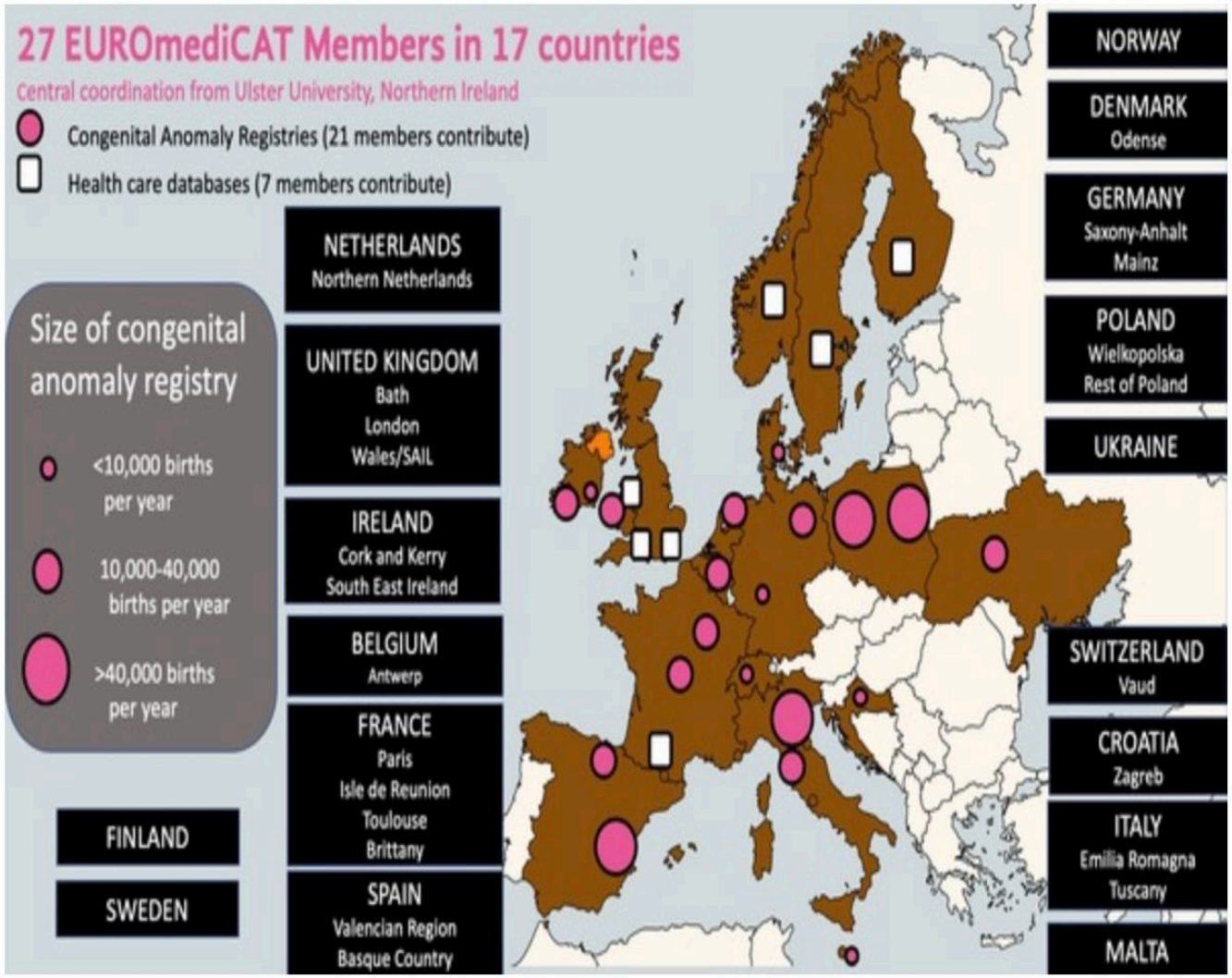


# Secondary use of Existing data



euromedicat

**www.euromedicat.eu**




- population-based congenital anomaly registries (including TOPFA and late diagnosed)
- + other pregnancy outcomes
- central database (750,000+births/year) and distributed data systems
- monitoring over time (EUROCAT, 30%EU)
- Case-control and cohort studies
- Signal detection studies using central database
- Antiepileptics, Antidepressants, antidiabetics, antiasthmatics, antibiotics, beta blockers, *sex hormones, multiple sclerosis, SLE, migraine, neuropathic pain……*
- Funding: EU FP7, EMA (via EUROmediSAFE), IMI (via ConcePTION), other

# Evidence Generation

| Primary data collection | Secondary use of existing data |
| --- | --- |
| Rapid real time collection as exposures occur | Often delays in availability |
| Smaller populations;  complex bespoke data | Very large populations; some data gaps |

**Hybrid**

# Primary Data Sources

| | |
|---|---|
| Spontaneous Adverse Event Reports (signal detection) | • Poor rate of reporting, poor knowledge of what to report, non-specific outome data, subject to bias |
| Pregnancy Exposure Registries | • Clinically led e.g. Epilepsy<br>• Teratogen Information Services (ENTIS)<br>• Industry pregnancy registries (single product) |
| Direct to consumer cohorts | • Use of apps, hybrid<br>• Issues of trust, confidentiality, data quality, counselling |

**Opportunities:**

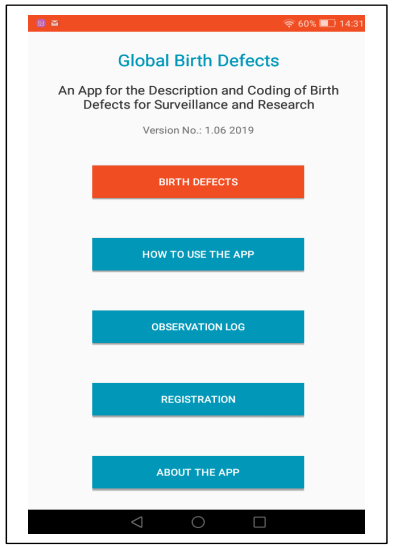
Technology (apps)

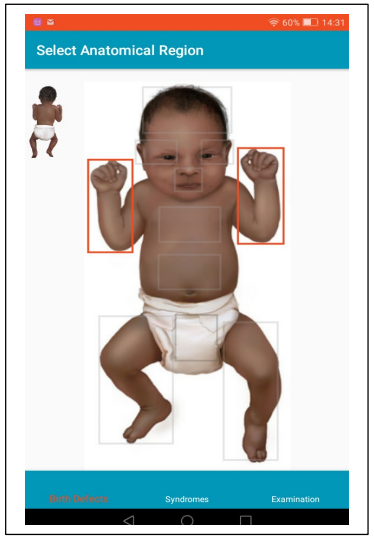
Improve and standardise reporting (IMI ConcePTION recommendations)

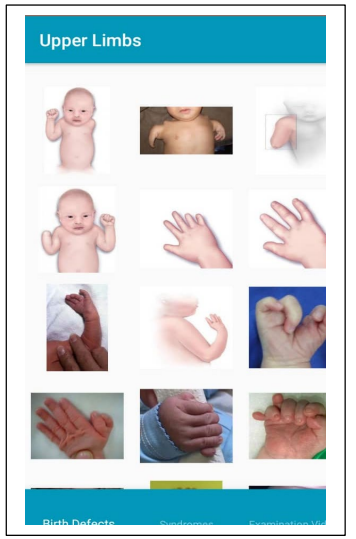
National pregnancy registries (single point of contact) for red zone and complex/rare exposures, ?mandatory reporting, European networking

# Global Birth Defects App

https://globalbirthdefects.tghn.org/download-birth-defects-surveillance-app/





# Evidence Generation: Scientific challenges

- Surrogate endpoints for earlier evaluation of outcomes
- Confounding by indication + other confounding
- Signal detection methods to increase sensitivity and specificity
- Drug interactions
- Treatment switching
- Paternal exposure
- Epigenetic  mechanisms
- Intergenerational effects (e.g. DES)
- Genetic factors & Personalised medicine

# Evidence Generation: System aspects

- System of signal detection and signal evaluation (confirmation/refutation)

- Responsibilities of stakeholders
  - Industry, regulators, patients, HCPs, academics
  - EncePP Code of Conduct for Scientific Independence and Transparency http://www.encepp.eu/code_of_conduct/index.shtml

- Funding
  - EncePP proposal - funding pregnancy pharmacovigilance by levy of pharma companies
    - Gain efficiencies in data collection and infrastructure
    - More disease-based analysis

# Evidence Dissemination (Risk reduction)

- HCP awareness and education

- Trusted portals for information & counselling
  - ENTIS network www.entis-org.eu
  - Opportunity: Prototype for single European knowledge bank : IMI ConcePTION
  - Bridge to the disease/condition-based benefit-risk approach
    - the Ondansetron debate

- Appropriate prescribing
  - prescribe medicines of benefit (proven efficacy)
  - Preconception care: start awareness and medication choice **prior to pregnancy** for chronic conditions

- Role of PILS/SPCs in signposting the above
- Emerging concerns: internet purchase e.g isotretinoin

- www.imi-conception.eu
- **Public-private partnership**
  - Project funded by the EU Innovative Medicines Initiative (IMI)
  - Co-led by Novartis and University Medical Center Utrecht
  - >200 researchers from 88 institutions including the European Medicines Agency, drug manufacturers, academia, small medium enterprises, public health organizations, women's health and teratology networks
  - Participation of EUROmediCAT, ENTIS and other networks
- **Duration**:
  - April 1, 2019-March 31, 2024
- **Methodologies and infrastructure development for evidence generation and dissemination, for pregnancy and lactation:**
  - use of existing data, including guidelines and informatic platform
  - primary data collection
  - European knowledge bank
  - pre-clinical models for lactation
  - European milk bank

https://www.imi.europa.eu/projects-results/project-factsheets/conception

# The paradigm shift

- EMA strategy: Raise ambition and targets for safety evidence availability and phasing

- Create regulator-healthcare bridge
  - from single product evaluation of safety to disease-based benefit-risk evidence

- Efficient diverse data collection and analysis
  - Avoid duplication of data collection while allowing diversity of data sources
  - Use new technological opportunities (electronic healthcare data, apps) without expecting technology to be a panacea
  - Address the data and scientific challenges

- Funding:
  - balanced and increased investment
  - Consider levy to pharma industry for pregnancy pharmacovigilance