PASS information

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Research question and objectives	Is routine surveillance for longer-term health and child neurodevelopment feasible, valid and accepted within already established pregnancy pharmacovigilance surveillance systems?
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Academic partners /ENTIS centres	UMAN, UZKN, UKTIS, UNEW, LAREB, UK and Ireland Epilepsy and Pregnancy Register, MHRA, UU.
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1. List of abbreviations and definitions

List of abbreviations

- ADHD Attention Deficit Hyperactivity Disorder
- ASD Autistic Spectrum Disorders
- ASQ-3 Ages and Stages Questionnaire – 3rd Edition
- EFPIA European Federation of Pharmaceutical Industries and Associations
- FVSD Fetal Valproate Spectrum Disorder
- IMI Innovative Medicines Initiative
- NaME Neurodevelopment of Babies Born to Mothers with Epilepsy
- MHRA Medicines and Healthcare products Regulatory Agency
- PASS Post Authorisation Safety Studies
- SPSS Statistical Package for the Social Sciences
- UMAN University of Manchester
- UK & I EPR UK and Ireland Epilepsy Pregnancy Register
- UKTIS UK Teratology Information Service
- UZKN University of KwaZulu-Natal
- WEB-RADR Web-Recognising Adverse Drug Reactions
- WP Work Package

List of definitions

- *Collaborating Group:* These are groups who undertake pregnancy pharmacovigilance studies pertaining to congenital anomaly data, who opt in to develop and pilot the LIFETIME System. Collaborating Groups may be disease or medication specific pregnancy registers or teratology information services.
- *Congenital anomaly:* Morphological, functional and/or biochemical developmental disturbance in the embryo or fetus whether detected at birth or not.
- *Fetus:* This term is used here with the broad definition of the term fetus, referring to the entire prenatal development from the conception until the birth.
- *Neurodevelopment:* The brain's development over time and its observable functions (e.g., milestone attainment, intellectual functioning, reading ability, social skills, memory, attention or focus skills).
- *Pharmacovigilance:* Science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.
- *Registry:* An organised system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition or exposure.
- *Risk-benefit balance:* An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks.
- *Signal:* Information arising from early investigations which suggests a potentially causal association between an exposure and an adverse event or set of outcomes.
- *Study Group:* The primary ConcePTION work package 2, demonstration 3 group.
- *Teratogens:* Environmental factors which can cause congenital abnormalities.

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3. Abstract

There is limited collection of data regarding longer-term child health and neurodevelopment following exposure in the womb to medications. This is despite the clear examples of deleterious impact of maternal medications on child health and development. The adaptation of already established pregnancy pharmacovigilance surveillance methods such as pregnancy registers or teratology information services, offers a route through which routine child health and neurodevelopmental screening could occur.

As part of the ConcePTION Study the LIFETIME System will be designed and piloted for feasibility, validity and acceptability. It will aim to be a cost-effective program, utilising parent reporting methods, which will allow for the standardised collection of longer-term child health and neurodevelopmental outcome data across different pregnancy pharmacovigilance surveillance sources (Collaborating Groups). Pregnancy and immediate birth outcomes recorded prospectively through the Collaborating Group's local procedures will be augmented with the LIFETIME follow up system, extending follow up from 6 months of age to 7 years of age. To be able to facilitate a more rapid accumulation of data, particularly for medications with a lower frequency of use, the feasibility of aligning and combining data from different Collaborating Groups using the LIFETIME System will be piloted.

If found to be feasible, valid and acceptable the LIFETIME System can be implemented into other pregnancy pharmacovigilance surveillance schemes throughout Europe to enable or enhance the collection of child health and neurodevelopmental screening data on a routine basis.

4. Amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1	24.01.2022	Timelines	Data collection for Stage 4 has moved to back to February 2022.	Study set up and approvals took longer than planned.

5. Milestones

Milestone	Planned date
Application for required ethics Start of data collection	Study Month: 3 ConcePTION Month: 31
Start of data collection	Study Month: 5 ConcePTION Month: 33
Progress report(s)/ Interim report(s)	
Stage 1: Internal report of the requirements of the Collaborating Groups.	Study Month: 1 ConcePTION Month: 29
Stage 2: LIFETIME design and questionnaire selection complete	Study Month: 2 ConcePTION Month: 31
Stage 3: Completion of the questionnaire pilot	Study Month: 6 ConcePTION Month: 34
Stage 4: Pilot data collection using the primary age questionnaire set in an already established cohort results	Study Month: 17 ConcePTION Month: 44
Stage 5: Results from the pilot of the prospective data collection using Lifetime	Study Month: 7 ConcePTION Month: 35
Stage 6: Results from the feasibility study regarding the combining of LIFETIME data collected from different groups	Study Month: 27 ConcePTION Month: 55
Registration in the EU PAS Register®	Study Month: 1 ConcePTION Month: 31
Final report of study results (all stages)	Study Month: 28 ConcePTION Month: 56

6. Rationale and background

Certain medications are associated with increased risks of both congenital anomalies and impact on fetal brain development [1]. However, the use of medication during pregnancy is often necessary for women with both chronic and acute conditions [2, 3] and the time taken to gather adequate data on risk or safety is too long [4]. While there are several established approaches to routine data collection for congenital anomalies, including disease and medication pregnancy registers, teratology information service cohorts and others [5, 6], there is currently a lack of routine surveillance for the impact an exposure may have on the developing fetal brain and associated long-term outcomes.

The medications sodium valproate and isotretinoin are two examples whereby a medication exposure can be associated with a deleterious impact on the developing brain [7-9]. These two medications, one an antiseizure medication and the other an oral retinoid for severe dermatological indications, highlight the high risk to the developing fetal brain which can be conveyed by diverse medication classes. Both medications are associated with increased rates of poorer early infant development and later an increased risk of intellectual disability [9, 10], but each has a characteristic and distinct pattern of cognitive deficits. For both medications there is a dose dependent association, with higher doses leading to increased risks of impairment [9, 11] and an association with physical symptoms of the exposure such as characteristic congenital anomalies and facial dysmorphia [7, 9]. However, despite these clear detrimental effects, little is known regarding the risk (or lack thereof) posed to the developing brain by the majority of medications commonly prescribed to women of child-bearing potential, including some for which structural effects have been identified.

Both health outcomes and neurodevelopmental deficits present a substantial cost to the individual, their family and to society through increased requirements for health and educational interventions and support. Given the severity of the

associated impact on the development and functioning of the child's body and brain, an expedited system of routine surveillance for child health and neurodevelopmental outcomes is required. This system must enable rapid collection and evaluation of safety data across large populations, but with high sensitivity to identify moderate to severe child neurodevelopmental and health difficulties.

Neurodevelopment is a term which covers a diverse range of brain functions including intellectual abilities, language, attention, executive functions and other cognitive abilities, as well as motor development and social skills. The development of the brain is a protracted process which begins *in utero* but continues to unfold and be influenced through the postnatal years. A child's health status is also dynamic and given this extended period of development, the complex functioning of the organs are not be fully evident at birth. The breadth of diversity and the elongated developmental phase of child health and neurodevelopmental outcomes may make them appear more nebulous than their structural anomaly equivalents. However, if considered as a set of interrelated but independent outcomes, measured by a standardised assessment and within the correct age range, the individual areas of child health and neurodevelopment can be clearly defined, objectively measured and effectively reported on.

A recently convened expert consensus group regarding the investigation of child outcomes following exposure to medications in utero highlighted the importance of longitudinal follow up studies utilising direct assessment of the child by a blinded trained assessor[12]. However, such methodological approaches are costly both in terms of time and finance and therefore have not, and are unlikely to become, fully embedded into routine surveillance systems. An alternative approach is to model what is currently undertaken in many national child health and developmental services. Parent completed standardised and validated questionnaires are used to act as a way of identifying children at risk of poorer health and developmental outcomes and who require more comprehensive, specialist assessments. Thus, there is the opportunity to investigate whether parent completed questionnaire data is a feasible option to allow for an adequate

system of routine surveillance for child health and neurodevelopment following exposure in the womb to a medication. It is not proposed that such studies replace gold standard longitudinal studies with blinded assessments by trained personnel, but that such a system is used to screen for signals of altered child health and neurodevelopment following exposure to medicinal products. Such early warning signals should then lead to intensive gold-standard investigation from which conclusions can be drawn and regulatory decisions made.

The Innovative Medicine Initiative (IMI) funded ConcePTION project aims to enhance the way medication use during pregnancy is studied [13] in order to provide clearer, more comprehensive data to a more appropriate timescale. This demonstration project will contribute to this aim through the investigation of feasibility of a system which would allow for cost effective, routine screening level investigation into the health and neurodevelopmental outcomes of children exposed to medications in utero. This will form the basis of a wider system of routine screening and comprehensive assessment of longer-term child health and neurodevelopmental outcomes.

7. Research question and objectives

The primary research question: Is a routine surveillance system for longer-term health and child neurodevelopment feasible, valid and acceptable for implementation within already established pregnancy pharmacovigilance surveillance systems?

The secondary research question: Is it feasible to combine data from multiple Collaborating Groups for analysis?

This study has the following objectives:

1. To identify what adaptions are required within already established pregnancy pharmacovigilance systems to extend data collection to include child health and neurodevelopmental outcomes.
2. To design a standardised and sustainable system ('LIFETIME System'), including data collection tools and technology infrastructure, that is

capable of collecting longer-term child health and neurodevelopmental outcome data within already established pregnancy pharmacovigilance surveillance programs.

3. To investigate the validity of the chosen questionnaires for the LIFETIME System to detect the health and neurodevelopmental difficulties associated with in utero exposure to sodium valproate.
4. To test the feasibility and acceptability of the LIFETIME Questionnaire Set, in already established research cohorts.
5. To pilot prospectively the LIFETIME System in established pregnancy pharmacovigilance surveillance programs such as disease specific pregnancy registers and teratology information services.
6. To develop the agreements, data flows and infrastructure required to combine data from different Collaborating Groups and to test the feasibility of data combining.

9. Timelines

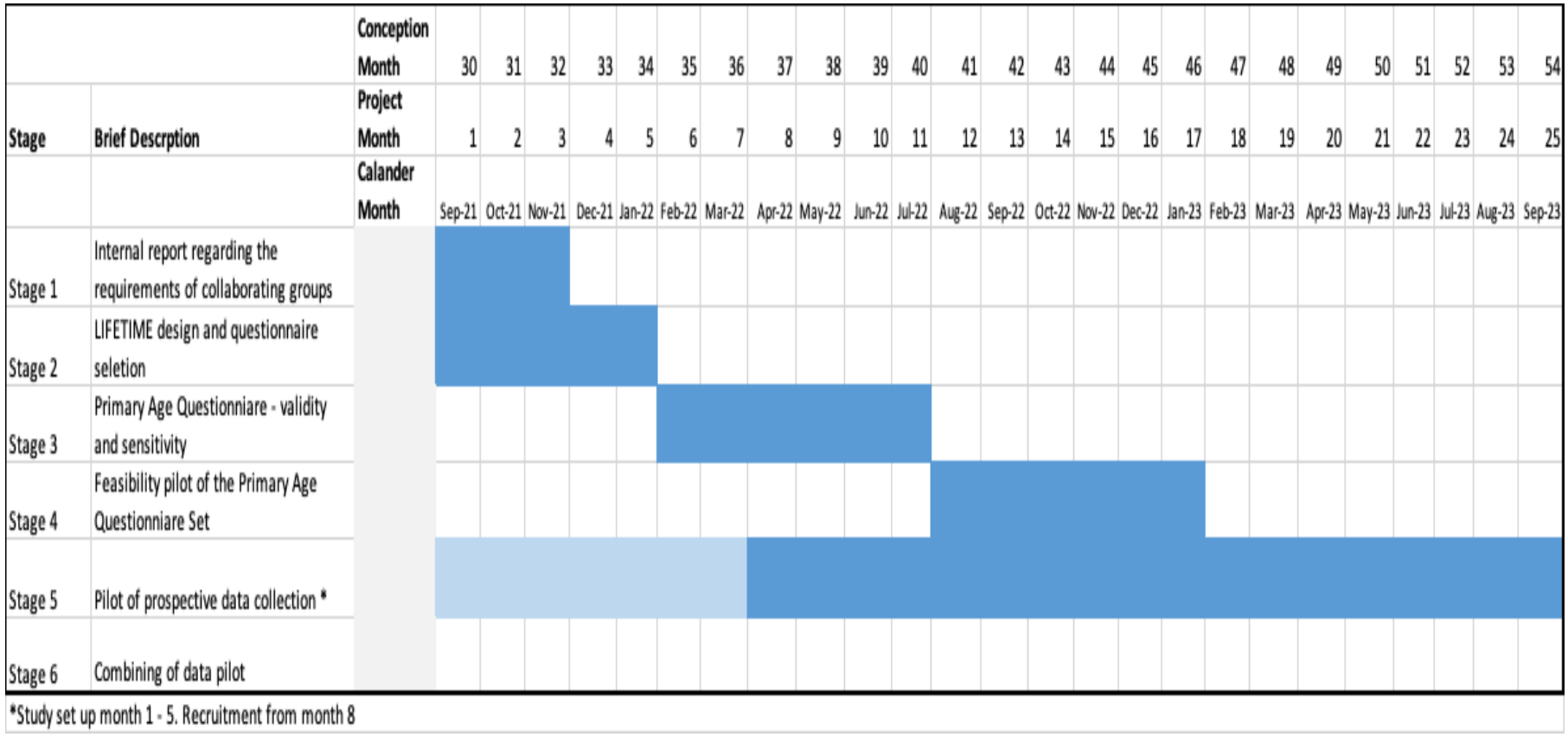
This demonstration project will run from September 2021 (month 30 of the IMI ConcePTION Study) until September 2023 (month 54 of the IMI ConcePTION Study). Figure 1 displays the timelines for each of the six stages of the project.

10. Research Design

This project is one of design and feasibility testing. Initially this project will focus on the development of the LIFETIME System: a set of questionnaires which will be the primary source of standardised data collection and the development of infrastructure to collect the data. Following this, three observational studies will be completed which will investigate validity and feasibility of the proposed system through the collection of primary data.

There are 6 stages to this investigation which will first develop and then feasibility test the new LIFETIME System. Table 1 provides a brief summary of each of the stage.

Figure 1. Demonstration project 3 timelines.



* Early work on this stage is required to establish procedures for recruitment during pregnancy with the collaborating groups.

Table 1. Summary of the objectives for each stage of the project

	Objective	Stage		
Stage 1.	To identify what adaptions are required within already established pregnancy pharmacovigilance systems to extend data collection to include child health and neurodevelopmental outcomes.	Development		
Stage 2.	To design a standardised and sustainable system (LIFETIME System) including data collection tools and technological infrastructure, that is capable of collecting longer-term child health and neurodevelopmental outcome data within already established pregnancy pharmacovigilance programs.			
Stage 3.	To investigate the validity of the chosen questionnaires for the LIFETIME System to detect the health and neurodevelopmental difficulties associated with *in utero* exposure to sodium valproate		Validity testing	
Stage 4.	To test the feasibility and acceptability of the LIFETIME Questionnaire Set in an already established research cohort.			Feasibility Testing
Stage 5.	To pilot prospectively the LIFETIME System in established pregnancy pharmacovigilance surveillance programs such as disease specific pregnancy registers and teratology information services.			
Stage 6.	To develop the agreements, data flows and infrastructure required to combine data from different Collaborating Groups and to test the feasibility of data combining.			

10.1. Stage 1: Identification of adaptions required within pregnancy pharmacovigilance surveillance systems to extend to longer term follow up.

Objective: To identify what adaptions are required within already established pregnancy pharmacovigilance systems to extend data collection to include child health and neurodevelopmental outcomes.

Months: 1-2.

The needs of potential end users of the LIFETIME System will be identified through a series of meetings and feedback sessions with possible collaborating Groups who have indicated an interest in piloting the LIFETIME System.

Information will be sought from primary pregnancy pharmacovigilance data collection schemes such as teratology information services and pregnancy registers as to current practices, data collection methods and likely barriers to extending their follow up periods and scope. A mapping exercise to identify common areas of need or challenges will be undertaken with the required adaptations identified and solutions identified. For example, in the preparation for this demonstration project, preliminary discussions with potential Collaborating Groups have identified that alterations to research approvals would be required. As part of this stage standard documentation will be produced for Collaborating Groups which would require personalisation for their specific data collection method and translations (where required).

Output(s) for Stage 1: An internal demonstration project report will be drafted documenting the technical, expertise, legal and ethical requirements of the different pregnancy pharmacovigilance surveillance systems to be considered in the design of the system. Additionally, a series of user guidance documents and information sheets will be prepared following these consultations to enable the participating Collaborating Groups to apply integrate the LIFETIME System into their already running data collection schemes.

10.2. Stage 2: The development of a system of longer-term child health and neurodevelopmental surveillance.

Objective: To design a standardised and sustainable system (LIFETIME System), including data collection tools and technology infrastructure, that is capable of collecting longer-term child health and neurodevelopmental outcome data within already established pregnancy pharmacovigilance surveillance programs.

Months: 1-3.

Identified through work already conducted in ConcePTION Study Task 2.3 and through preparatory work for this protocol, Collaborating Groups will require a flexible system which relies on limited financial and staff time commitments. Therefore, an approach which utilises a Collaborating Group's already collected pregnancy, maternal health and medication data but extends the period of follow up using a standardised system of parental completed questionnaires to ascertain the child's health and neurodevelopmental information will be designed and tested. Once developed and validated the ConcePTION LIFETIME System will also be suitable for use as a complete data collection system for new users.

There is a clear rationale for starting surveillance early in the child's life and with high frequency into the preschool years[12]. A framework for the proposed LIFETIME System has been developed as part of ConcePTION Study WP2, Task 2.3 and includes repeated contact with the parent early in the child's development. For this ConcePTION Study demonstration project, we would look to extend child follow up to seven years of age. Ideally the LIFETIME System follow up would run beyond the primary school years and into the second decade of life, but this is beyond the scope of the current project and is an area identified for future development.

Infant Questionnaire Set Choice (6 months – 4 years)

In order to obtain data from parents a cost-effective set of questionnaires will be selected as part of the development of this system. A mixture of standardised and adapted screening measures will be chosen based on availability, feasibility and

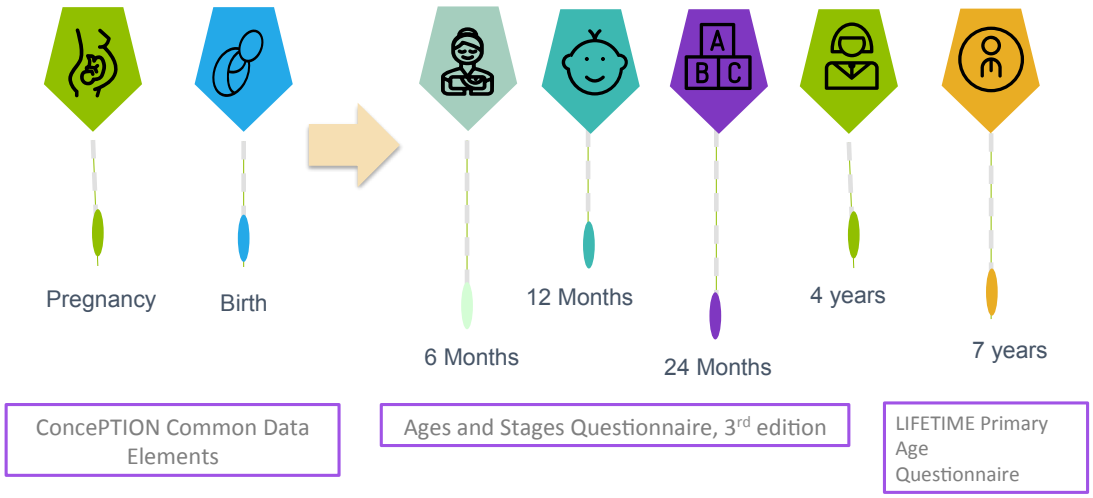
evidence of sensitivity. As part of the preparatory work for this protocol, through literature searches, author experience and alignment with other data collectors (e.g. US Organisation of Teratology Information Services [14]) there was a clear rationale for the utilisation of the Ages and Stages (ASQ-3) [15] questionnaire to be used for infant to early childhood follow up. The ASQ-3 is a caregiver-report that helps determine whether a child's development is on track or identifies children at risk for developmental delay. The ASQ-3 has been translated into a wide range of languages and has been shown to be feasible, as well as being sensitive to delays in development induced by teratogens [16, 17]. The ASQ-3 would provide information on the child's development in the following critical areas: Communication, Gross Motor, Fine Motor, Problem Solving, Personal and Social development. The use of the ASQ-3 will be utilized for the first four data collection time points (6 months, 12 months, 24 months, 4 years) along with questions about the child's health. As part of the development of this protocol discussions with the ASQ-3 publishers have been held about a license which will allow for the delivery of the ASQ-3 in a variety of formats (e.g., electronic or paper based, smartphone app).

Primary Age Questionnaire Set Development

At older ages development is more complex and multi-faceted, a broader set of measures are required. Given the financial and time restraints indicated by Collaborating Groups, large and expensive questionnaire sets are not feasible, if the LIFETIME System is to be adopted in the longer term as part of routine surveillance methods. Therefore, a bespoke questionnaire set will be designed specifically for this the LIFETIME System from low cost but standardized and validated measures already available. The LIFETIME System development team will include experts in child development (psychologists and pediatricians) and those with longitudinal cohort expertise and the final LIFETIME Primary Questionnaire Set will include questionnaire tools covering both the child's health and their neurodevelopmental status. Early reviews of possible questionnaires for the Primary Age Questionnaire Set include: MacArthur Health and Behaviour Questionnaire[18], Paediatric Symptoms Checklist[19], Patient-Reported

Outcomes Measurement Information System- Pediatric Bank v1.0 - Cognitive Function[20]. The final decision on the questionnaires will be made in month four of the project to allow for validity assessment in Stage 3.

Figure 2. Graphical display of the screening element of the LIFETIME System



Developing administration procedures for the LIFETIME System

The ability to provide a flexible system delivery through different collection formats is required for the LIFETIME System. Typically, longitudinal parent-reported child health and neurodevelopmental data are collected via in person, paper or telephone-based questionnaires. Whist these approaches may work in the context of certain services they may require too much resource for others (e.g., staff to complete telephone contacts with participants). To address these barriers, both web-based and App based delivery of the questionnaires will be trialed in the feasibility studies (stages 3 and 4) alongside more standardized completion, where needed.

As part of the ConcePTION Study, Work Package 2 partners including the Medicines and Healthcare products Regulatory Agency (MHRA) are repurposing

the WEB-RADR App (https://web-radr.eu/) to optimize it for pregnancy pharmacovigilance. WEB-RADR is an adverse event reporting App which will be extended as part of WP2 Demonstration Project 5 to create the ConcePTION App. This update will include an extension to include two key structured question sets: the ConcePTION Core Data Elements for pregnancy and immediate child outcomes, and the LIFETIME System questionnaires to provide the longer term follow up aspect of this initiative. The App will be utilized by some data collectors to deploy the questionnaires to participating women and send push notifications of relevant information and reminders.

Outputs Stage 2: The outputs from Stage 2 will be the developed questionnaire sets in electronic format and the delivery infrastructure (Web- based platform and App) for the feasibility and validity studies in Stages 3 and 4.

10.3. Stage 3: Assessment of the validity of the Primary Age Questionnaire Set.

Objective: To investigate the validity of the chosen questionnaire for the LIFETIME System to detect the health and neurodevelopmental difficulties associated with in utero exposure to sodium valproate.

Month: 3-6

Research Questions:

- Can the selected Primary Age Questionnaire Set detect the known neurodevelopmental difficulties associated with in utero exposure to sodium valproate?

The ASQ-3 has been trialed in the assessment of children exposed to certain medicines [21] and in infants born prematurely[22], as well as being used widely internationally as a general neurodevelopmental screening measure. However, because of the need for a more diverse set of measures as the child reaches 7 years of age a more bespoke set of measures will have to be selected and therefore

require trialing in a relevant population to determine that they are a sensitive and valid set of measurements to detect patterns of impairment associated with *in utero* exposure. Therefore, once assembled, the final LIFETIME Primary Questionnaire Set will be trialed by parents of children with Fetal Valproate Spectrum Disorder (FVSD) using a cross section observational cohort design. FVSD is a condition which can occur following prenatal exposure to the antiseizure medication sodium valproate and has a documented impact on child health and neurodevelopment[7]. Comparator data will be gathered from a set of non-exposed controls to ensure the Primary Questionnaire Set's ability to detect health and neurodevelopmental symptoms associated with a medication exposure.

Procedure

The finalized Primary Age Questionnaire Set will be re-created on an electronic platform hosted by the University of Manchester. Ethical approval will be obtained to promote this study through international charities which specialize in supporting families with children diagnosed with Fetal Valproate Spectrum Disorder [7], formally Fetal Valproate Syndrome. Parents of children and young people with Fetal Valproate Spectrum Disorder will be invited to take part in this study by the charities they are partnered with. Potential participants will respond to the invitation through an electronic link which will take the respondent to the Participant Information Sheet and the Consent Form. Following the provision of consent, participants will be asked to complete the Primary Questionnaire Set relevant to their child's age, through a Web-based platform. Using a standardized form at the end of the questionnaire, parents will also be asked to provide feedback regarding the acceptability of the questionnaire and its suitability to detect any difficulties their child experience.

Participating families will be asked at the end of the questionnaire if they or family members have children of a similar age to their young person who are unexposed to sodium valproate. They would be asked to complete the questionnaire for an unexposed sibling or to share a link to the study with their family member. Collection of data on siblings or family members where there is no history of exposure will allow for a comparator group to be established for this investigation.

Eligibility

Parents will be eligible for participation if:

- they are a parent of a child with Fetal Valproate Spectrum Disorder
    - or for the comparator group, they are related to the parent of a child without exposure in the womb to sodium valproate.
- their child is aged between 6 years and 8 years 11 months.
- they can read and respond in written English.
- they are able to provide informed consent to participate

Variables

In this stage to validate the use of the chosen questionnaires the following will be measured:

- **Feasibility** – the number of families who consent to complete the questionnaires.
- **Completion rates**- the number of successfully completed questionnaires.
- **Acceptability** – women will be asked to provide their opinions on the usefulness and the suitability of the questionnaires to provide the information they view as important.
- **Validity** – the pattern of reporting and whether it has the validity to detect health and neurodevelopmental outcomes known to be influenced by exposure to valproate versus the comparator group. Additionally, the validity of the questionnaires will be investigated through the pattern of responding and whether it is concordant with the known pattern of health and neurodevelopmental difficulties in Fetal Valproate Spectrum Disorder.

Data and analysis

Responses to the bespoke Primary Age Questionnaire Set will be collated and analyzed to determine recruitment rates, completion rates and acceptability.

Appropriate statistical tests (e.g., t-test and Chi-square) will be used to examine differences between the group with Fetal Valproate Spectrum Disorder and the control group (friends and family no exposure group); should large enough numbers be obtained, analysis adjusting for confounder and mediating factors will

be undertaken (e.g. multiple linear and logistic regression analyses). The Primary Age Questionnaire Set would be considered sensitive if it identifies the difficulties known to occur at a higher rate in valproate exposed children (e.g., poorer ascertainment of language and motor milestones, language and social functioning and increased risk of attention deficit hyperactivity disorder (ADHD) and autistic spectrum disorders (ASD).

Sample Size

The selected assessment measures from which the LIFETIME question set for assessment of age 4-7year olds are drawn will all have been previously validated. The current study will assess the validity and sensitivity of the LIFETIME derived Primary Age Questionnaire Set to detect differences between valproate-exposed and non-exposed individuals. Given that valproate is known to have a relatively large effect on development at 30-40% of exposed children[23], a sample size of 20-30 participants in each group will be sufficient to detect differences with 80% power and a significance level of $\alpha = 0.05$ [24].

Output(s) Stage 3: Following this validity pilot an internal Demonstration Study report will be drafted. Modifications to the LIFETIME Primary Age Questionnaire Set will be made where required, as indicated by feedback received from participants and any methodological issues that arise. The data collected from the parents of children and young people with Fetal Valproate Spectrum Disorder will be written up for publication demonstrating the suitability of the LIFETIME Primary Questionnaires Set to detect health and neurodevelopmental outcomes in the context of medication exposure.

10.4. Stage 4. To test the feasibility and acceptability of the LIFETIME Questionnaire Set, in already established research cohorts.

Objective: To test the feasibility and acceptability the LIFETIME Primary Age Questionnaire Set in an already established research cohort.

Months: 5-16

Research Questions:

- Is it feasible to collect data in middle childhood using the LIFETIME Primary Age Questionnaire Set?

- Are any developmental differences identifiable across the individual antiseizure medication exposure groups?

This stage will investigate the feasibility and the acceptability of using the LIFETIME Primary Age Questionnaire set for cross sectional neurodevelopmental and child data collection in an already established research cohorts. A small number of participating Collaborating Groups will be invited to take part in this set of investigations as well as the prospective feasibility pilot in Stage 5.

Procedure

Groups who wish to collaborate on this Stage's investigations will be supported through the provision of standardised documents that. Can be adapted or included in local study protocols and applications. Once approvals are in place, women enrolled in the Group's Study (e.g., their pregnancy register, cohort study or other) will be invited to participate. If agreeable, a link to the participant information sheet and online consent form will be provided. Once consent has been obtained, the LIFETIME Primary Age Questionnaire Set will be completed.

Eligibility

Women and their children will be eligible for this study if:

- they were enrolled in the specific collaborating project during pregnancy
- their child is aged between 6 years and 8 years 11 months

Variables

This study will collect the following feasibility variables:

- Process: is it feasible to collect longer term health and neurodevelopmental data by retrospectively approaching and obtaing data from women previously enrolled prospectively in pregnancy surveillance systems which were primary for the collection of congenital anomaly outcomes?
    - Does the pilot methodology lead to recruitment rates of greater than 50% of eligible mother-child pairs?
    - Can missing data be kept below 10% for questionnaire completion?

- Resources: what are the resources required for the set-up of retrospectively contacting families who were previously enrolled?
    - Were there any common barriers to establishing retrospective contact with participants for collaborating groups?
    - What was the number of months this process took?
- Management: what were the data management issues associated with this study?
    - What adaptions were required to ethical and data governance approvals? Were there are common barriers here?
    - What adaptions to data management were required?
- Scientific: What were the outcomes on the questionnaires in this context?
    - Was the data distributed as expected in terms of means, standard deviations and rates of below cut off scores?

Data and analysis

Data will be collected directly from the women either through a secure web-based platform or through the ConcePTION App, developed in Stage 2. Once complete the data will be downloaded into SPSS 25 for analysis. Feasibility of this as a data collection method will be measured by the time taken to establish data collection using the LIFETIME Primary Questionnaire Set for the Neurodevelopment in Babies Born to Mothers with Epilepsy (NaME) Study cohort (aged between 6 and 8 years of age), from ethical submission through to a complete data set for analysis. Acceptability will be measured through the completion rate. Defining a precise acceptable response rate is difficult as this can be influenced by a variety of factors, but a response rate of ~65% has been suggested as a good general marker for self-completion questionnaires[25]. Analysis of outcomes across the different antiseizure medication groups will be undertaken using logistic regression for categorical scores and linear regression where the outcome is measured in a continuous manner.

Sample size

This is a feasibility pilot to test retrospectively contacting families previously enrolled in surveillance systems to obtain longer term health and

neurodevelopmental data. The feasibility sample has been set at a minimum of 100 mother-child pairs, which is 10% of a full study, which includes several different medications.

Output(s) Stage 4: An internal study report will be written reporting the feasibility of using the LIFETIME System with a cross sectional methodology in an already establishing research cohort. Data regarding the pattern of outcomes for each of the included medications will additionally be written up for publication.

10.5. Stage 5. To pilot the system in 'real world' disease specific pregnancy registers and teratology information services

Objective: To pilot prospectively the LIFETIME System in established pregnancy pharmacovigilance surveillance programs such as disease specific pregnancy registers and teratology information services.

Month: 1-24

Research Questions:

- Is it feasible to use the LIFETIME System for the prospective collection of data in different settings?

From the work undertaken in Stage 1, 2 and 3 of the demonstration project, the prospective element of the LIFETIME System (summarized in Figure 1) will be piloted for feasibility and acceptability of administering the infant ASQ-3 questionnaires at 6, 12 and 24 months of age.

Setting

The pilot will take place in different Collaborating Groups, but at a minimum will be piloted in one disease specific pregnancy register and one teratology information service. The UK and Ireland Epilepsy and Pregnancy Register and The Netherlands Pharmacovigilance Centre Lareb have agreed to be Collaborating Groups for the LIFETIME System. Further Collaborating Groups will be identified during the undertaking of this demonstration project. The LIFETIME Research

Team will work with Collaborating Groups to identify the individual adaptions they specifically require, and the optimal route of data collection for their network.

Eligibility

Given that the aim of this demonstration project is to develop and trial the feasibility and acceptability of integrating longer term follow up routinely within already running pregnancy pharmacovigilance surveillance systems a wide ranging inclusion criteria will be employed.

- Women who are enrolled or in the process of being enrolled in one of the Host Systems
    - Women who are/were taking a medication at one or more times during their pregnancy
    - Women who have enrolled where they were not taking a medication during the pregnancy (where applicable and available in the Collaborating Groups)
- Women who are willing to provide information regarding their child's development

Procedure

Women will be recruited during pregnancy through the Collaborating Group's standard procedures. Consent to follow up with women for the extended period will be obtained through modifications to the Collaborating Group's information consent process, as required. Women will be followed prospectively through the series of data collection points outlined in Figure 1.

Data collection

The collection of exposure information including the medication, its route of administration and its dose will be collected using the Collaborating Groups current methods. This may include data collection from the mother or from medical/ pharmacy records. Pregnancy information will also be collected in this way. Work will be undertaken to map this information to the ConcePTION Common Data Elements, to ensure key information is available regarding the exposure and required confounders. Although data collection using the LIFETIME System will be standardized across Collaborating Groups in terms of the measures

used, variations in the systems used by Collaborating Groups and potential differences in the preferences of participants require a flexible approach to administration. Data will be collected from the mother in her native language. This flexible approach will be ensured by utilizing three different methods of data collection, including:

- The ConcePTION Study App (LIFETIME section) designed in Stage 1 or it's web-based interface.
- On paper, via post, or a web-based questionnaire
- Via the telephone (certain collaborating centres only)

The exact deployment method chosen will depend on the Collaborating Group's capabilities and information governance limitations. Where the Collaborating Group is able, women will be offered a choice regarding the data collection method. Completed information, however collected, will be owned by the Collaborating Group.

Each Collaborating Group will be provided with either a standardized local database for the LIFETIME data or the standardized LIFETIME fields to add to their own existing database. It is expected that this will vary across Collaborating Groups depending on their current infrastructure. Data collected via the ConcePTION App or it's wed-based interface will be held temporarily in the MHRA repository within the Amazon Cloud in a partitioned manner. Each Collaborating Group will be able to manually download their own participant data directly into their local database (e.g., questionnaire data completed over the phone for example) and will only access and view their own data. Further a shared workspace is being developed in collaboration with ConcePTION WP7 on the anDREa platform to all for the processing, analysis and storage of data from different data collectors. Each Collaborating Group will download the data from the MHRA repository periodically and store within their own database during and after the period of this demonstration project, to ensure sustainability.

Variables

This study will assess the feasibility of the LIFETIME System. Questionnaires will be sent to the Collaborating Groups to understand their experiences. Feasibility will be measured through the following domains:

- Process: Do the piloted procedures amount to a system capable of widespread international recruitment and longer-term child follow up?
    - What percentage of eligible women at the participating sites consent to longer term follow up with the LIFETIME System?
    - Once recruited, what are the retention rates until 24 months?
    - What are the levels of missing data for those who participate?
- Resources: What are the resources required to execute this methodology in individual Collaborating Groups?
    - What are the general infrastructure costs of the system?
    - What are the per participant costs for data collection from pregnancy through to 12 months of age?
- Management: What are the data management considerations associated with this study?
    - What adaptations to the Collaborating Groups current data flows, databases and data management plans are needed?
    - Are the proposed procedures compliant with the applicable data protection laws?
- Scientific: Are the questionnaire data consistent with the normative sample data for the ASQ-3?
    - Are the score ranges and distributions as expected?
    - Are the published cut off's applicable in this context?
    - What are the rates of below average development for the children assessed as part of this?

Study Size

This study is a feasibility study investigating the establishment of the LIFETIME longer term child health and neurodevelopmental surveillance system. As many women will be recruited to this through the Collaborating Groups as possible within the 24-month period in order to test feasibility of recruitment. However, due to the per person screening cost associated with the ASQ-3 a limit of 500 families will included, providing ratings at 6 and 12 months of age, across all Collaborating Groups.

Data Analysis

Data will be analyzed investigating the feasibility and the acceptability of the LIFETIME System from the questionnaire completed by Collaborating Groups. Frequency information will be provided with regards to number of women recruited in specific time periods by specific Collaborating Groups and as a total by medication type. Rates of completion of the ASQ questionnaires at each age point, stratified by key demographic variables will be calculated. Rates of questionnaire completion and missing data will also be calculated.

Output(s) Stage 5: An internal study report and academic publication will be written reporting to results of these feasibility pilot.

10.6. Stage 6. To develop and test a secure data sharing platform where data from different collecting programs can combine data

Objective: To develop the agreements, data flows and infrastructure required to combine data from different Collaborating Groups and to test the feasibility of data combining.

Months: 17-24

Research Questions:

- Is it feasible to combine standardised data collected through the LIFETIME System from different collaborators?

Once LIFETIME System data collection is established in more than one Collaborating Group's System, the ability to combine data from multiple Collaborating Group's will be piloted. Combining data which has been collected in a standardized manner across different Collaborating Groups offers an opportunity to reduce the time taken to obtain adequate sample sizes and therefore will reduce the time taken for data to be available for women, regulators and prescribers. The infrastructure for the combining of data, collected to the LIFETIME System specification, will therefore be developed as part of this demonstration project in collaboration with ConcePTION Study colleagues within WP7. The feasibility of data transfer into this infrastructure will be piloted.

Section 1.01 Study Design

This will be a feasibility study which investigates the combining data from individual Collaborating Groups. This will be trialed focusing on data regarding the development of children exposed to the antiseizure medications, due to the UK and Ireland Epilepsy and Pregnancy Register early commitment to the project. The exact exposures included will be determined by the data available during the project.

Procedure

Collaborating groups will be asked to provide information on what data they have collected using the LIFETIME System on the selected antiseizure medications. Collaborating Groups who have not collected pregnancy and immediate child outcomes data to the ConcePTION Common Data Elements will be sent a questionnaire to determine comparability of their pregnancy, exposure and demographic data against the ConcePTION Common Data Elements.

Data combining

The pilot would test the feasibility of combining data on development at 6 months of age as measured by the ASQ-3. Preparatory work will be undertaken with Collaborating Groups to understand the data management requirements generally as well as local information governance rules. Depending on the outcome of these investigations data would either be analyzed as a pre-written script and then the aggregate data uploaded, or analysis will be conducted centrally on the anonymized individual participant level data. Part of this process is to understand the feasibility of dealing with aggregate or participant level data in this manner.

Supported by ConcePTION WP7, a secure and compliant system will be created to allow for a joint workspace in which to combine and analysis data from the different Collaborating Groups.

Variables

This is an investigation regarding the feasibility of combining data from multiple Collaborating Groups who have collected longer term child health and development data using the LIFETIME System (6-month data collection timepoint only). This information will be collected from the Collaborating Groups via a questionnaire with the following variables considered:

- Process: Are the proposed processes feasible?
    - Is data alignment (pregnancy and exposure information) and combining feasible?
    - What are the steps involved with alignment and combining and what are the challenges?
- Resources: What are the resources required?
    - In the Collaborating Groups and at the lead site?
    - What data infrastructure was needed and what were the costs of this?
- Management: What are the data management steps associated with combining data across multiple Collaborating Groups?
    - What adaptations to current processes are needed?
    - Are the proposed procedures fully compliant with relevant data protection rules? Are there any country specific limitations for consideration?
- Scientific: Is analysis possible on combined data?
    - Is aggregate level data or participant level data the most appropriate?
    - Does the combined data produce means, standard deviations and cut offs within the expected ranges?
    - What at the rates of below average performance on the ASQ-3 at 6 months?

Output(s) Stage 6. The primary output from Stage 6 will be a written report on the feasibility and success of aligning and combining data from the LIFETIME System's Collaborating Groups for central analysis. A collaboration will be undertaken with ConcePTION WP8, to identify opportunities for sustainability of the LIFETIME System, should it be a sensitive, valid and feasible way forward for the routine collection of child neurodevelopment and health outcomes.

11. Data sources

A variety of different data sources will be utilised across the stages of this study. These are displayed in the table below.

Table 2. Data sources expected to be utilised for each of the objectives.

	Objective	Data sources
Stage 1.	Development Stages	
Stage 2.		
Stage 3.	To investigate the validity of the chosen questionnaire set to determine the health and neurodevelopmental difficulties associated with in utero exposure to sodium valproate	Data will be obtained through collaboration with Charities who support families of children with Fetal Valproate Spectrum Disorder. This will include international Charities but limited to English speaking countries.
Stage 4.	To test the feasibility and acceptability of the LIFETIME Primary Age Questionnaire Set in an already established research cohort.	Collaborating Groups will be identified who are interested in testing retrospective recruitment. This will include disease specific pregnancy registers and teratology information services.
Stage 5.	To pilot integration of the LIFETIME System into established prospective pregnancy pharmacovigilance programs such as disease specific pregnancy registers and teratology information service derived cohorts.	Collaborating Groups will be identified as part of Stage 1 of this Demonstration Study. Currently, the UK and Ireland Epilepsy and Pregnancy Register and The Netherlands Pharmacovigilance Centre Lareb are interested in collaborating on feasibility testing.
Stage 6.	To develop and test a secure platform where data from different LIFETIME System Collaborating Groups can be combined.	Data sources will be dependent on those identified and by the type of data (e.g., medication exposures they collect).

12. Quality control

In order to ensure quality over the development of the LIFETIME System and the pilot, monthly core group meetings will scheduled to occur every quarter. With each Collaborating Group collecting their own data, several audit principles will be drafted around the completion of data collection, recording and handling missing data.

13. Limitations of the research methods

The LIFETIME System is an ambitious plan to introduce routine child health and neurodevelopmental screening into teratology information services and prospective pregnancy registers in Europe. Given the novelty of this approach the aim is to test feasibility and acceptability rather than to collect data to investigate outcomes for specific medication exposures. However, if feasible and acceptable the system can continue to run following the pilot phase and will lead to the generation of adequately powered data sets to investigate child outcomes following specific exposures. The nature of this investigation also limits analysis of confounders and other potential biases. These will be investigated through future work.

Child development unfolds over a protracted period and therefore a complete prospective pilot stretching until the child is in the second decade of life cannot be ascertained in 24 months. In order to gain experiences with the types of data that will be collected at older ages, a retrospective cross-sectional data collection pilot in study 4 is being undertaken. Future work would test a prospective data system which starts in pregnancy and seamlessly follows the child up into the second decade of life.

Finally, signals of poorer outcomes must be followed up with more comprehensive investigations. The investigation of these additional follow ups are beyond the scope of this demonstration project but will be addressed in the ConcePTION Study Demonstration Projects 4 and 5.

14. Data management

Detailed data management plans will be drafted for Stages 1-6 of this project.
For example, Stages 3 and 4 will be conducted by the LIFETIME Research Group based at the University of Manchester. Specific ethical approval and data management applications will be made either through the University of Manchester (Stage 3) or the UK National Health Service (Stage 4) depending on the origin of the cohort to be utilised.

In Stage 5 and 6 Data will be collected by the Collaborating Groups who will be based in different European countries. Data management plans will need to be unique to Collaborating Groups, considering general principles determined by the Study Group in addition to local standard data management policies. Further, data management protocols may vary across individual participating centres depending on their current surveillance set up and how they choose to implement the LIFETIME System (e.g., App, electronic questionnaire etc). No identifiable information would be made available to the Lifetime Research Group, but analysis of data pertaining to recruitment, retention, completion and acceptability data will be made available to the LIFETIME Research Group as part of this Demonstration Project. Part of the approach into data combining will include consultancy on the required data management processes both internationally and at a local level for the Collaborating Groups. Currently, work is being undertaken to look at the anDREa platform.

The parties to this agreement and inviduals acting on their behalf hereby commit to adhere to the rules of the ENCePP Code of Conduct in their entirety.

15. Protection of human subjects

Given that this pilot will be taking part across several different countries, local policies regarding the protection of human subjects will apply. Each Collaborating Group must meet their country specific obligations.

16. Management and reporting of adverse events/adverse reactions

Data will be collected, processed and held at the Collaborating Group (e.g., the specific pregnancy register or teratology information service provision). The reporting of adverse events in relation to child development will be undertaken by the Collaborating Group as part of their local, already established processes.

17. Plans for disseminating and communicating study results

The results of the Lifetime System design and pilots will be written up for publication in relevant journals as well as in the ConcePTION Demonstration Project 3 reports. The data will be submitted to relevant conferences such as the European Network of Teratology Information Services and other disease specific conferences where the use of pregnancy registers is high (e.g., Epilepsy and Neurology Conferences). In order to maximize the impact and likely uptake of the final system we would also seek to engage directly with prospective Collaborating Groups of the system to obtain feedback and user experience. We will also work with industry and regulatory partners to ensure that the sustainability and up take of this system is maximized.

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Annex 1. ENCePP checklist for study protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Long-term **i**nvestigation **f**ollowing **e**xposure **t**o **i**ndividual **me**dicines in ut**e**ro: The LIFETIME system

EU PAS Register® number:
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				5
1.1.1 Start of data collection[1]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Progress report(s)	☒	☐	☐	
1.1.4 Interim report(s)	☒	☐	☐	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	

Comments:

This study is regarding the design and feasibility test of a novel methodological approach and therefore there is no *a priori* hypothesis.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	10
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	10
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	10.3, 10.4, 10.5 & 10.6
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☐	16

Comments:

There is no specification of measures of association as this is a design and feasibility study.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	10.3, 10.4, 10.5 & 10.6
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	
4.2.2 Age and sex	☐	☐	☒	
4.2.3 Country of origin	☐	☐	☒	
4.2.4 Disease/indication	☒	☐	☐	10.3, 10.4, 10.5 & 10.6
4.2.5 Duration of follow-up	☒	☐	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☐	☐	☒	

Comments:

This study is a design and feasibility study and therefore there are certain source and study population elements which are not applicable.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	10.5
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure categorised according to time windows?	☐	☒	☐	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Exposure information is not relevant to all stages of the investigation.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	10.3, 10.2, 10.4 & 10.5
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	10.3, 10.2, 10.4 & 10.5
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

This looks at feasibility in terms of process, resources, management and scientific methods; therefore there is no single primary outcome.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	

Comments:

This is a design and feasibility study and therefore biases are not being addressed.

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	10.5
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	10.4, 10.5, 10.6
9.1.3 Covariates and other characteristics?	☐	☐	☒	
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	10.5
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	10.5
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates and other characteristics?	☒	☐	☐	10.5
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Not all of the points in section 9 are applicable due to the nature of this study being one of design and feasibility investigations.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	10.3, 10.4, 10.5
10.2 Is study size and/or statistical precision estimated?	☐	☒	☐	
10.3 Are descriptive analyses included?	☒	☐	☐	10.3, 10.4, 10.5

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.4 Are stratified analyses included?	☒	☐	☐	10.5
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

Statistics are basic due to the type of investigations. There are no formal study size calculations as this study is investigating feasibility.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	10.4, 10.5
11.2 Are methods of quality assurance described?	☒	☐	☐	11
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

There is no system for independent review of the study results due to this being a design and feasibility study.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	
12.1.2 Information bias?	☒	☐	☐	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	10.5
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	10.3, 10.4, 10.5, 10.6

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.5, 15
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	14

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	4

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	15
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	15

Comments:

Name of the main author of the protocol: Dr Rebecca Bromley

Date: 30/08/2021

Signature :