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Linking Generations

Building Europe's Parent–Child Data Infrastructure for Drug Safety Evidence Generation



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Summary

Regulatory agencies, particularly the European Medicines Agency (EMA), have intensified their focus on reproductive and developmental safety monitoring, reflecting growing recognition that both maternal and paternal exposures may carry meaningful risks for offspring health. While maternal linkage is relatively well established in certain European countries, paternal linkage remains rare despite growing biological evidence supporting its relevance to offspring health outcomes. This piece highlights the value of scientific, regulatory, and infrastructural efforts to enable the use of father-child linked data within the broader field of parent-child linkage in post-authorization safety studies (PASS) in the EU and what it will take to get there.

Introduction:

The Regulatory Imperative

Evaluating medicine safety in offspring of women exposed during pregnancy is one of the most complex and urgent challenges regulators face. Pregnant women are systematically excluded from clinical trials, creating persistent evidence gaps that must be filled through real-world data (RWD)[1].

Parent–child linkage, connecting parental exposures to child health outcomes, is the primary methodological means by which these regulatory expectations can be met. It enables the identification of adverse offspring outcomes, neonatal complications, and long-term developmental outcomes extending into adulthood, as well as maternal and paternal health impacts. Collectively, these linkages provide a comprehensive safety profile across all family members, capturing both immediate and delayed risks.

Yet Europe's capability for such studies remains fragmented; some countries can link maternal health records to child outcomes, fewer can link paternal records, and coordinated multi-country efforts remain rare. This fragmentation leads to underpowered analyses, particularly for rare exposures or outcomes, and slows regulatory decision-making. Addressing this gap is both a scientific and regulatory priority, and one this piece sets out to examine.

Why Maternal Linkage is Not Enough

Maternal linkage has long been the primary focus. Recognition of the critical need to monitor medicine exposures during pregnancy and their effects on children, driven by the thalidomide scandal, gave rise to modern pharmacovigilance. Today, maternal record linkage - connecting maternal records to child health outcomes - has become the cornerstone of perinatal pharmacoepidemiology, informing both regulatory decision-making and clinical care. Landmark studies such as Nordic registry analyses of antiepileptic drug teratogenicity[2], the Clinical Practice Research Datalink (CPRD) pregnancy register in the United Kingdom (UK) evaluations of antidepressant use[3], and studies on maternal diabetes medication and neonatal outcomes using the PHARMO Perinatal Research Network[4] have shaped regulatory guidance and clinical practice across Europe.

But maternal linkage alone tells an incomplete story. A father's health, exposures, and medications prior to and around conception can affect offspring health through multiple biological pathways: germ cell damage, epigenetic modifications, and heritable genetic changes. Understanding the consequences of preconception paternal exposures requires longitudinal record linkage that extends well beyond pregnancy and birth, as effects on neurodevelopmental, immune function, endocrine health, and metabolic disease may only become evident later in childhood or adolescence. Both maternal and paternal perspectives are therefore relevant to provide a comprehensive picture of the safety of perinatal exposures.

Table 1 illustrates examples of complementary contributions of maternal and paternal record linkage to multiple concepts related to drug safety research.

Table 1: Key Safety Concepts for Maternal and Paternal Linkage.

Concept	Maternal relevance	Paternal relevance
Genotoxic or spermatotoxic medicines	Direct in-utero exposure to a known teratogen can cause malformation or developmental harm in the fetus.	A medicine with known effects on sperm quality or genetic integrity can plausibly affect offspring health even though the father is never pregnant.
Exposure during spermatogenesis	Maternal exposure risk is defined by gestational trimester, since the fetus is directly exposed throughout pregnancy.	Restricting paternal exposure to the ~3-month spermatogenesis window before conception allows researchers to test a precise, biologically defined period rather than a crude "ever exposed" classification.
Congenital and neurodevelopmental outcomes	Maternal use of a known teratogen during pregnancy carries a well-established risk of malformation and neurodevelopmental disorders in the child.	Paternal preconception use of the same drug class can be tested for an independent or shared risk pathway, since valproate is recognized as a cause of malformations and neurodevelopmental disorders when a mother takes it during pregnancy.
Negative-control analyses	Maternal exposure is the primary exposure under study, since the biological pathway from mother to fetus is direct and uncontested.	Because paternal antidepressant use during pregnancy is unlikely to result in fetal exposure, any observed association between paternal use and an offspring outcome suggests that the maternal association is influenced by confounding.
Control of familial and indication-related confounding	Maternal drug use during pregnancy can be confounded by the underlying condition being treated, as well as shared genetic and household factors.	Paternal linkage allows researchers to separate the drug's effect from the shared familial condition, by comparing outcomes among fathers with the same underlying indication but different exposure status.

Methodological Considerations

The scientific rationale for incorporating paternal linkage into studies of drug safety in offspring, based on pharmacoepidemiologic evidence but also on biological plausibility, is becoming increasingly compelling. Paternal linkage provides important complementary evidence for selected medicines and safety questions, particularly when paternal biological mechanisms or shared familial factors are plausible. Notably, several of the signals that have motivated this approach were identified in initial studies but not consistently replicated in subsequent research. Rather than weakening the rationale for paternal linkage, this pattern strengthens it, it demonstrates that paternal-linked real-world evidence is precisely the tool needed to test, challenge, and resolve safety signals, distinguishing true drug effects from confounding by indication, familial risk, or chance, rather than simply generating them.

At the same time, realizing this potential requires an objective assessment of its methodological considerations. While paternal linkage offers valuable complementary evidence, several limitations warrant consideration:

- paternal relationships are often inferred from administrative records rather than confirmed biologically, introducing a risk of inaccurate or incomplete linkage;
- residual confounding may persist after linkage due to unmeasured or poorly measured common causes of paternal exposure and offspring outcomes (e.g., genetic susceptibility, lifestyle, household environment). Maternal co-exposure is a key concern, if unmeasured or unreported, it may be correlated with paternal exposure and independently affect the outcome, making it difficult to attribute associations specifically to the father;
- confounding by indication persists where the condition prompting paternal treatment is itself related to offspring outcome;
- paternal exposure misclassification is a risk because the conception anchor date is often poorly defined or not harmonized across data sources, and paternal epigenetic effects are plausibly limited to the sperm lifecycle. In secondary data studies, exposure is reconstructed retrospectively for both parents, so even modest errors in the anchor date can misalign exposure with the relevant window;
- restricting analyses to live births, or to outcomes with incomplete ascertainment of losses and terminations, can introduce selection bias if the exposure independently affects survival. The direction and size of bias depend on how strongly exposure and outcome relate to selection, and are usually limited but can be material for high-mortality outcomes;
- paternal linkage may be less complete, particularly for births outside registered partnerships and for individuals born outside the country of registry. If missing paternal linkage is related to socioeconomic position, migration background, or family structure, which may also relate to exposure or outcome, this can introduce selection bias and limit generalizability.

Taken together, these constraints define the conditions under which it can be used responsibly — with transparent reporting of linkage quality, appropriate analytic designs (e.g., sibling comparisons, negative controls), and realistic expectations about which safety questions it can resolve. The remaining question is whether existing European data infrastructures and regulatory frameworks are equipped to evaluate the challenges above systematically.



Current European Landscape

The value of multinational paternal linkage in answering real regulatory safety questions has already been demonstrated. Despite growing evidence that parent–child linkage is essential for comprehensive drug safety research, capabilities across Europe vary considerably. Maternal linkage is available across multiple European health databases and registries and has long served as the foundation for perinatal pharmacoepidemiology research[5].

Paternal linkage, however, remains far less consistently available. Notably, the Nordic registries cover 100% of the Swedish, Danish, Norwegian, and Finnish populations through exact deterministic linkage, with father–offspring linkage rates exceeding 90% for live-birth outcomes. A population-based cohort study using Nordic registry data investigated the association between paternal valproate and the risk of neurodevelopmental disorders and congenital malformations in offspring, demonstrating that coordinated multi-country paternal linkage can generate regulatory-grade evidence[5].

Building on this foundation, a recent feasibility assessment of eleven European databases confirmed that the technical infrastructure for multi-country paternal linkage extends beyond the Nordics[7]. This reinforced that databases such as PHARMO and GePaRD can now offer comparable capabilities, covering approximately 20–25% of their respective national populations using probabilistic and deterministic algorithms.

However, even where linkage exists, structural and operational challenges persist, including data availability, sample size, data fragmentation, GDPR/Privacy governance, and paternal data completeness. The challenge is therefore no longer about feasibility, i.e., *whether* such linkage can be done, but about *how* it can be implemented more systematically.

A Proposed Path Forward – Federated Collaboration

Europe has already demonstrated that collaborative, multi-database medicines safety studies can generate regulatory-grade evidence while allowing data to remain under local governance. The next evolution of European drug safety research lies in coordinated collaboration between complementary family-linked healthcare databases. By combining harmonized methods with federated analysis, Europe can generate robust evidence for rare and long-term reproductive safety questions that are beyond the reach of any single data source.

Achieving this vision will require harmonized definitions, coding systems, common protocol, alongside robust governance frameworks to ensure comparable and valid evidence across countries. Federated analyses provide the scale and statistical power needed to investigate rare outcomes, while local data custodians, with their expertise in country-specific clinical practice and data provenance, remain essential underpinning validity of multinational research.

Initiatives like the SIGMA Consortium and TANGO study demonstrate that this is achievable. The Data Analysis and Real-World Interrogation Network (DARWIN EU), EMA's real-world evidence infrastructure, could become a more powerful tool for reproductive safety if the paternal linkage gap within its contributing data sources is addressed. PHARMO's parental linkage expertise and established relationships with European data custodians and governance bodies could contribute to broader European capacity-building efforts.

Conclusion

Maternal linkage has transformed our understanding of medicine safety in pregnancy. The next evolution point is to complement this foundation with paternal linkage where scientifically relevant enabling a more complete understanding of reproductive and developmental safety across the life course. PHARMO believes that collaborative paternal-linked real-world evidence represents the next frontier in reproductive safety research and is committed to working with partners across Europe to help realize that vision. By building on these proven models and infrastructures through coordinated collaboration, Europe can ensure regulatory decisions are informed by the most complete evidence possible, including comprehensive safety profiles for pregnancy and early life when future signals emerge.

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