IMI2 821520 - ConcePTION

WP2 – Improving the collection, analysis and interpretation of pregnancy pharmacovigilance data

D2.3 Report describing existing coding systems, schemes and regulatory guidelines of reported medication exposed pregnancies

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V0.1	10.01.2020	Draft	N/A
V0.2	17.02.2020	Draft	N/A
V0.3	19.02.2020	Comments returned	20.02.2020
V0.4	03.03.2020	Final draft	Submitted to Management Board for review.
V1.0	30.03.2020	Final draft	Submitted to IMI

Summary

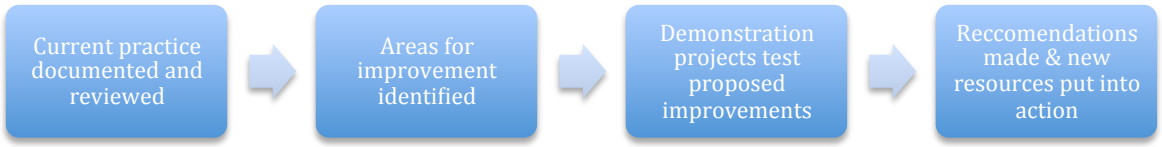
This report outlines a series of reviews completed with the aim of documenting current practice from which avenues of improvement can be identified and translated into future work undertaken by the ConcePTION project. The reviews focused on current regulatory guidelines pertaining to the collection of data on exposed pregnancies, on current large-scale data collection schemes, and on how data reported through industry pharmacovigilance systems is coded and communicated to regulators. A number of opportunities for the ConcePTION project to enhance data collection and patient safety are identified and discussed. One such improvement is the formation of an agreed set of Core Data Elements across different data collection schemes; the first stage of an optimized Common Data Element list including outcome at delivery is reported on here. A list of Common Data Elements for longer- term outcomes will be developed as part b of this task 2.3.

Introduction

A clear understanding across academic and industry partners regarding current practices in the detection of pregnancy related adverse events and accumulation of safety data relating to medication use in pregnancy is of paramount importance within the ConcePTION study. A review of current strategies to identify improvements is the first step towards implementing changes needed for a new system of pharmacovigilance to be developed by the ConcePTION project (Figure 1). Undertaken within Work Package 2, which aims to optimise the collection of data specifically for the purpose of pregnancy pharmacovigilance, this task reviewed current practice by both industry data collection and health/academic data collection schemes. (Figure 1). Three main aspects of current practice have been considered here:

- current regulatory recommendations on the collection of data elements pertaining to outcomes in medication exposed pregnancies,
- current data collection schemes including both industry and academic and their respective data elements,
- what common data elements should form a 'core set' that is central to all data collection schemes and how they should be defined.

Figure 1. Flow chart of task 2.3. Review through to change.



This main section of the report provides an executive summary of the work completed, with detailed reports on the individual reviews/areas accessible in the appendices.

- Appendix 1. Review of regulatory guidelines
- Appendix 2. Review of current data collection schemes
- Appendix 3. Data sources and coding schemes

- Appendix 4. Core data elements

Review of regulatory guidelines

This piece of work reviewed current regulatory guidance pertaining to the collection of data on medication exposed pregnancies, including both the recent Food and Drug Administration (FDA) and European Medicines Agency (EMA) draft guidance which were released for consultation last year. The review highlights that regulatory agencies recognise the importance of medication safety in this context. However, the lag between previous and new versions of guidance is notable, in an area which has evolved significantly in the last decade.

All reviewed documents highlight the challenges and complexities of medication exposure in pregnancy and the collection of outcome data in the child. There remained a focus on major congenital malformations at the expense of other endpoints such as fetal growth and longer –term child outcomes in all documents, including those recently out for consultation. In an area where there has been an expansion of methodological approaches to include large population based datasets there is little guidance on the core methodological requirements, the outcomes investigated and how they are reported. Further, breastfeeding offers an extended period of exposure to a medication following on from pregnancy or is a standalone time of exposure, yet there is limited focus on exposures through breastfeeding.

Our review included key recommendations for work which can be undertaken within the ConcePTION study. These recommendations centre around the harmonization of data collection through the creation of agreed Core Data Elements but also aligning of practices across different methodological approaches. There is also a call for the utilization of more novel methods of data collection and a change in the way industry collected data is utilized; including those with normal pregnancy outcomes. A call to extend the current focus on major malformations to include other child growth, health and developmental outcomes is made. Finally, it is noted that the ConcePTION study has brought

together important expertise, from diverse backgrounds, and that this group could contribute immensely to the updating of EMA pregnancy guidance in ICH-E2D(R1) (due for completion 2023), to reflect current practices, issues and challenges in medication use in pregnancy and breastfeeding.

Review of data collection schemes

To understand the data elements included in current large-scale data collection schemes a review of included data elements pertaining to the exposure, mother's history and child outcome was undertaken. Included schemes ranged from infinite data collection schemes such as EudraVigilance and Teratology Information Services to time limited studies focusing on a specific group of exposures such as disease specific pregnancy registers. Data was extracted from publically available information or was requested directly. Extracted fields were compared to the May 2019 FDA Guideline document[1] which sets out recommended data elements. Originally the comparator was set to be the EMA new draft guidance but a delay its in publication meant that this was not possible. However, the December 2019 EMA guidance on data elements is included and compared to the FDA document.

This review demonstrated variation across data collection schemes in comparison to the FDA recommendations and against each other. Additionally, reviewed schemes contained data elements not included in the FDA guidelines which are likely beneficial to the model which will be developed through the ConcePTION project. This review of data elements has been used to inform the Core Data Elements presented below.

The full report on this review can be found in Appendix 2.

Review of coding schemes

In order to make recommendations regarding more structured and harmonized collection of pregnancy exposure data within the new ConcePTION data model a

review of current practices was undertaken, led by the Work Package 2 EFPIA partners. There are multiple levels of data that need to be translated or 'coded' into a standardised format ranging from product administration information through to the adverse event being reported. Accurate data recording is essential and for that purpose a number of dictionaries and coding systems have been developed for pharmacovigilance. However, the lack of one system adopted by all leads to heterogeneity in reporting. This review covers old and limited systems through to the more widely utilized MedDRA and SNOMED systems. World Health Organisation (WHO) ICD codes are used frequently in pharmacoepidemiology and are much more familiar to academics and clinicians, but are infrequently used in pharmacovigilance practices within industry. The World Health Organisation (WHO) UMC Global Safety Database is the most comprehensive and actively used drug reference dictionary in the world in this context. The dictionary is used to identify drug names and to evaluate medicinal product information, including active ingredients and products' anatomical and therapeutic classifications.

It is recommended that a single unified approach is adopted which will best serve data collected from patients for the purpose of pharmacovigilance. The review recommends that the ConcePTION data system produced at the end of the project implement WHO Drug Global coding for the initial phase of product standard coding and that the MedDRA dictionary/ coding system is used for the coding of adverse events, indications for treatment, laboratory data and results. Other useful adoptions would be the Unified Code for Units of Measure (UCUM) for coding units and the EudraVigilance E2B (R3) lists of values (LoVs) associated with the core data fields for ConcePTION; however some modification may be needed. These recommendations from the Work Package 2 perspective will form the basis of future discussions within the wider ConcePTION project as to the optimal methods for diverse types of data.

The full review on coding systems can be found in Appendix 3.

Core data elements

The final component of this task was to define data that should be collected in reports of exposure to medication during pregnancy (e.g., through pharmacovigilance or pregnancy registries) in order to ensure optimal assessment of the fetal safety or risk profile of that medication with respect to its use during pregnancy.

Building on the review of current schemes of data collection and the diverse expertise within Work Package 2, which includes industry, academics, clinicians and teratology specialists, an optimal list of Core Data Elements required for the investigation of exposed children up to one year of age was created. The Core Data Elements comprised of demographic and exposure characteristic data along with the data required to reliably document outcomes such as major congenital malformations, fetal growth and maternal and child health up to the one year of age. Longer-term outcomes are the subject of a future report due to be delivered in month 24. The current document describing Core Data Elements for shorter-term outcomes is a live document and will be updated in line with ongoing discussions with ConcePTION project partners in the Definitions Task Force and colleagues in Work Package 1.

The aim of ConcePTION project is to improve not only the collection of data pertaining to pregnancy and breastfeeding exposures but also to improve communication of information to women and health care providers. For this purpose a set of proposals are made with regards to the format of reporting of outcome data.

For the full report please see Appendix 4.

Conclusions and looking forward

This series of reviews has identified a number of ways for the ConcePTION project to make improvements to the current pharmacovigilance system for medications used during pregnancy and in breastfeeding. Further work in Work

Package 2 will now develop these recommendations and test their implementation through the demonstration projects.

List of abbreviations

FDA – US Food and Drug Administration
EMA – European Medicines Agency

References

1 Food and Drug Administration. Post approval Pregnancy Safety Studies: guidance for industry. 2019. Available at https://www.federalregister.gov/documents/2019/05/09/2019-09527/postapproval-pregnancy-safety-studies-draft-guidance-for-industry-availability.

2 European Medicines Agency. Guidance on good pharmacovigilance practices (GVP) Product or Population –Specific Considerations III: Pregnant and breastfeeding women. EMA/653036/2019 DRAFT FOR PUBLIC CONSULTATION 2019. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-good-pharmacovigilance-practices-product-population-specific-considerations-iii_en.pdf.

Appendices

Appendix 1. Review of regulatory guidelines

Appendix 2. Review of current data collection schemes

Appendix 3. Data sources and coding schemes

Appendix 4. Core data elements

IMI2 821520 - ConcePTION

WP2 – Improving the collection, analysis and interpretation of pregnancy pharmacovigilance data

D2.3 Review of Regulatory Guidance pertaining to use of pharmaceutical products in pregnant and breastfeeding women

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V0.1	2019	Methodological approach	WP 2
V0.2	25 Feb 2020	First Draft	Dr Rebecca Bromley, University of Manchester, Dr Liat Greener, Teva Dr Michael Stellfeld, NovoNordisk
V0.3	03 Feb 2020	Second Draft	ConcePTION Management Board
V1.0	30 Mar 2020	Final Version	Submitted to IMI

Publishable Summary

The ConcePTION project aims to address the limitations of the current system for pharmacovigilance in pregnant and breastfeeding women. Review of pertinent regulatory guidance highlights recognition of the challenges and complexities of medication exposure in pregnancy and the collection of outcome data in the child. However, despite the publication of updated EU and FDA guidance in 2019, gaps remain. This review makes key recommendations for work which can be undertaken within the ConcePTION study to address these gaps and to harmonize data collection. These include delineation of Core Data Elements for data collection and proposals for aligning of practices within different methodological approaches. There is also a call for the utilization of more novel methods of data collection and a change in the way industry collected data are utilized; including those with normal pregnancy outcomes. Finally, it is noted that the ConcePTION study has brought together important expertise, from diverse backgrounds, and that this group could contribute immensely to the updating of pregnancy guidance in ICH-E2D(R1) due for completion in 2023.

Introduction

The average pregnant woman takes three medicines during her pregnancy, and four medications during breastfeeding. However, despite legislation mandating that marketing authorization holders (MAH) follow-up reports of pregnancy exposures, only around 5% of approved medicines contain safety information on use in pregnancy and/or breastfeeding based on human data. With the limited data available pertaining mainly to risk of congenital anomalies, information on longer term outcomes such as neurodevelopment, cancer or immune function is even more deficient.

Not only is lack of data a problem, but so too is the quality and completeness of the pregnancy PV data that are available, with data that have been collected over many years not infrequently of inadequate quality to support informed

assessment of benefit versus risk. A huge information gap therefore exists regarding the risks of maternal medication use to the fetus and child. This situation is surprising considering the diverse plethora of well-established data collection systems that include pregnancy registries, adverse event reporting systems, research cohorts, clinical databases and teratology information service network datasets.

The ConcePTION project aims to address the reasons for this system failure by bringing together individuals from both industry and academia who have the background experience in this field necessary to identify and address the limitations of the current system for pharmacovigilance in pregnant and breastfeeding women. As a starting point to systematically rebuilding and improving the system, from exposure reporting and data collection, through to analysis, change of product label and the communication of clinically relevant findings to health care professionals and pregnant / breastfeeding women, it is necessary to review and assess the regulatory guidance in which practical implementation of the applicable legislation is found.

Methods

Aim:

The aim of ConcePTION task 2.3 is to describe, evaluate & undertake a gap analysis of existing schemes, **regulatory guidelines** and coding systems for reporting medication exposure in pregnancy in order to propose changes to improve spontaneous and solicited primary data collection format and coding, and to assess the feasibility of mapping existing formats to those standards. This report focuses on the regulatory guidance pertaining to use of pharmaceutical products in pregnant and breastfeeding women.

Scope:

This review is restricted to aspects of regulatory guidance relating to the reporting of adverse events, or to the active collection of primary data on humans, for the purpose of pharmacovigilance in pregnant or breastfeeding

women i.e. data sources under consideration in the ConcePTION project by Work Package 2 (WP2). The main focus is on EU guidance, although international and non-EU guidance will be considered for the purpose of comparison. National guidance documents produced by regulators within individual EU member states, or by professional societies or organisations are not considered in scope. Guidance on the conduct of preclinical reproductive toxicity studies and pertaining to medication use in breastfeeding women are also considered out of scope.

Methodology:

Work Package 2 EFPIA (European Federation of Pharmaceutical Industries and Associations) and academic members proposed a list of regulatory guidance documents relating to the reporting, collection and analysis of pregnancy pharmacovigilance data that they considered, on the basis of real world experience, to be key. To ensure that no additional EU regulatory guidance documents of potential relevance to this review had been overlooked, guidance documents listed on the European Medicines Agency website (https://www.ema.europa.eu ,last accessed 16 Feb 2020) were screened by title and by entering the terms 'pregnan', 'breastfeed' and 'lact' into the website search function. Each EMA Good Pharmacovigilance Practice (GVP) module was screened for content relating to pregnant or breastfeeding women by inserting the terms above into the text search tool. Non-EU guidance was identified by searching the U.S Food and Drug Administration webpage for guidance documents (https://www.fda.gov/regulatory-information/search-fda-guidance-documents) using the term 'pregnan', and by conducting a Google and Pubmed search using '*regulatory guidance pregnancy pharmacovigilance'.* Regulatory guidelines published during the course of this task were assessed for relevance, and if regarded as in-scope by WP2 members, included in the review.

Results

We identified three EU regulatory pharmacovigilance (PV) guidelines specific to use of medication in human pregnancy, lactation and/or breastfeeding, and

several general PV guidance documents in which mention of pregnant or breastfeeding women was included, either as a discreet section within the document or within relevant sections of the general guidance. The guidance documents identified are listed below, categorized as EU or non-EU, and as 'Pregnancy and breastfeeding specific' or as 'General' within the two geographically defined groups:

1. **European Union**

PV Guidance specific to pregnancy and breastfeeding / lactation

1. CHMP Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: from Data to Labelling (EMEA/CHMP/203927/2005)1 – Endorsed https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-risk-assessment-medicinal-products-human-reproduction-lactation-data-labelling_en.pdf

2. CHMP Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Postauthorisation Data (EMEA/CHMP/313666/2005)2 – Endorsed https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-exposure-medicinal-products-during-pregnancy-need-post-authorisation-data_en.pdf

3. GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019) - draft for public consultation https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-good-pharmacovigilance-practices-product-population-specific-considerations-iii_en.pdf

General PV Guidance in which pregnancy and breastfeeding / lactation specifically mentioned

A number of the GVP modules include brief reference or specific sections that relate to specifically to pregnant or breastfeeding women. This includes details of the Pregnancy Prevention Program (PPP).

2. **Non-European Union/ Global**

PV Guidance specific to pregnancy and breastfeeding / lactation

1. Postapproval Pregnancy Safety Studies, Guidance for Industry (FDA, 2019) – draft status https://www.fda.gov/media/124746/download
2. Clinical Lactation Studies: Considerations for Study Design, Guidance for Industry (FDA, 2019) – draft status https://www.fda.gov/media/124749/download
3. Pregnant women; Scientific and Ethical Considerations for Inclusion in Clinical Trials (FDA, 2018) – draft status https://www.fda.gov/media/112195/download
4. Pharmacokinetics in pregnancy – Study design, Data Analysis, and Impact on Dosing and Labeling (FDA J:\!GUIDANC\5917dftcln2.doc 10/22/2004) – draft status https://www.fda.gov/media/71353/download

General PV Guidance in which pregnancy and breastfeeding / lactation specifically mentioned

1. Post -Approval Safety Data Management: Definitions and Standards for Expedited Reporting E2D (ICH) – adopted https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-12.pdf

2. Pharmacovigilance responsibilities of medicine sponsors, Australian recommendations and requirements (TGA, V2.1 June 2018) - adopted https://www.tga.gov.au/sites/default/files/190214_pharmacovigilance-responsibilities-medicine-sponsors.pdf

Description, evaluation and gap analysis of guidance documents regarded as in scope and key for the purpose of this task

1. CHMP Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: from Data to Labelling (EMEA/CHMP/203927/2005)1

Description

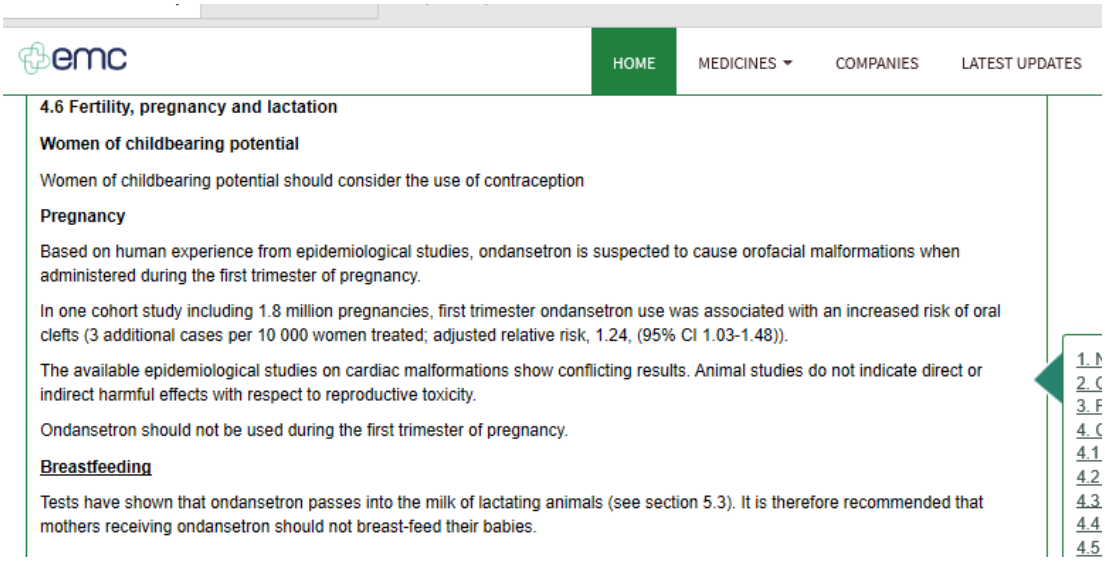
This guidance, released in draft mid-2005, was adopted by CHMP in July 2008 and came into effect in Jan 2009. It provides guidance on the integration of non-clinical and clinical data, and highlights the factors of importance for the assessment of the risk of an adverse reproductive/developmental effect in humans (fertility, pregnancy, health of the foetus and child), based on the assessment of reproductive toxicity studies in animals and human clinical data. It also outlines how to communicate the potential or identified risk of medicinal products for human use in product labeling and is intended for use in association with the CHMP Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Postauthorisation Data (EMEA/CHMP/313666/2005)2 (discussed below). Use of medication during pregnancy and lactation is covered.

Evaluation

At present, an update of the original version does not appear to be planned. Although the document is well structured and written, with much of its content still valid, it focuses primarily on risk assessment based on data relating to congenital malformations in isolation of other known teratological end points. Risk of adverse neurodevelopmental effects and other longer-term outcomes following exposure is referred to briefly (*section 6.2.2*) but the duration of follow-up is not stipulated. Far more prominence is given to the interpretation of malformation outcomes (*section 2.2.1*). 'Sufficient experience' from exposed pregnancies with neurodevelopment and other childhood outcomes is not defined, and as a consequence, guidance on labelling for these outcomes is not provided. Importantly, this guidance also provides suggested text in the *Guidance*

Appendix 3 for the purpose of product labeling. Examples of statements for use in *section 4.6 'Fertility, pregnancy and lactation'* of the summary of product characteristics for inclusion in the product label are based on assessment of risk. However, the case of ondansetron highlights issues regarding the implementation of this guidance.

Figure 1. Extract of Ondansetron SmPC (accessed online 2 Feb 2020)



Strong objections were raised to the use of the word *'cause'* in the SmPC (Figure 1.), in the context of what stakeholder groups considered a small increase in risk for a multifactorial malformation where the exposure is perhaps better considered one of many risk factors known to increase risk, and to the concluding statement that 'Ondansetron should not be used during the first trimester of pregnancy.', omitting the phrase '*unless the clinical condition of the woman requires treatment with (active substance)*', particularly given the existence in more than one country of guidelines for the treatment of hyperemesis in pregnancy recommending ondanseron as a second line therapy.

The current labeling recommending '*that mothers receiving ondansetron should not breast-feed their babies'* again does not appear consistent with current guidance which states that the recommendation regarding use during

breastfeeding should take into account human data of harm, and experience from use of the product in the neonatal population. No reference to human data is made in the label. Interestingly, a clinical trial exploring administration of ondansetron to women and their infants for the prevention of Neonatal Abstinence Syndrome (NAS) is currently enrolling (NCT01965704). https://clinicaltrials.gov/ct2/show/NCT01965704

Gap analysis

Review of the existing guidance (*text and Appendix 1. Integration table for risk assessment and recommendation for use*) suggests the following areas for improvement:

- Fetal growth and other longer term child outcomes should have more prominent coverage, in line with current thinking regarding the endpoints of exposed pregnancies.
- The number and timing of pregnancy exposures needed to classify a product risk for congenital malformation or other teratological outcome (neurodevelopment, growth, health) is required, if alignment with the new draft GVP guidance (EMA/653036/2019) is to be achieved regarding the definition of risk period and assessment of specific versus overall malformation rates.
- Consideration also needs to be given to the possibility of adverse fetal effects arising from exposure *in-utero* beyond the first trimester.
- When stipulating the number of first trimester exposed pregnancies for which data are available, the guidance does not take into account the possibility that exposure did not extend beyond week 4 of pregnancy and therefore did not occur during the main period of organogenesis and susceptibility to teratogenic effects. Discontinuation of a medication on recognition of pregnancy is commonly observed in clinical practice for new products where safety data are limited or absent. More precise consideration of the exposure window is required to establish whether a first trimester exposure is informative in terms of assessing the risk of major malformation with use of the product beyond week 4,

- The response from health professionals and patients to the revised labelling of ondansetron in 2019 raises the need for review of the application of and terminology used in the currently proposed standard statements for labelling through formal stakeholder consultation.

2. CHMP Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Postauthorisation Data (EMEA/CHMP/313666/2005)2

Description

Writing of EMEA/CHMP/313666/2005 commenced in October 2001, with a draft for consultation agreed by an ad-hoc expert group, and efficacy and pharmacovigilance working parties in June 2004. The final version was adopted by CHMP in November 2005, and came into effect in May 2006.

The guidance aims to provide criteria to select medicinal products for which active surveillance for collecting post-authorisation data in pregnancy is necessary. This document sets out guidance to advise on how to monitor accidental or intended exposure to medicinal products during pregnancy, to describe the specific requirements for reporting data and adverse outcomes of pregnancy exposure and to provide detailed recommendations regarding presentation of summary data collected on exposure in pregnant women. It also provides guidance on the reporting of paternal exposures (concern regarding risk to the fetus as a consequence of exposure to medications taken by the father at the time of conception or through semen during pregnancy).

Evaluation

Whilst recognizing the need for review and update, although written over a decade ago, this document continues to provide an excellent and coherent overview of the fundamental requirements of pregnancy pharmacovigilance for structural outcomes at birth. The scope of the document remains current in 2020 to a degree, but recommendations are relatively weaker in their focus with

regards to long term follow-up which is described as 'when possible and appropriate' rather than as 'essential when appropriate' and no longer term outcomes are defined in the document including in the 'Standardisation' section. The vast majority of examples and the list of outcomes focus predominantly on structural malformations whilst terms for neurodevelopment and other longer-term outcomes are neglected.

The potential benefits of disease registries compared to single product registries, and examination of offspring by clinicians blinded to exposure is recognised, along with the importance of collecting and recording data on normal pregnancy outcomes. Use of MedDRA codes for the recording of medical terms is requested and detailed operational instructions are provided to assist with the completion of the ICH E2B(R3) form for adverse event reports following pregnancy, breastfeeding or paternal exposure.

Importantly, this guidance includes 4 annexes of key information:

ANNEX 1 - QUESTIONNAIRE TO COLLECT INFORMATION ON PREGNANCY EXPOSURE
ANNEX 2 - INDIVIDUAL CASE SAFETY REPORTS (ICSR) OF PREGNANCY EXPOSURE
ANNEX 3 - SUMMARY TABLE OF PREGNANCY OUTCOME
ANNEX 4 – DEFINITIONS

Gap analysis

No further review of this guideline will be presented here as a large amount of the original content has been included in the draft of 'GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)', published for public consultation in December 2019 and discussed below.

3. GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Description

In July 2012 new legislation to strengthen and rationalise pharmacovigilance and increase patient safety was introduced in the European Union (EU) for which a set of guidelines entitled Good Pharmacovigilance Practices (GVP) was produced to support implementation.

The GVP guidance comprises a set of modules numbered I to XVI, grouped into two chapters, the first of which contains modules on 'Major Pharmacovigilance Processes', all of which have now been finalized. The second chapter focuses on Product- or Population-Specific Considerations. At the start of the ConcePTION project, guidance on vaccines, biological medicinal products and the paediatric population was available within this second chapter, with limited guidance for pregnant or breastfeeding women, and paternal exposure, included in a subset of the general PV modules of chapter 1 only.

Product- and Population- Specific Considerations Chapter P.III on 'Pharmacovigilance for the use of medicines by pregnant and breastfeeding women' was released in December 2019 and is open for public consultation until 28 February 2020. Existing guidance relating to pregnant and breastfeeding women from the various general GVP modules has been collated and summarized in the new pregnancy and breastfeeding draft (EMA/653036/2019), reviewed in the section below.

GVP Chapter P. III aims to provide guidance to marketing authorisation applicants/holders, competent authorities of Member States and the EMA for facilitating appropriate pharmacovigilance for medicinal products that may be used in pregnant or breastfeeding women. This new guidance introduces no new legislation and draws heavily on unchanged content from prior guidance. Readers or users of GVP Chapter P. III are asked to refer to earlier guidance,

suggesting that the intention is for this new GVP guideline to compliment rather than replace earlier guidance.

Evaluation

The addition of pragmatic, evidence based and expert reviewed guidance on contraception and pregnancy testing in the context of the Pregnancy Prevention Plan (PPP) is extremely helpful. Similarly, the collation of legislative guidance relating to pregnant and breastfeeding women from multiple general GVP modules into one document is welcomed. However the GVP Chapter P. III lacks provision of much needed added detail to improve the application and implementation of existing legislation and guidance.

The content of GVP Chapter P. III is also not aligned with the older guidelines which would benefit from simultaneous review and public consultation. This relates in particular to:

a) CHMP/203927/2005 CHMP Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation from Data to Labelling

b) CHMP/313666/2005 CHMP Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post authorisation Data (EMEA/CHMP/313666/2005), drafted 2005, published 2008.

There are a number of fundamental principles and definitions in the introductory section of the new guidance draft that need review for accuracy and alignment with the approaches used by the FDA and other EU data collectors. These include:

1. Gestational age at the time of exposure to a medicinal product during pregnancy is one of the most important factors in assessing teratogenic risk. To improve the quality of data that is collected reporters should be asked to report the exposure window as accurately as possible. The current draft document allows for greater uncertainty / vagueness in reporting than pre-

existing guidance. Reporters should be guided how to provide accurate information.

2. While the period of malformation risk stated in the draft (0 to 16 weeks) is not incorrect given the long period of fetal brain development, weeks 4 to 10 of pregnancy, and less specifically the first trimester, is usually regarded as the

   main period of susceptibility to human teratogens for major structural malformation. In order to avoid misinterpretation of the guidance, resulting in incorrect analysis of the data, precise definitions are required.

3. The concept of 'competing endpoints' is incorrectly described. This term refers to the fact that an outcome can only be viable or non-viable, with three subcategories of the latter ie. a pregnancy can only end in LB (Live Birth) or ETOP (Elective Termination of Pregnancy) or SA (Spontaneous Abortion) or SB (Still birth), however, any of these outcomes could involve a birth defect. Review of the wording is required.

4. No definition of trimesters is currently provided.

5. It is also key that lack of structural malformation is not taken to represent a lack of teratogenic effect. A product that does not cause structural malformations or dysmorphic features may still perturb brain development. This needs to be taken into consideration when deciding on the need for long term follow-up and the role of dysmorphology in future signal detection strategies.

6. Critically, the current EMA definition of a 'prospective' report, carried through from CHMP/313666/2005 introduces an inclusion bias that could prevent the recording of teratogenic effects. By virtue of this definition, only pregnancies that have had a normal prenatal scan will be represented in what is generally regarded as the 'gold standard' prospective cohort. The

presence or absence of an abnormal prenatal test should not be the determining factor for a report being prospective or retrospective, but rather whether or not a prenatal test has been done at the time of reporting. This is in line with the 2018 FDA guidance for PASS in pregnant women and previously used definitions of prospective versus retrospective, which depended on whether the birth outcome was known or unknown at the time of reporting or enrolment to a registry, NOT whether it was normal or abnormal. It should be also considered that for different endpoints the definition of prospective may alter. For longer term outcomes, which cannot be determined by prenatal imaging in the main, prospectively ascertained pregnancies could be up to delivery.

7.
8. The calculation of congenital malformation (CM) rate does not align with co-existing guidance that states that overall rates of CM need to be analysed given rarity of individual CMs. Harmonisation, across both EU and other international guidance, of the approach to assessment of risk for an outcome of this significance is key.
9. Dose adjustments are not informed by changes in plasma levels alone. Correlation with clinical features of the disease is key. Some conditions improve during pregnancy. Even if the serum concentration fell, a dose increase may not be indicated and potentially puts both fetus and mother at unnecessary increased risk. Oversimplification of this section carries the risk of the non-expert misinterpreting the background information.
10. The importance of signal detection is explained : 'The purpose of collection of pregnancy data is to detect certain trends in pregnancy outcome, which could be a signal for specific adverse effects. Therefore, such data should be analysed on a regular basis'. Clarification of what constitutes a signal and the signal detection method in the context of Pregnancy PV is required.
11. The description of study types is detailed and welcomed however the lean towards population-based cohort methodologies is in stark contrast to the FDA guidance which views them as 'complementary' due to the often poor ability to collect information on confounder variables.

Additional formal and extensive evaluation of GVP Chapter P. III was submitted to the EMA by the ConcePTION consortium and is available on request.

Gap analysis

The issuing of new guidance offers opportunities to improve data collection.

However, the *Questionnaire to collect information on pregnancy exposure, GVP Chapter P.III. Appendix 1*, is unchanged since the 2005 guidance issued 15 years ago. Given that these revised GVP modules aim to improve the implementation of the legislation and to improve PV practice, modification of the current ICH-E2B(R3) template to capture the required fields in a structured and systematic manner needs to be considered as a matter of priority. Further delineation of data fields considered necessary for longer term outcomes, in particular, what the document terms 'developmental delay' is required. The current suggestion that key listed information be provided in the narrative is suboptimal, both in terms of optimising the completeness and accuracy of data provided by reporters, as well as the readiness of data for automated signal detection and analyses. The addition of specific structured data fields/ elements for core pregnancy PV data elements to the existing ICH-E2B format is urgently needed to harmonise data collection and to ensure the meaningful collection of neurodevelopmental measures and for other long term outcomes such as cancer. The addition of recording of genetic test results that are thought to explain adverse outcomes in stillbirths, and other pregnancy losses as well as for live-births would further improve interpretation of reported cases.

Similarly, the table for submission of PSUR is unchanged from CHMP/313666/2005. Review of the required reporting format offers the opportunity to improve interpretation and contextualisation of the data, for example by capturing the number of cases 'Lost To Follow Up' , and requesting information on neurodevelopment or other long term outcomes. There is also opportunity to perhaps ask the reporter for summary statistics of their dataset (where applicable) to capture the total number of pregnancy reports they have received for the exposure in question, how many normal, abnormal etc, thereby establishing a denominator and insight into datasources of potential relevance should additional data be required following report of an early signal.

The table for requirements for the submission of ICSR with pregnancy exposure is unchanged from CHMP/313666/2005. It does not seem logical or conducive to accurate data analysis when an 'AR in mother + SA Or Foetal death without CM' is classed only as 1 case <mother>, with the same being true if there is No AR in the mother. This classification system seems to be focused around congenital malformation being the only marker of a teratogenic effect, and appears to ignore other key markers of harm such as spontaneous abortion or fetal demise. Reassessment of prior guidance needs to be part of this update, taking into account the usability of collected data, especially in regards to sections that have been incorporated in the new guidance.

This new guidance has been long awaited by industry and academic partners alike, for whom clarification regarding the implementation in daily practice and within the ConcePTION project of diverse legislative and academic guidelines poses a challenge. In particular, consideration of the following in the guidance would have been welcomed:

a) The ENCePP Code of Conduct is not currently referred to the 2019 draft GVP guidance and should be included in future dratfs (http://www.encepp.eu/standards_and_guidances/documents/ENCePP_Methods_Guide_Annex2.pdf.)
b) Guidance as to the minimum length and interval of follow-up for pregnancy registries or pregnancy case reports
c) Clarification as to which long term outcomes need to be surveyed for and at what ages
d) Guidance on the neurodevelopmental outcomes that need to be assessed e.g composite measures such as IQ versus measurement of component functions such as language, motor development etc versus outcomes such as ADHD, autism with presentation of results if available
e) Recommended assessment tools / questionnaires for neurodevelopmental assessment.

f) Guidance on longer term follow-up for pregnancy registries or surveillance programs that were closed on the basis that the number of first trimester exposures stipulated in existing guidance provide no evidence of increased risk for congenital malformations.

g) Development of *P.III. Appendix 1*. Questionnaire to collect information on pregnancy exposure (unchanged since 2005 guidance) from a high level list of categories to a more structured list of data fields for which a standardised coding system or unit of measurement is provided where appropriate

h) Methodological guidance as to how to analyse pregnancy or breastfeeding exposure surveillance data, taking into account the need for different methodological approaches for different study designs

i) A process through which to update the SmPC in order to incorporate the results of studies, published between scheduled PSURs, which identify no signal or harm but are considered to provide clinically useful data in support of safety. With this, suggested standardized text to unify the interpretation of limited data would be beneficial.

4. FDA Guidance documents relating to PV in pregnant and/ or breastfeeding women

The FDA register of guidelines currently includes four documents relating to PV in pregnant and/ or breastfeeding women, entitled:

- Postapproval Pregnancy Safety Studies, (2019)
- Clinical Lactation Studies: Considerations for Study Design (2019),
- Pregnant women; Scientific and Ethical Considerations for Inclusion in Clinical Trials
  (2018)
- Pharmacokinetics in pregnancy – Study design, Data Analysis, and Impact on Dosing and Labeling (2004)

Description

In contrast to EU guidance which aim to inform various audiences: regulators, the EMA and industry, the FDA guidelines listed above are written specifically for industry . They "do not establish legally enforceable responsibilities. Instead, the guidance describes the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited". The 2018 guidance regarding inclusion of pregnant women in clinical trials is also intended to stimulate further discussion and debate.

Evaluation

All four documents are currently in draft; while the two 2019 guidance documents replace *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format Guidance for Industry (Small Entity Compliance Guide) from 2015,* and the *Clinical trials Guidance* is a 2018 first revision, it would seem that the document on *Pharmacokinetics in pregnancy* was never adopted despite being drafted in 2004, over 15 years ago.

Formal evaluation and comment of the FDA *Postapproval Pregnancy Safety Studies, Guidance for Industry* 2019 draft has been provided by the ConcePTION consortium and is available on request. The document focuses on describing methodological considerations that are unique to the study of medication use in pregnant women. Importantly, it expands on the strength and weaknesses of the wide repertoire of study designs with which risk to the fetus could potentially be investigated. Alignment with the list of methodological approaches briefly outlined in EMEA/CHMP/313666/2005 is strong. The guidance provides valuable and much welcomed detail on optimising study design and quality however there are differences when compared to the EMA. The FDA document for example considers population based studies to be 'complimentary' studies due to their limited confounder adjustment and lack of blinding, whilst the EMA document suggests that these are central to post-market authorization studies.

Gap Analysis

Whilst there are clear descriptions of the different methodologies utilized in pregnancy pharmacovigilance there is no guidance as to the criteria for requiring additional studies and what format these should take.

The FDA *Pharmacokinetics in pregnancy* guidance is intended to promote an increase in the amount of useful data concerning how drug kinetics are affected by pregnancy and to further encourage the development of appropriate therapeutic treatments for pregnant women. Topics covered include ethical considerations associated with conducting PK studies in pregnant women, study

design, data analysis, labeling, and considerations for future research. Having been drafted in 2004, it predates a wealth of data and publications, such as the systematic review by Pariente et al. (1) An update and revision of the guidance to include focus on the importance of considering the clinical condition of the patient and not just the laboratory result, would make this a valuable guideline, both for those implementing pregnancy PK studies and to support informed clinical application of findings from PK studies in pregnant women.

5. Pharmacovigilance responsibilities of medicine sponsors, Australian recommendations and requirements (TGA, V2.1 June 2018)

Description

The Australian guideline, *Pharmacovigilance responsibilities of medicine sponsors, Australian recommendations and requirements* was identified by Google search and included in our review as, at the start of this task, it included the most recently published guidance relating to pregnant and breastfeeding women. It is a general PV document that is aligned with the *EMA Guideline on Good Pharmacovigilance Practices (GVP) Module VI—Management and reporting of adverse reactions to medicines*, except where requirements and

recommendations are specific to Australia. It outlines requirements for sponsor reporting and record-keeping, relevant legislation, and provides recommendations on the monitoring, collection and management of safety data to support 'best practice pharmacovigilance'.

Evaluation

In some sections of the document, very brief text outlining the specific requirements for pregnant and breastfeeding women is provided. For example, the section on '*Key data elements for adverse reaction reports*' states that the following additional information should be collected for adverse reaction reports of maternal/paternal or foetal exposure:

> "*– the gestation period at time of exposure*
>
> *– information about the parent such as their identity, age or date of birth, date of last menstrual period, weight, height, sex, relevant medical history and concurrent conditions, relevant past medicine history*
>
> - *Route of administration for the parent"*

The guidance also includes a one page section entitled '*Reports of exposure during pregnancy and breastfeeding*' under Reporting requirements for special situations. High level guidance with minimal operational detail is provided. Sponsors are urged to follow up all reported cases and to obtain as much information as possible. Legal requirements are stipulated as follows:

> *"You **MUST**:*
> - *report pregnancies that result in abnormal outcomes suspected to be related to the medicine as serious adverse reactions. Such cases include:*
> - *congenital anomalies or developmental delay in the foetus or the child*
> - *foetal death and spontaneous abortion*
> - *serious adverse reactions in the neonate.*

Note: A premature delivery (i.e. earlier than 37 weeks) is not considered an abnormal outcome unless it resulted in adverse reactions to the neonate or mother.

- *report suspected serious adverse reactions in infants following exposure to a medicine in breastmilk in accordance with the reporting requirements for serious adverse reactions.*
- *report any signal of a possible teratogenic effect, such as a cluster of similar abnormal outcomes, as a significant safety issue. "*

Gap Analysis

Whilst at first glance offering the advantage of clarity through the simplicity of content and wording, this guidance, like others lacks specificity as to how to achieve the recommendations. Prematurity is the only outcome that is defined, and differs by one week from the EMA GVP P.III guidance which defines delivery prior to 37 completed weeks as preterm.

6. ICH Topic E 2 D, Post Approval Safety Data Management ICH Harmonised Tripartite Guideline (CPMP/ICH/3945/03)

Description

ICH E2D "provides guidance on definitions and standards for post-approval expedited reporting, as well as good case management practices with the aim of establishing an internationally standardized procedure in order to improve the quality of post-approval safety information and to harmonise the way of gathering and reporting information." It focuses on providing guidance on definitions and standards for post-approval expedited reporting, as well as good case management practices. Definitions for Adverse Event (AE), Adverse Drug Reaction (ADR) and Serious AE/ADR are provided. 'Congenital anomaly/birth defect' is included in the list of Serious AE/ADRs.

Evaluation

The current 2003 guidance includes only one small section, included below, on pregnancy:

"5.4.1. Pregnancy Exposure

MAHs are expected to follow up all pregnancy reports from healthcare professionals or

consumers where the embryo/foetus could have been exposed to one of its medicinal

products. When an active substance, or one of its metabolites, has a long half-life, this should be taken into account when considering whether a foetus could have been exposed (e.g., if medicinal products taken before the gestational period should be considered)."

A business plan to revise ICH E2D to ICH E2D(R1) was endorsed by the Management Committee on 18 November 2019, the timescales for which are set out below. No specific mention to the need for additional focus on pregnant and breastfeeding women is included in this initial business plan.

Table 1. Project timeline for the revision of ICH E2D

Expected Completion date	Deliverable
Oct. 2021	Step 1 Consensus Building, Revisions of Guideline
Nov. 2021	Step 2a ICH Consensus/Endorsement of Revised Guideline/ Step 2b Adoption of the Revised Guideline
May. 2022	Step 3 Regulatory Consultation and Discussion
May 2023	Step 4 Adoption of ICH Harmonised Guideline

Gap Analysis

The need for ICH guidance in the area of pregnancy and breastfeeding is self-evident.

Discussion

This review highlights the recognition by regulatory agencies globally of the complexities and importance of improving PV in this population. Both the FDA and EMA issued new or updated draft guidance specific to pregnant and breastfeeding women within the last 12 months. What is notable is the time that development of these guidelines has taken, generally spanning a number of years with 2004 guidance still in draft form.

Each of these documents highlight that pharmacovigilance in pregnant and breastfeeding women presents a myriad of challenges over and above those already recognized for the general population and other specific populations.

The physiological changes of pregnancy alter drug pharmacokinetics and dynamics, sometimes unpredictably, impacting on both efficacy and adverse event risk in the mother. Added to this is the ever changing risk to the fetus.

Placental transfer varies at different stages of pregnancy, as does fetal susceptibility to teratogenic effects during different stages of development. Teratogenic effects are also often not predictable from the known therapeutic mechanism of action of a drug. Determining risk to the nursing infant with maternal medication use is no simpler. Precise recording of dose and interval between maternal mediation use, breast-feeding and infant health, taking into account the different composition of fore- or hind milk is required.

However, whilst recent guidance collates information and expands on theoretical considerations, there remains ambiguity as to when a post market authorization study would be required, what outcomes/ endpoints it would cover and what methodological approach should be used. Further, there is a pressing unaddressed need to improve the practical operability of data collection.

Systematic and structured collection of information specific to pregnancy and breastfeeding, in addition to that required for general adverse event reports, is key. In order to achieve this, expert consensus is required to clarify what is expected and how to collect and assess data for this special population. For example, guidance regarding the duration and intervals for long term follow-up of pregnancy or lactation exposures is lacking. Lack of specificity resulted in differences as to how guidance was interpreted amongst ConcePTION WP2 members.

It is notable that in all FDA guidance, the importance of investigators obtaining advice from experts in relevant fields, including but not limited to teratology, genetics, statistics, obstetrics and paediatrics, at the stage of study design is emphasised. All too often the need for specialised knowledge in this area of PV is not recognised, resulting in both academic and industry registry holders realising at the point of analysis that they lack the expertise required to analyse and interpret the data they have collected, and all too often finding that key information had not been requested in questionnaires.

It is also evident from review of the updated draft guidance that the current EU systems in place for adverse event reporting are not optimized for PV in pregnant and breastfeeding women, where information on both mother and offspring needs to be collected and recorded clearly and systematically. Commercial databases used by some industry partners do not contain basic fields essential for teratovigilance as standard. In contrast, while most academic partner registries have very well structured data collection systems, they are not beholden to the same reporting legislation as industry. As a consequence, pregnancy data of clinical value may not be visible. It is of interest and relevance that the pubmed search conducted at the start of this task failed to identify a single regulatory guidance document of relevance to pharmacovigilance in pregnant and breastfeeding women. Alignment between academia and industry is required.

Many industry partners have vast amounts of unpublished data on normal pregnancies that, under current guidance is not reported to Eudravigilance and therefore is not prioritized for inclusion in the product label unless the prevalence of an adverse outcome appears increased above that observed in the relevant background population. This results in a suboptimal situation where the regulatory response to a signal is frequently to advise against use of a certain medication in pregnancy or breastfeeding. For women with chronic conditions that require ongoing treatment, this often translates to the clinician needing to consider prescribing another medication for which published or analysed safety data are lacking. Where the magnitude of the signal is small or uncertain, this brings into question the true risks and benefits of discontinuing a therapy, which not uncommonly has been widely used in clinical practice. An accepted method for the analysis of existing datasets, potentially in a common data model, and a system for more timely inclusion in the product label of exposures with 'normal' outcomes in the future to support clinical decision making is required.

According to an FDA review based on 59 pregnancy registries, only a minority (12%) informed the label to adequately advise patients and healthcare professionals (HCPs), notwithstanding huge investments in funds and time by the sponsors (ConcePTION DOA). More concerning is that a further Pubmed search undertaken on 2 Feb 2020 during the write up of this report (using the terms 'Eudravigilance' and 'pregnan*') revealed only one publication in 2019 in which Eudravigilance data have been used to assess teratogenic risk (2).

In this study, data from four different PV databases were considered. The authors conclude that "*Pharmacovigilance databases have many limitations, most importantly lack of a clear denominator for patients exposed to the drug of interest and duplicate cases that are difficult to identify. Given widespread use of new antiretroviral drugs worldwide and anticipated use of new drugs, prospective follow-up of pregnant women and birth surveillance studies such as Tsepamo are critically needed. ……. Safety reports were inconsistent between databases and very hard to interpret.*"

Methodological studies are needed to assess the suitability of existing data sources for pregnancy PV.

Finally, despite the known impact of major human teratogens such as alcohol(3),valproate(4) and isotretinoin(5) on the developing brain, at doses lower that that required for structural teratogenesis, all reviewed regulatory documents still primarily focus on structural malformation outcomes.

This review suggests that there is therefore a disconnect between the resources being invested in optimizing the PV systems for pregnant and breastfeeding women and the demands currently being placed on stakeholders to support these systems. Reporting to multiple surveillance systems (adverse event systems, pregnancy exposure registries, disease registries, birth defect registries to name a few) is extremely resource intense and confusing for HCPs and women. The resulting multitude of datasets presents regulators and those trying

to make sense of fragmented but overlapping data with just as many challenges. The recently released GVP Chapter III Guidance does not address these issues. A far more radical review and update of regulatory guidance is required, with consideration given to less reliance on spontaneous reporting by the Marketing

Authorization Holder (MAH) and the possibility of systematic collated analysis of public and industry data to inform regulatory decision making.

The Final Business Plan for the E2D(R1): Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting (18 November 2019) highlights that since 2003:

> *"new sources of postapproval safety information have emerged and that the definitions and regulatory guidance in ICH E2D are no longer sufficient to provide guidance on the current practices and needs. Therefore, the definitions and standards for the management of post-approval safety*

information need to be revisited in order to support appropriate safety surveillance and actions…

In the current situation significant resources are being spent on handling increasing volumes of ICSRs that are of variable value to post market safety surveillance. There is a need to establish principles on how to manage these more effectively to support patient safety."

And that there is a need to:

"provide pragmatic solutions that can be adopted globally to ensure consistent collection, review, analysis and reporting of safety information from various data sources to ensure global data can be leveraged to optimise patient safety.

harmonize the way of reporting information from new or more frequently utilised sources of post-approval safety information. "

Of concern, the final business plan makes no reference to special populations such as pregnant or breastfeeding women, for whom all of the above apply. We feel strongly that a case needs to be made for the simultaneous development of

ICH guidance in this area. We also identify the opportunity for work being conducted within WP2 of the ConcePTION project to contribute to and form part of this guidance. In particular, WP2 aims to enhance safety data collection in pregnancy and the analysis of case reports to include:

1) Publication of standardised core data elements (when and what) to be collected 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 these deliverables will be regulatory accepted and be considered for implementation in the regulatory practice.

The time taken to develop pregnancy and breastfeeding guidelines is generally longer than that for general guidance and has to be taken into account. The ConcePTION project pulls the key experts around the table, however initiation by the EMA of formal public consultation on existing guidance such as CHMP/203927/2005 and CHMP/313666/2005 now, to align with feedback received on GVP Chapter III would greatly assist in addressing concerns around key topics not covered in GVP P. III, and which could then be addressed in ICH E2D(R1).

Recommendations

On the basis of this review, we recommend the following:

1. Development of internationally harmonized guidelines for medication use during pregnancy and breastfeeding that apply to both industry and academia so that data collected in different systems are comparable and combinable
2. Include in these guidelines an in depth focus on data fields for important wider outcomes such as cancer and neurodevelopment
3. Improve awareness of these guidance documents amongst academics, clinicians and public health bodies e.g. through publication in scientific journals
4. Data collection systems to be optimized and standardized for PV in pregnant and breastfeeding women
5. Streamlined and clear regulatory reporting pathways
6. Full capture centrally e.g. in Eudravigilance of data collected from different sources
7. Global standardisation and harmonization of data collection (what and when)
    - *standardised core data elements and protocol for collection of medication exposures in pregnancy AND breastfeeding*
    - *standardised core data elements and protocol for follow up of long term outcomes*

- *standardized definitions*
- *use of harmonised coding systems where appropriate*

8. Alignment of reporting requirements for both industry and academia
9. Involvement of experts in relevant fields, including but not limited to teratology, genetics, statistics, obstetrics and paediatrics, from the stage of study design or surveillance and data collection through to analysis, interpretation and communication/publication of findings
10. Methodological studies to assess the suitability of existing data sources for pregnancy PV
11. A mechanism by which findings other than adverse events / signals are fed back into the SmPC in a timely manner
12. Exploration of novel methods of data collection to reduce burden on reporter and data collector, and improve accuracy and completeness of data collected
13. Clarity for HCPs and patients as to how data they provide to regulatory agencies are analysed or assessed
14. Increased involvement of pregnant women in contributing to data collection

15. Consideration be given to the structure of the guidance e.g. Separate sections or documents for
    - legislative requirements
    - background/ theory
    - standardized protocols / methodological approaches
    - practical / operational info (ie. 'how to fill in the form')
    - standardized wording for labeling

List of abbreviations

CHMP	Committee for Medicinal Products for Human Use
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency

ENTIS	European Network of Teratology Information Services
FDA	Federal Drug Agency
GVP	Good Pharmacovigilance Practice
ICSR	Individual Case Safety Report
MAH	Marketing Authorisation Holder
SmPC	Summary of Product Characteristics
TGA	Therapeutic Goods Administration

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WP2 – Improving the collection, analysis and interpretation of pregnancy pharmacovigilance data

D2.3 Report describing existing schemes of reported medication exposed pregnancies.

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Summary

This document provides an overview of work undertaken within WP2, as a subtask of Task 2.3 to review currently recommended or 'in-use' data fields/ data elements for the collection of pregnancy exposure information and maternofetal outcomes. The aim of this analysis is to :

a) delineate and compare structured data collection across pregnancy PV systems b) assess whether there may be benefit to combining data from different data sources in a Common Data Model and

c) inform development of a list of Core Data Elements considered to be essential in pregnancy PV data collections systems .

Utilizing the U.S Food and Drug Administration (FDA) 2019 draft guidelines Postapproval Pregnancy Safety Studies Guidance for Industry as a reference, EU regulatory guidance and well established large data collection schemes were compared against these recommendations. Areas of commonality and divergence were reviewed and data elements absent from the FDA guidelines but notable in other collection schemes are highlighted. Recommendations for future work within the ConcePTION project are identified.

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Introduction

There is a wealth of diverse datasets currently in operation for the specific purpose of medication pharmacovigilance in pregnant women. These resources range from adverse event case reports and time limited academic cohort studies, which are often medication or disease specific, to on-going teratology information service network surveillance. The aim of this report was to:

a) delineate and compare structured data collection across pregnancy PV systems,

b) assess whether there might be potential benefit to combining existing data from different data sources in a Common Data Model (CDM),

c) inform development of a list of Core Data Elements considered to be essential in pregnancy PV data collections systems,

d) assess the potential for using existing databases such as Eudravigilance or the IMI Protect project pregnancy database as the basis of a CDM.

Initially, we had planned to undertake this analysis using the expected European Medicines Agency (EMA) GVP P. III guidance as the 'gold standard' for comparison. However, due to delays to the release of the EMA GVP P.III, the identified data collection schemes were instead compared to the May 2019 FDA draft guidance document[1] with the EMA draft guidance added in once it became available in December 2019[2].

Data element review

When collecting data on an exposed pregnancy there are a large number of data fields or data elements in addition to the reported outcome which are required in order to determine the potential role of the exposure in the outcome. Through discussion with Work package 2 member's major data collection schemes were identified and examples were selected to allow assessment of data collection

within that methodology (i.e. pregnancy register, teratology information service etc). Data was extracted from publically available information or was requested directly from each scheme. Selected data collection schemes for comparison included:

- FDA draft guidance[1]
- EMA 2005 and 2019 Guidance[2,3]

    a) Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations III: Pregnant and breastfeeding women EMA/653036/2019 DRAFT FOR PUBLIC CONSULTATION[2]

    b) CHMP Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post authorisation Data (EMEA/CHMP/313666/2005)[3]

    Both guidance documents list a high level of information that needs to be collected; this list is unchanged between documents.

- ENTIS[4] is a global collaborative network of Teratology Information Services. Member organisations consist of medical doctors, pharmacists, genetic counsellors and scientists all working together with the primary aim of preventing birth defects and developmental disorders which arise as a consequence of maternal or paternal perinatal exposures.

- OTIS /MotherToBaby[5] is a service of the non-profit Organization of Teratology Information Specialists, is dedicated to providing evidence-based information to mothers, health care professionals, and the general public about medications and other exposures during pregnancy and while breastfeeding.

- Protect[6] is the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) and was a collaborative European project to address limitations of current methods

in the field of pharmacoepidemiology and pharmacovigilance. It included a study on pregnancy which built a database for testing new ways of collecting information on lifestyle factors, health and use of medicines throughout pregnancy in a large number of pregnant women.

- BUMPS[7] is an online data collection system designed by the UK Teratology Information Service to enable patient self-reporting and longer term follow-up of children exposed to medications *in-utero.*

- PregNANT[8] is an online data collection system designed by Lareb, the Dutch Teratology Information Service to enable patient self-reporting and longer-term follow-up of children exposed to medications *in-utero.*

- EUdravigilance ICH-E2B[9] is the system for managing and analysing information on suspected adverse reactions to medicines which have been authorised or being studied in clinical trials in the European Economic Area (EEA). Data is collected through a structured format, ICH-E2B.

- VaMPSS[10] is a nationwide US post-marketing surveillance system established to comprehensively monitor the use and safety of vaccines and medications during pregnancy. It represents a unique collaboration the American Academy of Asthma, Allergy & Immunology (AAAAI), the Organization of Teratology Information Specialists (OTIS), the Harvard Pregnancy Research Group, and the Birth Defects Study (BDS) / Pregnancy Health Interview Study (PHIS) at the Slone Epidemiology Center at Boston University.

- EURAP[12] is a prospective observational study of pregnancies with antiepileptic drugs (AEDs), launched in Europe in 1999 by a consortium of independent research groups and later extended to several other nations worldwide.

Data elements for each of these schemes were plotted against the FDA requirements. Table 1 is a visual representation of the data elements from each data collection scheme in comparison to the elements recommended by the FDA. At first glance it is immediately obvious that despite consistency across many fields, there are areas of significant heterogeneity. There was good alignment between the proposed FDA and EMA requirements. EURAP and the teratology information centre schemes in Europe (ENTIS) and in the USA (OTIS), also aligned well with the FDA and with each other. The Protect study did not collect details on the women's obstetric history, or medication dose, route of administration and indication for use during pregnancy or information on neonatal outcome which represents a substantial deviation from the FDA recommendations. Eudra Vigilance had the least number of overlapping data elements with the FDA guidance, with a lack of collection in the areas of obstetric history, recreational drug and alcohol use and neonatal outcomes. Collection of longer-term child outcomes was weaker all schemes in comparison to structural child outcomes (i.e. malformations).

Table 1 : Comparison of data fields across different pregnancy surveillance and PV data collection systems

FDA	ENTIS	OTIS	PROTECT	bumps	pREGnant	Eudra Vigilance	EMA GVP	VAMPSS	EURAP
General									
Patient identifier		1							
Reporter name									
Date of initial contact									
Contact details of reporter			2	2			17		
Reporter source		3	3	3	3				
Demographics									
DOB				4					
Ethnicity					5				
BMI							15		
Occupation									
Obstetric History									
Number of past pregnancies									
Past parities							16		
Past spontaneous abortions							16		
Past terminations							16		
Past stillbirths							16	16	
Past extrauterine pregnancy									
Past pregnancy complications									
Birth defects in past pregnancies								18	
Neonatal problems in past pregnancies									
Pregnancy Details									
LMP Date									
Due Date (ultrasound guided)									19
Prenatal test results									
Maternal weight gain									
Pregnancy complications (incl. pre-existing disease course)									
Number of foetuses									
Maternal Exposures									
Medicines (incl. Rx, OTC)									
-Route of administration									
-Dose									
-Indication									
-Duration of use (in days)								20	
-SOP at exposure (from date of first use)						7	7		

Continued over the page…

Table 1 : Comparison of data fields across different pregnancy surveillance and PV data collection systems. Continued…

FDA	ENTIS	OTIS	PROTECT	bumps	pREGnant	Eudra Vigilance	EMA GVP	VAMPSS	EURAP
Dietary Supplements (incl. vitamins/minerals)									
Recreational Drugs									
Tobacco									
Alcohol									
Family Details									
History of birth defects and details (maternal/paternal)						8		8	
History of genetic disorders and details (maternal/paternal)				9		8	8	8	
History of multiple foetuses						8	8		
Pregnancy Outcome									
Reporter source			10	10	10				
Date of report									
Date of outcome					11				
Gestational age at outcome						8			
Outcome (incl. reason for ETOP)									
Infant sex									
Neonatal physical examination results									
Neonatal complications						12			
Malformations (at outcome or longer FU incl date reported)						12			
Developmental complications	14					12		21	
Infant illnesses						12			
Infant hospitalisation						12			
Infant medication use						12			

Key

- Yes
- No
- Unclear
- Partially collected or available through other data fields or by linking to other data sets

1 Initials only; 2 Email only; 3 Always pregnant women; 4 Age only; 5 country of birth only; 6 Workplace activity demands; 7 Can be calculated with LMP detail; 8 Could be available in relevant medical history field; 9 Only in infants with a history of birth defects; 10 Always pregnancy women; 11 DOB yes, others unknown; 12 Could be available in adverse event field; 13 Can be linked with national datasets; 14 Only in infants with a history of birth defects; 15 Can be calculated with height and weight detail; 16 From number of previous pregnancies and outcome item; 17 May be available from additional identification of the gynaecologist-obstetrician field; 18 Could be available in outcome of previous pregnancy field; 19 not always ultra sound guided 20 Can be calculated from exposure start and end date; 21 Communication, fine motor, gross motor, personal-social, problem solving, overall parental concern.

Working backwards from the comparison schemes a number of data elements were collected by the included schemes which were not in the recommended FDA list. These included data on additional exposures (e.g. hormone contraceptives, herbal remedies, occupational exposures), family background information such as parental years in education and family learning disability history and paternal exposure information. Figure 2 displays in detail these additional data fields.

Figure 2. Additional data fields common to the included surveillance schemes not included in the FDA guidance.

Common/useful additional data fields for consideration

Demographics
Education level, socioeconomic measures, country of birth

Pregnancy details
ART, breakthrough/unplanned pregnancy, menstrual cycle irregularities, date of first antenatal visit, maternal hospitalisations, consanguinity

Family medical history details
Learning difficulties (maternal or paternal)

Paternal data
Demographics, illnesses, medicines use (incl. 3 months prior), recreational exposures, occupational/environmental exposures

Maternal exposures
Continued birth control, homeopathic remedies, herbals, diagnostic or environmental radiation, occupational exposures, caffeine, vaccines, second hand smoke, anaesthetics

Pregnancy/infant outcome
Delivery details, Apgar scores, birth weight and length, head circumference, NICU admission, maternal admission/ ICU, infant identifiers (long term FU), developmental milestones, infant/childhood medical conditions, infant/ childhood hospital admissions

Looking to the future

Teratology information services are specialists in the collection and analysis of pregnancy exposure data and have been undertaking teratogen surveillance using a standardized method for over 30 years and this specialism is evidenced in their wide ranging data elements. This review raises questions about the suitability of using Eudra vigilance data in its current format for pregnancy PV

going forward. It suggests that additional data elements may need to be considered 'core' in order to create an optimal and flexible minimum dataset which is able to address risk for a wide range of maternal and child outcomes. Future work in Work package 2 will determine a set of core data elements, building on the FDA and EMA data fields, but incorporating key fields identified from ongoing data collection systems which will add benefit. In particular, little of the FDA guidance focused on data elements related to longer-term child health and neurodevelopmental outcomes, and information on additional confounder and outcomes data elements which would be required for investigation of these outcomes, despite there being life-long potential impacts in these domains.

Harmonization with other workpackages and tasks

The work from this review was utilised in the creation of the suggested optimal list of Core Data Elements for the first 12 months after pregnancy which is presented in appendix 3 of this report. The data from this task will be considered by colleagues in Work package 1 who are working on defining CDE for analyzing data from routine sources. This work will also feed into other aspects of the ConcePTION project and will underpin development of the Common Data Model (task 2.4) and will inform discussions and decisions within the Definitions Task Force.

List of abbreviations

FDA – US Food and Drug Administration
EMA – European Medicines Agency
ENTIS – European Teratology Information Services
OTIS – Organisation of Teratology Information Services
BUMPS – Best Use of Medicines in Pregnancy
PROTECT- Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium
pREGnant –The Dutch Pregnancy Drug Register
VAMPSS- Vaccines and Medications in Pregnancy Surveillance System
EURAP- European Registry of Antiepileptic Drugs and Pregnancy
ART – Assisted reproductive technology
FU – follow up
NICU – Neonatal intensive care unit

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IMI2 821520 - ConcePTION

WP2 – Improving the collection, analysis and interpretation of pregnancy pharmacovigilance data

D2.3 Coding systems, schemes and units of measurement in support of core data fields for reporting medication-exposed pregnancies and outcomes

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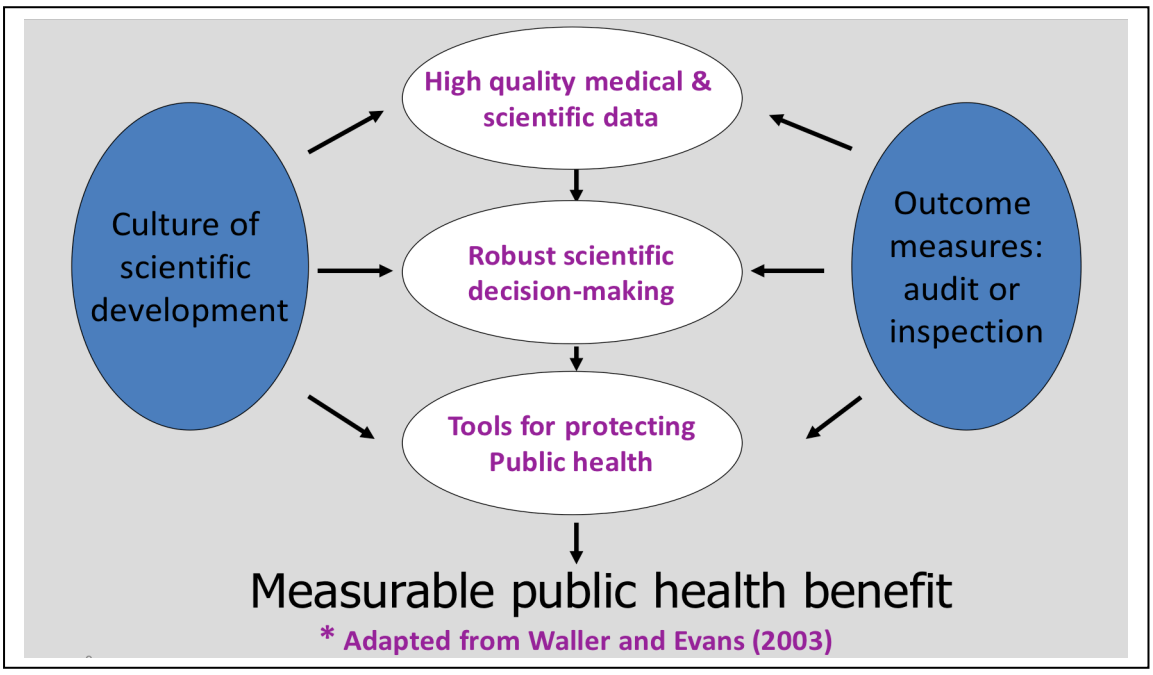
Background

Pharmacovigilance (PV) is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other problem associated with a medicinal product (1). The public private partnership, IMI ConcePTION (**Con**tinuum of **E**vidence from **P**regnancy Exposures, Reproductive **T**oxicology and Breastfeeding to **I**mprove **O**utcomes **N**ow) was formed under the aegis of the innovative medicines initiative in order to radically and rapidly to reduce uncertainty about the effects of medication used during pregnancy and breastfeeding. In order to maximise the value of the contribution of ConcePTION it is prudent to adopt a robust model for the management of safety data that will affect important medical decisions. Coding of safety data is often regarded as a mundane, even an unrewarding topic; nevertheless, it is an essential task and is essential to maintain data integrity and to provide standards that will facilitate medical and scientific evaluation of pharmacovigilance data. This will be achieved by adhering to the operating model shown in Figure 1.

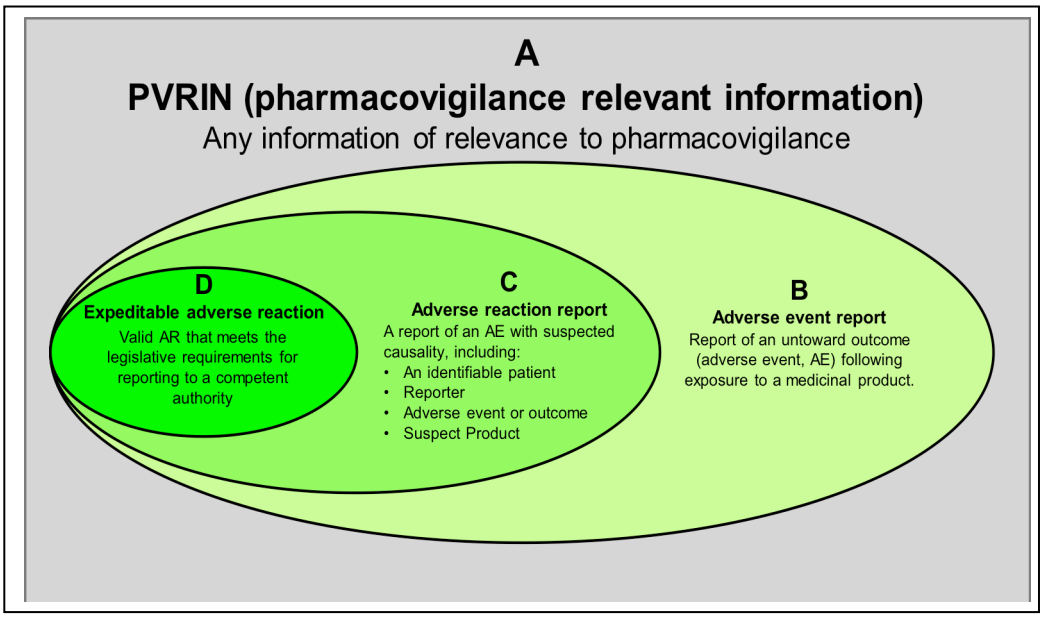
Figure 1. Model for excellence in pharmacovigilance



There are three main areas where ConcePTION Work Package 2 will contribute to the overall goal:

1. By detecting whether risks exist or not resulting from the exposure to medicinal products during pregnancy and when breastfeeding. Where medically important risks have been identified by evaluating, assessing, and confirming potential risk factors relating to harms caused by medicinal products; and
2. By providing accurate, up-to-date, current and evidence-based information about the risks of exposure to medicines during pregnancy and/or lactation thereby enabling patients, care providers and healthcare professionals to prevent the occurrence of harm; and
3. By promoting the safest and most effective use of medicinal products, in particular through providing timely information about both risks or the lack of evidence of harm caused by medicinal products used during pregnancy and/or lactation to patients, healthcare professionals and the public.

Figure 2. Venn diagram – broad classification of safety data



Post-marketing safety data related to pregnancy exposures and breastfeeding invariably comprises many incomplete reports (see Figure 2, area **A** – PVRIN: pharmacovigilance relevant information). Where insufficient information is available on either the patient or the source of the data, these case reports are lost to follow-up. Hence, the only useful information content is the identification of an association (or implied association between a medicinal product (or several products) with an adverse outcome. Thus, these data are largely only of use for large-scale signal detection via generation of hypotheses because of clustering or case series suggestive of a novel association. Where more detailed or extensive data exist within individual case reports, the evidence may be classified in various ways, for example (Figure 2):

- **B – Adverse event (AE) reports:** Case reports including an untoward (adverse) outcome following exposure to a specified medicinal product, or a combination of medicines;
- **C – Adverse reaction (AR) reports:** Reports with suspected causal association between a suspected medicinal product or products, an adverse event or syndrome, in a single, identifiable patient, with a recognised source, and;
- **D – Expeditable (regulatory reportable) adverse reactions**: Reports with a suspect medicinal product or products, an adverse reaction or syndrome, a uniquely identified source (to permit follow-up), and an identifiable patient. When such reports meet pre-determined criteria there is a legal obligation for manufacturers to submit these data in the form of individual case safety reports (ICSRs) to regulatory authorities.

It is important to screen and evaluate all PV data that may inform medical decisions, with a clear focus on prioritising reports related to serious outcomes in the mother, major congenital malformations in the offspring or related to serious outcomes of breastfeeding in the infant. Prioritisation of assessment of reports of medically serious outcomes is important. Serious reports are defined

as adverse events which:

- Result in death,
- Are life-threatening (patient was at risk of death at the time of the reaction),
- Require in-patient hospitalisation or prolong existing hospitalisation,
- Result in persistent or significant disability or incapacity, or
- A congenital anomaly or birth defect
- Any suspected transmission of an infectious agent via a medicinal product

Medical and scientific judgement will be exercised in deciding whether other situations are considered serious, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalisation or development of dependency or abuse (3).

It is the aim of Work Package 2 to contribute to the protection of patients' and public health by conducting research into aggregated patient safety data from multiple source systems, across many countries and several continents. Our aim is that the scientific evidence provided by the ConcePTION dataset will play a key role in supporting decision-making for pregnant women and their respective partners and/or breastfeeding women who require medical treatment (1). It is important that medicines with a proven positive benefit to risk assessment on an individual patient level are prescribed to pregnant and lactating women, and that both health professional and patient have up-to-date evidence based information on which to base such decisions (4).

Introduction

Patient safety data are diverse and complex due to the disparate nature of the sources.

Accurate recording of patient data is essential to support appropriate evaluation in order to inform medical decision-making. In essence, data standards, coding, and use of dictionaries are used to bring order from the huge diversity of unstructured medical and verbatim terms (5). Discipline is required to align the myriad of descriptive terms that HCPs and patients use when describing adverse reactions, for example. In fact, there are multiple areas where accurate, reproducible coding and precise units of measure are required:

1. **Medicinal products** including pharmaceuticals, biologicals, vaccines, advanced therapy medicinal products (ATMPs) and gene therapies
2. **Adverse reactions**
3. **Indications for treatment**
4. **Past medical history and concurrent medical conditions**
5. **Laboratory tests and associated test results**
6. **Lists of values** (also referred to as code lists i.e. typical values associated with variables in the core data fields such as route of administration of a medicinal product, age groups (of patients), outcomes (of adverse events), outcomes (of pregnancy).
7. **Units of measure**

Many other fields within the core data fields will also rely on the use of lists of values (LoVs), such as drug formulation and route of administration, hence it is important to propose a standard series of LoVs for adoption. Within each category, key aspects of information need to be separated into what are termed 'data fields'. For example, each relevant laboratory test will need a data field for:

a) The name of the test;
b) The date on which the test was performed;
c) The result as an absolute value or descriptive text;
d) The unit of measurement for the result;

e) The lower limit of the normal range for the test and laboratory;
f) The upper limit of the normal range for the test and laboratory.

To this end, various groups and organizations have established lists for units of measure (35) and lists of values (LoVs) for certain categories (e.g. drug formulation and route of administration) with a unique code assigned to each value. Use of different lists or coding systems presents a challenge when trying to pool data to improve analysis, hence it is important to propose a standard series of LoVs for adoption.

When conducting medical assessments it is imperative that coded data are carefully controlled and are subject to a single common set of data standards. Controlled use of these standards is essential when collecting, collating and aggregating safety data for evaluation and assessment, such that:

- Data are structured in a consistent and reproducible manner;
- Coding systems used must support detailed medical and scientific analyses;
- Terminology and coding schemes should be globally applicable;
- Standardised units are required to enable interpretation of test results;
- Where data are missing (field is set to null) there should be a capability to code the reason why, if the reason is known.

Coding and the strict adherence to agreed data standards make it possible to record patient safety data (case reports) effectively and concisely within a medical record and to store that record on a relational database. The use of a structured system in turn enables and facilitates searching, retrieval and outputting of ICSRs, aggregated data and summary tables. Despite this, it is of paramount importance to preserve unstructured text, such as the medical narrative which often accompanies an adverse event report. Preservation of verbatim text is essential to aid medical assessment, and this can also help to avoid coding biases or miscoding.

It should be borne in mind that the characteristics of dictionaries and terminologies selected, as well as the reporter's language and conventions used to code the source data may exert a profound effect on the interpretation of the safety data. Because accuracy and granularity of coding is vitally important to ConcePTION, it is important to avoid (for example) a medical dictionary that provides too few terms. This would result in compromises when coding the safety data. Almost equally important is the presence of structured relationships within the medical dictionary, so that valid medical, physiological, and biological principles are inherent within the structure. This is not always possible with the currently available dictionaries. Thus, it is important to have agreed conventions for coding and grouping terms when the hierarchy of the selected dictionary does not support logical groupings of similar medical concepts or otherwise related terms in all instances. For example, laboratory values may not be grouped with diagnostic terms in the dictionary. Similarly, coding of medicinal products should provide an accurate reflection of the therapeutic area, and class of the product and support a link to the indication for treatment, which may not be an approved use ('off label'). The selection of a dictionary may also provide too much specificity, but in the case of the ConcePTION project, this is not considered likely to occur.

With all of the above in mind, it limits the selection of dictionaries to code the ConcePTION data set. Whilst many dictionaries are in use in the context of pharmacovigilance and pharmacoepidemiology, this report considers only a subset as being potentially fit for purpose.

Methods

A literature research was conducted (see Annex 1). The aim of this research was to make a recommendation for consideration by ConcePTION concerning the adoption of specific coding dictionaries, terminologies, along with consensus conventions for their application, as well applicable as lists of values applicable to safety data related to the outcomes of exposure to medicinal products during

pregnancy and breastfeeding. The results were reviewed along with the regulations and guidelines applicable to collection, collation, and reporting of safety data including ICSRs. In addition, consideration was given to relevant high-level regulatory legislation and guidelines applicable to pharmacovigilance, particularly where coding systems were cited (Annex 2).

Results

Medicinal products

There is a continuously changing plethora of medicinal products available across the globe, which provides a significant challenge in the provision of a comprehensive, accurate, and up-to-date coding system. In order to make this task more manageable the focus of this assessment will be the coding of the therapeutic and pharmacological class, as well as the proprietary and trade names, and manufacturer. The following meta-data associated with medicinal products will be considered within the classification of lists of values:

- Formulation
- Dose forms
- Route of administration

The following coding systems were assessed at high-level; comments that are more detailed in nature have been provided for those coding terminologies and systems that appeared to offer a potential solution for the coding of data relevant to ConcePTION.

Anatomic-Therapeutic-Chemical Classification/Defined Daily Dose (ATC/DDD system)

This system was designed for coding of medicinal products associated with reports of suspected adverse reactions and the system is based on the site of

therapeutic effect, therapeutic indication, and pharmacological specificity. Updates are managed by the submission of requests for the addition of new chemical entities to the maintenance organisation of the ATC. This classification is useful for categorising and recording suspect medicinal products as well as concomitant medication and products used in the treatment of adverse reactions. The main ATC groupings are shown in Table 1 below

Table 1. Anatomic-therapeutic-chemical classification groupings

Code letter	ATC Group
A	Alimentary tract and metabolism
B	Blood and blood-forming organs
C	Cardiovascular system
D	Dermatologicals
G	Genitourinary system and sex hormones
H	Systemic hormonal preparations excluding sex hormones
J	General anti-infectives for systemic use
L	Antineoplastic and immunomodulating agents
M	Musculoskeletal system
N	Nervous system
P	Antiparasitic products, insecticides and repellents
R	Respiratory system
S	Sensory organs
V	Various

Each of the main groups comprises an arrangement of classes of medicinal products as sub-groups according to the therapeutic area or site of action. At the next level of specificity, products are broken down by pharmacological category. Further precision is conferred with additional codes under the broad pharmacological category based on precise pharmacology or chemical structure. An example of a typical ATC code is:

R03CC Selective β-adrenoceptor agonists, where:

R03 = Anti-asthmatics

R03C = Adrenergics for systemic use

Products with indications in multiple therapeutic areas or pharmacologically active at multiple sites of action are coded according to the primary indication or main site of action. This is a potentially significant deficiency in the coding system. This system has been adapted for use within the WHODrug Global dictionary, as described below.

World Health Organisation Drug Dictionary (WHODrug Global)

The WHO Uppsala Monitoring Centre (UMC) maintains a large product-coding dictionary comprising the proprietary names of over 75,000 authorised medicinal products. This is sufficiently comprehensive and flexible to support the VigiBase system that contains over 15 million ICSRs. The annual increment of products is in excess of 2,500 (13); updates are provided on a twice-yearly basis (0n 01 March and 01 September). The classification is inclusive of products available throughout the world, with over 150 countries contributing adverse reaction reports to the WHO Uppsala Monitoring Centre (UMC). Notably data from the National Competent Authorities (NCAs) in the countries which comprise the EEA are first submitted to EudraVigilance at the European Medicines Agency, and then these ICSRs are transferred en bloc to the WHO UMC. WHODrug Global is available in English and Chinese and is currently the most comprehensive and actively used drug reference dictionary in the world. The dictionary is used to identify drug names and to evaluate medicinal product information, including active ingredients and products' anatomical and therapeutic classifications. Coverage includes pharmaceutical medicines (i.e. prescription-only products (see Table 2), over-the-counter (OTC) and pharmacist-dispensed preparations), as well as biological (see Figure 3) and blood products, diagnostic substances and contrast media.

Figure 3. WHODrug Global structure (for a biological and biosimilars)

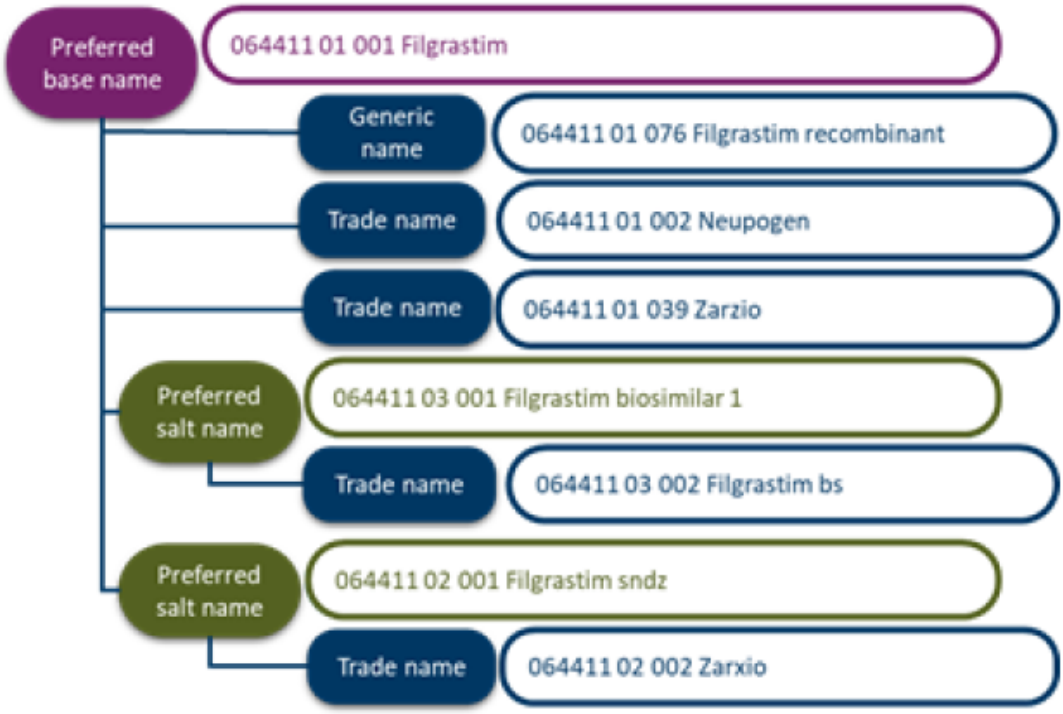


Table 2. Examples of 'umbrella terms' in WHODrug Global

Drug code	**Umbrella term**	**ATC**
901523 01 001	Immunotherapy	L03A, L04A
901517 01 001	Counterirritants	D11A, M02A
901522 01 001	Antivirals for treatment of HCV infections	J05AP
901518 01 001	Cancer vaccines	J07, L03AX
901519 01 001	Cancer vaccines, therapeutic	L03AX
901520 01 001	Cancer vaccines, preventive	J07
901521 01 001	Corticosteroids, topical	A01AC, A07EA, C05AA, D07A, R01AD, R03BA, S01BA, S02BA, S03BA
901524 01 001	Erythropoiesis-stimulating agents	B03XA

It is recognised that the same active substance may have a different status in different countries (e.g. in most countries amoxicillin is a prescription-only medicine, whereas in other countries amoxicillin is available OTC). Manufacturers work with the WHO in order to maintain the accuracy and completeness of WHO Drug Global. Products and substances registered by the US FDA and the EMA are routinely recorded. Compounded or magistral preparations are not included, although individual components may be included. Implementation support materials are available from the WHO UMC web resources (14).

WHODrug Global is maintained by the UMC; a dedicated team collects, validates and classifies drug information from a variety of international sources. The validation of trade names, inclusion of MAH (marketing authorisation holder) information, identification of substances, and determination of ATC assignments are performed for a significant proportion of entries. However, not all products in WHODrug Global contain a full 7-digit code, which may hinder at least some of the analyses that are required to be conducted by ConcePTION. This is a potential limitation of this dictionary. Changes to existing records in WHODrug are made or logged in order to meet pre-defined coding conventions. UMC applies standard operating procedures and change control mechanisms are in place, to aid quality control. Quality standards have been established to manage the coding process. The overall goal of the UMC is to ensure that WHODrug Global is produced to a high standard, with the notable exception of the incomplete 7-digit codes for a significant number of products.

A licence to WHODrug Global provides access to WHODrug Standardised Drug Groupings (WHODrug SDGs) and several analytical tools. WHODrug Global offers a subscription-based license that provides access to the suite of tools over a twelve-month period. The subscription model requires all organisations intending to use WHODrug Global to have a valid license. If ConcePTION were to use and share WHODrug Data between different partners this would require a valid license. Practically a subscription to WHODrug would allow ConcePTION to work with as many source data providers as required, as long as either the provides had a valid license themselves, or final coding to WHODrug was performed by licence holders within ConcePTION. The WHODrug SDGs group drugs according to their pharmacological effects or metabolic pathways. SDGs support the dictionary by helping users to:

- Identify medicinal products with similar properties
- Assign medications of interest

- Establish protocol violation lists for clinical trials

Recent additions to WHODrug include the browsing tool, WHODrug Insight. This is a dedicated, purpose-built browsing tool, which supports manual coding and user-generated queries. There is also an impact analysis tool, WHODrug CAT, which supports up-versioning of WHODrug. Finally, there is the tool WHODrug Change Request, which allows WHODrug users to request modifications to dictionary content in order to maintain currency and accuracy of the content of WHODrug Global.

ISO IDMP standards for the identification of medicinal products (IDMP)

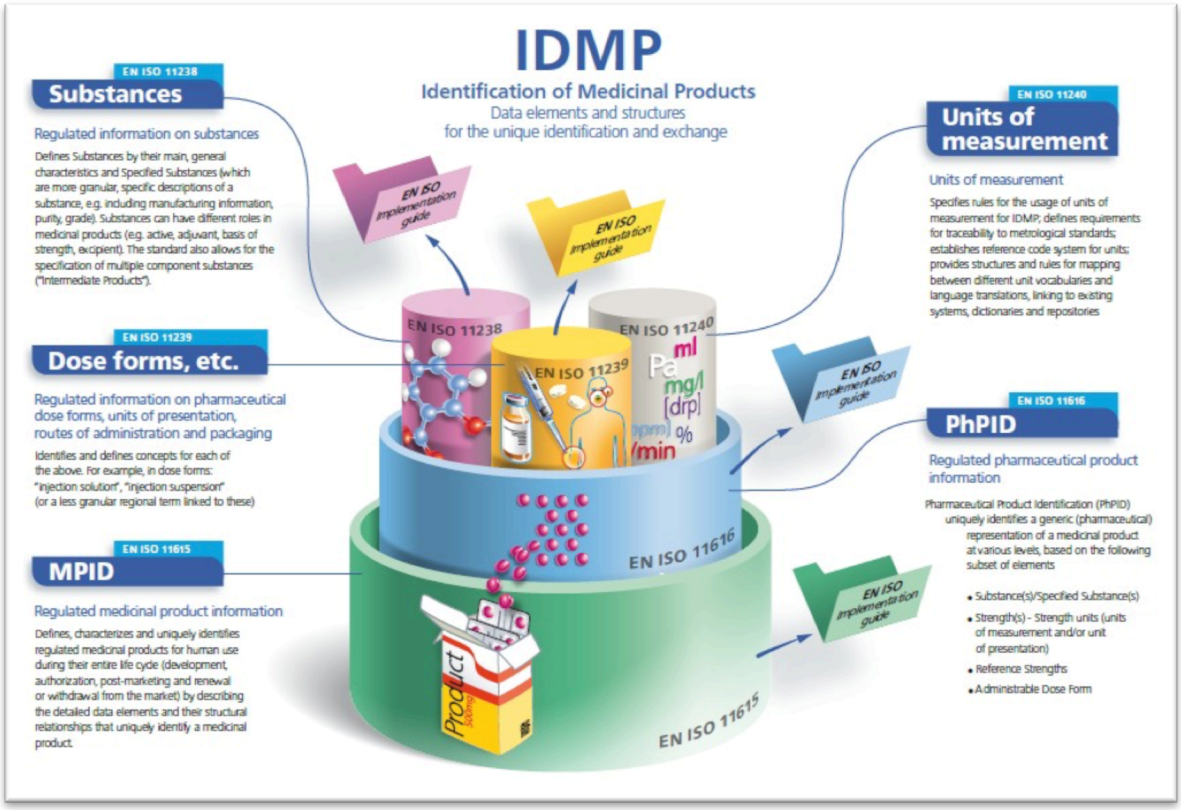
The International Standards Organisation (ISO) has compiled a series of standards which, when used together, form the IDMP (Identification of Medicinal Products) coding system (6). IDMP is a set of five ISO standards developed in response to a worldwide demand for internationally harmonized specifications for medicinal products. IDMP provides the basis for the unique identification of medicinal products, and facilitates jurisdiction of a variety of regulatory activities (development, registration, and life cycle management of medicinal products; pharmacovigilance and risk management). The European Medicines Agency (EMA) is currently in the process of implementing the ISO IDMP standards, and it is expected that IDMP will form the base for marketing authorization of medicinal products in Europe.

Five of these standards (see Figure 4) are applied to define the data elements and structures for the unique identification and exchange of medicinal products. The standards cover information on:

- Substances (ISO 11238);
- Pharmaceutical dose forms, units of presentation, routes of administration and packaging (ISO 11239):
- Units of measurement (ISO 11240);

- Regulated pharmaceutical product information (ISO 11616);
- Regulated medicinal product information (ISO 11615).

Figure 4. Identification of Medicinal Products Operating Model (7)



It has been anticipated that the ISO IDMP standards will bring benefits to patients and to the healthcare community because of simplification of the exchange of information between stakeholders (8). Improved interchange of data for the precise identification of medicinal products will enable enhancement of the interoperability of systems for the collection and collation of patient data. Consequently, it has been envisaged that IDMP will support the activities of medicines agencies worldwide. The IDMP has been designed to cover a variety of regulatory activities related to the:

- Development (chemical synthesis, derivation or source);
- Registration (authorisation);
- Manufacture (finished product), and
- Life-cycle management

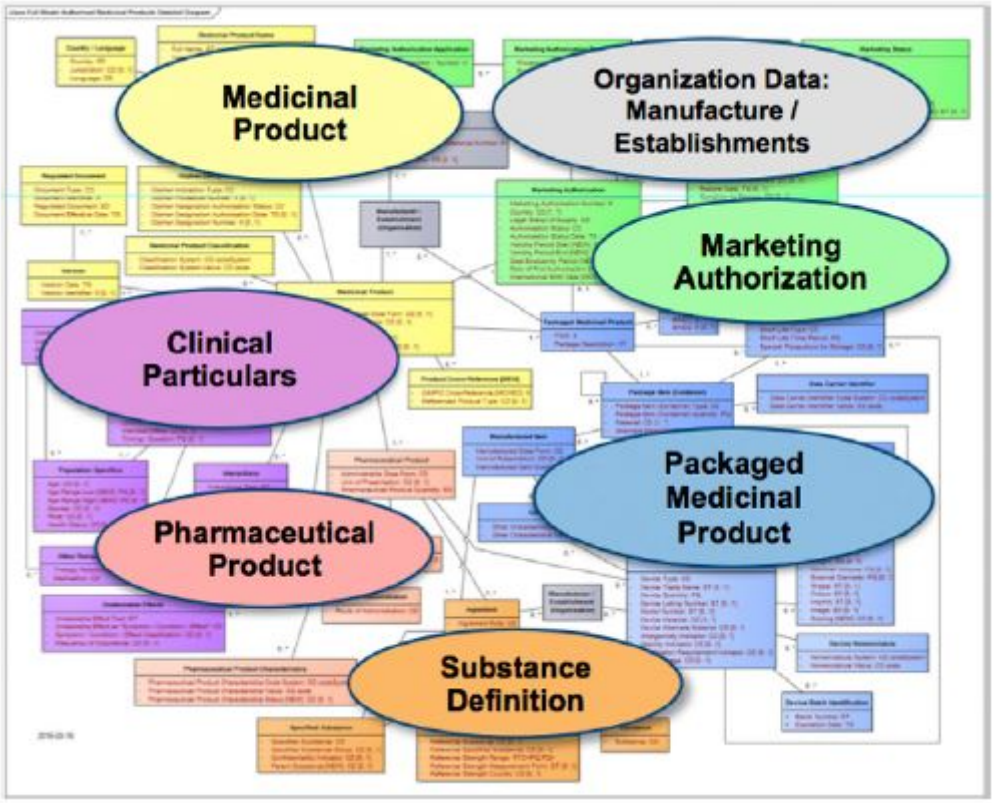
of medicinal products, including aspects of pharmacovigilance, pharmacoepidemiology and risk management. The ISO IDMP standards can also be applied to Investigational Medicinal Products (IMP) to support clinical studies from first time in human (FTIH) use through to submission of the marketing authorisation application.

The ISO IDMP standards cover the following aspects to describe a medicinal product:

- Medicinal product name
- Ingredient substances
- Pharmaceutical product (route of administration, strength)
- Marketing authorization
- Clinical particulars
- Packaging
- Manufacturing

The data model is complex (see Figure 5), comprising links between the seven entities described above. Each of the entities are described in detail, as well as their inter-relationships, within IDMP. Overall the aim is to provide unambiguous product identification on a global basis to improve pharmacovigilance by uniquely identifying specific medicinal products in ICSRs. In turn this will support safety signal detection related to medicinal products referenced in adverse event reports.

Figure 5. Data model for ISO Identification of Medicinal Products



Detailed specifications for the transmission of ICSRs are included as an integral part of the IDMP standards. Health Level Seven (HL7) Message Exchange are normative within the IDMP Standards. They describe and protect the integrity of the interactions for the submission of regulated medicinal product information in the context of the unique product identification. There is also the provision for acknowledgement of receipt of data including the validation of transmitted information. All of these features are vital to provide quality controls and to assure data integrity. IDMP Standards are provided with Implementation Guides (9), as well as with Technical Specifications (TS). For example, TS16791 provides guidance for the identification of medicinal products by using international supply chain Standards, securing traceability, safe supply chain, and other market requirements. Similarly, there are detailed Technical requirements (TR); TR 14872 specifies the requirements for the implementation of the standards for the identification of medicinal products for the exchange of regulated medicinal product Information.

Implementation of the IDMP standards will take place on a regional or national basis. Examples of the preparatory work that is ongoing can be seen on the EMA

web resources (10). The EMA has commenced the SPOR project; SPOR is derived from the **s**ubstance, **p**roduct, **o**rganisation, and **r**eferential data that are required in order to compile the master data for implementation of IDMP in the EEA. Updates to IDMP entries are first initiated by the original manufacturer of the product, and further updates will be required when generic manufacturers obtain marketing authorisations, Mandatory use of the ISO ICSR standard (based on the International Conference on Harmonisation (ICH) E2B(R3) modalities and the ISO IDMP standard terminology) was announced by the EMA Management Board on 19 December 2019. The ISO ICSR standard for the Agency, European NCAs, and Marketing Authorisation Holders becomes effective in the EEA on 30 June 2022 (11). In a separate, but parallel activity in the United States, the FDA has also commenced a project to implement IDMP (12). At the time of preparation of this report, there has been no formal announcement of the effective date in the US. Once the IDMP standards are in place and effective, it is anticipated that all data received from original sources and transferred to ConcePTION will be re-coded or at least mapped to the IDMP.

Product dictionaries in the form of point-solutions at company, agency, national & regional level

a) **Industry: Marketing Authorisation Holder-based systems**
b) **Regional systems {e.g EMA's Extended EudraVigilance medicinal product dictionary (XEVMPD)} (15)**
c) **National Competent Authority-based systems (e.g. FDA, MHRA)**

It is recognised that there are many other coding dictionaries available for the management of medicinal products. No further systems were reviewed in depth due to limitations of scope (e.g. a. and c.), and worldwide availability (a., b. and c.).

Adverse events, indications for treatment, laboratory data and associated results

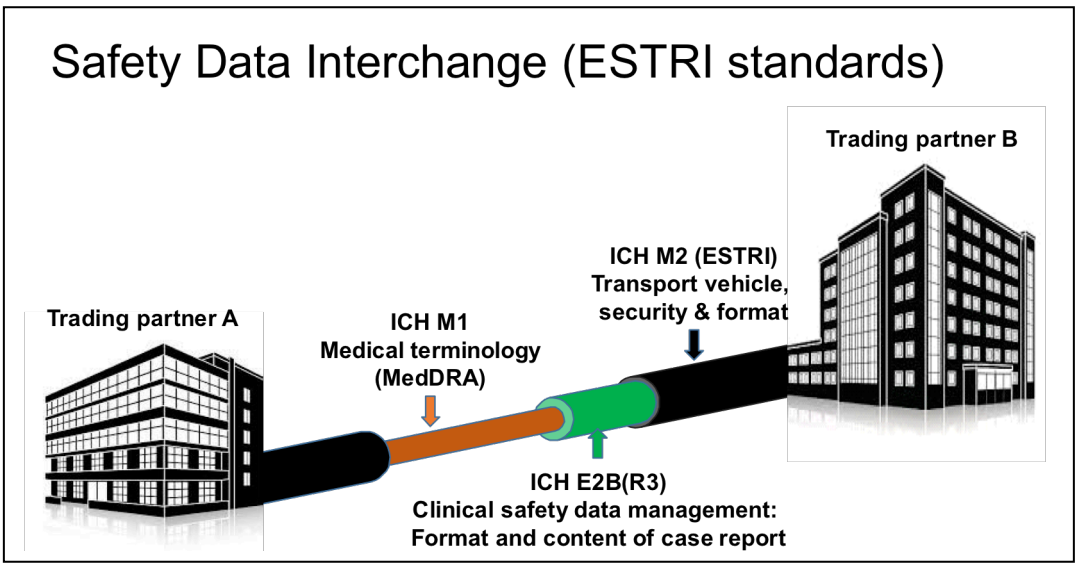
Medical Dictionary for Regulatory Activities (MedDRA®)

MedDRA is a structured thesaurus of medical terms that is open to any organisation that would like to use it (16). MedDRA has been in widespread use since March 1999. On its initial implementation, most users were based in Europe, Japan, and USA. Today, use has grown worldwide, as it has been adopted by regulatory authorities, global pharmaceutical companies, clinical research organisations, and health care professionals, facilitating global protection of patient health. MedDRA is a rich and highly specific standardised medical terminology developed by ICH to facilitate sharing of regulatory information internationally for medical products used by humans. It is used for registration, documentation and safety monitoring of medical products both before and after a product has been authorised for sale. Products covered by the scope of MedDRA include pharmaceuticals, vaccines, and drug-device combinations.

MedDRA was implemented as an international standard according to the ICH M1 guideline (17). MedDRA was designed for use with other ICH standards, including ICH E2B (18) and ICH M2 (19) for the exchange of data according to the Electronic Standards for the Transfer of Regulatory Information (ESTRI). The ICH ESTRI standards operate together to form a secure pipeline between organisations that wish to exchange or transfer regulatory information, in the form of ICSRs, product registration dossiers, and other regulated information. Figure 6 shows a representation of the ESTRI standards in operational use. At either end of the virtual pipeline are two organisations (trading partners) who wish to exchange safety data. The link between the two partners is drawn-up according to the ESTRI standards. ICH M2 provides the security, as well as detailed information on the sender and intended receiver of the information. ICH E2B(R3) defines the content of each ICSR, including specifications of each data

field, the field format, and content. ICH M1 is the medical content, in the form of unique 8-digit MedDRA codes.

Figure 6. Diagrammatic representation of ESTRI standards in operation



Under the governance of the MedDRA Management Committee, MedDRA is continuously enhanced to meet the evolving needs of regulators and industry around the world. The *s*cope of MedDRA is broad; the examples provided within this document are focused on pregnancy exposures and congenital anomalies, but MedDRA is a wide and varied terminology enabling the coding of an immense variety of medical conditions. Translations of MedDRA based on the original English version are available in Chinese, Czech, Dutch, French, German, Hungarian, Italian, Japanese, Korean, Portuguese, Russian, and Spanish. Other translations may be considered, should interest be expressed to the MedDRA Management Committee. The MedDRA Maintenance and Support Services Organization (MSSO), contracted by ICH with technical and financial oversight by the MedDRA Management Committee, is tasked to maintain, develop, and distribute MedDRA. The terminology is free for all regulators worldwide, academics, and health care providers while paid subscriptions are on a sliding scale linked to annual turnover of companies. In order to facilitate the correct implementation and consistent use of MedDRA, free training is offered. The

MedDRA MSSO reports that there are over 5,000 MedDRA subscribers from over 125 countries.

Structure of MedDRA

MedDRA is organized systematically into a five-level hierarchy, which is described below. System Organ Class (SOC) groupings (n=27) including, of relevance to ConcePTION:

- Congenital, familial and genetic disorders
- Pregnancy, puerperium and perinatal conditions
- 25 other SOCs for the representation of:
    - Suspected adverse reactions
    - Medical terms applicable to the indication for treatment & medical history
    - Laboratory and diagnostic tests and results

  All twenty-five SOCs are directly applicable to the coding of medical terms in either of the parents, or in the offspring.

High-level group terms (HLGTs), used primarily for retrieval and reporting, including, for example for congenital, familial, and genetic disorders (n = 28):

- Blood and lymphatic system disorders congenital
- Cardiac and vascular disorders congenital
- Musculoskeletal and connective tissue disorders congenital
- Renal and urinary tract disorders congenital
- Skin and subcutaneous tissue disorders congenital

And for pregnancy, puerperium, and perinatal conditions (n = 8) including, for example:

- Abortions and stillbirth
- Foetal complications
- Neonatal and perinatal conditions, and
- Postpartum and puerperal disorders

High-level terms (HLTs) again used primarily for retrieval and reporting, including in total more than 1,700 terms. Preferred terms (PTs), somewhat akin to a medical diagnosis, including more than 15,000 terms with essential terms for ConcePTION, such as (for congenital disorders):

- Ankyloglossia congenital
- Cataract congenital
- Hypospadias
- Talipes

And for pregnancy, puerperium and perinatal conditions PTs include:

- Pregnancy
- Aborted pregnancy
- Complication of pregnancy
- Exposure during pregnancy
- First trimester pregnancy (second and third trimester are also discrete terms)

Lowest level terms (LLTs) which are synonyms for a specified Preferred Term (more than 70,000) including for example 87 terms linked to the stem 'abort-':

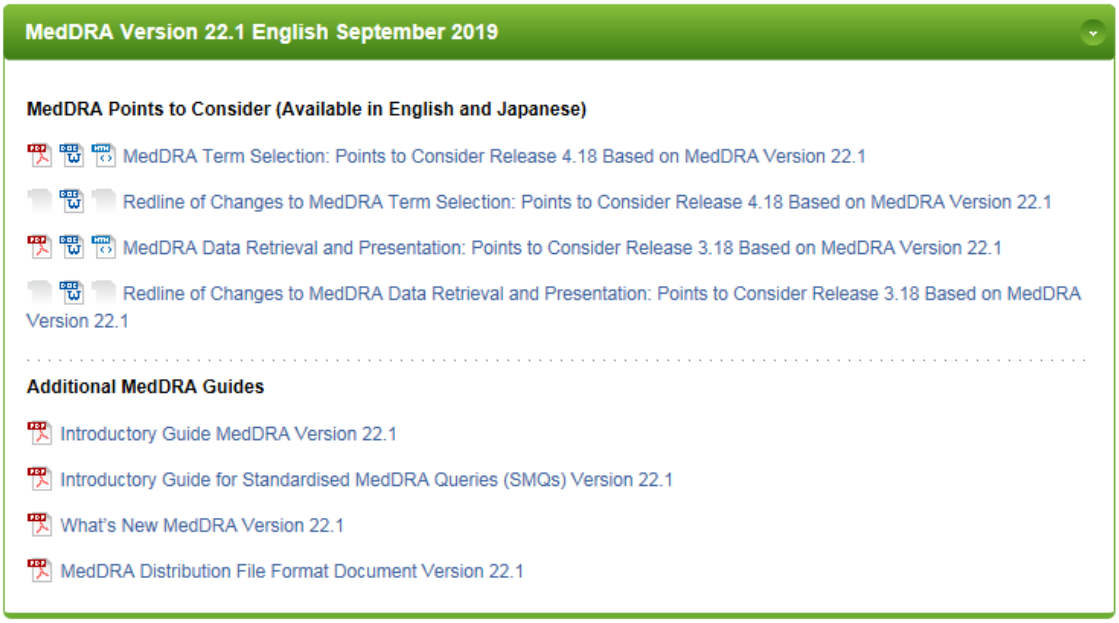
- Aborted pregnancy
- Abortion late
- Elective abortion
- Spontaneous abortion
- Therapeutic abortion
- Threatened abortion

Most of the above terms are retained in each subsequent version of MedDRA, but it must be borne in mind that terms are subject to change or be repositioned in the hierarchy as part of the routine maintenance process.

Supporting Documentation

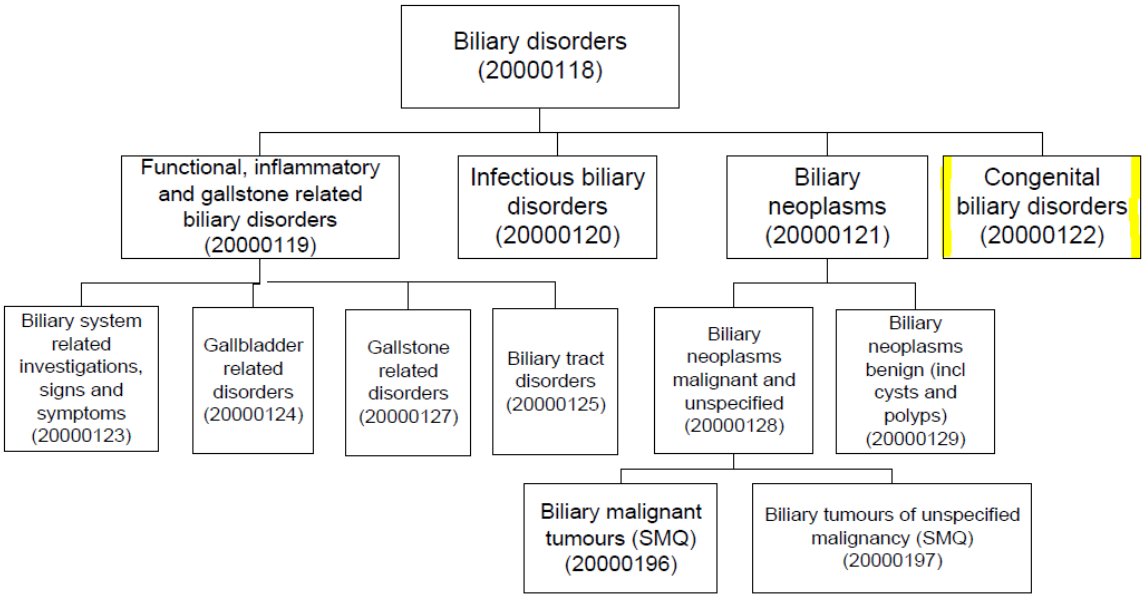
There is a range of supporting documentation available for MedDRA (see Figure 7, 20).

Figure 7. Supporting documentation for the MedDRA dictionary



The MedDRA MSSO develops and maintains two important 'Points to Consider' (PtC) documents concerning the use of MedDRA for data entry (coding) and data retrieval or data analysis. The latter includes guidance on the use of Standardised MedDRA Queries SMQs (21), which are powerful tools for assisting with data retrieval and safety signal detection. Both documents are updated twice a year, with every MedDRA release. SMQs are available for 'Congenital, familial and genetic disorders', for 'Congenital and neonatal arrhythmias', for 'Congenital, familial, neonatal and genetic disorders of the liver', and for 'Congenital biliary disorders' (see Figure 8).

Figure 8. Structure of a hierarchical SMQ (including congenital biliary disorders)



There is also a very broad SMQ for 'Pregnancy and neonatal topics' which includes 'Lactation related topics' (incl neonatal exposure through breast milk). This broad search is further inclusive of two sub-SMQs covering 'Functional lactation disorders' (SMQ) and 'Neonatal exposures via breast milk' (SMQ)

MedDRA mapping

There is notable collaboration between ICH (via the MedDRA MSSO) and the WHO. MedDRA is fully implemented in the WHO global safety database (VigiBase) allowing entry and retrieval of information in either MedDRA or WHO-ART. A mapping bridge was introduced between the WHO and ICH, to allow conversion of WHO-ART coded data into MedDRA, allowing users to readily convert their data and use MedDRA. This mapping is historic and it is no longer actively maintained.

Systematized Nomenclature of Medicine - Clinical Terms (SNOMED CT)

SNOMED Clinical Terms (22) is a systematically organized collection of medical terms providing codes, terms, synonyms, and definitions used in clinical documentation and reporting. The terminology is designed for use in healthcare

systems utilising computer-based processing of medical data. SNOMED CT has been described as the most comprehensive, multilingual clinical healthcare terminology available (23, 24). The primary purpose of SNOMED CT is to encode health information and to support the effective clinical recording of data. SNOMED CT contains over 100,000 unique concepts and many synonyms and abbreviations. The overall aim is to improve patient care. SNOMED CT provides a core general terminology for electronic health records. Coverage includes: clinical findings, symptoms, diagnoses, procedures, body structures, organisms, and other etiologies, substances, pharmaceuticals, medical devices and specimens. SNOMED CT is maintained and distributed by SNOMED International, an international non-profit standards development organization, located in London, UK. The governance organisation is International Health Terminology Standards Development Organisation (IHTSDO), established in 2007.

The SNOMED CT coding system provides for consistent information interchange and enables interoperability of electronic health records. It provides a consistent means to index, store, retrieve, and aggregate clinical data across specialties and sites of care. The dictionary supports organisation of the content of electronic health records systems by reducing the variability in the way that health data are captured, encoded, and used for clinical care of patients and research (25). The terminology can be used to record clinical details of individuals in electronic patient records. SNOMED CT provides the user with a number of links to clinical care pathways, shared care plans and other knowledge resources, in order to facilitate informed decision-making, and to support long-term patient care. Automated coding tools and services, are provided, which can return a ranked list of SNOMED CT descriptors to encode any clinical report; these tools help users to navigate the terminology. Recently there has been research into the potential for the use of SNOMED CT to support the reporting of adverse reactions, and for the purposes of signal generation (26). The approach used was to map SNOMED CT to MedDRA and, whilst the results were promising, the mapping requires validation and evaluation of the overall quality and consistency. SNOMED CT is cross-mapped to other international standards and

classifications (27) including MedDRA (28). Specific language editions are available which augment the international edition and can contain language translations, as well as additional national terms and codes. A mapping of certain adverse event terms between MedDRA and SNOMEDCT is part of the IMI WEB-RADR 2 project (28).

International Classification of Diseases versions 9, 10 & 11 (ICD-9, -10, -11)

The International Classification of Disease, Ninth Revision (ICD-9) is a system of medical coding created by the World Health Organization (WHO). ICD-9 was used for documenting diagnoses, diseases, signs and symptoms and social circumstances. It remains in use in some countries. The caveat is that the ICD-9 code structure has been in place for almost 40 years. Thus, the terms used in ICD-9 have become outdated, obsolete and are inconsistent with current medical practices. On this basis, for the purposes of the ConcePTION project, ICD-9 will be considered as a legacy terminology, even though it is still in use by some institutions.

ICD 10 (published in 1992, (289) is in widespread use in support of national and regional healthcare systems. Whilst version 10 is in use, ICD 11 is available (it was released on 18 June 2018), and is supported by the WHO (30). ICD-11 contains over 55,000 codes, compared to the more than 14,400 codes which exist in ICD-10. Thirty-one countries played a role in field-testing ICD-11. ICD-11 is described by the WHO as:

"...a system of categories to which morbid entities are assigned according to established criteria..."

The application of ICD 10 is widespread, as the system is accepted as a global standard. Predominant usage is for epidemiology and pharmacoepidemiology with very limited applicability to pharmacovigilance. ICD has also been used for coding baseline medical history and diagnoses in clinical trials and occasionally for the recording of adverse events. It has to be made clear that the system was

not designed for this purpose, and thus the hierarchy, the description of conditions and their groupings is suboptimal for this purpose.

WHO Adverse Reaction Terminology (WHO-ART)

This adverse reaction dictionary was originally constructed by the WHO UMC in support of VigiBase, but it is no longer maintained. Whilst it was extensively used by regulatory authorities and industry alike it has, largely, been superseded by MedDRA and SNOMED. With the advent of IDMP, it is likely that this system will become even more limited in use. It will not be considered further in this report because of the restricted usage and availability.

Read Codes

Read codes are a coded thesaurus of clinical terms (31). They were introduced to the National Health Service (NHS) in the United Kingdom (UK) in 1985. There are two versions: version 2 (v2) and version 3 (CTV3 or v3). Both versions provided the standard vocabulary for clinicians to record patient findings and procedures, in health and social care IT systems across primary and secondary care in the UK. This was the standard clinical terminology system used in the UK before 1 April 2018; SNOMED CT was implemented from that date. Read Codes were incorporated into SNOMED CT. Because of the limitations described, this coding system will not be considered further.

ICPC

The International Classification of Primary Care, Second edition (ICPC-2) has been adopted by the WHO (32). It has been used as a classification terminology for primary care or general practice wherever deemed applicable. ICPC-2 classifies patient data and clinical activity in the domains of General/Family Practice and primary care, taking into account the frequency distribution of problems observed in these domains. It allows classification of the patient's reason for encounter (RFE), the problems and/or diagnosis managed interventions, and the ordering of these data within an episode of care structure.

Due to the restriction in use to primary care systems, this coding terminology will not be considered for adoption by ConcePTION.

LOINC

LOINC (Logical Observation Identifiers Names and Codes) is a database and universal standard for identifying medical laboratory observations (33). It was first developed in 1994 by the Regenstrief Institute, a US nonprofit medical research organization. The LOINC system is maintained by the organisation that created it. Whilst this system has been described as "…key to the development and use of the WHO Essential Diagnostics List…", it must be used in tandem with a medical coding terminology (34), hence it will not be considered further for use by ConcePTION.

Units of measure (applicable to all variables)

Units of measure applied to variables should be standardised to support data integrity and facilitate accurate electronic data interchange (EDI). It is proposed that ConcePTION should adopt and apply standards for all relevant units of measure being contemporarily used in medical science. In order to provide an illustrative example, consider the field 'birth weight'. The result may be represented as a single figure with units, or series of figures with units and a decimal point or a comma, or as a series of figures each with different units, and so on. Hence the results might be:
2,750 grams, 2.75 kilograms, 6.93 pounds (or lbs), or 6 pounds (lbs) and 10 ounces

It is important to ensure that the numeric value reported by the source of the data is accompanied by the correct units of measure. Use of the correct units will also facilitate review for outliers (e.g most babies born between 37 and 40 weeks' gestation will weigh somewhere in the range of 2.5 and 4 kilograms.

Unified Code for Units of Measure (UCUM)

The Unified Code for Units of Measure (UCUM) was developed by Regenstrief Institute (35). UCUM is described as an "…unambiguous system of units and their combinations…" (35). UCUM is a coding system that claims to include all units of measures in contemporary use in international science (including medicine and pharmaceutics, engineering, and business). The purpose is to facilitate unambiguous electronic communication of quantities together with their units. UCUM was designed to facilitate electronic communication between computers, as opposed to communication between humans, and has been adopted for use in ICH E2B(R3) ICSR messages. A typical application of UCUM is electronic data interchange (EDI), as it is suitable for use in various types of machine communication. UCUM has been adopted internationally by organizations including LOINC and HL7, and is included within the ISO 11240:2012 standard. Several important features are available for users:

Online validation & conversion of UCUM units. Users can enter UCUM expressions on the page and validate them or convert them to other expressions;

Batch validation of UCUM units. Users can submit a CSV (a spreadsheet format) file with a column of UCUM unit expressions, and the validator will return another CSV file with the addition of a column that reports on the validity of each unit expression;

Examples of commonly used UCUM codes. This document is based on real-world usage of UCUM in data from Intermountain Healthcare.

In addition, there are additional services provided to facilitate computer programming:

Validation and Conversion: A web service for validating and converting UCUM units, and for obtaining base unit information;

Autocompletion and searching: A web service for searching the UCUM unit data. Includes synonomy;

UCUM-LHC: A library providing application programming interfaces (APIs) for validating and converting UCUM units as a downloadable package. Includes a suggestion feature for incorrectly typed units.

Lists of values (LoVs)

It is important that a finite set of permitted values (terms and codes) is defined for use with the core data fields for ConcePTION. The ICH E2B(R3) implementation package (18) has an associated series of regionally defined allowed values for specific data elements. For ICH these code lists are identified by object identifiers (OIDs) and in some instances they are constrained, so all included terms should not always be used Pre-specified lists of values support clear definitions of pharmaceutical and clinical concepts when used in association with the core data fields. For example it is important to standardise the collection and collation of values associated with variables such as: dose form, route of administration, age groups, outcomes of adverse events, outcomes of pregnancy, nature of the exposure to drug (suspect, concomitant, treatment), etc. In order to demonstrate the complexity, a full list of available values can be viewed at the NCI Term Browser (36). In order to maintain the consistency of data as many of the core data fields as possible should have an assigned list of permitted values. The NCI Term Browser provides access to more than 6,700,000 terms (85 terminologies) in the NCI Metathesaurus, so the specific term list is often constrained for a specific use such as the use case presented by ConcePTION.

Null values

It is well documented that in the post-marketing environment many spontaneous reports have missing information. When this occurs, it is preferable to represent the lack of information in a consistent manner. Null flavours may be

used to describe the primary reason for missing data. Based on the null flavours adopted for use in association with the ICH E2B(R3) format message the following table of null flavours has been prepared (Table 3).

Table 3. Null flavours for use with the core data fields for ConcePTION

Code	Name	Description
ASKU	Asked but unknown	Data not present but requested on follow-up
MSK	Masked	Data hidden for privacy or due to lack of consent
NA	Not applicable	Not relevant to this case report
NASK	Not asked	Data not present and not requested
NAV	Temporarily unavailable	Data are unavailable for valid reasons and may be sought on follow-up
NI	No information	No data available
UNK	Unknown	Sender has no data and is unaware of availability
OTH	Other	Data are missing for other reasons -

Discussion

It is worth reminding the reader of the overall objective of ConcePTION, which is:

"To build an ecosystem for better monitoring and communicating the safety of medicinal products in pregnancy and breastfeeding" (37)

The importance of validated and regulatory endorsed coding systems to support rapid evaluation, and the optimised generation of scientific evidence cannot be overstated. Equally, there are certain fields that must not be coded, and the original data must be preserved in verbatim format and in context. In some instances it may be helpful, or even important, to include both the verbatim/reported term and the coded term.

It is recognised that quality checks of data and database normalisation (38) will be required in order to allow use of various data sources and comparison of data within various sources for better decision making. Database normalization is the

process of structuring a relational database in accordance with the series of normal forms proposed by ConcePTION in order to reduce data redundancy and improve data integrity. Normalization entails organizing the data content within the database to ensure that the dependencies are properly enforced by edit checks and database integrity constraints. It is proposed to accomplish this by applying formal rules and using a standard process of conversion. For example, birth weight may be represented in a variety of units, such as pounds and ounces, pounds and fractions of a pound, kilograms or grams. Normalisation would entail converting all units to a single standard, such as kilograms with no more than two units after the decimal point. Hence, a baby weighing eight pounds and five ounces (8 lbs 5 ozs) at birth would be represented as 3.77 kg.

Recommendations

Proposed approach is to build a coding system based on current need and coding systems that are immediately available, but to consider the following options with a view to the future and sustainability in particular. An assumption has been made that English will be the standard language for final coding. It is recommended that the following coding systems are adopted:

1. Implement **WHODrug Global** for the initial phase of product coding. It has been assumed that ConcePTION will code all suspect medicinal products and all concomitant medicines, biologicals or vaccines.

    a. Commence planning for transition to IDMP (SPOR) during Year 2.
    b. Implement a test instance of IDMP (SPOR) during Year 3.
    c. Map all relevant medicinal products to IDMP (SPOR) from 30 June 2022(11)

2. Implement **MedDRA** for the coding of adverse events, indications for treatment, medical history, laboratory data, and results. It has been assumed that for the purposes of complete and thorough evaluation

ConcePTION will code all signs, symptoms, and relevant laboratory results. As a secondary activity it is highly recommended that additional SMQs are created for use in connection with specific congenital anomalies, for example neurodevelopmental delay. These SMQs should be constructed under the guidance of the medical experts within ConcePTION.

3. Implement the **Unified Code for Units of Measure** (UCUM) for coding units.

4. Implement the **EudraVigilance E2B(R3) lists of values** (LoVs) associated with the core data fields for ConcePTION.

5. Adopt the **null flavours** shown in Table 2 for use with the core data fields.

Agreement was reached that these are the most pragmatic solutions available for consideration in the context of the requirements of ConcePTION. Wherever possible preferences have been based upon alignment with current and future European (and indeed global) healthcare and regulatory systems.

Future considerations

There is the potential for many improvements to be considered once the basic coding systems have been implemented, for example to:

- Use the UMLS code mapper (39) to map verbatim terms;
- Apply machine learning to:
    - Adverse event coding
    - Medicinal product coding
    - Data cleaning
    - Translation (use Google Translate)

If there is a desire to assess and validate new technologies ConcePTION could consider:

- Coding medicinal products based on bar-coding (3D) or QA codes
- Photographic recognition of medicinal products and facial phenotypes

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Annex 1

Pharmacovigilance Coding Literature Review

Method

- Search conducted
- Search term, "pharmacovigilance AND coding" → 55 papers
- Search term, "pharmacovigilance AND clinical coding" → 32 papers

Results

- 55 unique papers
- 25 papers retrieved from Abstract review
- Three excluded: one discussing product packaging bar codes (PMID: 15154829); one commentary on the complexity of MedDRA and how its poorly evaluated performance make it susceptible to manipulation, errors of interpretation and bias (PMID: 30645835); one demonstration of a deep learning approach to extracting data from medical texts (PMID: 31546016)

Author & Year	**PMID**	**Focus of paper**	**Coding systems discussed**
Brown et al. 1999	10082069	Introducing MedDRA terms	Medical Dictionary for Regulatory Activities (MedDRA)
Meyboom et al. 2000	10945372	Discussing the value of reporting therapeutic ineffectiveness as an adverse drug reaction	WHO Adverse Reaction Terminology (WHOART)
Klepper 2004	15154828	Use of periodic safety update report as a pharmacovigilance tool	MedDRA
Bousquet et al. 2005	15649103	Appraisal of the MedDRA conceptual structure for describing and grouping adverse drug reactions	MedDRA
Bousquet et al. 2005	15955732	Statistical computing automated signal generation methods	MedDRA
Thiessard et al. 2005	16048358	Trends in spontaneous ADR reports to the French PV system	Anatomical Therapeutic Chemical (ATC) and MedDRA
Henegar et al. 2006	16185681	Formulation of an ontology of ADRs to describe semantics of MedDRA terms	MedDRA
Alecu et al. 2008	19007441	Improving the WHO-ART structure by integrating the associative relationships included in SNOMED CT	MedDRA and Systematized Nomenclature of Medicine Clinical Terms (SNOMED-CT)
Lu 2010	19900576	Industry approaches to eCRF design (including coding considerations)	MedDRA

Overhage et al. 2011	22037893	Details of the OMOP CDM dictionary of standardised terminologies	International Classification of Diseases (ICD) 9, Current Procedural Terminology (CPT-4), Healthcare Common Procedure Coding System (HCPCS) Logical Observation Identifiers Names and Codes (LOINC), National Drug Code (NDC), and SNOMED
Paul and Robinson 2012	23705134	An overview of capturing and documenting coded data on adverse drug reactions	ICD-10
Emmendorfer et al. 2012	22302257	Monitoring adverse drug reactions across a nationwide health care system	MedDRA
Avillach et al. 2013	22955495	Harmonization process for the identification of medical events in eight European healthcare databases	Unified Medical Language System
Inacio et al. 2015	25596069	Comparing verbatim reports (in Portuguese) with MedDRA codes	MedDRA
Harmark et al. 2016	27379887	Explaining the limitations of PV coding systems when using data reported from patients	MedDRA, Common Terminology Criteria for Adverse Event (CTCAE - used in oncology ref 30)
Souvignet et al. 2016	27369567	Creating a functioning ontology for pharmacovigilance ADRs by mapping between MedDRA terms and SNOMED-CT	MedDRA and SNOMED-CT
Bhangale et al. 2017	29109938	Describing processes involved in pharmacovigilance case processing	MedDRA and WHO Drug Dictionary (WHO DD)
Ammann et al. 2018	29446185	Chart validation study of disease code data held in the Sentinel Distributed Database (SDD)	ICD-9
Ly et al. 2018	29860093	Natural language processing (NLP) tools to assist automated extraction and MedDRA mapping of AE terms in drug product labels	MedDRA
Lai et al. 2018	30100761	OMOP CDM in Asian databases	LOINC, SNOMED-CT, ICD-9, CPT-4, HCPCS, RxNorm and WHO ATC
Brajovic et al. 2018	30131314	A framework for coding patient reported ADR data	MedDRA
Bousquet et	31551780	Analysis of the potential of reuse	MedDRA and SNOMED-

al. 2019		of ontological and non-ontological resources for generating definitions for MedDRA	CT

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Work package 2 Improving the collection, analysis and interpretation of pregnancy pharmacovigilance data

D2.3 Core data elements

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Summary

Work package 2 of the concePTION project aims to improve the collection, analysis and interpretation of exposed pregnancy data. As part of this work we looked to define data elements that should be collected in prospective reports of exposure to medication during pregnancy (e.g., through pharmacovigilance or pregnancy registries) in order to ensure optimal assessment of the fetal safety or risk profile of that medication with respect to its use during pregnancy. A series of core data elements have been proposed which extend from the prenatal period through to the end of the first postnatal year. Further, to aid future dissemination of results a set of proposals are made regarding the format of reporting of outcomes.

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Introduction

The purpose of this document is to define data that should be collected in prospective reports of exposure to medication during pregnancy (e.g., through pharmacovigilance or pregnancy registries) in order to ensure optimal assessment of the fetal safety or risk profile of that medication with respect to its use during pregnancy. Although pregnancy outcomes and fetal outcomes are the focus here, the overall safety profile of a given medication used during pregnancy also requires collection of data on important maternal outcomes.

Data to be collected are referred to here as "Core Data Elements". These may be placed into context by considering the reasons for collecting them; namely to be able to calculate "core statistics" to support the "core statements" needed to investigate and characterise the safety profile of the medication(s) under review. Consequently, three levels of information are considered:

1. Core statements to be delivered to appropriate target audiences (regulatory authorities, healthcare professionals, pregnancy support groups, etc.).

2. Core statistics to be displayed in appropriate summary data tables or visual displays. Core statistics form the evidence needed to support the core statements and are determined by those statements.

3. Core data needed to be collected to enable direct derivation and tabulation of the core statistics.

Each level needs definition / derivation / conventions to be specified to enable creation a Common Data Model, compilation Statistical Analysis Plans and Programming Specifications, and to ensure consistency within and between research activities.

Scope of this document

The scope of the research focus guiding the selection of core data elements is as follows:

In scope:

- Potential short-term effects (conception to one year of age) on the baby / foetus and mother of *in-utero* exposure to medicines taken or used by the mother during or just before pregnancy.
- Effects of potential co-morbidities (where available) on the baby / foetus and mother.

Not in scope:

- Effects on the baby / foetus of medicines taken by the father and of risk factors based on paternal demographic data.
- Effects of medicines on the baby and mother during breastfeeding.
- Long-term outcomes Core data elements concerning long-term infant outcomes (e.g., neuro-developmental) beyond 1 year of age are covered by the long-term outcomes Task Force (Manchester University).

Note that this document should be viewed as a living document that will be updated as the project evolves in alignment with new input from other work packages and work streams, in particular the Definitions Task force, the Work Package 2 Task 2.3 Coding Systems, Work Package 2 Task 2.4 (Common Data Model), and Work Package 2 demonstration projects.

Core statements

Research questions underlying any data study will result in a set of core statements to be delivered to the target audience of that research (regulatory authorities, healthcare professionals, pregnancy support groups, etc.). Examples of these core statements can be considered to be of the following skeletal form:

1. The proportion of [Outcome (e.g., major malformations)] in [Subgroup: (e.g., prospectively-reported live births)] with exposure to [Treatment X (e.g. medicine X)] in pregnancy [Period (e.g., trimester one)] is xx.x% (95% CI: xx , xx).

2. The corresponding proportion in [Reference population] reported in [Source] with exposure to [Treatment Y (e.g., medicine Y / or unexposed)] in pregnancy [Period (e.g., trimester one)] is xx.x% (95% CI: xx , xx).
3. The observed proportion seen for [Treatment X] is (greater than/ less than / not different from/ not distinguishable from) that seen for [Treatment Y] based on (e.g.):
    - estimated statistical contrast (ERR/ Difference/ OR/ HR, etc.) = xx.x (95% CI xx , xx)
    - for which covariate / confounders /risk factors x, y, z, etc (as appropriate) were considered.

The exact form of the statements and of the necessary evidence underlying them is subject to the variables investigated and the characteristics of the data analysed, and the manner in which they were collected (e.g., controlled versus uncontrolled, prospective versus retrospective) but each of the components ("outcome", "period", "medicine X", etc.) requires specific patient-level data to be collected.

Note: Although statements carry considerably more scientific weight if confirmed by a statistical test, the appropriate statistical methodology underlying these types of statements and guidance on the medical assessment of the results leading to conclusions and recommendations (often also in lay language) to the intended audiences are not a topic of this document.

Core statistics

Core statistics are determined by and support the chosen core statements. Examples of core statistics are displayed within summary tables, examples of which are shown in Section 6.

Core data

Core data needed to be collected to be able to calculate the core statistics to support the core statements are described below in terms of "source", "purpose", and "definition".

Source

The "Source" of each of the core data items in the following lists is categorised as:

- Reported – the data item is entered to the database directly through a data collection tool (case report form, spontaneous report, targeted checklist, electronic capture, etc.)
- Derived - the data item is derived from other data fields in the database (as indicated in brackets) according to a defined algorithm

According to the data source and completeness of data, a data item could be "reported" or "derived" or, depending on the data collection tool and completeness of data, could be available in both ways.

Purpose

A data element can have more than one potential purpose. In the following lists the "Purpose" is grouped as follows:

Data set creation: the element is used to establish the analysis dataset(s)

Derivation: the element is used to derive other elements indicated in brackets (e.g. height is used to derive BMI)

Statistic: according to the presence of the attribute represented by this element, cases can be counted or summarised (for example mean age, number of live births, proportion of live births with a malformation). A data summary table in which this statistic might appear or be used is suggested in brackets. Such statistics would appear in the data summary tables and serve as evidence for core statements, conclusions, and recommendations.

Subsetting: the element is used to subset or stratify a dataset for example for a sub-group analysis

Risk factor: the element is a potential risk factor or confounder for maternal or child outcomes of interest and could be used in a statistical model or in a medical assessment of individual pregnancy cases

If the purpose of a variable is "subsetting" or "risk factor", that variable could be used for one or more of the following:

- Formation of sub-group analyses or tables of subsets of a larger dataset
- For (covariate) adjustment of a statistical analysis model
- For identification of fetal safety risks and confounders
- For interpretation of individual pregnancy cases of concern in a medical review (e.g., those associated with a fetal malformation) to assess causality.

Definition

For each data element a clinical definition and technical definition is offered. Technical definitions consist of:

- Permitted values that the element may take (e.g., Yes / No, Major / Minor / Other). The "value" of an element may have several levels; e.g., Value 1=Yes / No, and if "Yes", then Value 2=Before pregnancy reported / After pregnancy reported.
- Data coding, measurement system, or units used to describe the data element (e.g., if ICD10 or MedDRA is used to code adverse events, or units to record weight).

Both clinical and technical definitions presented here were reviewed within Work Package 2 and will be reviewed further in collaboration with Task 2.3 Coding Systems, Task 2.4 Common Data Model, and the Definitions Task force team.

List of core data elements

Note that elements in the tables below are labelled as:

Essential (Essential = Y): these are considered essential for every data collection process in order to provide data which can be analysed statistically to address core statements on the risks of adverse pregnancy or fetal outcome following medication use in pregnancy.

Not essential (Essential = N): these are not considered essential for every data collection process but may be important for specific reporting activities which for example would allow more detailed evaluation of the data considering covariate risk factors, indication-specific research, or specific data collection situations (e.g., large prospective patient registries with extensive data collection forms).

a) *Table 0-1 Core data: Case type*

Variable	Clinical definition	Technical definitions and values	Essential	Source	Purpose	Notes
Pregnancy	Person carrying a developing embryo or fetus; either suspected from missed menstrual period and/or positive result on an over-the-counter beta-HCG urine test, or confirmed by any clinical method (e.g. beta-HCG blood test, ultrasound or Doppler examination etc.)	Values: Y/N	N	Reported	Dataset creation	Only relevant for datasets collecting reports outside pregnancy. Would not be needed in pregnancy registries for example
Data collection source	Name of organisation collecting the pregnancy reports	Free text	Y	Reported	Dataset creation	
Mother case identifier	Unique identifier for the pregnant woman	Alphanumeric	Y	Reported	Dataset creation	
Baby case identifier	Unique identifier for each fetal record	Alphanumeric	Y	Reported	Dataset creation	
Mother-Baby case identifier/link	Common unique identifier linking mother with fetus/fetuses or child/children (same identifier located on both maternal and fetal/offspring records)	Alphanumeric	Y	Reported	Dataset creation	
Primary reporter	Type of reporter providing the information (Patient or HCP: GP, Midwife, Obstetrician, Other)	Values: Mother / HCP / GP/ midwife / obstetrician / gynaecologist / other (detail)	Y	Reported	Subsetting	The primary reporter is assumed to collect information from evolving sources during pregnancy
Primary reporter details	Name and contact details for the primary reporter	Free text	Y	Reported	Follow-up/case queries	Contact details may include postal and/or

Variable	Clinical definition	Technical definitions and values	Essential	Source	Purpose	Notes
Mother's date of birth	Mother's date of birth	dd/mm/ yyyy	Y	Reported	Dataset creation Derivation (age at LMP)	Availability depends on local law
Mother's age at LMP	Mother's age (in years) on the first day of the last menstrual period prior to the pregnancy	Integer	Y	Reported Derived (Maternal DOB, Date of LMP)	Subsetting/ Risk factor	Availability depends on local law
LMP (last menstrual period)	Date of the first day of the last menstrual period prior to conception	dd/mm/ yyyy	Y	Reported Derived (EDD, or gestational age at delivery)	Derivation (Pro-/retrospective status) Derivation ("Exposure timing")	This refers to the LMP associated with this pregnancy (not with earlier cycles)
EDD (Expected date of delivery)	Expected date of delivery based on 280 day gestation length (using the LMP date) or 266 day gestation length (using estimated date of conception from US fetal measurements)	dd/mm/ yyyy	Y	Reported Derived (LMP, date of conception)	Derivation (Pro-/retrospective status) Derivation (Pre-term / post-mature) Derivation ("Exposure timing" if LMP n/a)	
Source of reported EDD	Clinical calculation of EDD could be based on LMP, Date of embryo transfer, Ultrasound Measurement, or any other obstetric evaluation	Values: LMP / , date of embryo transfer / ultrasound / Other	Y	Reported	Derivation (Pro-/retrospective status) Derivation (Pre-term / post-mature)	
Date of end of	Date at which the pregnancy completes. For live	dd/mmm/yyyy	Y	Reported	Derivation	The date of completed

Variable	Clinical definition	Technical definitions and values	Essential	Source	Purpose	Notes
pregnancy	births, this will be the date of delivery. For terminations/evacuation of retained products of conception, this will be the date the procedure was performed. For spontaneous abortions or stillbirths, this will be the date when the fetus died if known or estimated from crown rump length (CRL) on autopsy/last ultrasound, last fetal movements, or any other.				(Pro-/retrospective status) Derivation ("Exposure timing") Derivation ("Gestational age at pregnancy outcome")	pregnancy and the date at which the fetus died may differ considerably
Prenatal test(s)	Any prenatal examination or test performed to investigate fetal medical conditions	Value 1: Y/N Value 2: Before/After reporting the pregnancy Value 3:Date test performed Value 4: Approx. gestational age when test performed (if date not known) Value 5: Type (see notes) Value 6: Details/ Diagnosis	Y	Reported	Derivation (Pro-/retrospective status) Derivation (Malformation status)	Tests to be reported here are only those that could identify anomalies and malformations in the fetus. Value 5 options for tests include: 1. Chorionic Villous Biopsy, 2. Amniocentesis, 3. Cordocentesis, 4. 2d USS, 5. 4d USS, 6. Maternal blood tests, 7. Nuchal translucency, 8. Maternal serum (alpha fetal protein etc.), 9. Other
Prospective status	Prospective - Report of any exposure which occurs during pregnancy/peri-LMP period whilst the patient is still pregnant Retrospective - Report of any exposure which occurs during pregnancy/peri-LMP period after the pregnancy has ended	Values: Prospective / Retrospective / Unknown	Y	Reported Derived (Report date, Date of end of pregnancy, Pre-natal test (timing/diagnoses)	Subsetting (to eliminate reporting bias)	Where required, alternative definitions of pro-/retrospective can be constructed from the information collected at "Pre-natal tests" together with the "Initial report

Variable	Clinical definition	Technical definitions and values	Essential	Source	Purpose	Notes
						date
True Prospective status	True prospective: - Report of any exposure which occurs during pregnancy/peri-LMP period whilst the patient is still pregnant but before any prenatal screening capable of identifying congenital anomalies has been performed True retrospective: - Report of any exposure which occurs during pregnancy/peri-LMP period after the pregnancy has ended, or a report of any exposure which occurs during pregnancy/peri-LMP period whilst the patient is still pregnant but after any prenatal screening capable of identifying congenital anomalies has been performed	Values: True prospective / True retrospective / Unknown	Y	Derived ("Status", Pre-natal tests", Initial report date")	Subsetting (to eliminate reporting bias)	Prenatal screening tests are those which may be capable of identifying congenital anomalies listed in the notes of "Prenatal test(s)" variable

b) Table 0-2 Core data: Drug exposure

Variable	Clinical definition	Technical definitions and values	Essential	Source	Purpose	Notes
Drug name(s)	International Non-proprietary drug name (i.e. active ingredient(s) of the medicinal product)	Coding guidance needed.	Y	Reported	Dataset creation	Includes the drug(s) targeted for investigation and concomitant drugs
Drug start date	Date at which the medication used during pregnancy was started	Values: Date 1 (dd/mmm/yyyy) Values: Date 2 (dd/mmm/yyyy) Etc.	Y	Reported	Derivation (Period of exposure: Peri-LMP, Trimester1, Trimester2, Trimester3)	Multiple dates can be collected; dates needed are those relevant to exposure in pregnancy Coding guidance needed
Drug stop date	Date at which the medication used during pregnancy was stopped (dd/mm/yyyy)	Values: Date 1 (dd/mmm/yyyy) Values: Date 2	Y	Reported	Derivation (Period of exposure:	Multiple dates can be collected; dates needed are those relevant to

Variable	Clinical definition	Technical definitions and values	Essential	Source	Purpose	Notes
		(dd/mmm/yyyy) Etc. Coding guidance needed.			Peri-LMP, Trimester1, Trimester2, Trimester3)	exposure in pregnancy
Drug indication(s)	Specific indication for which the medication was prescribed	Coding guidance needed.	Y	Reported	Dataset creation Subsetting/ Risk factor	This is needed only to check completeness of (or to merge with) the concomitant conditions / comorbidities field
Peri-LMP exposure	5xT1/2 of specific medication	Values: Y/N	Y	Reported Derived (Drug start/stop dates, Date of LMP)	Statistic / Timing of exposure table	Def TF to confirm. Product-specific definition needed dependent on half-life of drug of interest. CHMP (Exposure to Medicinal Products During Pregnancy): "For medicinal products with long half-lives, data on exposure before the start of pregnancy should also be provided, with an appropriate time frame to be chosen according to the pharmacokinetics of the individual drugs".
Trimester 1 exposure	Any exposure occurring in the first trimester (from date of LMP to LMP+90 days)	Values: Y/N	Y	Reported Derived (Drug start/stop dates, Date of LMP)	Statistic / Timing of exposure table	Exposure to the medicine in question during Trimester 1. This could be derived and reported by the HCP from gestational ages at start /stop

Variable	Clinical definition	Technical definitions and values	Essential	Source	Purpose	Notes
Trimester 2 exposure	Any exposure occurring in the second trimester (from LMP+91 days to LMP+188)	Values: Y/N	Y	Reported Derived (Drug start/stop dates, Date of LMP)	Statistic / Timing of exposure table	Exposure to the medicine in question during Trimester 2. This could be derived and reported by the HCP from gestational ages at start /stop
Trimester 3 exposure	Any exposure occurring in the third trimester (from LMP+189 days onwards)	Values: Y/N	Y	Reported Derived (Drug start/stop dates, Date of LMP)	Statistic / Timing of exposure table	Exposure to the medicine in question during Trimester 3. This could be derived and reported by the HCP from gestational ages at start /stop
Route of exposure	Route by which the medication is administered	Values: 1. Aural, 2. Inhalation, 3. Ocular, 4. Oral, 5. IV, 6. IM, 7. Rectal, 8. Topical, 9. Vaginal, 10. Other (free text)	N	Reported	Subsetting	
Dose per use	Amount of medication administered per use (e.g. 250 mg or 2 x 500 mg)		N	Reported	Subsetting Derivation (Total daily dose)	Coding guidance needed
Frequency of use	Number of times the medication is taken or administered in a 24 hour period	Values: Possible stat dose/single dose, once daily (od),	N	Reported	Subsetting Derivation (Total daily dose)	Coding guidance needed

Variable	Clinical definition	Technical definitions and values	Essential	Source	Purpose	Notes
		twice daily (bd), three times daily (tds), four times daily (qds), five times daily and when required (prn), once weekly, once bi-weekly, once per month, any other (free text)				
Total Daily Dose	Total amount of the medication used in a 24 hour period		Y	Reported Derived (Dose per use, Frequency of use)	Subsetting	Coding guidance needed.

c) Table 0-3 Core data: Pregnancy outcome

Variable	Clinical definition	Technical definitions and values	Essential	Source	Purpose / Destination	Notes
This section to be completed for each foetus in the pregnancy						
Pregnancy outcome information	Pregnancy outcome details have been reported to the system	Values: Known /pending / Lost-to-follow-up / missing	Y	Reported	Statistic / Disposition table	
Live birth	Delivery of a fetus, irrespective of the duration of the pregnancy, which after separation shows signs of life, such as beating of the heart, breathing, pulsation of the umbilical cord, or	Values: Y/N	Y	Reported	Statistic / Outcomes table	Stratification by gestational age at birth should be attempted.

Variable	Clinical definition	Technical definitions and values	Essential	Source	Purpose / Destination	Notes
	definite movement of voluntary muscles					
Stillbirth	Death of a fetus prior to the complete expulsion or extraction from its mother, after the 22nd completed week (≥154 days) of pregnancy; the death is indicated by the fact that after such separation the fetus does not breathe or show any other evidence of life, such as beating of the heart, pulsation of the umbilical cord or definite movement of voluntary muscles	Values: Y/N	Y	Reported	Statistic / Outcomes table	
Induced termination	Induced abortion (either medical or surgical) of a pregnancy for any reason	Values 1: Y/N Values 2 (If Yes) Reason for termination: - 1. Non-medical reason, - 2. Medical reason (maternal indication) - 3. Medical reason (foetal indication) - 4. Other, - 5. Unknown	Y	Reported	Statistic / Outcomes table	Collection of the specific reasons is not in scope
Spontaneous abortion	Death of a fetus prior to the complete expulsion or extraction from its mother, before the 22nd completed week of pregnancy (≤153 days).	Values: Y/N	Y	Reported	Statistic / Outcomes table	Definitions TF to decide whether to add this text to the definition: “The death is indicated by the fact that after such separation the fetus does not breathe or show any other evidence of life, such as beating of the heart, pulsation of

Variable	Clinical definition	Technical definitions and values	Essential	Source	Purpose / Destination	Notes
						the umbilical cord or definite movement of voluntary muscles” This text would clearly distinguish SA from LB however lack of breathing (etc.) might not be reported for many SAs. Also, the definition for live birth includes “irrespective of age” and all the signs of life caveats, so confusion is unlikely to arise. “Extraction” is to cover cases in which a demised fetus is not expelled naturally and requires assisted delivery.
Ectopic pregnancy	Implantation outside of the endometrial cavity (including tubal, cervical, caesarean scar, interstitial, cornual, ovarian, abdominal, hetertopic or of unknown location) confirmed by transvaginal ultrasound.	Values: Y/N	Y	Reported	Statistic / Outcomes table	
Molar pregnancy	A non-viable product of conception which can be either a 'complete mole' arising after single sperm fertilisation of an ovum lacking genetic material, or a 'partial mole' which arises as a consequence of multi-sperm fertilisation of a healthy ovum. An invasive mole (formerly known as chorioadenoma destruens) is a hydatidiform mole that has grown into the muscle layer of the uterus	Values: Y/N Values (if YES): - Hydatidiform Mole (complete or partial) / - Invasive Mole / - Mole of Unknown Type	Y	Reported	Statistic / Outcomes table	
Blighted ovum	A non-viable pregnancy in which the embryo either never develops, or begins to develop and	Values: Y/N	Y	Reported	Statistic / Outcomes	

Variable	Clinical definition	Technical definitions and values	Essential	Source	Purpose / Destination	Notes
	is reabsorbed. Diagnosis requires ultrasound examination to establish a gestational sac diameter of >25mm with no fetal pole detected				table	
Gestational age at EOP (end of pregnancy)	Gestational age at the time the pregnancy ended	Days	Y	Reported Derived (LMP, Date of EOP)	Derivation (Gestational timing of live birth, SGA)	Calculated as either post first day of the LMP or from prenatal US scan (always reported /40 weeks). Guidance needed from coding or Def TF
Gestational timing of live birth	Live birth of a preterm, term, or post-term infant Preterm is <37 weeks (<259 days). Full-term is ≥37 to <42 weeks (≥259 and <294 days) Post-term is ≥42 weeks (≥294 days)	Values: - pre-term, - full term, - post-term	Y	Reported Derived (Birth type outcome, Date of LMP, Date EOP)	Statistic / Outcomes table Subsetting	Def TF to confirm definitions.
Labour onset	How labour began	Values: - Natural onset - membrane sweep - amniotomy - vaginal prostaglandin tablet, - pessary or gel - mifepristone - misoprostol - other	N	Reported	Subsetting/Risk factor	
Mode of delivery	The method by which the fetus was delivered from the mother	Values: - Spontaneous vaginal delivery (incl. vertex / breach) - Assisted vaginal delivery	N	Reported	Subsetting/ Risk factor	

Variable	Clinical definition	Technical definitions and values	Essential	Source	Purpose / Destination	Notes
		(incl. forceps / ventouse) - Emergency C-section (post-labour / pre-labour) - Elective C-section				

d) Table 0-4 Core data: Fetal outcome (at birth, possibly updated at follow-up visits)

Variable	Clinical definition	Technical definitions and values	Essential	Source	Purpose	Notes
This section to be completed for each foetus in the pregnancy						
Fetal outcome information	Pregnancy outcome details have been reported to the system	Values: Known / pending / unknown (Lost-to-follow-up) / missing)	Y	Reported	Statistic / Disposition table	
Congenital anomaly (CA)	Structural or functional anomalies in the fetus that occur during intrauterine life and can be identified prenatally, at birth or later in life	Values 1: Y / N Values 2: (if yes): - no known genetic/cytogenetic aetiology - known genetic/cytogenetic aetiology - suspected	Y	Reported Derived (Outcome of pre-natal test, Infant SAE)	Statistic / Outcomes table	Anomalies are considered to have genetic/cytogenetic aetiology if there is laboratory evidence supporting the diagnosis, or if either parent of the case child also has clinical manifestations of the suspected genetic/chromosomal

Variable	Clinical definition	Technical definitions and values	Essential	Source	Purpose	Notes
		genetic/cytogenetic aetiology Values 3: (if yes): - Major malformation - Minor malformation - NOS - Unknown				condition. Anomalies are coded as major or minor as per EUROCAT standards.
Type of CA	Details of the anomalies present in the exposed fetus/fetuses	Values: - Diagnosis (free text description) - Unknown - not applicable	Y	Reported Derived (Infant adverse events)	Statistic / Outcomes table Subsetting	Coding support needed. Coding of diagnosis according MedDRA, EUROCAT, ICD9, etc. is required. consider mapping to EUROCAT from MedDRA or others. It is important to confirm what the baby had through postnatal exam / investigation or post mortem.
Other fetal problems	Problems with the baby or fetus that cannot be diagnosed as congenital anomaly	Values: - Diagnosis (free text description) - Unknown - not applicable	Y	Reported Derived (Infant adverse events)	Statistic / Outcomes table Subsetting	Problems with the offspring that cannot be diagnosed as congenital anomaly, e.g., positional deformity, maturity related, other.
Neo-natal complications	Any complication experienced in the neonatal period (first 28 days of life)	Values 1: Y/N Values 2: Diagnosis	Y	Reported Derived (Outcome of pre-natal test, Infant adverse events	Statistic / Outcomes table	Coding of diagnosis according MedDRA, EUROCAT, ICD9, etc. to be decided

Variable	Clinical definition	Technical definitions and values	Essential	Source	Purpose	Notes
Infant birth weight	Weight of the offspring at delivery	Integer (in grams)	Y	Reported	Statistic / Infant details Table	
Infant sex	Sex of the offspring at birth	Values: Male / Female / Undetermined / Unknown	Y	Reported	Statistic / Infant details Table	
Infant head circumference	Occipito-frontal circumference (i.e. the widest circumference of the skull from the broadest part of the forehead (above the eyebrow and ears) to the most prominent part of the rear of the head), measured using a non-stretchable flexible tape - to be recorded in cms	Integer (in centimeters)	Y	Reported	Statistic / Infant details Table	
Infant birth length	Heel to crown (knees flat) measurement of recumbent infant length - to be recorded in cms	Integer (in centimeters)	N	Reported	Statistic / Infant details Table	
Small for Gestational Age at delivery	An infant born with a birth weight less than the 10th percentile on population-level infant birth weight charts (these may be customised for various factors including gestational age at delivery as a minimum and additionally maternal BMI, parity and ethnicity, and infant sex).	Values Y/N	Y	Reported	Statistic / Infant details Table	Def TF to consider how this information can be derived Derived from infant weight, Sex, Gestational age at EOP, and Norm tables. Infants born with a birth weight for gestational age <3rd percentile are considered as severe SGA
Large for Gestational Age at Delivery	An infant born with a birth weight greater than the 10th percentile on population-level infant birth weight charts (these may be customised for various factors including gestational age at delivery as a minimum and additionally maternal BMI, parity and ethnicity, and infant	Values Y/N	Y	Reported	Statistic / Infant details Table	Def TF to consider how this information can be derived Derived from infant weight, Sex, Gestational age at EOP, and Norm tables.

Variable	Clinical definition	Technical definitions and values	Essential	Source	Purpose	Notes
	sex)					
Fetal Growth Restriction	Fetuses/neonates may be diagnosed as growth restricted if they have not reached their genetically defined growth potential considering various contributory factors to fetal growth (including for example maternal BMI, parity and ethnicity, and infant sex). Fetal growth restriction (FGR) is not synonymous with SGA.	Values: Y/N/unknown	Y	Reported	Statistic / Infant details Table	Def TF to review the definition. Do we lack the following phrasing: "less than the 10th percentile for gestational age" in our definition? Proposal: "Intrauterine growth retardation (IUGR) will be defined as estimated fetal weight below the 10th percentile for GA"
Apgar score	Apgar score at 1 minute post-delivery	1-Min Score Value 1: Known / Unknown Value 2 (If Known): Integer (0-10) 5-Min Score Value 1: Known / Unknown Value 2 (If Known): Integer (0-10) 10-Min Score Value 1: Known / Unknown	N	Reported	Statistic / Infant details Table	A clinical scoring system used to establish the clinical status of the newborn at one and five minutes post-delivery, and every additional five minutes until 20 minutes in infants with ongoing Apgar scores <7. The scoring system comprises five components investigating: Appearance (skin colour), Pulse (heart rate), Grimace (reflexes), Activity (muscle tone) and Respiration (respiration rate). Scores of between 0 and 2 are provided for each component depending on the clinical

Variable	Clinical definition	Technical definitions and values	Essential	Source	Purpose	Notes
		Value 2 (If Known): Integer (0-10) 15-Min Score Value 1: Known / Unknown Value 2 (If Known): Integer (0-10) 20-Min Score Value 1: Known / Unknown Value 2 (If Known): Integer (0-10)				features of the newborn, providing summary scores of between 0 and 10. Scores of 7-10 are reassuring, 4-6 moderately abnormal, and 0-3 as low

e) Table 0-5 Core data: Infant outcome (during infant follow-up phase)

Variable	Clinical definition	Technical definitions and values	Essential	Source	Purpose	Notes
This section to be completed for each foetus in the pregnancy						
Death of live born infant	Death of a live born infant	Values: Yes/No Values 2 (If Yes): - Neonatal death (Age at death: 0-27 days),	Y	Reported	Statistic / Infant outcomes follow-up	

Variable	Clinical definition	Technical definitions and values	Essential	Source	Purpose	Notes
		- Infant death (Age at death: ≥28d) Values 3 (If Yes): Date of death (dd/mm/yyyy)			Table	
Age at death of neonate/infant / child	Age of the child on the day of death	Record in days for children <1 month old, record in months for children <2 years old and years in children ≥2 years	Y	Reported/Derived	Derivation (Neo-natal death)	
Product/disease-specific outcomes	Offspring outcomes specific to the investigated product, to be decided ad-hoc	Values: Y/N	N	Reported	Statistic / Infant follow-up Table	Outcomes specific to the investigated product Coding ICD?
Developmental delay		Values: Y/N	N	Reported	Statistic / Infant follow-up Table	Def TF: No definition provided, this variable is likely to change into a group of sub-variables Coding ICD? Product specific Define at which time-points?

f) Table 0-6 Core data: Maternal illnesses and complications

Variable	Clinical definition	Technical definitions and values	Essential	Source	Purpose	Notes
Maternal death	Death of a woman while pregnant or ≤42 days of the end of the pregnancy (including live/stillbirth delivery, ectopic pregnancy,	Values 1: Y/N Values 2 (If Y): Date of death	Y	Reported	Statistic / Maternal outcomes Table	Coding support needed: MedDRA/ICD/etc.? N.B.: A death that occurs

Variable	Clinical definition	Technical definitions and values	Essential	Source	Purpose	Notes
	miscarriage or termination) from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes.	dd/mmm/yyyy Values 3 (If Y): Cause of death				more than 42 days but less than one year after the end of pregnancy is referred to as “late maternal death”; this is not collect.
Maternal pre-pregnancy medical conditions (history)	Any maternal medical condition present prior to pregnancy	Values 1: Y/N Values 2 (If Y): Details	Y	Reported	Statistic / Demographics table Subsetting/ Risk factor	Def TF: Coding support needed. Any pre-existing conditions which may act as risk factors are to be defined. Information may also come from drug indication or concomitant drugs
Maternal medical conditions arising in pregnancy	Any maternal medical condition arising during pregnancy	Values 1: Y/N Values 2 (If Y): Details (free text) Values 3 (If Y): Gestational age condition diagnosed	Y	Reported	Statistic / Maternal outcomes Table Subsetting/ Risk factor	
Maternal complications during / after delivery	Any maternal complications arising during or after delivery	Values: Y/N Values (if yes): Details/ Diagnoses	N	Reported	Subsetting/ Risk factor	To be completed as appropriate for the pregnancy outcome
Maternal post-partum complications	Any maternal complication occurring post-delivery.	Values 1: Y/N Values 2 (If Y): Details (free text)	N	Reported	Statistic / Maternal outcomes Table	Def TF: Coding support needed. A time limit of 42 days should be sufficient for the majority of maternal complications. However, maybe not for “Maternal depression” which could be an important endpoint in some of our demonstration projects. Suggest avoiding

Variable	Clinical definition	Technical definitions and values	Essential	Source	Purpose	Notes
						specification of time limit at this point.
Product/disease-specific outcomes	Maternal outcomes specific to the investigated product, to be decided ad-hoc	Values 1: Y/N Values 2 (If Y): Details	N	Reported	Statistic / Maternal outcomes Table	Outcomes specific to the investigated product Coding ICD?

g) Table 0-7 Core data: Source of information, maternal and obstetric history

Variable	Clinical definition	Technical definitions and values	Essential	Source	Purpose	Notes
Maternal Height	Height (cm) of the mother at the time of conception	Integer (Convert from feet and inches, etc.)	N	Reported	Subsetting/ Risk factor	
Maternal Weight pre-pregnancy	Actual or approximate weight (kg) of the mother at or around the time of conception	Integer (Convert from stones and pounds, etc.)	N	Reported	Subsetting/ Risk factor	
Maternal BMI pre-pregnancy	Maternal BMI at the time of conception (kg/m2)	Values 1: - Actual BMI kg/m2 - Unknown	N	Reported Derived (Maternal height, Maternal weight)	Subsetting/ Risk factor	Def TF: Should we add a second collection possibility: Values 2 (If known): Underweight (<18.5), normal (18.5-24.9) overweight (25-29.9), obese 1 (30-34.9), obese 2 (35-39.9), obese 3 (≥40)
Country of case origin	Country in which the mother resides at the time of reporting	NATO codes	N	Reported	Subsetting/ Risk factor	
Smoking in pregnancy	Maternal smoking of tobacco during pregnancy	Values 1: (Y/N) Values 2 (If Y): Details of use if available	N	Reported	Subsetting/ Risk factor	

Variable	Clinical definition	Technical definitions and values	Essential	Source	Purpose	Notes
Alcohol in pregnancy	Maternal alcohol consumption during pregnancy	Values (Y/N) Values 2 (If Y): Details of use if available	N	Reported	Subsetting/ Risk factor	
Illicit drugs in pregnancy	Maternal recreational drug use in pregnancy (details of drugs, approximate daily amount ingested, duration of use in pregnancy)	Values (Y/N) Values 2 (If Y): Details of use if available	N	Reported	Subsetting/ Risk factor	
Family history of congenital anomalies	The presence of any congenital anomaly (major or minor) in a sibling, or the mother or the father of the reference pregnancy, or their immediate/ first degree relatives (grandparents, aunts or uncles of the reference pregnancy)	Values 1: (Y/N) Values 2 (If Y): Details (free text - record details of anomaly, and relationship to the affected family member)	N	Reported	Subsetting/ Risk factor	
Relevant family history of genetic disorders	The presence of any genetic disorder in a relative thought to be the explanation or of relevance to the abnormalities reported in the reference pregnancy.	Values 1: (Y/N) Values 2 (If Y): Details (free text - record details of the disorder, and relationship to the affected family member)	N	Reported	Subsetting/ Risk factor	
Plurality	Number of foetuses in current pregnancy	Values: 1, 2, >2	Y	Reported	Subsetting/ Risk factor	
Number of previous pregnancies	Number of previous pregnancies (including non-live births) experienced by the mother only	Integer	N	Reported	Subsetting/ Risk factor	
Number of previous live births	Number of previous live births	Integer	N	Reported	Subsetting/ Risk factor	An important risk factor for outcomes related to birth weight
Number of previous spontaneous abortions	Number of previous spontaneous abortions	Integer	N	Reported	Subsetting/ Risk factor	
Number of previous	Number of previous induced terminations (for any reason)	Integer	N	Reported	Subsetting/ Risk factor	

Variable	Clinical definition	Technical definitions and values	Essential	Source	Purpose	Notes
induced terminations						
Number of previous stillbirths	Number of previous stillbirths	Integer	N	Reported	Subsetting/ Risk factor	
Previous pregnancies with congenital anomalies	Details of any previous pregnancies which resulted in fetuses/offspring with congenital anomalies (include description of birth defect(s) for each affected fetus/child)	Values 1: (Y/N) Values 2 (if Y): Details (include whether any of these anomalies occurred due to genetic/chromosomal disorders)	N	Reported	Subsetting/ Risk factor	
Assisted conception	Assisted conception technique utilised for this pregnancy	Values: (Y/N)	N	Reported	Subsetting/ Risk factor	
Maternal blood type	Maternal blood type	Values: A+, A-, B+, B-, O+, O-, AB+, AB-	N	Reported	Subsetting/ Risk factor	
Blood group incompatibility	Maternal anti-D antibodies identified in pregnancy	Values: (Y/N)	N	Reported	Subsetting/ Risk factor	
Folic acid use	Maternal folic acid use in pregnancy	Values 1: None, pre-conception, first trimester, other Values 2 (If not None): Dose - 400 mcg, 5 mg or other	N	Reported	Subsetting/ Risk factor	

Core summary tables – Example table shells

Case disposition

Table 1-1 (Page 1 of 1)
Case disposition
PRIM: All fetus cases

Status	(N=xxxx)
Birth type outcome pending	xxx (xx.x %)
Birth type outcome not known *	xxx (xx.x %)
Birth type outcome known	xxx (xx.x %)
Fetal outcome known	xxx (xx.x %)
Fetal outcome unknown **	xxx (xx.x %)
Not live birth	xxx (xx.x %)
Live birth	xxx (xx.x %)
Major malformations in live births	x (xx.x %)

Notes: * Lost to follow-up.
** Although the birth type is known, the fetal outcome is either: Outcome pending, Lost to follow up, Infant status unknown, or data missing.

Demographics

Table 1-2a (Page 1 of 1)
Patient demographics
PRIM: All pregnancy cases

	(N=xxxx)
Age at last menstrual period (LMP) (years)	
n	xxx (xx.x %)
Mean (SD)	xxx (x.x)
Median	xxx
Min, Max	xxx, xxx
Predominant race	
n	xxx (xx.x %)
Caucasian	xxx (xx.x %)
Black	xxx (xx.x %)
Asian	xxx (xx.x %)
Hispanic	xxx (xx.x %)
Oriental	xxx (xx.x %)
Other	xxx (xx.x %)
Unknown	xxx (xx.x %)
Region	
n	xxxx (xxx %)
USA and Canada	xxx (xx.x %)
Europe	xxx (xx.x %)
Japan	xxx (xx.x %)
Other	xxx (xx.x %)
Pre-pregnancy BMI (kg/m2) *	
n	xxx (xx.x %)
Mean (SD)	xx.x (x.x)
Median	xx.x
Min, Max	xx.x, xx.x

Notes: * BMI measurements may be in early pregnancy for PRIM.
n is the number of cases with non-missing data.

Gestational age at reporting

Table 1-3a (Page 1 of 1)
Gestational age at reporting
PRIM: All pregnancy cases

	(N=xxxx)
Gestational age (days)	
n	xxx (xx,x %)
Mean (SD)	xxx (xx)
Median	xxx
Min, Max	xxx, xxx

Notes: n is the number of cases with non-missing data.

Exposure to drug

Table 1-4a (Page 1 of 1)
Drug exposure during and shortly before pregnancy
PRIM: All fetus cases

Timing of exposure in pregnancy	
N	xxxx (100 %)
Peri-LMP only *	xxx (xx.x %)
At least 1st trimester **	xxx (xx.x %)
Only after 1st trimester	xxx (xx.x %)
Exact timing in pregnancy unknown	xxx (xx.x %)
Other categories	xxx (xx.x %)

Notes: * From 8 weeks before LMP to LMP.
** 1st trimester is the period starting on the first day of LMP and ending on the date of LMP + 84 days.
** At least 1st trimester category may include cases with exposure also in other periods.

Selected pregnancy outcomes by exposure period

Table 1-5a (Page 1 of 1)
Summary of selected pregnancy outcomes by exposure period
PRIM: Fetus cases with known outcome

	Overall N	(%)	Timing of exposure in pregnancy: Peri-LMP only * N	(%)	At least 1st ** trimester N	(%)	Only after 1st trimester N	(%)	Unknown # N	(%)
All pregnancies with known outcome										
Ectopic pregnancy										
Spontaneous abortion ##										
Hydatidiform mole										
Elective terminations										
With congenital malformations (TOPFA)										
Without congenital malformations or unknown										
Still births										
With congenital malformations										
Without congenital malformations or unknown										
Live births										
With congenital malformations										
Without congenital malformations or unknown										

Notes: * From 8 weeks before LMP to LMP.
** 1st trimester is the period starting on the first day of LMP and ending on the date of LMP + 84 days.
# Exact timing in pregnancy unknown.
Spontaneous abortion includes fetal outcome cases of Fetal death / intrauterine death and blighted ovum.
There may be other combinations of known timing of exposure not displayed in this table but included under Overall; therefore columns do not add up to the total.

Prevalence of major malformations by exposure period

Table 1-7a (Page 1 of 1)
Prevalence of major malformation (including chromosomal anomalies) by exposure period
PRIM: Fetus cases with known outcome

Timing of exposure in pregnancy	Denominator: Population	N	Major malformation and/or chromosomal abnormalities: n	Prevalence % (95% CI)
Overall	Live births			
	Live births, still births, and TOPFA			
Peri-LMP only *	Live births			
	Live births, still births, and TOPFA			
At least 1st trimester **	Live births			
	Live births, still births, and TOPFA			
Only after 1st trimester	Live births			
	Live births, still births, and TOPFA			
Unknown #	Live births			
	Live births, still births, and TOPFA			
Overall except unknown ##	Live births			
	Live births, still births, and TOPFA			

Notes: * From 8 weeks before LMP to LMP.
** 1st trimester is the period starting on the first day of LMP and ending on the date of LMP + 84 days.
# Exact timing in pregnancy unknown.
All cases except those with exact timing in pregnancy unknown.
TOPFA: Termination of pregnancy due to fetal anomaly.
Still births not including spontaneous abortions.
There may be other combinations of known timing of exposure not displayed in this table but included under Overall.