

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

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Conflict of interest: SC, MLK are employees of Sanofi, JL and LF are contractors of SANOFI. RP is an employee of RTI Health Solutions, which is a unit of RTI International, a nonprofit organisation that conducts work for government, public, and private organisations, including pharmaceutical companies.

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Background



Abstract as submitted

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.

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.



The SIGMA Consortium is the European hub for real-world evidence generation (<https://sigmaconsortium.eu/>)

Methods

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 (SIDIAPI)
- **Sweden** - Swedish Registries
- **UK** - Clinical Practice Research Data Link (CPRD Aurum)

CPRD's assessment was based on a literature review



Figure 1 – Feasibility: 11 European countries

Results

❖ Infant-father-mother linkages

All databases have an established mother-infant linkage.

Father-infant linkage is a key element of the PASS on paternal valproate (VPA) exposure (Table 1). Father-infant linkages are **available 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

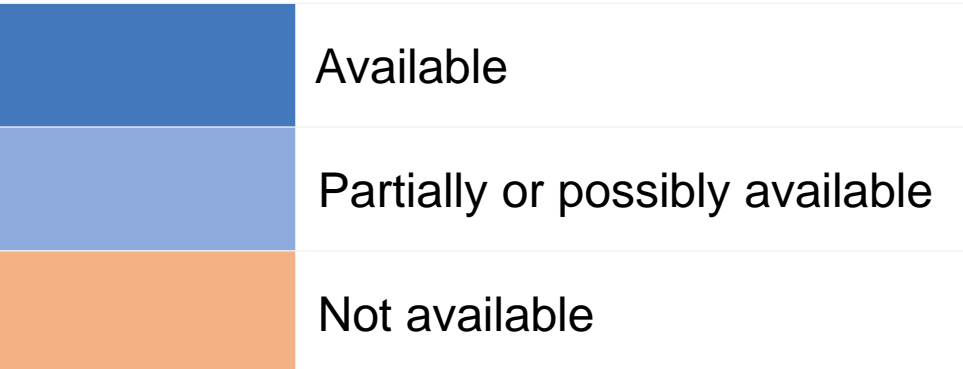
	Danish Registries	Swedish Registries	Norwegian Registries	CPRD Aurum	GePaRD	Finnish Registries	PHARMO Data Network
Father-infant link & years of availability	1995-2022	2005-2023	2010-2023	2003-2023	2004-2022	1995-2023	2000-2023
Father-infant linkage rate for live birth outcomes	>90%	>90%	>90%	50-70%	25%	>90%	>20%
Father-infant linkage rate for non live birth outcomes	>90%	No	>90%	50-70%	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	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 (8)	NR (Likely to be almost complete)	57,000	NR	NR (500,000 for 2004-2022)	40,000-55,000	8,000

❖ 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.



* Only available if captured in maternal records.

Conclusion

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**.

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Poster