Topic: ConcePTION – Continuum of Evidence from Pregnancy Exposures, Reproductive Toxicology and Breastfeeding to Improve Outcomes Now

All information regarding future IMI Call topics is indicative and subject to change. Final information about future IMI Calls will be communicated after approval by the IMI Governing Board.

Topic details

Action type	Research and Innovation Action (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

Information to guide decision making for safe and effective use of medications during pregnancy and lactation is a large unmet need that hinders optimal care of women of childbearing potential. Pregnant women with serious illness may need medicines to maintain their health, to treat conditions that affect them during pregnancy to prevent irreversible damage and for healthy pregnancies. These patients, together with their healthcare professionals (HCPs), are invariably interested in better information on the risks that their disease and/or medication can pose to the foetus as well as to babies during breastfeeding.

Prescribing information leaflets generally lack clear information to inform decision making. Very often pregnancy is listed either as a contraindication, or a warning or advice to use effective contraception to avoid pregnancy and stop medication in case of pregnancy. It is common to have statements such as, *"[drug] should not be used during pregnancy unless clearly necessary"* and *"It is not known whether [drug] or metabolites are present in breast milk; caution should be exercised when administered to a nursing woman*" rather than useful scientific information [1]. In the absence of scientific data to inform decision making, the treating physicians often take a risk avoidance approach and advise women with chronic disease to avoid becoming pregnant or to stop or not start treatment during pregnancy and breastfeeding. In some situations, when the treatment is stopped, the disease itself may cause even more damaging effects for both the foetus and the mother than the medication, and this may lead to higher disease burden, poor quality of life and more healthcare costs.

After a marketing authorisation has been granted, pregnancy registries may be proposed by the Marketing Authorisation Holder (MAH) or mandated by the Medicines Agencies or National Competent Authorities to better characterise the foetal risk in a real-world setting. Over time it has become evident that product-specific pregnancy registries often have their own shortcomings, as evidenced by the lack of published data from

these sources, and according to the FDA review based on 59 pregnancy registries, only a minority (12%) informed the label to adequately advise patients and healthcare professionals (HCPs) [2], notwithstanding huge investments in funds and time by the sponsors.

The major reason why most pregnancy registries end up being non informative is that they do not achieve the targeted number of pregnant women and commonly lack internal comparator groups to aid data interpretation. Hence, many compound-specific pregnancy registries close several years after initiation woefully under-enrolled, despite efforts by the sponsors to increase the recruitment. Alternative ways of characterising disease and compound mediated adverse foetal outcomes, like teratology information services cohorts, retrospective database or case control studies are increasingly used for hypothesis testing, but there are still gaps in knowledge about the best methods to use. In addition, there is no consistent standard of data quality (data collection and analytical methods) recognised as warranting inclusion in product labels.

The situation is even worse concerning breastfeeding. There is a large information gap for patients and HCPs on the risk to the breastfed child from the medication given to the mother. Often, due to lack of data, and even when some data exists, due to difficulties with predictability of animal data to humans, women are advised to avoid breastfeeding, despite the proven benefit of breastfeeding. The majority of current drug labels follow this approach which is more based on risk avoidance than on risk/benefit assessment. However, certain compounds, due to their physicochemical properties, are either not excreted in the milk, or are found at concentrations well below any biologically active concentrations. As there are no broadly accepted ways of generating such data and there is no requirement that such data/calculations are generated, these data are often not available. Although there are many different biological sample banks in the EU, there is no biobank for human breast milk. Such a biobank, when in place, would increase the human milk research as well as the assessment of medication concentrations in human milk.

This topic addresses the unmet need for a science and data driven approach to define the standards for generating data on medicines used during pregnancy and breastfeeding. The resulting better and more complete scientific information on drug effects on pregnancy and lactation will be used to inform treatment decisions and will increase the quality of care for women.

Need and opportunity for public-private collaborative research

Historically, the two sources of data about medicine use and effects in pregnancy and lactation have been academia and industry. The former had a more disease focus, the latter more a product focus. Both sources and approaches combined have essentially failed to fill the knowledge gap with relevant, timely and adequate information. Today there are three new and positive elements that can fundamentally change this current unsatisfactory status quo. Firstly, the expectations of the public and the regulators about better information connecting risks associated with disease and medication are rising (Pregnancy and Lactation Labelling Rules (PLLR) in the USA, guidelines in EU are expected). Secondly, new data analytics and data sources, such as remote data capture devices and electronic health records allow efficient access to and learning from much larger pregnant populations. And thirdly, there is a growing consensus among all stakeholders in healthcare that collaboration is the way forward when facing a challenge that is too large or complex for any one player to address, like this one.

The magnitude and complexity of the challenges mentioned above are such that they can only be addressed by a strong and dedicated collaboration between stakeholders. A public-private partnership involving a variety of stakeholders equipped with complementary areas of expertise and working together with a multi-disciplinary integrated approach provides a unique scientific opportunity in finding game-changing solutions to this huge unmet medical and societal need affecting millions of women world-wide every year.

IMI2 JU provides the ideal neutral framework for such a sensitive matter to ensure maximum transparency and buy-in by all stakeholders, and is an established forum where different stakeholders' needs can be put forward. It also provides the frame to share data in a secure environment as well as for interaction with different health authorities which is essential to guide and advice on guidance documents and consensus papers envisaged by the project as well as gain broad acceptance of methods and criteria for the predictive models generated as part of the proposed project.

Scope

The scope of this topic is to better inform the use of medicines during pregnancy and breastfeeding. To change current practices, the overall objective is to provide improved tools and methods to generate more valuable, reliable and timely information to HCPs and pregnant and lactating women to enhance optimal care.

More specifically the aims are to:

- define more timely and efficient approaches than pregnancy registries to better estimate disease background rates and treatment-related rates of adverse pregnancy and birth outcomes, including long-term outcomes in children. Improved information enables HCPs and pregnant patients to make informed decisions regarding medication use and enhances care;
- harmonise data elements collected during routine pharmacovigilance and enhance the collection of spontaneous reports (rate and the quality) of pregnancy cases. The standardised data elements will be also applicable for patients who get pregnant during clinical trials and for use in clinical practice;
- develop and validate a new animal lactation model in a species that more closely parallels human lactation physiology. Develop a physiologically based pharmacodynamic model for translation between the medication concentration in animal and human breast milk. These data will provide more reliable information for the initial product label than the currently existing prediction based on the presence or absence of medication in human milk mainly using the rat model;
- establish a non-commercial, Europe-wide breast milk biobank to be built on an already existing biobank setup with existing governmental support and an analytical centre for analysis of drug concertation in milk. The biobank will be able to host clinical breast milk samples from healthy breastfeeding volunteers as well as patients taking prescription medications;
- disseminate through various channels educational material for HCPs on the importance of reporting pregnancy cases though the pharmacovigilance system as well as why the follow up is needed. Educational information will be provided to patients on how to read and interpret relevant sections of the label, how to obtain relevant information from HCPs on treatment during pregnancy and breastfeeding and why clinical research in this field is needed.

Expected key deliverables

The deliverables are as follows:

- **Moving beyond pregnancy registries to enhance our understanding of disease related pregnancy birth/infant outcomes, medication use and safety in pregnancy**
    1) Comprehensive catalogue of existing data sources and approaches to capturing maternal medication exposure in pregnancy and subsequent pregnancy and birth outcomes including long-term outcomes in children building on existing catalogues;
    2) Publication of common data elements across data sources proposing a common data model for consolidating information across multiple sources, regions and countries;
    3) Consensus on key data elements to allow the assessment of medication utilisation and safety in pregnancy to meet regulatory requirements and standards for inclusion in product labelling;
    4) Proposal for a governance structure to enable de-identified data sharing across participating data sources under the common data model (leveraging experience of relevant IMI projects);
    5) Publication of guidance outlining standards for conducting drug utilisation studies in pregnant women (data collection and analytic standards) and conducting demonstration projects for established and newly marketed products;
    6) Publication of guidance outlining standards for conducting medication safety studies in pregnancy (data collection and analytic standards) using secondary data approaches (e.g. from claims data or similar large non-registry sources). Conducting demonstration projects for established and newly marketed products;
    7) Published guidance on appropriate disease based comparators (untreated and standard of care treated) with reference to demonstration projects and a range of diseases of varying prevalence using

the literature and patient data from clinical trials and primary data collected through pregnancy registries;

8) Published overall guidance on the application of different data approaches to study medicine safety in pregnancy based on the knowledge gained through the project;

9) Published aligned recommendations on how to prepare for pregnancy and medication use during pregnancy for HCPs, patients and general public.

It is expected that the deliverables will be regulatory accepted and be considered for implementation in the regulatory practice.

- **Enhance safety data collection in pregnancy and the analysis of case reports**

1) Publication of standardised core data elements (when and what) for pregnancy and follow-up applicable globally across industry and clinical practice;
2) Publication of a standardised method for data analysis for aggregate reviews across individual cases from different sources (e.g. spontaneous and clinical studies).

It is expected that the deliverables will be regulatory accepted and be considered for implementation in the regulatory practice.

- **Enhance data generation about lactation during medicine use and standardise approaches to human lactation studies**

1) Publication of a well characterised in silico and/or physiology-based pharmacokinetic (PBPK) model;
2) Translatable animal model to human;
3) Developed standards for conducting animal lactation studies;
4) Best practice document for conducting animal lactation studies;
5) Best practice document on how the results can be implemented when studying medication related lactational risks and develop algorithm when human lactation studies are indicated;
6) Best practice document on developed standards for conducting human lactation studies;
7) Aligned general recommendations on medication use during breastfeeding for HCPs, patients and general public.

It is expected that the deliverables will be regulatory accepted and be considered for implementation in the regulatory practice.

- **Establish a non-commercial, Europe-wide breast milk biobank building on an already existing biobank setup with existing governmental support and an analytical centre for analysis of drug concertation in milk**

1) A self-sustaining Europe-wide human milk biobank (building on an existing biobank with existing governmental support) for voluntary donor and study collected samples;
2) Europe-wide human milk sample analytical centre(s) able to comply with quality standards capable of measuring medication concertation in milk.

- **Dissemination and education for HCPs, pregnant and breastfeeding patients and general public**

1) Partnering to provide online centralised and verified information on medicines use during pregnancy and breastfeeding as well as risks associated with untreated diseases;
2) Network to deliver and maintain accurate and current information on good scientific and registry practice;
3) Guidelines addressing data privacy balancing spontaneous comments affecting benefit-risk profile, use of social media including electronic tools and ethical questions related to cross-border communication on pregnancy and breastfeeding;

4) Education and training programmes enhancing HCPs, patients and general public's ability to understand / comprehend information provided in labels regarding medication use in pregnancy and breastfeeding;.

5) Aligned general recommendations for medication use during pregnancy and breastfeeding for HCPs, patients and general public.

Expected impact

It is expected that the funded project will deliver: 1. broadly acceptable methodologies for generating event rates of adverse foetal and birth outcomes, including long-term outcomes in children, as well as rates for selected diseases; 2. promote alternatives to primary data collected through pregnancy registries for timely generation of medication-related adverse foetal and birth outcomes including long-term outcomes in children to inform the labels; 3. enhanced and harmonised way for dealing with pharmacovigilance pregnancy reports; 4. advanced methodology on how compound milk transfer can be better characterised in animals to inform the initial label with more relevant data and communication on standards for conducting human lactation studies, and 5. a EU centralised breast milk biobank and an analysis centre to enable research on medication transfer into human milk.

According to United Nations statistics [3] there were around 230 million pregnancies worldwide in 2012. According to the Eurostat data [4] in 2014, 5.1 million children were born in the EU-28 and around 6 million in the US (CDC). The proportion of pregnant women using medicines during pregnancy in developed countries varies in the published literature, the estimates being lowest in Northern European countries (44% to 47%), around 50% in the US and highest in France (93%) and Germany (85%, [5]). When only conservatively taking the lowest reported proportion of medication use in pregnancy in Nordic counties of 40%, the population which will benefit from the outcomes of this private public partnership would be around 2 million pregnant women only in the EU every year.

The short-term impact of the funded project is that regulatory bodies will be reviewing data generated by individual sponsors, including Small- and Medium-sized Enterprises (SMEs), that use broadly acceptable methodologies, hence making review of the individual product datasets easier. The faster and more efficient way of producing data to assess medication related adverse pregnancy outcomes will enable regulatory bodies to include enhanced information into the label, providing prescribers and patients with much needed information to guide treatment decisions for the benefit of women and children. Better characterisation and prediction of excretion of medicines in breast milk will deliver more reliable data to inform the initial label and the breast milk biobank and the analytical centre will allow for future milk research regarding drug transfer to human breast milk as well as milk research in general. The project is expected to deliver scientifically sound and validated information for implementation into the regulatory guidelines, which will lead to better information for HCPs and patients and generally improve the health of our next generation. Better and healthier next generation is expected to reduce health burden to the society and contribute to economic growth. In the absence of the information generated through the project, the diseased pregnant and breastfeeding population will continue to be underserved.

Potential synergies with existing Consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts and funding.

Example of such IMI and non-IMI projects include:

- **EUROCAT** (http://www.eurocat-network.eu) has existed for decades and includes most member states in collecting pregnancy and congenital anomalies data. Collaboration with EUROCAT will eliminate any duplicative work on pregnancy registries, collaboration will be synergistic and will provide outcomes that will be more conclusive, timely and less costly for all stakeholders.

- **EUROMEDICAT** (http://euromedicat.eu/) is an European system for the evaluation of safety of medication use in pregnancy in relation to the risk of congenital anomalies.
- **IMI EUPATI** project (https://www.eupati.eu/) focuses on education and training to increase the capacity and capability of patients to understand and contribute to medicines research and development and also improve the availability of objective, reliable, patient-friendly information for the public.
- **ISRHML** (International Society for Research in Human Milk and Lactation, https://isrhml.net) is a non-profit organisation dedicated to the promotion of excellence in research and the dissemination of research findings in the field of human milk and breastfeeding.
- **IMI PROTECT** project (http://www.imi-protect.eu). Although the project has ended, its legacy lives on in the knowledge and tools for monitoring the benefits and risks of medicines generated by the project.
- **GAIA**-Consortium (http://gaia-consortium.net) aims to improve programmes of immunisation in pregnancy by harmonising maternal, pregnancy, foetal, and neonatal health outcome assessment.
- **European Network of Teratology Information Services (ENTIS)** (https://www.entis-org.eu) has the general objective to coordinate the activities of the different Teratology Information Services (TIS), and to collect and evaluate data in order to contribute to the primary prevention of birth defects and developmental disorders.
- IMI **eTOX** project (http://www.etoxproject.eu). The principles developed by the IMI eTOX project for sharing data, both public and private, through the combination of legal (IP), IT and honest broker concepts would be in principle applicable to the project selected under this topic.
- IMI **EHR4CR** project (http://www.ehr4cr.eu) that provides adaptable, reusable and scalable solutions (tools and services) for reusing data from Electronic Health Record systems offering large opportunities for the advancement of medical research, improvement of healthcare, and enhancement of patient safety.
- To help improve access to these patient-level data, the IMI European Medical Information Framework (**EMIF**) (http://www.emif.eu) project develops common technical and governance solutions and improves access and use of health data.
- Future IMI project resulting from the topic European Health Data Network (EHDN) IMI2 Call 12; http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2Call12/IMI2_Call12_CallText.pdf.
- The US based **Mommy's Milk Human Milk Research Biorepository** (https://mommysmilkresearch.org) is the first human milk biobank that makes easier for scientists to perform research with standardised, sterile and indexed human breast milk samples.
- **BBMRI-ERIC** (http://www.bbmri-eric.eu/) operates a pan-European distributed research infrastructure of biobanks and biomolecular resources in order to facilitate access to resources.
- **IMEDS** (https://blogs.fda.gov/fdavoice/index.php/2017/01/introducing-imeds-a-public-private-resource-for-evidence-generation/) framework provides governance that allows private sector entities to gain access to the FDA Sentinel System's distributed data making the scientific methods and tools available for entities outside of FDA.

Industry consortium

The industry consortium will bring extensive expertise in pharmacoepidemiology and pharmacovigilance, experience in collecting additional information on spontaneous pregnancy case reports, prospective data collection, statistical analysis of spontaneous reports, legal and ethics experts, extensive expertise in animal lactation studies, reproductive toxicology, physiologically based modelling and simulation expertise, expertise in bioanalytical methods, assay development, sample collection and handling expertise, sampling protocol development, legal, ethical, financial expertise, expertise in medical communications, patient affairs, drug labelling, experience in monitoring social media, experience of translating highly technical information into usable information for health care providers and patients, as well as experience with interacting with regulatory authorities.

More detailed industry consortium contribution is presented under the section suggested architecture of the full proposal (see below).

Indicative duration of the action

The duration of the action is 60 months.

Future Project Expansion

Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking may, if exceptionally needed, publish at a later stage another Call for proposals restricted to the consortium already selected under this topic, in order to enhance and progress their results and achievements by extending their duration and funding. The consortium will be entitled to open to other beneficiaries as they see fit.

A restricted Call may be launched as part of a future IMI2 JU Annual Work Plan to carry out further on the correlation/analysis between animal reproductive toxicology data and human adverse pregnancy outcomes safety data.

Applicant consortium

The applicant consortium will be selected on the basis of the submitted short proposals.
The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2. This may require mobilising the following expertise, including from SMEs:

- expertise in design and analysis of existing data sets, electronic health records;
- teratology and birth defect experts, scientific societies working with malformations;
- experience in legal, ethics and privacy law across regions;
- expertise in gynaecology and neonatology, representatives of patient's advocacy groups and professional medical associations, breastfeeding advocacy groups;
- expertise in animal and human lactation physiology and physiologically based modelling and simulation, capabilities to develop animal lactation models as well as conducting animal lactation validation studies, ability to host a non-commercial breast milk biobank with already existing governmental support and analytical centre, expertise in assay development and adaptation of medication assays to milk;
- financial experts on advising for sustainability;
- experience in use of different communication channels to different interest groups and professional associations, ability to communicate and translate complex medical information into lay language, expertise in handling and dissemination of information through internet and social media, expertise in qualitative analysis of social media feedback, web designer and web site maintenance experience;
- regulatory expertise, experience dealing with regulatory agencies, professional expertise managing complex multi-stakeholder projects, professional project management capability and experience.

The expected applicant consortium contribution expertise is presented under the section suggested architecture of the full proposal (see below).

Suggested architecture of the full proposal

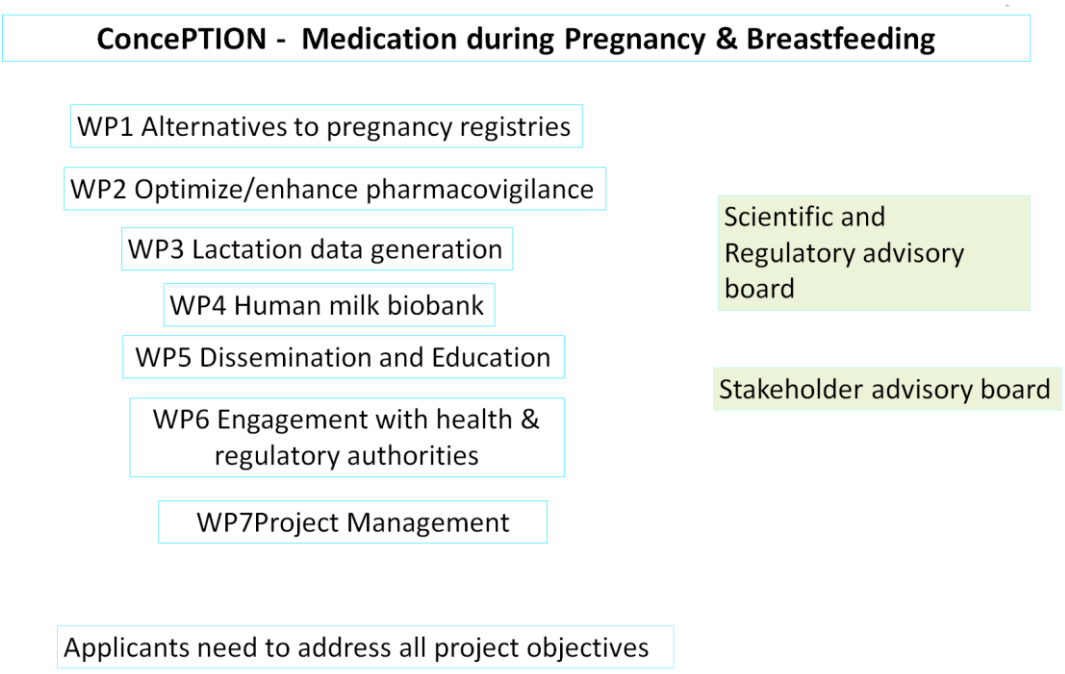
The applicant consortium should submit a short proposal which includes their suggestions for creating full proposal architecture, taking into consideration the industry contributions and expertise provided below.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the

consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

The architecture outlined below for the full proposal is a suggestion. Different innovative project designs are welcome, if properly justified.



The consortium is expected to have a strategy on the translation of the relevant project outputs into regulatory practices, clinical and healthcare practice. A plan for interactions with Regulatory Agencies/health technology assessment bodies with relevant milestones and resources allocated, should be proposed to ensure this e.g. qualification advice on the proposed methods for novel methodologies for drug development, qualification opinion.

Sustainability

A plan for aspects related to sustainability, facilitating continuation beyond the duration of the project should also be proposed.

It is important to recognise that certain project deliverables are expected to endure beyond the timescale of the project, and particular emphasis should be put on ensuring the sustainability of these deliverables.

It is important that the following deliverables of the project are made sustainable after the completion of the project:

- Human breast milk biobank;
- Dissemination and educations;
- Website and social media communication infrastructure and content support.

The list of activities within the work packages below gives more detailed insight into the activities which are proposed in order to achieve the project objectives.

Work package 1 – Moving beyond pregnancy registries to enhance our understanding of disease related pregnancy outcomes, medication use and safety of use during pregnancy

1. Develop a comprehensive catalogue of existing data sources and approaches capturing maternal medication exposure in pregnancy and subsequent pregnancy outcomes building on existing catalogues;

2. Review and publish common data elements across identified data sources building a proposal for a common data model for consolidating data across multiple data sources, regions and countries building on existing knowledge;

3. Propose and gain consensus on key data elements to allow assessment of medication utilisation in pregnancy as well as medication safety data to meet regulatory requirements and standards for inclusion in product labelling;

4. Propose a governance structure for de-identified data sharing across participating data sources under the proposed common data model;

5. Conduct Strengths, Weaknesses, Opportunities, Threats (SWOT) analysis of approaches to assessing medication utilization and medication safety in pregnant populations: primary data collection (e.g. product specific pregnancy registries versus alternative approaches (secondary data collection) or hybrid approach;

6. Based on SWOT analysis, agree standard data collection and analytical methods and publish guidance for conducting drug utilisation studies in women of childbearing potential;

7. Based on SWOT analysis agree standard data collection and analytical methods and publish guidance for conducting medication safety studies in pregnancy using secondary data collection approaches and conduct demonstration projects (case studies) for established and newly marketed products;

8. Develop and publish guidance on appropriate disease based comparators (untreated and standard of care treated) with reference to demonstration projects and a range of diseases of varying prevalence (e.g. examples for frequent (e.g. Hyperemesis); common (e.g. Depression) and rare (e.g. Breast cancer or Lupus);

9. Publish a guidance document on application of different data approaches to study medicine safety in pregnancy based on the knowledge gained through the project;

10. Prepare aligned recommendations on how to prepare for pregnancy and medication use during pregnancy for HCPs, patients and general public.

Industry contribution:

Expertise in pharmacoepidemiology; drug regulatory experience; legal and ethics expertise; experience conducting databases/registry studies. The industry consortium will share placebo clinical trials pregnancy cases and non-treated/standard of care treated patients data from pregnancy registries (as far as available); experience and challenges as well as roadblocks encountered during primary data collection and use of alternative approaches as well as sharing of experience of what worked well.

Expected applicant consortium contribution:

Experience in leveraging alternative data sources; experts in analysis of large data sets like electronic health records; teratology experts; statisticians; data modelling; legal, ethics and privacy law experience; expertise in gynaecology and neonatology; patients' advocacy groups; representatives of professional medical associations; regulatory experience.

Work package 2 – Enhance safety data collection in pregnancy and the analysis of case reports

1. Conduct cross-company inventory on handling pharmacovigilance (PV) pregnancy case reports;
2. Develop and standardise core data elements (when and what) for pregnancy and infant follow-up. This core set should apply across industry and clinical practice and be applicable globally;
3. Develop standardised method for data analysis for aggregate reviews across individual cases from different sources (e.g. spontaneous reports and clinical studies);
4. Publish standards for handling PV pregnancy case reports in peer review journal(s);
5. Prepare aligned information on importance of reporting pregnancy cases though PV system for HCPs in order to stimulate data reporting and create a safe environment for reporting pregnancy cases with compounds without appropriate safety information in labels.

Industry contribution:

Extensive expertise in pharmacoepidemiology and pharmacovigilance; experience in collecting additional information on spontaneous pregnancy case reports; prospective follow up data collection; statistical analysis of spontaneous reports; legal, and ethics experts. The industry consortium will also share pharmacovigilance pregnancy data under the Honest Broker concept to better inform the feasibility of the outcome.

Expected applicant consortium contribution:

Expertise in design and analysis of existing data sets; teratology and birth defect experts; legal, ethics and privacy law experience; expertise in gynaecology and neonatology; representatives of patient's advocacy groups and professional medical associations.

Work package 3 – Enhance data generation about lactation during medicine use and standardise approaches to human lactation studies

1. Review the literature and evaluate the existing animal lactation models for comparison to human physiology and milk composition and/or develop animal lactation model;
2. Conduct experiments to validate the selected or new animal lactation model – respecting the Reduce, Refine, Replace (3Rs) principle;
3. Develop a well-characterised in silico and/or PBPK model(s) based on physicochemical properties of drugs and preclinical data to better predict human milk transfer of drugs and to derive concentrations of drugs in milk, permitting a more accurate prediction of Relative Infant Dose (RID); where justified, also using available human lactation data;
4. Validate that the developed model(s) can predict the known human lactation data;
5. Define factors that should be considered when calculating neonatal exposure e.g. gastro-intestinal maturation;
6. Develop and publish standards and best practices in peer reviewed journals;
7. Develop a guidance document when generating human data might still be justified;
8. Propose consensus on minimal amount of any breastfeeding data to meet regulatory requirements for inclusion in the label;

9. Publish the guidance document in peer reviewed journal(s) on best practice for conducting human lactation studies;

10. Prepare aligned recommendations on medication use during breastfeeding for HCPs, patients and general public.

Industry contribution:

Expertise in animal lactation studies; general and reproductive toxicology; physiologically based modelling and simulation expertise; expertise in bioanalytical methods; capabilities to develop animal lactation models and conduct animal lactation studies. The industry will also share relevant preclinical and/or clinical lactation data under the Honest broker concept.

Expected applicant consortium contribution:

Expertise in animal and human lactation physiology and physiologically based modelling and simulation; capabilities of conducting animal lactation studies and/or develop animal lactation models; expertise in bioanalytical methods; expertise in gynaecology and neonatology; patients advocacy groups; representatives of professional medical associations; breastfeeding advocacy groups and experts in legal, ethics and privacy laws.

Work package 4 – Establish a non-commercial, Europe-wide breast milk biobank building on an already existing biobank setup with existing governmental support and an analytical centre for analysis of drug concertation in milk

1. Investigate the legal basis of establishing a Europe-wide human milk biobank from healthy breastfeeding women and women taking medicines;

2. Utilise and expand on existing tissue biobank structure/collaboration;

3. Identify the population and stakeholder for breast milk collection;

4. Develop human milk sample collection and handling methodology guidance (sampling, storage shipment, health data needed from breastfeeding women) and model informed consent form (ICF);

5. Suggest a biobank Scientific Board structure to review and approve requests for milk samples for research purposes;

6. Develop analytical methodology for human breast milk adaptable for drug product analysis;

7. Propose the potential financing structure to ensure sustainability, in addition to the existing governmental support;

8. Generate charters for collaboration between industry and academia based on the Good Pharmacovigilance Practice (GVP) Module 8 and Council for International Organizations of Medical Sciences (CIOMS).

Industry contribution:

Expertise in bioanalytical methods and assay development; analytical capabilities, sample collection handling and transportation expertise; biological material sampling protocol development; legal, ethical, financial expertise.

Expected applicant consortium contribution:

Ability to host a non-commercial human milk biobank, building on existing biobank structure with already existing and sustainable governmental support, milk samples analytical capabilities preferably in the same

country able to set up and analyse medications in human milk and capable to comply with all necessary analytical quality standards; expertise in assay development and adaptation of medication assays to milk; experts in regulatory environment related to collection and transport of biological material; experts in ethics, experts on advising for sustainable financial support.

Work Package 5 – Dissemination and education for HCPs, pregnant and breastfeeding patients and general public

1. Inventory of possible communication means to HCPs and patients using different professional and patient associations and selection of the most appropriate ones for the project purpose;

2. Inventory of existing social media communication channels, including electronic tools to HCPs, pregnant and breastfeeding women and general public;

3. Analysis of information searched and feed-back on the quantity, utility and clarity by HCPs, pregnant lactating women and breastfeeding women and general public;

4. Partnering to provide online information packages on points to consider when preparing for pregnancy and medication use during pregnancy and breastfeeding to HCPs, patients and general public and generation of communication guidelines and customise information packages for different target audiences;

5. Engage HCPs, pregnant and breastfeeding women and general public to set expectations and stimulate pregnancy reporting through PV system and participation in research;

6. Communication tools for internal and external communication.

Industry contribution:

Expertise in medical communications; patient affairs; drug labelling; experience in monitoring social media; experience of translating highly technical information into usable information for HCPs and patients.

Expected applicant consortium contribution:

Experience in use of different communication channels to different interest groups and professional associations, ability to communicate and translate complex medical information into lay language, expertise in handling and dissemination of information through social media, expertise in training and continuous medical education, expertise in the area of legal and ethical questions across regions, expertise in psychology and sociocultural aspects, expertise in qualitative and quantitative analysis of social media feedback and machine learning, hosting and webmaster capacities, patient organisations, regulatory expertise, scientific societies working with malformations and experts on advising for sustainable financial support.

Work Package 6 – Engagement with health and regulatory authorities

1. Interact with work package leaders on the need for health authorities (HA) input;

2. Assist Work Package leaders in using correct regulatory language;

3. Organise HA interaction webinars, teleconferences and/or meetings;

4. Share the regulatory interaction knowledge gained through the process with other Work Packages;

5. Regulatory support to milk biobank establishment.

Industry contribution:

Expertise in drug labelling and interaction with the regulatory authorities as well as experience in use of real world evidence generated data.

Expected applicant consortium contribution:

Experience in regulatory communication, experience in using real world data for scientific purposes as well as labelling expertise.

Work package 7 – Project management

1. Participate in joint governance structure;
2. Implementation and management of the project, setting-up regular meetings and interaction between sub-groups and teams, coordination of the work efforts, preparing meeting minutes;
3. Manage collaboration with external stakeholders and synergies with other related projects;
4. Communication and information dissemination within the project;
5. Coordinate activities across all work packages tracking of deliverables, ensure deliverables are achieved according to plan, on time and budget;
6. Ensure meetings and interactions between work packages and consortium governance bodies to coordinate and follow-up on work effort.

Industry contribution:

Support in work package project management within the company leading a work package.

Expected applicant consortium contribution:

The applicant consortium should bring proven record of professional project management capabilities; expertise and experience in managing complex and long lasting projects, such as this one.

References

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