# Studying paternal drug exposures and offspring outcomes: feasibility assessment of large European databases

**EPH220**

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## INTRODUCTION

Recent studies highlighted the importance of investigating the safety of paternal drug exposures with respect to offspring health.

A new PASS (TANGO) aims to further investigate the risk of neurodevelopmental disorders and major congenital malformations in offspring of fathers exposed to valproate (VPA), an anti-seizure medication (ASM), before conception: large databases are needed for sufficient statistical power and generalizability.

Abstract

## OBJECTIVE

**To assess the fitness for purpose of large European databases in the SIGMA Consortium for estimating the effect of paternal drug exposures on offspring health.**

SIGMA CONSORTIUM

The hub for real-world evidence studies

The SIGMA Consortium is the European hub for real-world evidence generation (https://sigmaconsortium.eu/). This collaborative research initiative was assembled to enable multi-country studies using common analyses to study responses to treatments in large populations.

## METHOD

Mother-father-offspring linkage was assessed in 11 relevant data sources to determine:

- Availability & completeness of mother-father-offspring link for live and non-live birth outcomes
- Key information relevant to the TANGO objective and its methodological challenges

### Data sources

- **Denmark** - Danish Registries
- **Finland** - Finnish Registries
- **France** - French Nationwide Healthcare Claims Database (SNDS)
- **Germany** - German Pharmacoepidemiological Research Database (GePaRD)
- **Italy** - ARS Toscana, THIN, Caserta Regional Database
- **Netherlands** - PHARMO Data Network
- **Norway** - Norwegian Registries
- **Scotland** - Scottish Prescribing Information System
- **Spain** - The Information System for the Development of Research in Primary Care (SIDIAP)
- **Sweden** - Swedish Registries
- **UK** - Clinical Practice Research Data Link (CPRD Aurum). *CPRD's assessment was based on a literature review*


**Figure 1 – Feasibility in 11 European countries**

## RESULTS

### Infant-father-mother linkages

**All databases have an established mother-infant linkage.**

**Table 1** presents all data sources where **father-infant linkage is available.**

Father-infant linkages are **available (or potentially available, CPRD Aurum) for all data sources included in this feasibility study except French, Italian, Scottish and Spanish data sources** which either do not have the linkage or would not have it in time to participate in the TANGO study**.** A separate feasibility was performed in France by EPI-PHARE, the ANSM-CNAM group (French national drug and insurance agencies) and communicated at EMOIS Conference March 21st, 2025.

**Table 1 – Father-infant linkage characteristics in data sources where it is available**

| | Danish Registries | Swedish Registries | Norwegian Registries | CPRD Aurum | GePaRD | Finnish Registries | PHARMO Data Network |
|---|---|---|---|---|---|---|---|
| Years of availability | 1995-2022 | 2005-2023 | 2010-2023 | 2003-2023 | 2004-2022 | 1995-2023 | 2000-2023 |
| Father-infant linkage rate for live birth outcomes | >90% | >90% | >90% | 50-70% [1] | 25% [1] | >90% | >20% |
| Father-infant linkage rate for non live birth outcomes | >90% | No | >90% | Unknown | Unknown | Unknown | No |
| Method used to link the father and infant | Direct via paternal identifier | Direct via Swedish Tax Agency | Direct via national ID | Deterministic algorithm using Household ID and GP Practice ID | Direct via health insurance ID | Direct via family link in population register | Deterministic Algorithm |
| Live births with maternal link, per year (estimated) | 60,000 | 100,000 | 57,000 | Cannot be publicly disclosed | 70,000-140,000 | 45,000-60,000 | 6,000 |
| Live births with paternal link, per year (estimated) | 60,000 | NR (Likely to be almost complete) | 57,000 | NR | NR (500,000 for 2004-2022) | 40,000-55,000 | 8,000 |

[1] Estimate for linkage rate of fathers to mother-offspring pairs

### Comparison of key variables relevant to TANGO between data sources with paternal link

**Table 2 – Summary of discriminant data source characteristics**

| | Danish Registries | Swedish Registries | Norwegian Registries | CPRD Aurum | GePaRD | Finnish Registries | PHARMO Data Network |
|---|---|---|---|---|---|---|---|
| Biological *vs.* Adoptive | | | | | | | |
| ASM dispensing date (for exposure window calculations) | | | | ** | | | |
| Diagnoses for stillborn infants *(i.e., diagnosis associated with code for stillbirth)* | | | | * | | | |
| Identification of spontaneous abortion | | | | | | | |
| Diagnoses for spontaneous abortion *(i.e., medical reason for spontaneous abortion)* | | | | * | | | |
| Identification of elective abortion | | | | | | | |
| Diagnoses for elective abortion *(i.e., medical reason for elective abortion)* | | | | * | | | |
| Paternal / Maternal congenital malformation | | | | | | | |
| Identification of siblings | | | | | | | |

Variables are classified according to their availability in each data source with an established father-mother-infant linkage.

Available

Partially or possibly available

Not available

** Only available if captured in maternal records.*
*** Date of ASM prescription by GP available*

## CONCLUSIONS

From the performed feasibility assessment:

**GePaRD**, **Nordic Registries**, **PHARMO**, and potentially **CPRD** are considered fit for purpose databases to study the effects of paternal drug exposure on offspring. Due to a preferred exact father-offspring linkage, **Nordic Registries** and **GePaRD** were selected for **TANGO**.

## CONTACT INFORMATION

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