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Study Protocol

Impact of EU label changes and revised pregnancy prevention programme for oral retinoid containing medicinal products: utilization and prescribing trends

Version 1.2

17 December 2021

CONTENTS

1.TITLE

Impact of EU label changes and revised pregnancy prevention programme for oral retinoid containing medicinal products: utilization and prescribing trends (EU PAS Register number: 31095).

2. MARKETING AUTHORISATION HOLDER

Not applicable

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4. ABSTRACT

Title:

Impact of EU label changes and revised pregnancy prevention programme for oral retinoid containing medicinal products: utilization and prescribing trends (EU PAS Register number: 31095).

Version 1.2 – 17 December 2021

Main authors:
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Rationale and background:
Oral retinoids are used to treat dermatological conditions like severe acne vulgaris (isotretinoin) psoriasis (acitretin) and chronic hand eczema (alitretinoin), some oral retinoids are also used to treat skin manifestations of T-cell lymphoma (bexarotene) and acute promyelocytic leukaemia (tretinoin). All oral retinoids are highly teratogenic and must not be used during pregnancy. The PRAC has taken risk minimization measures including pregnancy prevention and testing. The study plan has been developed under the Framework service contract (nr. EMA/2017/09/PE/04) with regard to the re-opening of competition no.4.

Research question and objectives:

The aim of this study is to investigate the use of oral retinoid containing medicinal products authorised in the EU before and after implementation of the 2018 revised measures for pregnancy prevention in clinical practice.

While the MAH should conduct a Post Authorization Safety Study (PASS) to evaluate the risk minimization measures, EMA has requested the conduct of an analysis on the use of oral retinoid containing medical products authorized in the EU before and after implementation of the 2018 revised measures for PPP.

Objective 1: To determine drug utilization and prescription patterns of oral retinoid containing medicinal products in females of childbearing potential, and to investigate whether significant changes in prescribing patterns occurred.

Objective 2: To determine prescribers' compliance with the recommendations in the SmPC for oral retinoids-containing medicinal products, by indication (i.e. dermatological conditions including acne, psoriasis and eczema), by age group, by duration of use, and by database.

Objective 3: To determine, in so far as is possible, patients' use of effective contraception in compliance with recommendations in the SmPC for oral retinoid containing medicinal products, by indication (i.e. acne, psoriasis and eczema), by age group, by method of contraception and by database.

Objective 4: To determine drug utilization and prescription patterns over time for alternative medicines prescribed in females of childbearing potential and females becoming pregnant where oral retinoid-containing medicinal products had previously been prescribed or discontinued, by indication, by age group and by database.

Objective 5: To estimate the effectiveness of the 2018 risk minimization measures for oral retinoids.

Study design:
The study design for the different objectives will be a time series study, where outcomes (drug utilization, pregnancy prevention measures, pregnancy) are assessed every month. The study period will run from January 1, 2010 - December 31st, 2020.

Population:
Female subjects of childbearing potential (age 12-55 years)

Variables:
All Objectives: Exposure to oral retinoid containing medicinal products: Acitretin, Alitretinoin, and Isotretinoin; Indication for retinoid containing medicinal products; duration of time on therapy; discontinuation of retinoid containing medicinal product use; pregnancy; depression; age.
Objective 1: Use and discontinuation of oral retinoids. Reason for retinoid discontinuation
Objective 2: Pregnancy testing; contraceptive measures, procedures causing infertility.

Objective 3: Pregnancy: date of conception, pregnancy outcomes.
Objective 4. Alternative medicines used concomitantly with retinoids or after stopping retinoids.

Data sources:
The study will be performed in the following data sources: PHARMO (Netherlands), Danish National Registries, ARS (Italy), BIFAP (Spain), FISABIO (Spain), and Caserta (Italy) data sources.

Study size:
Approximately 15-20 million female subjects of childbearing age.

Data analysis:
Objective 1:
Descriptive: Monthly period prevalence estimates (MPP), monthly incidence of oral retinoid use, stratified by indication, age group, duration on therapy, and database. MPPs of discontinuers, estimated as the number of discontinuers divided by the number of users in the prior quarter stratified by indication, age group, reason for discontinuation.

Hypothesis testing: Interrupted time series analysis of incidence and prevalence of retinoid prescriptions before and after regulatory intervention, by type of retinoid.

Objective 2:
Descriptive: Prescriber compliance, measured by pregnancy test observed by healthcare professional and prescribing of effective contraception. The number and percentage of retinoid prescriptions meeting these criteria will be reported by type of retinoid, period of RMM (before, during, after intervention), age category, duration on therapy prior to prescription, and database.

Hypothesis testing: Interrupted time series analysis of the rate of physician compliant prescriptions before and after regulatory intervention, by type of retinoid.

Objective 3:
Descriptive: Patient compliance to effective contraception, measured by observed pregnancies in women prescribed effective contraception. Types of contraceptives used by women of childbearing age who are current or previous (at any point during the study period) users of retinoids will be described by type of retinoid, period (before, during, after intervention), age group, database, and prior or current use of retinoid. The number of pregnancies during or after a retinoid prescription will be reported by type of retinoid, period (before, during, after intervention), contraceptive type, age group, database, and prior or current use of retinoid.

Objective 4:
Descriptive: Counts and percentages of prescriptions with concomitant use of alternative medicines during retinoid prescriptions stratified by age category, type of retinoid, and database. Counts and percentages of prescriptions with a switch to an alternative medicine during or after discontinuation of a retinoid

prescription stratified by age category, type of retinoid, and database. MPP of treatment switchers estimated as the number of women who switched to an alternative medication divided by the total number of retinoid users in the prior quarter.
Hypothesis testing: Interrupted time series analysis of incidence of retinoid prescriptions with a concomitant alternative medication before and after regulatory intervention, by type of retinoid. Interrupted time series analysis of incidence of retinoid prescriptions with a switch to an alternative medication before and after regulatory intervention, by type of retinoid.

Objective 5:
Synthesis: Description of findings from objectives 1-4 to estimate the effectiveness of the 2018 risk minimization on use of effective contraception, appropriate use of pregnancy testing, incidence of pregnancies in retinoid exposed women.

Milestones:
Final study report will be available in December 2021.

5. AMENDMENTS AND UPDATES:

Date	Amendment	Justification	Protocol Section
03 December 2021	Changes in the study investigators	This accounts for changes in the team structures over the study period.	3. Responsible parties
	Monthly instead for quarterly analysis.	This is motivated by two factors: 1) Due to COVID-19, the validity of time series data after February 2020 is debatable. Therefore, we need to maximize yet number of time points before this, after implementation of the PPP in order to run the ITS analysis 2) Not all data sources can provide data up to 2020 (for example end of 2018 or end of 2019). Therefore, monthly intervals helps to maximize the number of time points after the PPP for the ITS analysis.	4. Abstract 9.7 Data analysis
	Text correction from women to females	The description of study subjects is changed from “women” to “female subjects” to recognize that minors under the age of 18 are included in the study	All sections.
	Study design text corrected	The study design text previously described was erroneously describing a longitudinal cohort, when in fact the analyses were for a time-series design measuring repeated cross-sections over a period of time.	9.1 Study Design 4. Abstract
	Changes in the study investigators	This accounts for changes in the team structures over the study period	3. Responsible parties
	Minor changes to internal timelines (no	More time was needed to run the interim quality checks (level 1 checks) and complete the ETL, due	6. Deliverables and milestones

	changes to deliverable timelines)	to the time required to run the quality checks and due to unexpected delays in access to data for some data sources.	
	Inclusion of the phrase, "having at least one year of valid data" in the study design description	This detail was missing in the first protocol, but is essential to define the study population with the available data	9.2 Setting
	Segmented regression methodology corrected	Due to the limited post-intervention period in some data sources and analyses, and due to the variable implementation length of implementation period across data sources, a 2-segmented regression analysis is proposed, as it will have more power to detect change due to the PPP. Second, the exact start months of the PPP in each country will be used as the intervention date, instead of July 2018, as this is more accurate. Therefore this will be the primary analysis.	9.7 Data analysis
	Pregnancy algorithm	It was originally proposed that pregnancies would be identified in all data sources using the Matcho algorithm. Two changes are proposed: 1) Data sources are now flexible to use registry data, if available, to define pregnancies together with or instead of diagnostic codes, if they believe this will be more accurate (PHARMO, CPRD, ARS); 2) the Matcho algorithm has since been extended by members of this consortium by integrating the existing pregnancy algorithm for the BIFAP data source.	
	Clarified description of how treatment duration will be estimated	The previous description was imprecise and not sufficiently specific. We now provide a more precise description of the prescription and dispensing length across data sources.	9.3.1 Exposure definition
	Common data models tables update	The final analysis will use the latest version of the ConcePTION CDM (V2.2). The full tables are available in a link provided in the Appendix.	Annex 3
	Typographical corrections	Minor typos (such as repeated words), where detected, have been corrected. In some sections, text has been reworded to make it less ambiguous.	
	Delete of sensitivity analysis: "Objective 3: Use of a different algorithm for detection of pregnancy, with removal of requirement of an observed pregnancy outcome."	A unique algorithm for identification of pregnancies across data sources has been defined.	Section 9.7
	Delete of sensitivity analysis: "Objectives 1,	A unique ITS analysis model will be applied.	Section 9.7

	2, 4: Level change models will be used for the ITS analyses to investigate the robustness of the findings to an alternative impact model.		
	Inclusion of additional sensitivity analysis to exclude COVID-19 pandemic period from analyses	The COVID-19 pandemic may influence the rates of prescribing, and other study outcomes, violating the assumptions of the ITS analysis. Therefore, sensitivity analyses will be conducted to examine the effect of excluding this period of time form each ITS analysis. We describe this as a limitation now in section 9.9	Section 9.9 Section 9.7.7
	Exclusion of University of Bordeaux and University of Messina/Palermo as data access providers.	Exclusion of University of Bordeaux and University of Messina (Palermo data source) as data providers due to impossibility of deliver data on time for this study. These actions have been communicated to and approved by EMA.	Several sections across the protocol.
	Delete limitation: "At the planned analysis stage, BIFAP will only be able to provide data through 31 December 2019. This will impact our ability to conduct ITS in BIFAP alone and to draw conclusions in database-stratified analyses regarding BIFAP. However, data provided by BIFAP in the post-intervention period through 31 December 2019 will contribute to pooled ITS analyses for all time points through the end of 2019."	AEMPS has confirmed data availability until 2021 Q2-3	Section 9.9
	Change in data availability – Danish National Registers can only provide prescribing information until 2018;	Due to severe delays in access to the Danish data source, as a result of prioritization of COVID-19-related projects by the data holder, only a portion of the expected Danish National Register data will be available by the study end date. A readily available data set, including only prescribing data up until the end of 2018 will be used for objectives 1,2,4. As a result, neither objective 3 (pregnancy), nor the analyses stratified by diagnostic information (indication,	9.4.2 Data availability 9.9 Limitations

		reason for discontinuation) can be reported on within the study period. A more extensive description of this has been provided to the EMA. We describe this limitation now in section 9.9	
	Change in data availability for ARS Toscana	It was found that pregnancy testing is insufficiently well-captured in the ARS Toscana data source to be used in this study (as pregnancy tests are not reimbursed). It was found that only **acitretin** is reimbursed and captured in the ARS data source.	9.4.2 Data availability

6. DELIVERABLES AND MILESTONES:

Deliverables

Deliverable	Date
1. Preliminary study plan	25th April 2019
2. Draft Study protocol submitted to EMA	12th July 2019
3. Study report	25th Dec 2021
4. Manuscripts	25th Feb 2022
5. Slide set	25th Feb 2022

Month	April 2019	July 2019	February 2020	August 2020	December 2020	June 2021	July 2021	August 2021	September 2021	December 2021	February 2022
1. Preliminary study plan*											
2. Draft study protocol*											
3. Data specification + statistical analysis plan, final study protocol on EU-PAS											
4. First data extraction & harmonization											
5. Interim analysis**											
6. Updated data extraction and transformation finalized											
7. Verification of pregnancy outcomes and review finished											
8. Statistical analysis results ready											
9. Study report finished*											
10. Manuscripts and slide set drafted*											

* Deliverables required by EMA. All other milestones are internal milestones.

** Rounds of data extraction, transformation and quality checking will be conducted throughout 2020 to facilitate an efficient final extraction in July 2021.

7. RATIONALE AND BACKGROUND

The protocol has been developed under the Framework service contract (nr. EMA/2017/09/PE/04). The topic of this study is to investigate the use of oral retinoid-containing medicinal products authorised in the EU before and after implementation of the 2018 revised measures for pregnancy prevention in clinical practice.

7.1 BACKGROUND

Retinoids are natural or synthetic vitamin A derivatives that regulate cell differentiation, proliferation and apoptosis and include the active substances acitretin, adapalene, alitretinoin, bexarotene, isotretinoin, tazarotene and tretinoin. Oral retinoids are used to treat dermatological conditions like severe acne vulgaris (isotretinoin) psoriasis (acitretin) and chronic hand eczema (alitretinoin), some oral retinoids are also used to treat skin manifestations of T-cell lymphoma (bexarotene) and acute promyelocytic leukaemia (tretinoin).

All oral retinoids are highly teratogenic and must not be used during pregnancy. Retinoic acid embryopathy include central nervous system abnormalities (hydrocephalus, microcephaly), external ear abnormalities (anotia, microtia or absent external auditory meatus), cardiovascular abnormalities (septal wall and aortic defects), facial dysmorphia (cleft palate), eye abnormalities (microphthalmia), thymus gland and bone abnormalities (Lipson AH, et al. (1993). Human data on congenital malformations after oral retinoid exposure shows a significant risk of retinoid embryopathy (of up to 30% of fetuses exposed); furthermore it is known that approximately one-third of pregnant patients will undergo spontaneous abortions (Nao H., at al (2001)). Pregnancy is an absolute contraindication for all oral retinoids in the EU.

In 1990, a *dear doctor* letter was issued regarding acitretin, since the elimination half-life was longer than expected requiring that women should not be pregnant for at least two years after cessation, the effects were limited (Sturkenboom M et al. 1995). A pregnancy prevention programme (PPP) launched in 2003 for isotretinoin has been introduced for other oral retinoids for the treatment of dermatological conditions. The effectiveness of these PPPs has been closely reviewed despite a reduction in the number of pregnancies exposed to retinoids cases of pregnancy exposure continued to occur, raising concerns about compliance and the effectiveness of the PPPs in clinical practice and inconsistencies and variation in PPP across manufacturers and member states. Several studies have considered the effectiveness of the PPP for isotretinoin and several publications describe poor compliance particularly with the pregnancy testing and use of contraception (Crijns, H. J., et al. (2012); Veyries, M. (2015); Henry, D., et al. (2016)).

Concerning acitretin, a cohort study (Raguideau, F., et al. (2015) conducted in France between 2007 and 2012 also highlighted concerns about poor compliance with pregnancy testing requirements for acitretin.

The number of pregnancies since the date of first marketing, as presented by the MAHs to PRAC as part of the referral procedure, was assessed cumulatively and respectively as follows:

• Acitretin: 442 pregnancy cases (132 related to conception during treatment, 260 after completing treatment);

• Alitretinoin: 17 pregnancy cases (12 related to conception during treatment, 4 more than one month after stopping treatment);

• Isotretinoin: 7968 pregnancy cases from all sources (the majority of cases from USA).[1]

In June 2018 a referral procedure (EMEA/H/A-31/14462) under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data confirmed the already known teratogenic risks associated with the use of oral retinoids in pregnant women.

To ensure compliance to the PPP, harmonized warnings about the teratogenic risk, including a boxed warning on the outer package and in the product information, and precautions of use have been required for oral retinoids (acitretin, alitretinoin and isotretinoin) with changes to sections 4.3, 4.4, 4.6 and 4.8 of the SmPC reinforcing the *contraindication in pregnancy* and, unless all of the conditions of the PPP are met, in women of child-bearing potential, and *a direct healthcare professional communication.* To ensure healthcare professionals and patients are informed about the risks in pregnant women and women of child-bearing potential, *changes to educational materials* have been introduced, including a patient reminder card, a physician checklist and acknowledgement form, and a pharmacist checklist. These revised materials should effectively *encourage contraception use, regular pregnancy testing and inform about the shared responsibility between patients, doctors and pharmacists in adhering to the PPP*. To ensure consistent and effective communication for all retinoid containing products distribution, electronic channels such as Quick Response (QR) codes and websites have been recommended.

7.2 PREGNANCY PREVENTION PROGRAM

The PRAC made the following measures to the marketing authorization holders of oral retinoid containing medicinal products (from Assessment report 2018) mandatory:

- Individual patient and prescriber discussion should take place to guarantee patient engagement, discuss therapeutic options and ensure the patient understanding of the risks and the measures needed to minimize the risks.
- The hazards and necessary precautions associated with retinoid use during pregnancy are presented in the risk acknowledgement form and the patient reminder card which should be provided to the patients.
- The prescribers must ensure that the patient has understood and acknowledged the risks of congenital malformations including the magnitude of these risks for children exposed to a retinoid in utero.
- Pregnancy testing should be performed prior to initiation of treatment, ideally monthly during treatment and after stopping treatment. For alitretinoin and isotretinoin pregnancy testing needs to be performed one month after stopping treatment. For acitretin, women should undergo pregnancy test periodically with 1-3 monthly intervals for a period of 3 years after stopping treatment. The patient should be capable of complying with an effective contraceptive treatment/method, without interruption during the entire duration of treatment with oral retinoids acitretin, alitretinoin, isotretinoin and for 1 month [3 years for acitretin] after the end of treatment
- These patients must be provided with comprehensive information on pregnancy prevention programme measures and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user independent form such as an intra- uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case, when choosing the contraception method involving the patient in the

[1] https://www.ema.europa.eu/documents/referral/retinoid-article-31-referral-prac-assessment-report_en.pdf

discussion, to guarantee her engagement and compliance with the chosen measures. In case of amenorrhea, the women should also be on effective contraception.

- In case of pregnancy while using the oral retinoids acitretin, alitretinoin, isotretinoin, the treatment must be stopped and the patient be immediately referred to a physician specialized or experienced in teratology for evaluation and advice.
- Guidance and details on the conditions of the pregnancy prevention programme are reflected accordingly in the product information and in the updated educational materials (Physician's checklist, pharmacist's checklist and patient reminder card) described in this report.

7.3 FURTHER INFORMATION

The PRAC also imposed a post-authorization safety study (PASS) to assess the effectiveness of the updated risk minimization measures in women of childbearing potential for oral retinoids with a PPP. The study required in context of this tender is complementary to the drug utilization study imposed on marketing authorization holders of oral retinoids acitretin, alitretinoin and isotretinoin. A search on the EU PAS database did not reveal a PASS protocol as of yet (November 2018).

8. RESEARCH QUESTION AND OBJECTIVES:

EMA has requested to conduct an analysis on the use of oral retinoid-containing medicinal products authorized in the EU before and after implementation of the 2018 revised measures for PPP.
The study should be carried out in at least five EU countries with the following objectives:

Objective 1.
To determine drug utilization and prescription patterns of oral retinoid containing medicinal products (ATC codes: D05BB02 (acitretin), D11AH04 (alitretinoin), D10BA01(isotretinoin)) in females of childbearing potential, and to investigate whether significant changes in prescribing patterns occurred in the pre- vs post-intervention period. This study will give particular focus to:

1.1 Prescription of oral retinoid containing medicinal products, by indication (i.e. dermatological conditions including acne, psoriasis and eczema; indications will be assumed based upon drug prescribed), by incident and prevalent users, by age group, by therapy duration and by data source;
1.2 Discontinuation of oral retinoid containing medicinal products, by indication, by age group, by reason for discontinuation (i.e. pregnancy or others) and by data source;
1.3 Time trends in prescribing over a minimum of at least three years before the regulatory intervention and including data up to 2020;

Objective 2.
To determine prescribers' compliance with recommendations included in sections 4.3, 4.4 and 4.6 of the SmPC for oral retinoid-containing medicinal products, by indication (i.e. dermatological conditions including acne, psoriasis and eczema), by age group, by therapy duration and by data source;

Objective 3.
To determine, in so far as is possible, patients' use of effective contraception in compliance with sections 4.4 and 4.6 of the SmPC for oral retinoid containing medicinal products, by indication (i.e. dermatological conditions including acne, psoriasis and eczema), by age group and by country (data source).

Objective 4.
To determine drug utilization and prescription patterns over time for alternative medicines prescribed in women of childbearing potential and women becoming pregnant where oral retinoid containing medicinal products had previously been prescribed or discontinued, by indication, by age group and by database.

Objective 5.
Based on the results of above objectives, to estimate the effectiveness of the 2018 risk minimization measures for oral retinoids in terms of:

5.1 Appropriate use of retinoid containing medicinal products in females of childbearing potential in line with SmPC recommendations;
5.2 Appropriate use of pregnancy testing prior to treatment initiation, during treatment and after stopping treatment;
5.3. Use of effective contraception in retinoid exposed females of childbearing potential;
5.4. Occurrence of pregnancies in retinoid exposed females of childbearing potential and pregnancy outcomes (live/stillbirths, spontaneous abortions, induced terminations).

9. RESEARCH METHODS

9.1 STUDY DESIGN

The study design for the different objectives will be a time series study, where outcomes (drug utilization, pregnancy prevention measures, pregnancy) are assessed every month. An interrupted time series analysis will be conducted for hypothesis testing.

9.2 SETTING

The study will be conducted in childbearing potential females (age 12-55 years) between 01 January 2010 and 31 December 2020. Females will be followed from the latest of the following dates: start of the study period having at least one year of valid data in the data source, or reaching 12 years of age. Follow-up will end at the earliest of the following dates: end of study period, last data draw down, death or reaching 56 years of age.

Data from eight sources are included: Netherlands (sample, nationally representative), Denmark (national), Italy regional databases (Tuscany, Campania) and Spain (multiple regions, and regional Valencia), covering more than 80 million source population (approximate estimate: 15-20 million childbearing age females).

All databases capture GP prescribing, 5 capture also specialists prescriptions, allowing us to investigate the difference. The Italian administrative databases have difficulty assessing oral contraceptives in general, as these are not reimbursed. Invasive pregnancy prevention methods (e.g. hysterectomy, sterilization) can be measured. Pregnancy outcomes can be measured in all (see Section 9.3.2.5 Pregnancy and for details). Mother-child linkage and or a pregnancy/perinatal registry is available in 3 of the 6 databases and this linkage will be utilized to assess performance of pregnancy detection algorithms (if additional diagnostic, procedural and medical observation codes are used to detect pregnancies) and to identify outcomes of pregnancies (live birth, still birth, spontaneous abortion, interruption, ectopic pregnancy) that occurred during a period of oral retinoid exposure. Reasons for discontinuation beyond pregnancy and experience of selected adverse drug reactions will not be retrievable.

9.2.1 DATA SOURCES

Table 1 Current overview of databases to be used for the study

Characteristic	PHARMO Nationally representative	Danish National Registries*	ARS Tuscany**	BIFAP Multi-regional	FISABIO Valencia	Caserta Campania
Handling partner	PHARMO	University of Copenhagen	ARS	AEMPS	FICF/FISABIO	University Messina
Country (pop. size in million)	Netherlands (17.0)	Denmark (5.8)	Italy (59.8)	Spain (46.5)	Spain (46.5)	Italy (59.8)
Type of database	EMR	ADM	ADM	EMR	EMR	ADM
# in DB	4.2 million (prior to linkage)	5.8 million	3.6 million	9 million	5.1 million	0.9 million
Date in	Yes	Yes	Yes	Yes	Yes	Yes
Date out	Yes	Yes	Yes	Yes	Yes	Yes
Updates	Annual	Annual	Monthly	Annual	Monthly	Annual
GP Rx	Yes	Yes	Yes	Yes	Yes	Yes
Outpatient Rx spec.	Yes	Yes	Yes	No	Yes	Yes
Private Rx	No	No	No	No	No	No
Inpatient hospital Rx	Yes (not utlilised in this study)	No	No	No	No	No
Date of Rx	Yes	No	No	Yes	Yes	Yes
Date of Dispensing	Yes	Yes	Yes		Yes	
Quantity	Yes	Yes	Yes	Yes	Yes	Yes
Duration	Yes	Yes	Based on DDD	Yes	Yes	Based on DDD
Strength	Yes	Yes	Yes	Yes	Yes	Yes
Brand/generic	Yes	Yes	Yes	Yes	Yes	Yes
Indication of retinoids	Diagnosis codes in history*	Diagnosis codes in history	Diagnosis codes in history	Linked to prescription and diagnosis codes in history	Diagnosis codes in history	Diagnosis codes in history
Coding of drugs	ATC	ATC	ATC	ATC	ATC	ATC
Dosing regimen	Yes	No	no	Yes	Yes	No
Oral contraceptives	Yes	Yes	No	Yes (only those publicly funded)	Yes (only those publicly funded)	No
Duration	Yes	DDD based	No	Yes	Yes	no
Observed pregnancy test dx	No	No	No	No	Unclear for retinoids	Unclear for retinoids

Date fitted	Yes	Date of prescription fill (not copper IUD)	No	No	No	No
Date removed	Yes	No	No	No	No	No
Date inserted	date of prescription fill	date of prescription fill	No	Not systematically	Yes	No
Date removed	Proxy based on date of prescription fill	No	No	Not systematically	No	No
Date injected	Not marketed	Not marketed	No	Yes (norethisterone enantate only)	No	No
Date injected	Proxy based on date of prescription fill	date of prescription fill	No	Yes	Yes	No
Written record of OC advise	Free text potentially	No	No	Free text potentially	No	No
Hysterectomy	Yes*	Yes	Yes	If recorded by GP	Yes	Yes
Oophorectomy	Yes*	Yes	Yes	If recorded by GP	Yes	Yes
Sterilization	Yes*	Yes	Yes	If recorded by GP	Yes	Yes
Partner vasectomy	No	No	No	Not	No	No
Completed Menopause	Free text potentially	No	No	If recorded by the GP and Free text potentially	No	No
Reasons for stopping Retinoid	No	No	No	From EMR,Free text potentially	No	No
Coding of disease	ICPC, ICD-9, ICD-10, *	ICD-10	ICD-9 CM/ICD-10	ICPC-2, ICD-9, SNOMED?	ICD-9CM/ICD-10CM	ICD-9CM
Pregnancy outcomes	Linkage to perinatal registry*	Linkage to birth register	Linkage to birth register /interruption registry/spontaneous abortions registry	Mother's records if recorded by the GP	Linkage to perinatal registry	Mother's records
# of pregnancies/ year	29,000 linked pregnancies per year	60,000	Unknown yet	Not known yet	45.000	Not known yet

ADM = Administrative; ATC = Anatomical Therapeutic Chemical; EMR = Electronic Medical Records; ICD= International Classification of Disease, ICPC = International Classification of Primary Care. DDD=defined daily dose

* Due to data access delays for the Danish National Registers, diagnosis, procedure and pregnancy information will not be available during the study; only information on prescriptions will be available

* Only acitretin is captured in the ARS database, as isotretinoin and alitretinoin are not reimbursed.

9.3 VARIABLES

9.3.1 EXPOSURE DEFINITION

The exposure of main interest for objectives 1-5 are oral retinoid containing medicinal products: acitretin, alitretinoin and isotretinoin.

Additionally, exposure to oral contraceptives, intrauterine devices, vaginal rings, contraceptive patches, and contraceptive injections will be retrieved for assessment of appropriate contraception.

Exposure to folic acid supplements will be used for ascertainment of pregnancy wish.

Exposure to antidepressant medications will be used as part of the algorithm employed in ascertainment of depression.

Alternative prescribed medicines for treatment of eczema are defined as: emollients, topical or oral steroids, calcineurin inhibitors (cyclosporine, pimecrolimus, tacrolimus), and PDE4 inhibitors (crisaborole), phototherapy (UVB), biologicals (e.g.dupilumab), keratolytics, methotrexate.
Alternative prescribed medicines for treatment of psoriasis are defined as [2]: Topical: emollients, corticosteroids, vitamin D analogs (calcipotriene, calcitriol), tazarotene, calcineurin inhibitors (ciclosporin), anthralin, pimecrolimus, tacrolimus, apremilast, biological agents (etanercept, infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab, certolizumab pegol), dimethyl fumarate
Alternative prescribed medicines for treatment of acne are defined as[3]: topical retinoids, azelaic acid, topical antimicrobials (benzoyl peroxide, erythromycin, nadifloxacin, and clindamycin, sulfacetamide, dapsone), oral antibiotics (doxycycline, minocycline, and tetracycline), macrolides, hormonal therapy.

Operationalization for all drug exposures
Drugs will be extracted from the drug files by ATC code and/or product name. A list of authorized medicinal products and their ATC codes is attached in the Annex I.

Treatment initiation for all drug exposures
Treatment initiation will be defined as the date of the first record of the specific (ATC level) prescription or dispensing in the follow-up period. When both prescription and dispensing dates are available, the dispensing date will be used.

[2] https://www.uptodate.com/contents/treatment-of-psoriasis-in-adults#H33
[3] https://www.uptodate.com
https://www.uptodate.com/contents/treatment-of-acne-vulgaris#H3949564526

Duration of treatment for all exposures

Duration is defined as the number of days of therapy from initiation to discontinuation of therapy. Since duration is often not provided, it will be derived. The theoretical duration of each prescription will be estimated based on the preferred method for each individual database. Each data access partner (DAP) will recommend the approach that is expected to minimize exposure misclassification in their database, given their available data. For example, this may be based on the number of units prescribed/dispensed and the dosage regimen (prescribed daily dose), or, when information on dosage regimen is missing, based on either the typical period for prescribing medicines for chronic diseases in the country (e.g., 30 or 7 days) or the duration based on the assumption that one defined daily dose (DDD) will be used per day. The algorithms used for each database and rationale will be reported in the final report and manuscript. The date based on the start of the prescription/dispensing plus the estimated duration of the dispensing/prescription is considered the end date of the drug. If the start of a next prescription of the same drug (same ATC code) falls during treatment duration of the prior prescription/dispensing, we will consider this as the start of that prescription.

Treatment discontinuation for all exposures

Patients not receiving any other prescription or dispensing of the same drug (same ATC code) within 90 days after the calculated end date, with at least these days of follow-up, will be considered as discontinuers (a sensitivity analysis may be conducted with 30 days).

Incidence and prevalence of use

Drug users will be included in calculation of incident use if no prescription or dispensing for the same drug was recorded in the one year prior to that prescription/dispensing. Drug users will be included in calculation of prevalent use during a period if one or more days of a prescription duration fall within the period of interest.

Switching of retinoid to alternative medications and concomitant use of alternative medications

Switching of retinoids to alternative medication is defined as the discontinuation of the specific retinoid (see definition above) and the incident use of an alternative medication during the last prescription of the retinoid or after discontinuation as defined above (See figure 1).

Concomitant use of alternative medication is defined as use of a medication (any day of overlap) during a retinoid prescription, if not classified as a switch.

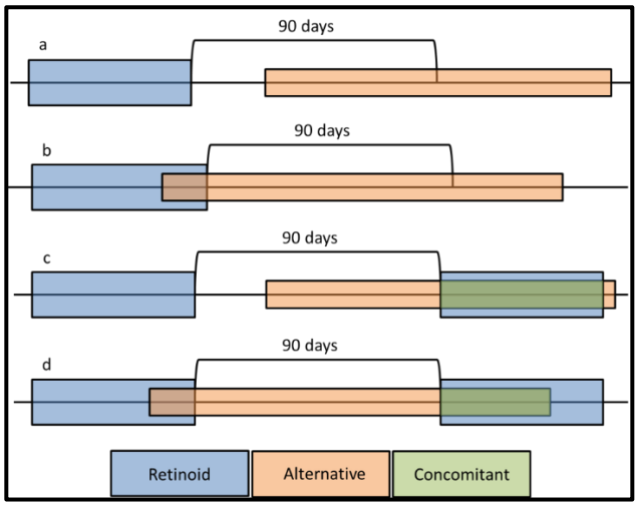


Figure 1. Scenarios of switching to an alternative medication. In each scenario, use of the alternative medication is incident (no use in the prior year)

Locally the extracted prescription/dispensing data will be transformed into a common input file structure on prescriptions. See the Exposures CDM table in Annex III.

9.3.2 OUTCOME(S) & FOLLOW-UP OPERATIONALIZATION

9.3.2.1 Reason for discontinuation (Objective 1)

The reason for discontinuation will be assessed by electronic medical records and categorized as pregnancy wish (folic acid use), pregnancy, adverse reactions, multiple or unknown during the 90 days preceding discontinuation. Reasons for discontinuation will be based on coded information.

The default reason for discontinuation will be unknown. If we can measure within the follow-up time any of the other events (see below), this will become the reason for discontinuation, if multiple criteria apply these will counted.

Reasons for discontinuation will be considered to be:

- Pregnancy wish if within the 90 days following discontinuation of alitretinoin or isotretinoin a female is prescribed folic acid. A 90-day lookback window will be used, instead of a longer window, to increase the specificity of this category. See Annex I for ATC mapping of folic acid.
- Pregnancy will be assumed as the reason for discontinuation if a pregnancy event is observed during a prescription or discontinuation period which ends with discontinuation of the retinoid.
- Discontinuation will be assumed to be for adverse reactions if a known serious retinoid-associated ADR event is recorded during the duration of a prescription which ends with discontinuation.

Only serious adverse events will be considered as minor events may not lead to discontinuation. See Annex II for section 4.8 Undesirable Effects and lists of serious adverse events for each retinoid. See Annex IV for mapping of codes for serious ADRs as well as mapping for depression (serious ADR for all retinoids under study).

Because specific codes for drug ineffectiveness do not exist in the coding systems used by the data sources in this study and ineffectiveness cannot be assumed from repeated codes for drug indications, ineffectiveness will not be assessed.

Depression

Depression, as a known serious adverse reaction to retinoids, will be identified from the medical history prior to retinoid start and during follow-up using ICPC/ICD-9/10/SNOMED codes as well as use of antidepressants (See Annex I for drug codes and Annex IV for diagnosis codes).

9.3.2.2 Pregnancy testing (Objective 2)

Pregnancy testing is defined as a health care professional-witnessed pregnancy test. Recorded pregnancy testing will be obtained from the electronic medical records of GPs or specialists if available.

Pregnancy testing will be labelled as *appropriate* if pregnancy testing is performed prior (within 14 days) to initiation of treatment (incident users) and monthly during the duration of treatment. For alitretinoin and isotretinoin, pregnancy testing needs to be performed also one month after stopping treatment. For acitretin, women should undergo pregnancy test periodically with 1-3 monthly intervals for a period of 3 years after stopping treatment. We will count the number of recorded pregnancy tests per retinoid prescription and the gaps between recorded testing. See Annex IV for mapping of codes for pregnancy testing.

Appropriate pregnancy testing will be defined as follows for each prescription of each drug:

Acitretin: Witnessed pregnancy testing prior to initiation of treatment (within 14 days to start), witnessed pregnancy testing once per month for the duration of the prescription, witnessed pregnancy testing at least four times per year in the three years following the date defined by the end of the discontinuation period for prescriptions ending in discontinuation.

Alitretinoin/isotretinoin: Witnessed pregnancy testing prior to initiation of treatment (within 14 days to start), witnessed pregnancy testing once per month for the duration of the prescription, witnessed pregnancy testing in the month following the date defined by the end of the discontinuation period for prescriptions ending in discontinuation.

Lack of adherence to the retinoid specific testing will be classified as *inappropriate* pregnancy testing.

9.3.2.3 Contraceptives measures (Objective 2 & 3)

Effective contraception at each retinoid prescription and monthly after discontinuation is defined as at least one user independent method applied to the woman (permanent or non-permanent), or a hormone-based method combined with a barrier method.
Barrier methods cannot be assessed reliably from healthcare databases so will not be considered. Effectiveness of contraception will therefore be categorized as follows.

Non-use of contraception is defined as absence of evidence of all:

- Prescribed/dispensed hormonal contraception AND
- Permanent method AND
- User-independent non-permanent measure

Ineffective use of contraception is defined as evidence of:

- Prescribed hormonal contraception AND

Absence of evidence of:

- Permanent method AND
- User-independent non-permanent measure

Effective use of contraception is defined as evidence of:

- Permanent method OR
- User-independent non-permanent measure

Barrier, user dependent methods:
Contraceptive diaphragm or cap, male condom, female condom will not be ascertainable from data sources.

Hormone based user dependent methods
Vaginal ring (21 days, one week off), contraceptive patch (weekly for 3 weeks, one week off), progestogen only pill or desogestrel progestogen-only pill (28 days continuously), combination pills (21 days one week off)

User independent non-permanent methods

Contraceptive implant (progestogen releasing: 3 years), contraceptive injection (progestogen releasing 8-13 weeks), intrauterine device (coil: 5-10 years), intrauterine system (progestogen releasing 3-5 years)

User independent permanent methods
Female sterilization and hysterectomy. Because the data sources used do not allow for family linkage, male partner sterilization (vasectomy) will not be considered. All observation time following occurrence of a procedure or diagnosis code for female sterilization or hysterectomy will be classified as a period of effective contraception coverage.

See Annex I for ATC codes for contraceptive methods and Annex IV for mapping of codes for permanent methods

9.3.2.4 Duration of use (Objective 2)

Duration of use will be defined as the time from initiation of treatment based upon the first recorded prescription or dispensing in the look-back or study periods until discontinuation. Women meeting criteria for discontinuation may re-initiate, leading to multiple episodes of treatment.

9.3.2.5 Pregnancy (Objective 3)

A woman is considered to be pregnant if she reports a pregnancy to the GP/ obstetrician / dermatologist, which is confirmed by a positive pregnancy test, ultrasound, or if there is linkage to a pregnancy/birth record. To properly identify pregnancies across databases, we will apply a pregnancy algorithm developed by Gini R., et al., within the framework of the ConcePTION project.

Briefly, the proposed pregnancy algorithm allows the identification of past and ongoing pregnancies from 4 main streams: perinatal or birth registries, administrative data banks using diagnosis codes, European registry of congenital abnormalities (EUROCAT) and a tailored-combined stream (itemsets). Within this framework, four of the six participating databases can identify pregnancies through linkage to a perinatal or birth register (PHARMO, Danish National registries, ARS, and FISABIO).

In all the other databases, pregnancies will be identified using an algorithm. The stream aiming to identify diagnosis codes is based in the algorithm published by Matcho et al. (Matcho et al (2018). The Matcho based algorithm uses identification of pregnancy outcomes as a first step in pregnancy identification. Briefly, the algorithm first detects any record of live birth, stillbirth, ectopic pregnancy, abortion, or delivery. These events then represent the set of pregnancies in the data source and pregnancy start dates are assessed for each of these pregnancy outcomes using LMP, recorded gestational age, and fertility procedure, ultrasound, amniocentesis, amenorrhea, and pregnancy test dates. The algorithm therefore does not capture any pregnancies for which an outcome has not been recorded.

For each woman who becomes pregnant during or after use of oral retinoids we will assess the outcome from the available data. Pregnancy outcomes will be measured in the mother's record. In case of deliveries we will try to link to infants records which will be conducted deterministically where possible (in data sources where there is linkage to a perinatal or medical birth registry is available). Where information on child outcomes available in a perinatal or medical birth registry indicates a congenital anomaly, this will be reported.

9.3.3 OTHER VARIABLES

9.3.3.1 Age (Objectives 1-4)

Age groups for each objective will be defined as follows:

12 to 20 years of age
21 - 30 years of age
31 - 40 years of age
41 - 55 to < 46 years of age

For study baseline measurements, a female's age will be defined as the year of entry into the study. For objectives 1-4, age will be defined as the age at which the prescription occurs.

9.3.3.3 Intervention Implementation Periods (Objectives 1-5)

Country implementation periods of the updated pregnancy prevention programs will be defined as follows:

Country	Start date	End date
Netherlands	10-08-2018	12-12-2018
Denmark	16-07-2018	11-10-2018
Italy	08-08-2018	02-10-2018
Spain	24-07-2018	01-12-2018

-

Prescriptions will be categorized as occurring pre, during and post intervention based upon the period during which the prescription began.
Pregnancy prevention measures were already in place for retinoids prior to the 2018 revised measures (which were mostly re-inforcing educational materials), which may mitigate the measurable impact of the 2018 measures.

9.3.2.7 Effectiveness of RMM (Objective 5)

Results of objectives 1-4 will be synthesized in objective 5 to estimate the effectiveness of the 2018 risk minimization measures for oral retinoids in terms of:

5.1 Appropriate use of retinoid containing medicinal products *in childbearing potential females* in line with SmPC recommendations (are there any contra-indications)
5.2 Appropriate use of pregnancy testing prior to treatment initiation, during treatment and after stopping treatment (see above);
5.3. Use of effective contraception in retinoid exposed women of childbearing potential (see above)
5.4 Occurrence of pregnancies in retinoid exposed women of childbearing potential and pregnancy outcomes (live/stillbirths, spontaneous abortions, induced terminations)

9.4 DATA SOURCES

9.4.1 DESCRIPTION OF DATA SOURCES

Spain: FISABIO

The region of Valencia, with 5 million inhabitants, is part of the Spanish National Health System, a universal public healthcare system. Information will be obtained from the population-based electronic information systems of the Valencia Health Agency (VHA) and the regional Government of Valencia: (1) The Population Information System (SIP) provides an identification number for each person under Valencian Health Service (VHS) coverage, and registers some demographic characteristics, and dates and causes of VHA discharge, including death. (2) The Minimum Basic Dataset (MBDS) at hospital discharge is a synopsis of clinical and administrative information on all hospital discharges, including diagnoses and procedures (all electronic health systems in the VHS use the ICD-9-CM). (3) The Emergency Department module (ED) including ED dates of visit and discharge and reason for discharge. (4) The electronic medical record (EMR) for ambulatory care, available in all primary healthcare centers and other ambulatory settings. It has all the information on patients regarding diagnoses, their personal and family medical history, laboratory results, lifestyle, etc. (5) The pharmaceutical module (prescription information system), part of EMR, includes information about both physician prescriptions and dispensations from pharmacy claims. (6) The Corporate Resource Catalogue (CRC) provides information about the geographical and functional organization of VHS, its health centers, health services provided and professionals in healthcare. Specific public health registries are available and linkable at an individual level (such as the perinatal registry and the congenital anomalies registry, from which pregnancy outcomes can be obtained) All the information in these systems can be linked at an individual level through the SIP number.

Spain: BIFAP

BIFAP (Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria), a computerized database of medical records of primary care (www.bifap.aemps.es) is a non-profit research project funded by the Spanish Agency for Medicines and Medical Devices (AEMPS). The project started in 2001 and currently includes clinical information of 6,857 physicians 5,862 General Practitioners (GPs) and 995 pediatricians). Nine participant Autonomous Region send their data to BIFAP every year. BIFAP database currently includes anonymized clinical and prescription/dispensing data from around 9 million patients representing 70% of all patients of those regions participating in the database, and 16% of the Spanish population. Mean duration of follow up in the database is 7.2 years. Diagnoses are classified according to the International Classification of Primary Care (ICPC)-2 and ICD-9 code system. BIFAP does not overlap with FISABIO. A mother-child linkage has not been made so far and no private/specialist prescribing is available.

Netherlands: PHARMO Database Network & Netherlands Perinatal Registry

The PHARMO Database Network is a population-based network of electronic healthcare databases and combines data from different primary and secondary healthcare settings in the Netherlands. These

different data sources, including data from general practices, in- and out-patient pharmacies, clinical laboratories, hospitals, the cancer registry, pathology registry and perinatal registry, are linked on a patient level through validated algorithms. Detailed information on the methodology and the validation of the used record linkage method can be found elsewhere (van Herk-Sukel et al 2010).

The longitudinal nature of the PHARMO Database Network system enables to follow-up more than 4 million (25%) residents of a well-defined population in the Netherlands for an average of ten years. Data collection period, catchment area and overlap between data sources differ. Therefore, the final cohort size for any study will depend on the data sources included. As data sources are linked on an annual basis, the average lag time of the data is one year. All electronic patient records in the PHARMO Database Network include information on age, sex, socioeconomic status and mortality. Other available information depends on the data source. To address the objectives of the present study the following PHARMO databases will be used: General Practitioner Database, Out-patient Pharmacy Database and Pregnancy Register.

The General Practitioner (GP) Database comprises data from electronic patient records registered by GPs. The records include information on diagnoses and symptoms, laboratory test results, referrals to specialists and healthcare product/drug prescriptions. The prescription records include information on type of product, prescription date, strength, dosage regimen, quantity and route of administration. Drug prescriptions are coded according to the WHO Anatomical Therapeutic Chemical (ATC) Classification System. Diagnoses and symptoms are coded according to the International Classification of Primary Care (ICPC), which can be mapped to ICD codes, but can also be entered as free text.

The Out-patient Pharmacy Database comprises GP or specialist prescribed healthcare products dispensed by the out-patient pharmacy. The dispensing records include information on type of product, date, strength, dosage regimen, quantity, route of administration, prescriber specialty and costs. Drug dispensings are coded according to the WHO Anatomical Therapeutic Chemical (ATC) Classification System. Oral contraceptives are mostly prescribed by GPs, but can also be obtained directly in the pharmacy, this will be captured in PHARMO as was proven before (Bezemer et al 2016).PHARMO is listed under the ENCePP resources database (www.encepp.eu/encepp/resourcesDatabase.jsp).

The Netherlands Perinatal Registry is maintained by Perined and comprises data on pregnancies, births and neonatal outcomes of births in the Netherlands, voluntarily collected by perinatal caregivers, mainly for benchmarking. Records include information on mothers (e.g. maternal age, obstetric history, parity), pregnancy (e.g. mode of conception, mode of delivery) and children (e.g. birth weight, gestational age, Apgar score). Diagnoses and symptoms are coded according to the Perinatal Registry code lists. For more information: www.perined.nl. For research purposes the data can be linked with the PHARMO Database Network via a trusted third party (TTP). Permission on a project basis is needed from PHARMO as well as Perined to obtain these data. Combined Out-patient Pharmacy and data from the Netherlands Perinatal Registry currently cover a catchment area representing 0.5 million residents for the data cut up to 2015 (to be updated). Additional linkages to the other PHARMO databases can be performed on a patient-level. Data collection period, catchment area and overlap between data sources differ. Therefore, the final cohort size for any study will depend on the data sources included.

Denmark: Danish National Registries

Denmark has a tax-funded health care system ensuring easy and equal access to health care for all its citizens, and all contacts with the system are recorded in administrative and medical registers. The records

carry a unique personal identification number, called the CPR-number, assigned to every Danish citizen. Linkage between registers at an individual level is possible because this CPR-number is used in all Danish registers. All registers have a nationwide coverage and an almost 100% capture of contacts covering information on currently 5.8 million inhabitants plus historical information. For the purpose of the study we will obtain information from the following registries. The Danish National Prescription Registry (DNPR) includes data on all drugs dispensed from Danish pharmacies from 1995 and onwards, including dispensing date, Anatomical Therapeutic Chemical (ATC) code, product code and amount. Sociodemographic data is available from the Danish Civil Registration System, such as gender, date of birth, migration, vital status and civil status recorded since 1968. The Medical Birth Register captures pregnancies ending in a live birth and data on stillbirth. The Patient Register contains diagnoses from hospitalisation and contacts to hospital outpatient clinics that can also be used as a proxy for the indication.

Italy: Caserta claims database

The Caserta database is an administrative claims databases containing patient-level data from the city of Caserta, in the Campania region. The coverage of these databases in the respective catchment areas is very high because they consist of Italian National Health Service (NHS) data and practically all the persons living in the catchment areas are NHS beneficiaries. The databases therefore contain data related to healthcare claims covered by the NHS, covering a wide variety of healthcare services.

The data in Caserta accounts for approximately 15% of the Campania regional population. This database has been previously used in multi-database projects with other databases where harmonized methods were applied to Caserta database. Catchment area population from 2005-2017 in Caserta consists of 907,410 persons. The Caserta linkage databases consists of several databases which are linked through a unique patient identifier: a demographic registry, containing demographic patient information as well as first and last date of contact with National Health Service (NHS), out-patient pharmacy claims database with information on concerning all dispensed drugs reimbursed by the Italian NHS, as well as hospital discharge diagnose databases, emergency department admissions database, claims for diagnostic and laboratory tests ordered, and a registry of patients exempt from reasons for healthcare service co-payment exemptions (e.g. diabetes mellitus, dementia, and other chronic diseases), emergency department visit diagnoses and diagnostic tests. Patient level data from this claim database, including other drugs reimbursed by the NHS and dispensed by community pharmacies, can be linked together, using a unique patient identifier.

Italy: ARS database

The Italian National Healthcare System is organized at regional level: the national government sets standards of assistance and a tax-based funding for each regions, and regional governments are responsible to provide to all their inhabitants. Tuscany is an Italian region, with around 3.6 million inhabitants. The Agenzia regionale di sanit`a della Toscana (ARS) is a research institute of the Tuscany Region. ARS' database comprises all the tables that are collected by the Tuscany Region to account for the healthcare delivered to its inhabitants. Moreover, ARS collects tables from regional initiatives. All the tables in the ARS' data source can be linked with each other at the individual level, through an pseudoanonymous identifier. ARS' database routinely collects primary care and secondary care

prescriptions of drugs for outpatient use, and is able to link them at the individual level with hospital admissions, admissions to emergency care, records of exemptions from copayment, dispensings of diagnostic tests and procedures, causes of death, mental health services registry, birth registry, spontaneous abortion registry, induced terminations registry. A pathology registry is available, mostly recorded in free text, but with morphology and topographic Snomed codes. Mother-child linkage is possible through the birth registry. Vaccine data is currently available but still incomplete.

9.4.2 DATA AVAILABILITY

Table 2: Data available for each data source by milestone 6 for objectives 1-5*

Data Type	Data Source	PHARMO national	Danish National	ARS Tuscany	BIFAP multiregional	FISABIO Valencia	Caserta Campania
Prescriptions	Outpatient	Q3 2021	Q3 2018	Q2 2021	NA	Q2 2021	Q1 2021
	In-hospital	NA	NA	NA	NA	NA	NA
Diagnoses	GP	Q3 2021	Q4 2016	NA	Q2-3 2021	Q2 2021	Available up to December 2014
	Specialist outpatient	NA	Q4 2016 (hospital clinics only)	NA	Q2-3 2021	Q2 2021	Q1 2021
	Emergency room	NA	Q4 2016	Q2 2021	Q2-3 2021	Q2 2021	Q1 2021
	Hospitalization	Q4 2021	Q4 2016	Q2 2021	Q2-3 2021	Q2 2021	Q1 2021
	Death record	Q4 2021	Q4 2016	Q2 2021	Q2-3 2021	Q2 2021	Q1 2021
Free text notes	GP charts/records	Q3 2021	NA	NA	Q2-3 2021	NA	NA
	Hospital charts	NA	NA	Q1 2021	Q2-3 2021	NA	NA
Perinatal registry/ Birth register/ Spontaneous abortions/ Induced terminations	With mother-child linkage	Q4 2019	Q4 2016	Q2 2021	Q2-3 2021	Q2 2021	Q1 2021
	Without mother-child linkage	NA	NA	NA	Q2 2022	NA	NA

*Date of availability for data through 31 December 2020. Data unavailable at any time for a data source should be indicated with NA. Data will be extracted up until the end of the study period (31 December 2020). Data unavailable at any time for a data source is indicated with NA.

Table 3. Data availability and last available data per database and objective

Database	Availability	1) Drug Utilization	2) Pregnancy Testing	3) Effective Contraception			4) Alternative medicines	Pregnancy
				User-dependent non-	User-independent non-	Permanent Methods		

				permanent methods	permanent methods			
PHARMO	Available (Y/N)	Yes	Yes (mainly OTC))	Yes	Yes	Yes	Yes	Yes
	Last available data Q3 2021	Q4 2019	Q4 2019	Q4 2019	Q4 2019	Q4 2019	Q4 2019	Q4 2019
Danish National	Available (Y/N)	Yes	No	Yes	Yes	Yes	Yes	Yes
	Last available data Q3 2021	Q4 2016	Q4 2016	Q4 2016	Q4 2016	Q4 2016	Q4 2016	No (pregnancy data is not linked to available prescribing data)
ARS Tuscany	Available (Y/N)	Yes	Unclear	No	No	Yes	Yes	No
	Last available data Q3 2021	Q4 2020	Q4 2020	NA	NA	Q4 2020	Q4 2020	NA
BIFAP Multiregional	Available (Y/N)	Yes	No	Yes	No	Yes	Yes	Yes
	Last available data Q3 2021	Q4 2019	Q4 2019	Q4 2019	NA	Q4 2019	Q4 2019	Q4 2019
FISABIO Valencia	Available (Y/N)	Yes	Unclear	Yes	No	Yes	Yes	Yes
	Last available data Q3 2021	Q4 2020	Q4 2020	Q4 2020	NA	Q4 2020	Q4 2020	Q4 2020
Caserta Campania	Available (Y/N)	Yes	Unclear	No	No	Yes	Yes	Yes
	Last available data Q3 2021	Q4 2020	Q4 2020	NA	NA	Q4 2020	NA	Q4 2020

9.5 STUDY SIZE

All eligible subjects will be included in the study. Source population includes approximately 15-20 million childbearing age females over the 11 year study period, divided across the contributing centres as follows:

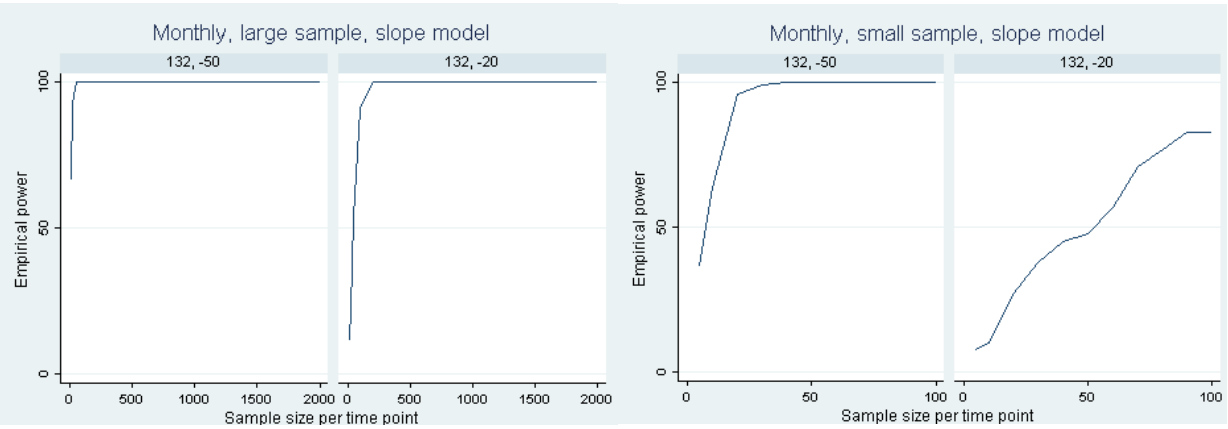
PHARMO: 0.5 million
Denmark: 1.592 million
ARS: 1.352 million
BIFAP: 2.508 million
FISABIO : 1.0 million
Caserta: 0.318 million

9.5.1 SAMPLE SIZE ESTIMATION

A minimum of 10 pre- and post-intervention time points may be required for ITS (Ramsay et al (2003)). Given an approximate date of intervention of July 01 2018, 102 monthly pre-intervention time points and 30 monthly post-intervention time points will be available, which exceeds this minimum requirement.

As described by Hawley et al, additional factors such as the number of subjects or amount of persontime per time point, type of impact of the intervention (level change or slope change), effect size of the intervention impact, pre-intervention incidence, and location of the intervention in the time series can impact power in an interrupted time series analysis. To examine the impact of additional factors on the power to detect an effect with ITS, power calculations were conducted based on Monte Carlo simulations in Stata/SE 14.1, as previously described (Hawley et al (2019)). Simulations (100 replicates) were based on ordinary least squares linear "slope" segmented regression models, assuming a constant pre-intervention cumulative outcome incidence of 10%, 102 pre- and 30 post-intervention time points, a background 10% variation in the outcome incidence across time points, and an effect size of a 20% or 50% reduction in the cumulative outcome incidence after intervention (this is hypothetical) The results in Figure 2 suggest the study will be sufficiently powered to detect an effect on common outcomes (period prevalences/incidence of prescriptions), but may be underpowered to detect an effect on uncommon outcomes (pregnancy). Therefore ITS will be restricted to the main analyses of objectives 1, 2, and 4, stratified by database and indication for prescription outcomes.

Figure 2 Empirical power calculations for given sample sizes per time point.



9.6 DATA MANAGEMENT

This study will be conducted in a distributed manner using a common data model and common analytics. This process was used successfully in several other European multi-database projects (see Trifiro et al 2014) (see figure 3). It maximizes the involvement of the data providers in the study by utilizing their knowledge on the characteristics and the process underlying the data collection and makes analysis more efficient.

First, to harmonize structure of the data sets held by each partner, a shared syntactic foundation will be built. This is described in Annex III and is referred to as the 'Level 1 CDM'. In this common data model, codes are linked to concepts but remain in their original format.

To reconcile differences across terminologies a shared semantic foundation will be built for the definition of events under study by mapping disease concepts using the Codemapper tool (see Becker et al.). Based on the relevant diagnostic codes and key words (for free text search in BIFAP only), a mapping algorithm will be constructed to identify each event based on the consensus of the individual data providers. This algorithm will then be implemented by all databases against data in the Level 1 CDM and verified using quality assessment processes (see below) This will result in a Level 2 CDM (See below)

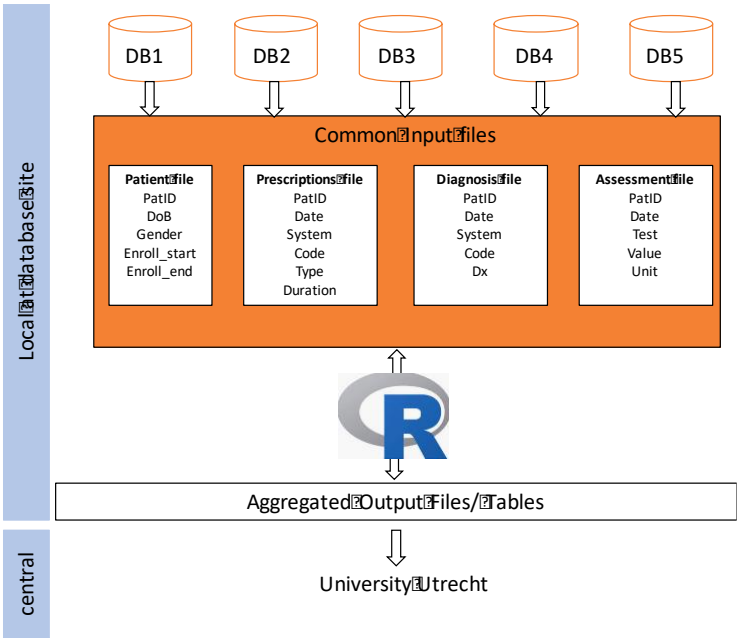


Figure 3: data management plan

9.6.1 DATA EXTRACTION

Each database extracts the study data locally using their software (Stata, SAS, R) and transforms them into a simple common data model structure (see annex III). These data remain local.

9.6.2 DATA PROCESSING/TRANSFORMATION

Data processing and transformation will be conducted using R code against the low level common data model. The R code will be created and tested centrally and sent to the data access providers, code will be documented for verification. The data access providers will run the R code locally and sent the aggregated output to the UU server using a secure file transfer protocol. On the server, data will be further plotted, inspected (for quality assessment) and pooled (if needed) for final reporting.

9.6.3 *Software and Hardware*

All the final statistical calculations will be done in R and/or SAS, programs will be shared with all sites for verification

9.6.4 *Storage*

Aggregated data will be stored YODA, Utrecht University's institutional research data repository, registered at RE3DATA.org. YODA complies with Utrecht University's information security policy for data classified as public, internal use or sensitive. All YODA data is stored in at least two geographically spread locations. The data is stored and transmitted in an encrypted format.

9.6.5 *Access*

All researchers who need access to YODA are trained and monitored by the data management group. Data management is also responsible for granting access to file-directories of specific datasets. Data analyses on aggregated data that are shared by partners will be performed on a dedicated stand-alone desktop located in the division's secure data laboratory that is only accessible by access card and access key to relevant personnel, with output data being written to the YODA platform. Access to this desktop is only possible using a university account and password.

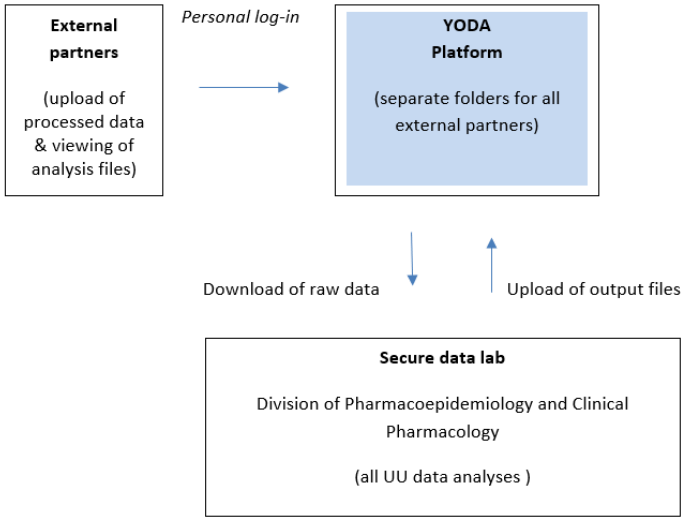


Figure 4: Representation of the infrastructure for data access and storage using YODA

9.6.6 *Archiving and Record Retention*

The final study dataset and statistical programs will be archived and stored on a secured, access limited computer driver locally. The validation of the quality control (QC) of the statistical analysis will be documented. The final study protocol and possible amendments, the final statistical report, statistical programs and output file will be archived on a specific and secured drive centrally.

Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced will be retained for a period of 5 years in accordance with GPP guidelines. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement between study partners. It is the responsibility of the principal investigator to inform the other investigators/institutions as to when these documents no longer need to be retained. Study records or documents may also include the analyses files, syntaxes (usually stored at the site of the database), and questionnaires.

9.7 DATA ANALYSIS:

9.7.1 ANALYSIS OF DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The source population and study population for the different objectives will be described in numbers and person-time by age, database, and calendar year. Retinoid users (first prescription/dispensing in follow-up) and use (each prescription/dispensing) will be described on the basis of baseline characteristics (one year prior to start) with the following variables: age, prior depression, indication, incident/prevalent use and concomitant use of alternative treatments (prescribed before and lasting until first retinoid prescription/dispensing). Frequency tables will be generated for categorical variables.

9.7.2 HYPOTHESES

The purposes of the objectives differ.

Objective 1: To determine drug utilization and prescription patterns of oral retinoid containing medicinal products.

Null hypothesis (H0): utilization and prescription patterns (on a prescription level) of oral retinoids in women of childbearing age (as in section 4.4 and 4.6) have not changed over time (pre-post 2018 RMM).

Alternative hypothesis (H1): utilization and prescription patterns of oral retinoids in women of childbearing age (as in section 4.4 and 4.6) varies over time.

Objective 2: To determine prescribers' compliance with recommendations included in sections 4.3, 4.4 and 4.6 of the SmPC for oral retinoid containing medicinal products.

Null hypothesis (H0): the compliance of prescribers with the 2018 PPP measures (as defined by witnessed pregnancy testing and use of effective contraception for each prescription) in oral retinoid users of childbearing age (as in section 4.4 and 4.6) has not changed over time (pre-post 2018 RMM).

Alternative hypothesis (H1): the compliance of prescribers with the new PPP measures (as defined by witnessed pregnancy testing and use of effective contraception) in oral retinoid users of childbearing age (as in section 4.4 and 4.6) varies over time (pre-post 2018 RMM).

Objective 3 (descriptive): To determine, in so far as is possible, patients' use of effective contraception in compliance with sections 4.4 and 4.6 of the SmPC.

Objective 4: To determine drug utilization and prescription patterns over time for type and number of alternative medicines prescribed in women of childbearing potential and women becoming pregnant where oral retinoid containing medicinal products had previously been prescribed or discontinued.
Null hypothesis (H0): drug utilization and prescription patterns over time for alternative medicines prescribed in women of childbearing potential and women becoming pregnant where oral retinoid containing medicinal products had previously been prescribed or discontinued (as in section 4.4 and 4.6) has not changed over time (pre-post 2018 RMM).
Alternative hypothesis (H1): drug utilization and prescription patterns over time for alternative medicines prescribed in women of childbearing potential and women becoming pregnant where oral retinoid containing medicinal products had previously been prescribed or discontinued (as in section 4.4 and 4.6) varies over time (pre-post 2018 RMM).

Objective 5 (synthesis): to estimate the effectiveness of the 2018 risk minimization measures for oral retinoids is a written synthesis of evidence generated in objectives 1-4.

9.7.3 STATISTICAL METHODS

Interrupted time series analysis

To test the effect of the 2018 risk minimization measures on outcomes, interrupted time-series analyses (ITS) will be conducted. Segmented Poisson regression analysis will be used to compare the pre-intervention (2010-2018) and post-intervention (2018-2020) trends in each of the tested outcomes: i) incident and prevalent retinoid use per month year, ii) incidence of pregnancy testing compliant prescriptions, iii) incidence of contraception non-compliant (ineffective contraception) prescriptions, and iv) treatment discontinuation in retinoid users, v) switches from retinoids to alternative medications per month year. The precise timing of intervention is defined as the month in which EMA interventions were implemented in each country (described in Section 9.3 Intervention). For the main analyses, a slope and level-change model with two segments will be considered: segment 1 models constant pre-intervention outcome levels, segment 2 models models post-intervention outcomes. Slope change will be tested using a time*intervention period interaction term (Bernal et al (2016)). Pre-post intervention change will be tested with the Wald statistic; regression coefficients, confidence intervals and p-values will be estimated. Incidence rate ratios for tested outcomes i-v will be calculated for the post vs. pre-intervention period using the same Poisson regression models. For all analyses, data will be used from January 1st 2010 until the last date of available information (see Section 9.4 for details).

Key assumptions of the Poisson regression models will be tested. First-order autocorrelation will be tested with the Durbin-Watson statistic and graphically with autocorrelation function plots (Durbin et al. (1950)). Second, overdispersion of the Poisson models will be checked according to the dispersion parameter. If overdispersion is detected, negative binomial regression models will be used instead of Poisson models for the segmented regression analyses.

Pooled analyses

ITS analyses will be presented separately per data source, using forest plots, as well as pooled. Data from each centre will be analysed together centrally in a 1-stage approach. The time scale of each centre will

be centred with intervention at time zero, so that change point in the ITS analysis is consistent across centres. Mixed effects Poisson regression models will be fitted with a random intercept and slope per country to account for between-centre heterogeneity in the baseline incidences of outcomes and the effects of the intervention. Pooled incidence rate ratios for tested outcomes i-v will be calculated for the post vs. pre-intervention period using the same Poisson regression models. In a sensitivity analysis, we will pool results from different data sources in a 2-stage approach using random effects meta-analysis (See section 9.7.7 Sensitivity analysis).

9.7.4 STATISTICAL ANALYSIS

Objective 1: Utilization patterns

Monthly incidence rates of retinoid use will be estimated as the number of new users per year (no use in year prior) divided by the number of person-years of follow-up in that quarter. Calculations will be stratified by age categories, indication, therapy duration and database. All incidences will be standardized by age according to the European standard population 12-55 years of age if needed.

Period prevalence

Monthly period prevalence estimates (MPP) will be estimated and defined as the number of female retinoid users of childbearing age during the month of interest (with at least one day of use in the period) divided by the total number of females-of-childbearing-age-years per calendar month. For all MPP, direct standardisation by age will be performed based upon the European standard population 12-55 years of age if needed. Poisson regression will be used to estimate the 95% confidence intervals around the prevalence.

ITS analyses will be conducted to compare i) the monthly prevalence of retinoid use and ii) monthly incidence rate of retinoid use before and after the period of intervention (as described in Section 9.7.2), stratified by database and indication, and pooled where appropriate. Incidence rate ratios comparing incident retinoid use in the post vs. pre-intervention period will be calculated using the Poisson regression models developed for ITS analyses, with the same stratifications.

To assess discontinuation, the frequency of discontinuation (as defined in section 9.3) divided by number of retinoid users in the previous quarter will be calculated stratified by database, year of start, type of retinoid, age group, duration of therapy and reason for discontinuation (adverse drug reaction, pregnancy, pregnancy wish, unknown). A Kaplan-Meier curve for drug "survival" (the proportion of patients still being treated after a given number of days) will be produced for each period as defined by PPP implementation. Start of follow-up for this analysis will be the treatment initiation during follow-up. Log rank tests will be applied to test for differences between subgroups of interest (indication, age, database).

ITS analyses will be conducted to compare the monthly incidence of retinoid discontinuations (numerator comprises of discontinuation by females who were users of the retinoid in the prior month (denominator)) before and after the period of intervention stratified by database and indication and pooled where appropriate. Incidence rate ratios comparing discontinuation in the post vs. pre-intervention period will be calculated using the Poisson regression models developed for ITS analyses, with the same stratifications.

Objective 2: Compliance of prescribers

Compliance of prescribers with recommendations for retinoid containing medicinal products will be analysed on a prescription level (each retinoid prescription) and assessed by analysing contraceptive coverage and pregnancy testing confirmed by healthcare professional before retinoid prescription and monthly during use.

First, incidence of witnessed pregnancy testing in periods before and after the intervention will be calculated for women of childbearing age using persontime in women of childbearing age as the denominator.

Second, the proportions of retinoid prescriptions with which a physician-confirmed pregnancy test was recorded i) up to 14 days prior to the date of prescription or dispensing and ii) once per month for the duration of the prescription and monthly for an additional three years following discontinuation for acitretin will be calculated per quarter, stratified by database, indication, age group, and treatment duration. Prescriptions which do not meet pregnancy testing compliance will be described in terms of missingness of testing prior to prescription or dispensing, during the prescription, or after discontinuation. An ITS analysis will be conducted to test for a change in the proportion of prescriptions compliant with pregnancy testing (according to criteria i and ii above) before and after the intervention, with time points per month year. Incidence rate ratios comparing pregnancy testing compliant prescriptions in the post vs. pre-intervention period will be calculated using the Poisson regression models developed for ITS analyses, with the same stratifications.

Third, to establish whether prescribers were compliant with recommendations for contraception, we will calculate the proportion of retinoid prescriptions that are fully covered with effective contraception (constructed as described in section 9.3.2.3) per month, stratified by database, indication, age group, treatment duration and by effectiveness of contraception (ineffective contraception coverage, effective contraception coverage). ITS analyses will be conducted to test for a change in the proportion of effectively compliant (during a period of effective contraception coverage,) and ineffectively compliant (during a period of ineffective contraception coverage) retinoid prescriptions after the intervention, with time points per quarter year. Incidence rate ratios comparing effective contraception compliant prescriptions in the post vs. pre-intervention period will be calculated using the Poisson regression models developed for ITS analyses, with the same stratifications.

Objective 3: Compliance with contraceptive use

The incidence of pregnancies overall in retinoid-exposed females of childbearing potential will be calculated, stratified by retinoid and period. The numerator will be the number of pregnancies, denominator the person-time of women years of follow-up in the following mutually exclusive categories: during retinoids, post-exposure at risk (1 month for isotretinoin and alitretinoin and 3 years for acitetrin), post-risk (> 1month after stopping isotretinoin and alitretinoin, > 3 years after acitretin). Type of outcome of the pregnancy and root cause analysis will be described as counts and narratives. Because we expect a very low incidence of pregnancies in oral retinoid users, incidence rate ratios comparing pregnancies in the post vs. pre-intervention period will not be calculated.

Objective 4: Alternative medicines

The rate and type of switching to an alternative medication will be calculated stratified by database, age group and indication. The monthly incidence of treatment switches (as defined in section 9.3) will be estimated as the number of switches divided by the number of retinoid users in the previous quarter, per retinoid. ITS analyses will be conducted to test for a change in frequency of switches alternative medications after the intervention, with time points per month year. Incidence rate ratios comparing switches to alternative medications in the post vs. pre-intervention period will be calculated using the Poisson regression models developed for ITS analyses, with the same stratifications.

Objective 5: Effectiveness of risk minimization

An overall assessment of the effectiveness of the 2018 risk minimization measures will be made based on the results of the analyses within objectives 1-4. Descriptive findings will be interpreted in accordance with the definition of appropriate and inappropriate use according to the CMDh (21 March 2018), as far as possible given the data available within the included databases.

The intervention will be determined to be effective if there is no pregnancy after the 2018 RMP. Should pregnancies be detected, counts and rates of pregnancies before and after the intervention will be described. Reasons for ineffectiveness will be listed.

9.7.5 MISSING DATA

Since the underlying data represent attended medical care we generally assume that absence of information of clinical events means absence of that condition. No imputation will be done for missing data.

9.7.7 SENSITIVITY ANALYSIS

Sensitivity analyses will be conducted on the definitions of effective contraception and the definition of discontinuation.
The following sensitivity analyses will be conducted in addition to the main analyses:

- Objectives 1,4: The discontinuation period for gaps between retinoid prescriptions for the definitions of switching and discontinuation will be reduced from 90 to 30 days
- Objectives 1,4: The study period will be restricted to end at February 2020, to investigate the impact of excluding the period of time affected by the COVID-19 pandemic, which is known to have impacted on health care seeking behaviour and collection of prescriptions.
- Objectives 1, 2, 4: Inclusion of previously defined lag time in the post-intervention period.
- Objectives 1, 2, 4: Two-stage pooling of database-specific results will be conducted using a random effects meta-analytical approach, if appropriate.
- Objective 3: Limitation of denominator to those women who were prescribed contraceptives.

The sensitivity analyses will be conducted individually and not in combination.

9.8 QUALITY CONTROL:

9.8.1 QUALITY MANAGEMENT

The study will be conducted according to the guidelines for Good Pharmacoepidemiology Practice (GPP) (International Society for Pharmacoepidemiology 2008) and according to the ENCePP code of conduct (European Medicines Agency 2018). All data access providers have experience in conducting pharmacoepidemiological research and research is done by researchers trained in pharmacoepidemiology. All programs will be programmed according to agreed coding standards and will be validated by double programming or source code review with second programmer involvement. Only validated software (Stata, R and/or SAS version 9.4, SAS Institute Inc., Cary, NC) will be used for statistical analyses

The Division of Pharmacoepidemiology & Clinical Pharmacology at Utrecht University is working according to a quality management system based on ISO 9001 principles, at the moment in development towards certification. The quality management system is system and process oriented and based on continuous improvement. The system is based upon standard operating procedures implemented throughout the division with regular internal audits as well as external audits that lead to certification. The quality management system is based on national and international external quality requirements where available and pertinent, including the guidelines for Good Pharmacoepidemiological Practices, ENCePP Guide on Methodological Standards in Pharmacoepidemiology, Good Clinical Practice, and Good Clinical Datamanagement Practice as well national and international guidelines and legislation concerning data-handling and privacy issues. The Division of Pharmacoepidemiology & Clinical Pharmacology (the division) uses a Virtual Desktop Infrastructure (VDI) to ensure secure and safe access to research data. This infrastructure has been designed and built by the Information Technology Services (ITS) of Utrecht University (https://www.uu.nl/en/organisation/information-and-technology-services-its), together with IT-servicepartner Axians (https://www.axians.nl/). Principles of the design of the infrastructure were security (access control), safety (continued access and backup of data) and flexibility of use (remote access for researchers).

9.8.2 DATA QUALITY

Data quality will be assessed according to the United States FDA Sentinel System data quality indicators[4,5]. The data quality and characterization checks described below will take place in collaboration with partners. All data will remain local and only summary measures described below will be inspected in collaboration with study statisticians. This process will proceed iteratively in collaboration with each data partner until concensus regarding acceptable data quality and fitness for purpose has been reached.

Level 1 data checks review the completeness and content of each variable in each table to ensure that the required variables contain data and conform to the formats specified by the CDM specifications (e.g., data types, variable lengths, formats, acceptable values, etc.).

[4] https://www.sentinelinitiative.org/sentinel/data-quality-review-and-characterization

[5] https://www.sentinelinitiative.org/sites/default/files/data/distributed-database/Sentinel_DataQAPractices_Memo.pdf

This is a check conducted in collaboration with partners to verify that the extract, transform, and load (ETL) procedure to convert from source data to the CDM has been completed as expected. Formats for all values will be assessed and compared to a list of acceptable formats. Missingness for core variables such as date of birth or sex will be assessed at this stage. Frequency tables of variables with finite allowable values will be created to identify unacceptable values. Counts of codes for events and exposures of interest in each data source will be tabulated. Distributions of dates of birth to assess identify rounding will be constructed.

Level 2 data checks assess the logical relationship and integrity of data values within a variable or between two or more variables within and between tables

At this stage we may check for consistency between variables such as date of delivery and date of birth for a linked mother-child pair and verify that all health encounters occur on or after a subject's date of birth.

Level 3 data checks examine data distributions and trends over time, both within a Data Partner's database (by examining output by year and year/month) and across a Data Partner's databases (by comparing updated CDM tables to previous versions of the tables). For example, a level 3 data check would ensure that there are no large, unexpected increases or decreases in records over time.

In this check, we will calculate person-time in women of child-bearing potential by calendar year and database. We may also calculate incidence of events and retinoid prescriptions by calendar year, database, and indication, as well as incidence of contraception prescriptions by contraceptive type, calendar year, and database. By comparing these types of summary measures across data sources and over time, anomalies and errors which can be corrected in partnership with data sources will become apparent.

9.9 LIMITATIONS OF THE RESEARCH METHODS:

9.9.1 LIMITATIONS RELATED TO THE DATA SOURCES

For all databases, it should be noted that the primary aim of data collection is patient management and not medical research. This implies that only events are collected which are deemed to be relevant for patient care. No single European data source contains all the information required in this study.

Due to severe delays in access to Danish data, as a result of the prioritization of COVID-19 studies by the data controlled, analyses with Danish data can only be completed in part by the date of the final deliverables. This means that only the main analyses of objectives 1, 2 and 4 can be conducted, as no information will be available in time on diagnostic or pregnancy information. In addition, the available data only extends to the end of 2018, which means limited inferences on the impact of the PPP in this data source can be drawn by the date of the final deliverable.

Pregnancy outcomes can be linked in PHARMO, Denmark, FISABIO, and ARS. In other databases the mothers' record will be utilized to identify pregnancy. Where possible and allowed by the IRB, the medical doctor will be contacted to collect information on pregnancy outcomes and the reason why in spite of the PPP the woman became pregnant. However, due to privacy constraints in many data sources, access to maternal records to conduct root cause analysis for detected pregnancies will not be possible.

Reasons for stopping treatment cannot be directly obtained. A proxy of pregnancy wish is made (e.g. start of folic acid), but will be highly underestimated.

Use of contraceptives and pregnancy testing may be underestimated, especially in those databases in which contraceptives are not reimbursed (See Charlton et al. 2015). This is particularly so for administrative databases such as in Italy. We will use available data and conduct analyses within database, so that time trends (even in presence of incomplete data) can be observed.

Anticipated missingness of specific variables is described below.

- Contraceptives:
    - Barrier contraceptives used without a prescription will not be ascertained.
    - For data partners in Italy, oral contraceptives and intrauterine devices are not reimbursed and therefore may not be ascertainable. Our definitions of effective and ineffective contraception, due to inability to ascertain barrier methods, mean that effective contraception will be defined across all data sources including those in Italy as presence of a permanent or user-independent non-permanent method (see 9.3.2.3). This will allow Italian sites to be included in analysis of effective contraception, although the rates of effective contraception will be underestimated.
- Reasons for discontinuation:
    - Reasons for discontinuation cannot be determined from free text and we therefore rely upon coded information. Using coded information, we can infer pregnancy wish (based upon prescribed folic acid as a proxy), pregnancy, or severe adverse drug reactions as reasons for discontinuation. Pregnancy wish can unfortunately not be inferred from cessation of contraception, as cessation of contraception may occur due to discontinuation of retinoids. There is likely to be misclassification in inference of reasons for discontinuation. The default reason for discontinuation will be 'unknown' and it is likely that for most women, none of the three methods for ascertaining reasons for discontinuation will be applicable.
- Alternative medications:
    - Some alternative medications (emollients, phototherapy) may not have a corresponding ATC code and will therefore not be detected.

Misclassification of outcomes:

Misclassification of endpoints is possible. For the different databases that will be used, validation studies have shown that coding is reliable in the databases and that these databases are suitable for pharmacoepidemiological research [6]. Misclassification is unlikely to be differential by time period.

[6] PHARMO: Lau, Hong S., et al. "Validation of pharmacy records in drug exposure assessment." *Journal of clinical epidemiology* 50.5 (1997): 619-625, Goettsch, W. G., et al. "Results from a rosuvastatin historical cohort study in more than 45 000 Dutch statin users, a PHARMO study." *Pharmacoepidemiology and drug safety* 15.7 (2006): 435-443..
Danish National: Johannesdottir, Sigrun Alba, et al. "Existing data sources for clinical epidemiology: the Danish National Database of Reimbursed Prescriptions." *Clinical epidemiology* 4 (2012): 303., Adelborg, Kasper, et al. "Positive predictive value of cardiac examination, procedure and surgery codes in the Danish National Patient Registry: a population-based validation study." *BMJ open* 6.12 (2016): e012817.
ARS: Valkhoff, Vera E., et al. "Validation study in four health-care databases: upper gastrointestinal bleeding misclassification affects precision but not magnitude of drug-related upper gastrointestinal bleeding risk." *Journal of clinical epidemiology*67.8 (2014): 921-931., Gini, Rosa, et al. "Identifying type 2 diabetes, hypertension and ischaemic heart disease from data sources with incomplete diagnostic information: a population-based validation study in Italian Administrative Databases." *Rosa Gini*: 67.
BIFAP: Gil, Miguel, et al. "Validation study of colorectal cancer diagnosis in the Spanish primary care database, BIFAP." Pharmacoepidemiology and drug safety 28.2 (2019): 209-216., Saiz, L. C., et al. "Validation and incidence of community-acquired

However, inspection of trends over time during the harmonization process may reveal changes in care or coding practice over the study period. These will be inspected and algorithms modified if necessary (see 9.8.2 Data Quality)

Selection bias:

Selection bias is mitigated by the inclusion of all women of childbearing age registered in each data source at any time during the study period. Additionally, each retinoid-specific cohort is defined as the set of all women of childbearing age registered in each data source at any time during the study period with any use of the retinoid at any time during the study period. However, generalizability of study results is limited by the selection of study data sources, which all represent western European populations.

Residual/Unmeasured confounding:

Residual and unmeasured confounding is controlled by design. However, unmeasured effect modification may occur. Prescribing patterns of the retinoids under study may have changed over time for reasons unrelated to the PPP. Additionally, coding practices may have changed over time, leading to misclassification of outcomes. Trends in preferred contraceptive methods unrelated to the PPP may have impact our findings.

As part of the statistical analysis plan, we will further define the event identification algorithms and also will provide availability of validation studies previously conducted for the events of interest.

Finally, there are differences in timing of data updates in the various databases (medical records are continuously updated, administrative databases are updated only once per year in most instances).

Covid-19 Pandemic

The COVID-19 pandemic has likely impacted on the rates of healthcare visits and prescribing, and may have influences the behaviour of individuals when ordering repeat prescriptions. This is likely to have an impact on the trends seen from February/March 2020 onwards. To explore the impact of this, we will conduct a sensitivity analysis (for all ITS analyses) where we end the study period at January 31st 2020.

9.9.2 LIMITATIONS IN THE METHODOLOGY

Although the ITS design is considered the best available method to evaluate the impact of policy changes where a control group is not available, causality cannot be established. Other external factors unrelated to the EMA PPP may influence the utilization of oral retinoids and cannot be accounted for. Finally, the PPP is not a clearly defined intervention and was in place already for long time. The staggered implementation of the 2018 changes across Europe makes it challenging to assess the impact of the PPP on the various outcomes under study. As it is not possible to fully establish precise dates of implementation in each of the countries due to variation at the regional and practice-levels, we decided

pneumonia in patients with type 2 diabetes in the BIFAP database." Epidemiology & Infection 145.14 (2017): 3056-3064.
FISABIO: --
Caserta Campania: Oteri A, Trifiro G, Gagliostro MS, Tari DU, Moretti S, et al. (2010) Prescribing pattern of anti-epileptic drugs in an Italian setting of elderly outpatients: a population-based study during 2004–07. Br J Clin Pharmacol 70: 514–522, Alacqua M, Trifiro G, Cavagna L, Caporali R, Montecucco CM, et al. (2008) Prescribing pattern of drugs in the treatment of osteoarthritis in Italian general practice: the effect of rofecoxib withdrawal. Arthritis Rheum 59: 568–574.

to model an implementation period of 6 months for the ITS analyses, which aims to broadly capture the stepwise implementation. Nonetheless, this decision may influence the results of the ITS analysis.

Finally, because interventions to prevent pregnancy were already in place prior to the 2018 intervention, change in trend may be minimal, meaning reduced power to detect impact of the intervention.

10. PROTECTION OF HUMAN SUBJECTS:

For this study, participants from various EU member states will process personal data from individuals which is collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All of the databases used in this study are currently already used for pharmacoepidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to.

According to these regulations, rather than combining person level data and performing only a central analysis, local analyses will be run, which will generate non identifiable data with less detailed information that will be pooled across databases.

The output files are stored at Utrecht University. These output files do not contain any data that allow identification of subjects included in the study. In fact, each record is completely anonymous and does not contain any identifier key. The protocols will be reviewed by the Institutional Review Boards (IRBs) of the respective databases.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS:

As this is a non-interventional study based on secondary use of data (from various EU electronic healthcare databases), safety monitoring and safety reporting, where there is a safety relevant result, is provided on an aggregate level only; no reporting on an individual case level is required. In studies based on secondary use of data with a safety relevant result, reports of adverse events/adverse reactions should be summarized in the study report, i.e. the overall association between an exposure and an outcome. Relevant findings from the study report will be included in the periodic aggregated regulatory reports submitted to Health Authorities

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS:

Upon study completion and finalization of the study report, the results of this non-interventional study will be submitted for publication and posted in the EU PAS publicly accessible database of results. Publications will comply with the International Committee of Medical Journal Editors (ICMJE) guidelines.

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14. ANNEXES

ANNEX I. MAPPING OF EXPOSURES TO ATC CODES

RETINOIDS

D05BB02: acitretin

D11AH04: alitretinoin

D10BA01: isotretinoin

RETINOID ALTERNATIVE MEDICATIONS

COMPOUND	**ATC**	**INDICATION**		
		PSORIASIS	ACNE	CONTACT DERMATITIS
Retinol (vit A)	A11CA01	0	1	0
Vitamin A and D in combination	A11CB	0	1	0
Dithranol	D05AC01	1	0	0
methoxsalen (topical)	D05AD02	1	0	0
Fumaric acid	D05AX01	0	1	0
methoxsalen (systemic)	D05BA02	1	0	0
Dimethylfumarate	D05BX51	1	0	0
methylprednisolone	D07AA01	0	1	0
clobetasone	D07AB01	1	0	1
hydrocortisone butyrate	D07AB02	1	0	1
flumetasone	D07AB03	1	0	1
fluocortin	D07AB04	1	0	1
fluperolone	D07AB05	1	0	1
fluorometholone	D07AB06	1	0	1
fluprednidene	D07AB07	1	0	1
desonide	D07AB08	1	0	1
triamcinolone	D07AB09	1	0	1
alclometasone	D07AB10	1	0	1
hydrocortisone buteprate	D07AB11	1	0	1
dexamethasone	D07AB19	1	1	1
clocortolone	D07AB21	1	0	1
combinations of corticosteroids	D07AB30	1	0	1
betamethasone	D07AC01	1	0	0
fluclorolone	D07AC02	1	0	0
desoximetasone	D07AC03	1	0	0
fluocinolone acetonide	D07AC04	1	0	0
fluocortolone	D07AC05	1	0	0
diflucortolone	D07AC06	1	0	0

fludroxycortide	D07AC07	1	0	0
fluocinonide	D07AC08	1	0	0
budesonide	D07AC09	1	0	0
diflorasone	D07AC10	1	0	0
amcinonide	D07AC11	1	0	0
halometasone	D07AC12	1	0	0
mometasone	D07AC13	1	0	0
methylprednisolone aceponate	D07AC14	1	0	0
beclometasone	D07AC15	1	0	0
hydrocortisone aceponate	D07AC16	1	0	0
fluticasone	D07AC17	1	0	0
prednicarbate	D07AC18	1	0	0
difluprednate	D07AC19	1	0	0
ulobetasol	D07AC21	1	0	0
clobetasol	D07AD01	1	0	0
halcinonide	D07AD02	1	0	0
Fluorometholone	D10AA01	0	1	0
Methylprednisolone	D10AA02	0	1	0
Dexamethasone	D10AA03	0	1	0
Benzoyl peroxide (local)	D10AE01	0	1	0
Clindamycin (local)	D10AF01	0	1	0
Erytromycin (local)	D10AF02	0	1	0
clindamycin/benzoyl peroxide	D10AF51	0	1	0
Erytromycin- Zn complex	D10AF52	0	1	0
Azzelaic acid	D10AX03	0	1	0
Tacrolimus	D11AH01	1	0	1
Pimecrolimus	D11AH02	1	0	1
Cromoglicic acid	D11AH03	0	1	0
Dupilumab	D11AH05	0	1	0
Crisaborole	D11AH06	0	1	0
aldosterone	H02AA01	0	1	0
fludrocortisone	H02AA02	0	1	0
desoxycortone	H02AA03	0	1	0
betamethasone	H02AB01	0	1	0
dexamethasone	H02AB02	0	1	0
fluocortolone	H02AB03	0	1	0
methylprednisolone	H02AB04	0	1	0
paramethasone	H02AB05	0	1	0
prednisolone	H02AB06	0	0	1
Prednisone	H02AB07	0	0	1
triamcinolone	H02AB08	0	1	0
hydrocortisone	H02AB09	0	1	0
cortisone	H02AB10	0	1	0

prednylidene	H02AB11	0	1	0
deflazacort	H02AB13	0	1	0
cloprednol	H02AB14	0	1	0
meprednisone	H02AB15	0	1	0
cortivazol	H02AB17	0	1	0
Doxycycline	J01AA02	0	1	0
Tetracycline	J01AA07	0	1	0
minocyclin (systemic)	J01AA08	0	1	0
erytromycin (systemic)	J01FA01	0	1	0
Clarithromycin	J01FA09	0	1	0
azithromycin (systemic)	J01FA10	0	1	0
Apremilast	L04AA32	1	0	0
Etanercept	L04AB01	1	0	0
Infliximab	L04AB02	1	0	0
Adalimumab	L04AB04	1	0	0
certolizumab pegol	L04AB05	1	0	0
Ustekinumab	L04AC05	1	0	0
Secukinumab	L04AC10	1	0	0
Brodalumab	L04AC12	1	0	0
Ixekizumab	L04AC13	1	0	0
Guselkumab	L04AC16	1	0	0
Tildrakizumab	L04AC17	1	0	0
Ciclosporin	L04AD01	1	0	1
Azathioprin	L04AX01	0	0	1
Methotrexate	L04AX03	0	0	1
Dimethylfumarate	L04AX07	1	0	0

HORMONE BASED CONTRACEPTIVE PRODUCTS (USER DEPENDENT)

Vaginal ring (21 days, one week off), contraceptive patch (weekly for 3 weeks, one week off), progestogen only pill or desogestrel progestogen-only pill (28 days continuously), combination pills (21 days one week off).

Progestagens and estrogens, fixed combinations (G03AA)

G03AA01	etynodiol and ethinylestradiol
G03AA02	quingestanol and ethinylestradiol
G03AA03	lynestrenol and ethinylestradiol
G03AA04	megestrol and ethinylestradiol
G03AA05	norethisterone and ethinylestradiol
G03AA06	norgestrel and ethinylestradiol
G03AA07	levonorgestrel and ethinylestradiol

G03AA08	medroxyprogesterone and ethinylestradiol
G03AA09	desogestrel and ethinylestradiol
G03AA10	gestodene and ethinylestradiol
G03AA11	norgestimate and ethinylestradiol
G03AA12	drospirenone and ethinylestradiol
G03AA14	nomegestrol and estradiol
G03AA15	chlormadinone and ethinylestradiol
G03AA16	dienogest and ethinylestradiol
G03AA17	medroxyprogesterone and estradiol

Progestogens and estrogens, sequential preparations (G03AB)

G03AB01	megestrol and ethinylestradiol
G03AB02	lynestrenol and ethinylestradiol
G03AB03	levonorgestrel and ethinylestradiol
G03AB04	norethisterone and ethinylestradiol
G03AB05	desogestrel and ethinylestradiol
G03AB06	gestodene and ethinylestradiol
G03AB07	chlormadinone and ethinylestradiol
G03AB08	dienogest and estradiol
G03AB09	norgestimate and ethinylestradiol

Progestagens (G03AC)

G03AC03	levonorgestrel
G03AC04	quingestanol
G03AC05	megestrol
G03AC07	norgestrienone
G03AC09	desogestrel
G03AC10	drospirenone

VAGINAL RINGS

G02BB01
G02BB02

CONTRACEPTIVE PATCH

G03AA13	norelgestromin and ethinylestradiol

IMPLANT

G03AC08	etonogestrel subcutaneous implant

INJECTION

G03AC06	medroxyprogesterone

INTRA-UTERINE DEVICES*

G02BA01	plastic IUD

G02BA02	plastic IUD with copper
G02BA03	plastic IUD with progestogen

*Diagnosis codes for insertion of Intra-uterine devices will also be used to identify IUD contraception (See Annex Iv)

FOLIC ACID

B03BB01	folic acid
B03BB51	folic acid, combinations
B03AE02	iron, multivitamins and folic acid
B03AE01	iron, vitamin B12 and folic acid

ANTIDEPRESSANTS

N06AA01	desipramine
N06AA02	imipramine
N06AA03	imipramine oxide
N06AA04	clomipramine
N06AA05	opipramol
N06AA06	trimipramine
N06AA07	lofepramine
N06AA08	dibenzepin
N06AA09	amitriptyline
N06AA10	nortriptyline
N06AA11	protriptyline
N06AA12	doxepin
N06AA13	iprindole
N06AA14	melitracen
N06AA15	butriptyline
N06AA16	dosulepin
N06AA17	amoxapine
N06AA18	dimetacrine
N06AA19	amineptine
N06AA21	maprotiline
N06AA23	quinupramine
N06AB02	zimeldine
N06AB03	fluoxetine
N06AB04	citalopram
N06AB05	paroxetine
N06AB06	sertraline
N06AB07	alaproclate
N06AB08	fluvoxamine
N06AB09	etoperidone
N06AB10	escitalopram
N06AF01	isocarboxazid
N06AF02	nialamide

N06AF03	phenelzine
N06AF04	tranylcypromine
N06AF05	iproniazide
N06AF06	iproclozide
N06AG02	moclobemide
N06AG03	toloxatone
N06AX01	oxitriptan
N06AX02	tryptophan
N06AX03	mianserin
N06AX04	nomifensine
N06AX05	trazodone
N06AX06	nefazodone
N06AX07	minaprine
N06AX08	bifemelane
N06AX09	viloxazine
N06AX10	oxaflozane
N06AX11	mirtazapine
N06AX12	bupropion
N06AX13	medifoxamine
N06AX14	tianeptine
N06AX15	pivagabine
N06AX16	venlafaxine
N06AX17	milnacipran
N06AX18	reboxetine
N06AX19	gepirone
N06AX21	duloxetine
N06AX22	agomelatine
N06AX23	desvenlafaxine
N06AX24	vilazodone
N06AX25	Hyperici herba
N06AX26	vortioxetine

ANNEX II. ORAL RETINOID SMPCS, SECTION 4.8 (UNDESIRABLE EFFECTS)

ACITRETIN SMPC (UK) SECTION 4.8

4.8 Undesirable effects

Possible side effects of Acitretin occur in varying degrees from patient to patient. Most of the side effects are dose-related and usually reversible with reduction of dosage or discontinuation of therapy.

At the start of treatment with Acitretin there may be a transient worsening of the psoriasis symptoms.

The skin and mucous membranes are most commonly affected, and it is recommended that patients should be so advised before treatment is commenced.

The reported adverse reactions are listed below by system organ class and by frequency.

	Very common	Common	Uncommon	Rare	Very Rare	Unknown
	(≥ 1/10)	(≥ 1/100 < 1/10)	(≥ 1/1000, < 1/100)	(≥ 1/10,000 < 1/1000)	(<1/10000)	
Blood and lymphatic system disorders						
Immune system disorders						Type 1 hypersensitivity
Endocrine Disorders						
Psychiatric disorders						
Nervous system disorders				Increase of intracranial pressure (pseudotum or cerebri)		
Eye disorders	Conjunctivitis, visual disturbances, e.g. xerophthalmia, blurred vision, impaired night vision			Inflammation or ulcers of the cornea		
Ear and labyrinth disorders						

Vascular disorders						Capillary Leak Syndrome / retinoic acid syndrome
Respiratory, thoracic and mediastinal disorders						Dysphonia
Gastrointestinal disorders				Gastrointestinal symptoms (e.g. nausea, vomiting, abdominal pain, diarrhoea, dyspepsia)		
Hepatobiliary disorders					Hepatitis and jaundice	
Skin and subcutaneous tissues disorders	hypervitaminosis A as e.g. dry lips and possibly inflamed lips, dry mucous membranes of mouth and nose, peeling of skin, especially the palms of the hands and soles of the feet, rhinitis, nose bleed, scaling and thinning of healthy skin with increased sensitivity, erythema, pruritus, sensation of “burning skin”, sensation of “sticky skin”, dermatitis, hair loss, inflammation of the nail wall, nail fragility	rhagades, inflammation of oral mucosa and gingiva associated with taste disturbances, blistering of the skin, change in pigmentation of the skin and hair, change in growth rate of hair, change in hair structure		Increased sensitivity of the skin to light		Madarosis and exfoliative dermatitis

Musculo-skeletal and connective tissue disorders			Myalgia, arthralgia and bone pain			
General disorders and administration site conditions	Thirst and feeling of cold		Peripheral oedema, sensation of heat, dysgeusia, headache			
Investigations						Elevation of triglycerides, total cholesterol, SGPT, creatine phosphokinase, SGOT, γ-GT, alkaline phosphatase, direct bilirubin, lactate dehydrogenase and uric acid, Lowering of HDL cholesterol

SERIOUS ACITRETIN ADRS TO BE EXTRACTED[7]

Cardiovascular: Thrombosis

Hepatic: Hepatitis, Jaundice

Neurologic: Pseudotumor cerebri

Octic: Ototoxicity – deafness, tinnitus

Other: Capillary leak syndrome, retinoic acid syndrome

[7] IBM Micromedex

ALITRETINOIN SMPC (UK) SECTION 4.8

4.8 Undesirable effects

The safety and efficacy of Alitretinoin in patients with severe chronic hand eczema (CHE) unresponsive to treatment with potent topical corticosteroids has been evaluated in two randomised, double blind, placebo-controlled clinical studies (see section 5.1).

The most frequent adverse drug reactions (ADRs) observed under alitretinoin therapy are headache (30 mg: 23.9%; 10 mg: 10.8%), erythema (30 mg: 5.5%; 10 mg: 1.7%), nausea (30 mg: 5.1%; 10 mg: 2.4%), flushing (30 mg: 5.9%, 10 mg: 1.6%), and laboratory changes consisting of increased levels of triglycerides (30 mg: 35.4%; 10 mg: 17.0%), increased cholesterol (30 mg: 27.8%; 10 mg: 16.7%), decreased levels of thyroid stimulating hormone (TSH, 30 mg: 8.4%, 10 mg: 6.0%) and decreased levels of free T4 (30 mg: 10.5%; 10 mg: 2.9%). These reversible ADRs are dose dependent and may therefore be alleviated by dose reduction.

	Very common (≥ 1/10)	**Common (≥ 1/100 < 1/10)**	**Uncommon (≥ 1/1000, < 1/100)**	**Rare (≥ 1/10,000 < 1/1000)**	**Very Rare (<1/10000)**	**Unknown**
Blood and lymphatic system disorders		Anaemia, increased iron binding capacity, monocytes decreased; thrombocytes increased				
Immune system disorders						Anaphylactic reactions, hypersensitivity
Endocrine Disorders		TSH decreased, free T4 decreased				
Psychiatric disorders				Depression, depression aggravated, aggressive tendencies, anxiety, mood alterations	Suicide, suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour	
Nervous system disorders	Headache	Dizziness		Benign intracranial hypertension		
Eye disorders		Conjunctiviti	Blurred			Decreased

		s, dry eye, eye irritation	vision, cataract			night vision
Ear and labyrinth disorders		Tinnitus				
Vascular disorders		Flushing, hypertension		Vasculitis		
Respiratory, thoracic and mediastinal disorders			Epistaxis			
Gastrointestinal disorders		Nausea, dry mouth, vomiting	Dyspepsia			Inflammatory bowel disease
Hepatobiliary disorders		Transaminase increased[1)]				
Skin and subcutaneous tissues disorders		Dry skin, dry lips, cheileitis, eczema[1)], dermatitis[1)], erythema, alopecia	Pruritus, rash, skin exfoliation, asteatotic eczema	Nail disorders, photosensitivity reaction, hair texture changes		
Musculo-skeletal and connective tissue disorders		Arthralgia[1)], myalgia[1)]	Exostosis, (hyperostosis), ankylosing spondylitis			
General disorders and administration site conditions		Fatigue				Peripheral oedema
Investigations	Hypertriglyceridemia, high density lipoprotein decreased, hypercholesterolemia	Blood creatinine phosphokinase increased				

[1)] The overall incidence of adverse events was not higher than those observed in the corresponding placebo group.

The following adverse events have not been observed in clinical trials with alitretinoin, but have been observed with other retinoids: diabetes mellitus, colour blindness (colour vision deficiencies), and contact lens intolerance (see section 4.4).

Changes in bone mineralization and extra-osseous calcifications have been associated with systemic retinoid treatment. In clinical studies with alitretinoin, degenerative changes of the spine and ligamentous calcifications were frequent findings in patients with chronic hand eczema before treatment (baseline), with minor progression in a small number of patients during treatment. These observations were consistent with age dependent

degenerative changes. Assessments of bone density (DXA) did not indicate a dose dependent effect on bone mineralization.

SERIOUS ALITRETINOIN ADRS TO BE EXTRACTED[8]

Psychiatric: Aggressive behavior, Depression, Injury due to suicide attempt, Psychotic disorder, Suicidal thoughts, Violent behavior

Gatrointestinal: Inflammatory bowel disease

Immunologic: Anaphylaxis, Hypersensitivity reaction

Neurologic: Cerebrovascular accident, Pseudotumor cerebri

Ophthalmic: Cataract, Blurred vision

Other: Vasculitis

ISOTRETINOIN SMPC (UK) SECTION 4.8

4.8 Undesirable effects

Some of the side effects associated with the use of isotretinoin are dose-related. The side effects are generally reversible after altering the dose or discontinuation of treatment, however some may persist after treatment has stopped. The following symptoms are the most commonly reported undesirable effects with isotretinoin: dryness of the skin, dryness of the mucosae e.g. of the lips (cheilitis), the nasal mucosa (epistaxis) and the eyes (conjunctivitis).

Infections:	
Very Rare (≤1/10 000)	Gram positive (mucocutaneous) bacterial infection
Blood and lymphatic system disorders:	
Very common (≥1/10) **Common (≥1/100, <1/10)** **Very Rare (≤1/10000)**	Anaemia, Red blood cell sedimentation rate increased, Thrombocytopenia, Thrombocytosis Neutropenia Lymphadenopathy
Immune system disorders:	
Rare(≥1/10000,<1/1000)	Allergic skin reaction, Anaphylactic reactions, Hypersensitivity
Metabolism and nutrition disorders:	
Very Rare (≤1/10000)	Diabetes mellitus, Hyperuricaemia
Psychiatric disorders:	
Rare (≥1/10000,<1/1000) **Very Rare (≤1/10000)**	Depression, Depression aggravated, Aggressive tendencies, Anxiety, Mood alterations Abnormal behaviour, Psychotic disorder, Suicidal ideation, Suicide attempt, Suicide

[8] IBM Micromedex

Nervous system disorders:	
Common (≥1/100,<1/10) **Very Rare (≤1/10 000)**	Headache Benign intracranial hypertension, Convulsions, Drowsiness, Dizziness
Eye disorders:	
Very common (≥1/10) **Very Rare (≤1/10000)**	Blepharitis, Conjunctivitis, Dry eye, Eye irritation Blurred vision, Cataract, Colour blindness (colour vision deficiencies), Contact lens intolerance, Corneal opacity, Decreased night vision, Keratitis, Papilloedema (as sign of benign intracranial hypertension), Photophobia, Visual disturbances
Ear and labyrinth disorders:	
Very Rare (≤1/10 000)	Hearing impaired
Vascular disorders:	
Very Rare (≤1/10000)	Vasculitis (for example Wegener's granulomatosis, allergic vasculitis)
Respiratory, thoracic and mediastinal disorders:	
Common (≥1/100,<1/10) **Very Rare (≤1/10000)**	Epistaxis, Nasal dryness, Nasopharyngitis Bronchospasm (particularly in patients with asthma), Hoarseness
Gastrointestinal disorders:	
Very Rare (≤1/10000)	Colitis, Ileitis, Dry throat, Gastrointestinal haemorrhage, haemorrhagic diarrhoea and inflammatory bowel disease, Nausea, Pancreatitis (see section 4.4 "Special warnings and special precautions for use")
Hepatobiliary disorders:	
Very common (≥1/10) **Very Rare (≤1/10000)**	Transaminase increased (see section 4.4 "Special warnings and special precautions for use") Hepatitis
Skin and subcutaneous tissues disorders:	
Very common (≥1/10) **Rare (≥l/10000,<l/1000)** **Very Rare (≤1/10 000)** **Frequency unknown***	Cheilitis, Dermatitis, Dry skin, Localised exfoliation, Pruritus, Rash erythematous, Skin fragility (risk of frictional trauma) Alopecia Acne fulminans. Acne aggravated (acne flare), Erythema (facial), Exanthema, Hair disorders, Hirsutism, Nail dystrophy, Paronychia, Photosensitivity reaction, Pyogenic granuloma, Skin hyperpigmentation, Sweating increased Erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis.
Musculo-skeletal and connective tissue disorders:	
Very common (≥1/10) **Very Rare (≤1/10 000)** **Frequency unknown*:**	Arthralgia, myalgia, back pain (particularly in children and adolescent patients) Arthritis, Calcinosis (calcification of ligaments and tendons), Epiphyses premature fusion, Exostosis, (hyperostosis), Reduced bone density, Tendonitis Rhabdomyolysis
Renal and urinary disorders:	
Very Rare (≤1/10 000)	Glomerulonephritis
Reproductive system and breast disorders:	
Frequency unknown*	Sexual dysfunction including erectile dysfunction and decreased libido, Gynaecomastia
General disorders and administration site conditions:	
Very Rare (≤1/10 000)	Granulation tissue (increased formation of), Malaise
Investigations:	

Very common (≥1/10) **Common (≥1/100, <1/10)** **Very Rare (≤1/10000)**	Blood triglycerides increased, High density lipoprotein decreased Blood cholesterol increased, Blood glucose increased, Haematuria, Proteinuria Blood creatine phosphokinase increased

* cannot be estimated from the available data

SERIOUS ISOTERINOIN ADRS TO BE EXTRACTED[9]

Cardiovascular: Thrombosis of blood vessel, Vasculitis

Dermatological: Stevens-Johnson syndrome, Toxic epidermal necrolysis

Gastrointestinal: Gastrointestinal hemorrhage, Inflammatory bowel disease, Pancreatitis

Hematologic: Agranulocytosis, Neutropenia, Thrombocytopenia

Hepatic: Hepatitis

Immunologic: Anaphylaxis, Hypersensitivity reaction

Musculoskeletal: Rhabdomyolysis

Neurologic: Cerebrovascular accident, Pseudotumor cerebri, Seizure, Syncope

Ophthalmic: Optic neuritis, Visual disturbance

Otic: Hearing loss

Psychiatric: Aggressive behavior, Depression, Injury due to suicide attempt, Psychotic disorder, Suicidal thoughts, Violent behavior

Respiratory: Bronchospasm

Gatrointestinal: Inflammatory bowel disease

[9] IBM Micromedex

ANNEX III. LEVEL 1 COMMON DATA MODEL, SYNTACTIC HARMONIZATION

This study will make use of the ConcePTION CDM, version 2.2 - available to view here: https://docs.google.com/spreadsheets/d/1hc-TBOfEzRBthGP78ZWIa13C0RdhU7bK/edit#gid=413205035).

Partners will be asked to extract all available data of relevance for the study population and convert these data into the ConcepTION Common Data Model (CDM) using their preferred software for syntactic harmonization (see figure 5 below).

Metadata – contains general information about the data source that describes the data, and can be used to develop characterization programs based upon presence or absence of CDM tables.

CDM_SOURCE - In this table, a high-level, machine-readable description of the instance of the CDM is contained. The scripts of the studies that are deemed to run on this instance will use this information to tailor some choices to the specific DAP and data source

INSTANCE - This table displays the list of the tables and columns of the origin data dictionary that are mapped to the instance of the CDM, together with date of last update (both in terms of when the data was accessed by the DAPs, and when the data was actually recorded and can be considered complete). This is to be used, together with a machine-readable version of the ETL, to match the inclusion of the study population and the creation of the study variables to the actual data loaded in the CDM instance. The list is restricted to tables and columns of the origin data dictionary that are included in the current ETL document.

Person – contains stable information on a person: date of birth, sex at birth, ethnicity

ObservationPeriods – contains information on the period of follow-up period per person with multiple observation periods per person possible.

Medicines – contains information on medicines prescribed or dispensed to a person.

Products - This table collects the information associated to each marketed product that may have been prescribed, dispensed or administered to a patient. It contains one row per product

Events – contains information on events characterised by a date and a code belonging to a coding system for a diagnosis, a sign, a symptom, each record will contain information on its coding system and on its provenance;

Procedures – contains information regarding medical procedures/inquiries characterised by a date and by a description with a result/outcome and units if applicable

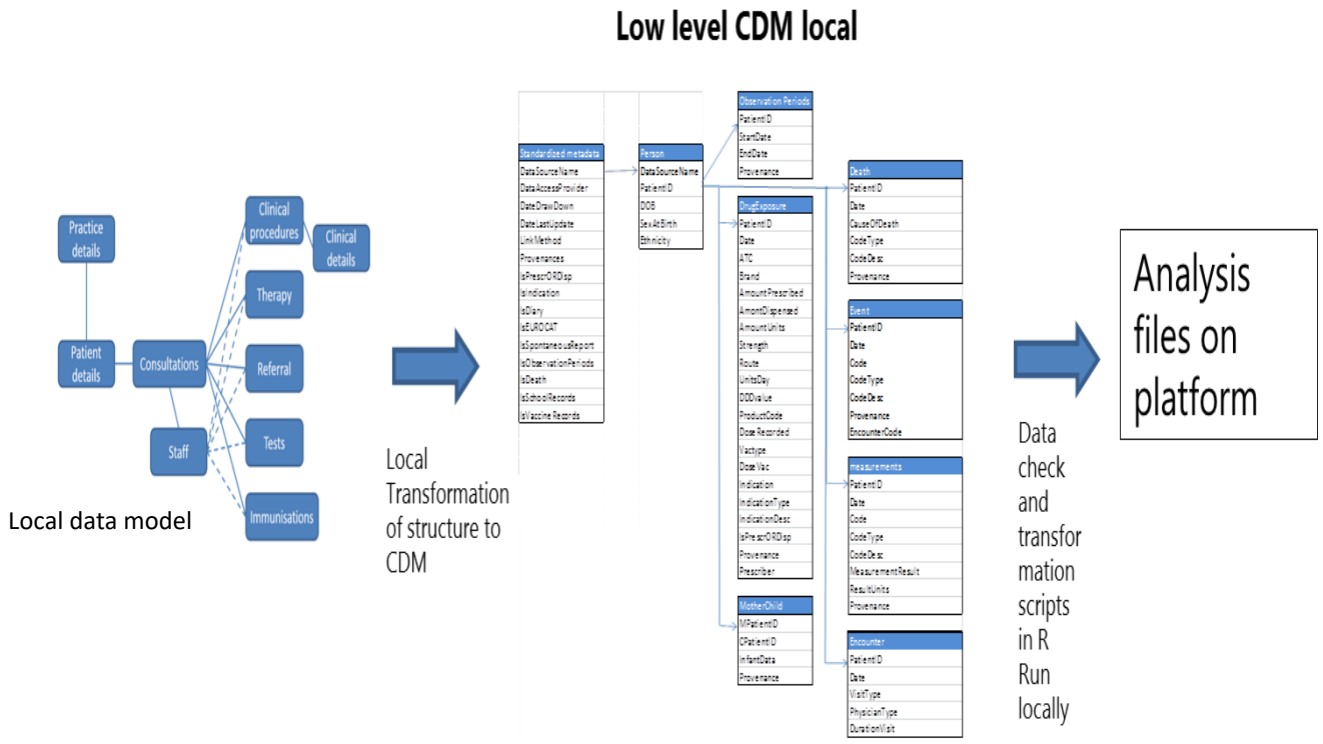
Death - contains records of death from any source including medical records, death registries, hospital discharge records, etc.

Mother-child linkage - contains identifiers for mother-infant pairs and data on methodology used to link each pair.

PERSON_RELATIONSHIP - contains identifiers for mother-infant pairs and data on methodology used to link each pair.

SURVEY_ID – contains identifiers for persons recorded in surveys captured in the SURVEY_OBSERVATIONS table.

SURVEY_OBSERVATIONS – contains data collected to record data related to an event or episode (i.e. a medical birth registry)



ANNEX IV. DRAFT CODE LISTS

NOTE: All code lists included here are initial proposals. Code list harmonization will be conducted with study partners until consensus is reached, following which code lists will be finalized.

PREGNANCY TESTING

Coding system	Code	Code name	Concept name
ICD10	Z32	Pregnancy examination and test	Pregnancy examination and test
ICD10CM	Z32	Encounter for pregnancy test and childbirth and childcare instruction	Encounter for pregnancy test and childbirth and childcare instruction
ICD10CM	Z32.0	Encounter for pregnancy test	Encounter for pregnancy test
ICD10CM	Z32.00	Encounter for pregnancy test, result unknown	Encounter for pregnancy test, result unknown
ICD10CM	Z32.00	Encounter for pregnancy test NOS	Encounter for pregnancy test
ICD10CM	Z32.01	Encounter for pregnancy test, result positive	Encounter for pregnancy test, result positive
ICD10CM	Z32.02	Encounter for pregnancy test, result negative	Encounter for pregnancy test, result negative
ICD9CM	V72.4	Pregnancy examination or test	Pregnancy examination or test
ICD9CM	V72.40	Pregnancy examination or test, pregnancy unconfirmed	Pregnancy examination or test, pregnancy unconfirmed
ICD9CM	V72.41	Pregnancy examination or test, negative result	Pregnancy examination or test, negative result
ICD9CM	V72.42	Pregnancy examination or test, positive result	Pregnancy test positive
ICPC2P	W60001	Test;result(s);pregnancy	Pregnancy test finding
RCD2	6211.	Pregnant - urine test confirms	Pregnancy test positive
RCD2	ZV724	[V]? pregnant examination/test	Pregnancy examination or test, pregnancy unconfirmed
RCD2	ZV729	[V]Pregnancy examination/test	Pregnancy examination and test

FEMALE STERILIZATION

Coding system	**Code**	**Code name**	**Concept name**
ICD9CM	66.51	Removal of both fallopian tubes at same operative episode	Removal of both fallopian tubes at same operative episode
ICD9CM	V25.2	Sterilization	Encounter due to sterilization

MTHICD9	V25.2	Encounter for sterilization	Encounter due to sterilization
MTHICD9	V25.2	Admission for interruption of fallopian tubes or vas deferens	Admission for interruption of fallopian tubes or vas deferens
ICD9CM	V26.51	Tubal ligation status	Encounter due to tubal ligation status
ICPC2P	W52002	Tubal ligation;procedure	Tubal Ligation
ICD10	Z30.2	Sterilization	Encounter due to sterilization
ICD10CM	Z30.2	Encounter for sterilization	Encounter due to sterilization
ICD10CM	Z98.51	Tubal ligation status	Encounter due to tubal ligation status
RCD2	ZV252	[V]Sterilisation	Encounter due to sterilization
RCD2	ZV252	[V]Sterilisation	Encounter due to admission for tubal ligation

HYSTERECTOMY

Coding system	Code	Code name	Concept name
ICD10CM	Z90.710	Acquired absence of both cervix and uterus	Encounter due to acquired absence of both cervix and uterus
ICD9CM	65-71.99	OPERATIONS ON THE FEMALE GENITAL ORGANS	Gynecologic Surgical Procedures
ICD9CM	68.3	Subtotal abdominal hysterectomy	Subtotal abdominal hysterectomy
ICD9CM	68.4	Total abdominal hysterectomy	Total abdominal hysterectomy
ICD9CM	68.5	Vaginal hysterectomy	Vaginal hysterectomy
ICD9CM	V88.01	Acquired absence of both cervix and uterus	Encounter due to acquired absence of both cervix and uterus
ICPC2P	X52009	Hysterectomy;abdomin;subtotal	Subtotal abdominal hysterectomy
ICPC2P	X52010	Hysterectomy;abdomin;total	Total abdominal hysterectomy
ICPC2P	X52011	Hysterectomy;vaginal	Vaginal hysterectomy
ICPC2P	X52018	Hysterectomy	Hysterectomy
MTHICD9	68.9	Hysterectomy NOS	Hysterectomy
MTHICD9	V88.01	Acquired absence of uterus NOS	Encounter due to acquired absence of uterus NOS
RCD2	7E04.	Abdominal excision of uterus	Abdominal hysterectomy
RCD2	7E043	Total abdominal hysterect NEC	Hysterectomy
RCD2	7E044	Subtotal abdominal hysterect	Subtotal abdominal hysterectomy
RCD2	7E046	Radical hysterectomy	Radical hysterectomy
RCD2	7E04C	Laparoscopic hysterectomy	Laparoscopic hysterectomy
RCD2	7E04G	Tot abdo hyst conserv ovar	Total abdominal hysterectomy
RCD2	7E04z	Abdominal excision uterus NOS	Abdominal hysterectomy
RCD2	7E05.	Vaginal excision of uterus	Vaginal hysterectomy
RCD2	7E05z	Vaginal excision uterus NOS	Vaginal hysterectomy
RCD2	7F1A0	Caesarean hysterectomy	Cesarean hysterectomy

INTRAUTERINE DEVICE

Coding system	Code	Code name	Concept name
ICD10	Z30.1	Insertion of (intrauterine) contraceptive device	Encounter due to Intrauterine contraceptive device fitted
ICD10	Z97.5	Presence of (intrauterine) contraceptive device	Encounter due to presence of intrauterine contraceptive device
ICD10CM	Z97.5	Presence of (intrauterine) contraceptive device	Encounter due to presence of intrauterine contraceptive device
ICD9CM	V45.51	Presence of intrauterine contraceptive device	Encounter due to presence of intrauterine contraceptive device
ICD9CM	69.7	Insertion of intrauterine contraceptive device	Intrauterine coil insertion
ICPC	W12	Family planning/IUD	Intrauterine contraception
ICPC2P	W12004	Insertion;IUCD	Intrauterine coil insertion
ICPC2P	W12003	Contraception;IUD	IUD contraception
RCD	ZV251	[V]Coil insertion	Encounter due to Intrauterine contraceptive device fitted
RCD	ZV455	[V]Intraut.contrac.dev.present	Encounter due to presence of intrauterine contraceptive device
RCD	6151.	Intrauterine contraceptive device fitted	Intrauterine coil insertion
RCD	7E090	Introduction of intrauterine contraceptive device	Intrauterine coil insertion
RCD	XaDbF	Intrauterine contraception	Intrauterine contraception
RCD	6153.	Intrauterine contraceptive device re-fitted	Intrauterine contraceptive device re-fitted
RCD	615F.	IUD check	Intrauterine device check

RCD	XM15M	Intrauterine device check	Intrauterine device check
RCD	615G.	IUD in situ	IUD contraception
RCD	XaDbJ	IUD contraception	IUD contraception
RCD	ZV254	[V]IUCD reinsertion	Reinsertion of coil

ACITRETIN ADRS

Concept name	Coding system	Code	Code name
Capillary Leak Syndrome	RCD	X50B1	Capillary leak syndrome
Coronary Thrombosis	ICD10CM	I21	coronary (artery) thrombosis
Coronary Thrombosis	ICD10CM	I22	coronary (artery) thrombosis
Coronary Thrombosis	ICPC2P	K75008	Thrombosis;artery;coronary
Coronary Thrombosis	RCD	X200E	Coronary thrombosis
Coronary Thrombosis	RCD	X203v	Coronary artery thrombosis
Deafness	ICD10CM	H91.9	Deafness NOS
Deafness	ICPC	H86	Deafness all degrees NOS
Deafness	ICPC2P	H86003	Deafness
Deafness	RCD	XE0s9	Deafness
Deafness	RCD	XE17P	Deafness NOS
Deep Vein Thrombosis	ICD10CM	I82.40	Deep vein thrombosis NOS
Deep Vein Thrombosis	ICPC2P	K94004	Thrombosis;deep venous
Drug ototoxicity - deafness	RCD	XE17O	Ototoxicity - deafness
Drug ototoxicity - deafness	RCD	XM1QG	Drug ototoxicity - deafness
Hearing Loss, Partial	RCD	1C132	Partial deafness

Hearing problem	ICPC2P	H02006	Problem;hearing
Hearing problem	RCD	Xa7SQ	Hearing problem
Hearing problem	RCD	Xa7SW	Disorder of hearing
Hepatitis	ICD10	K75.9	Inflammatory liver disease, unspecified
Hepatitis	ICD10CM	K75.9	Inflammatory liver disease, unspecified
Hepatitis	ICD9CM	573.3	Hepatitis, unspecified
Hepatitis	ICPC2P	D72002	Hepatitis
Hepatitis	ICPC2P	D97008	Hepatitis
Hepatitis	RCD	J633.	Hepatitis unspecified
Hepatitis	RCD	J633z	Hepatitis unspecified NOS
Hepatitis	RCD	X306T	Inflammatory liver disease
Icterus	ICD10	R17	Unspecified jaundice
Icterus	ICD10CM	R17	Unspecified jaundice
Icterus	ICPC	D13	Jaundice
Icterus	ICPC2P	D13001	Jaundice
Icterus	RCD	R0241	[D]Icterus NOS
Icterus	RCD	X769z	Jaundice
Icterus	RCD	XM0z9	Icterus [D]
Intracranial Hypertension	ICPC2P	N29023	Raised intracranial pressure
Intracranial Hypertension	RCD	XM04c	Raised intracranial pressure
Portal vein thrombosis	ICD10	I81	Portal vein thrombosis
Portal vein thrombosis	ICD10CM	I81	Portal vein thrombosis
Portal vein thrombosis	ICD9CM	452	Portal vein thrombosis

Portal vein thrombosis	ICPC2P	K94003	Thrombosis;portal
Portal vein thrombosis	RCD	G81..	Portal vein thrombosis
Pseudotumor Cerebri	ICD10	G93.2	Benign intracranial hypertension
Pseudotumor Cerebri	ICD10CM	G93.2	Benign intracranial hypertension
Pseudotumor Cerebri	ICD9CM	348.2	Benign intracranial hypertension
Pseudotumor Cerebri	RCD	F282.	Idiopathic intracranial hypertension
Thrombosis	RCD	XC0fW	Thrombosis
Tinnitus	ICD10	H93.1	Tinnitus
Tinnitus	ICD10CM	H93.1	Tinnitus
Tinnitus	ICD10CM	H93.19	Tinnitus, unspecified ear
Tinnitus	ICD9CM	388.3	Tinnitus
Tinnitus	ICD9CM	388.30	Tinnitus, unspecified
Tinnitus	ICPC	H03	Ringing/buzzing/tinnitus
Tinnitus	ICPC2P	H03003	Noises in;ear
Tinnitus	ICPC2P	H03004	Ringing (in);ear
Tinnitus	ICPC2P	H03006	Tinnitus
Tinnitus	RCD	1C2..	Noises in ear
Tinnitus	RCD	1C23.	Ringing in ear
Tinnitus	RCD	1C2Z.	Tinnitus symptom NOS
Tinnitus	RCD	F5830	Unspecified tinnitus
Tinnitus	RCD	F583z	Tinnitus NOS
Tinnitus	RCD	Xa7Rv	Observation of tinnitus
Tinnitus	RCD	XE17L	Tinnitus
Venous Thrombosis	ICD10CM	I82.90	Thrombosis (vein) NOS
Venous Thrombosis	ICPC2P	K94008	Thrombosis;venous

Venous Thrombosis	RCD	Xa0l8	Venous thrombosis
Venous Thrombosis	RCD	XE0Vb	Thrombosis of vein NOS

ALITRETINOIN ADRS

Concept name	Coding system	Code	Code name	Tags
Aggressive behavior	ICPC2P	P80001	Aggression	
Aggressive behavior	RCD	X7651	Aggressive behaviour	
Aggressive behavior	RCD	X78wl	Aggressive	
anaphylaxis	ICD10	T78.2	Anaphylactic shock, unspecified	
anaphylaxis	ICD10CM	T78.2	Allergic shock	
anaphylaxis	ICPC2P	A12004	Shock;anaphylactic	
anaphylaxis	ICPC2P	A92005	Shock;anaphylactic	
anaphylaxis	RCD	SN50.	Systemic anaphylaxis	
Blurred vision	ICPC2P	F05011	Blurred;vision	
Blurred vision	RCD	X75bj	Blurring of visual image	
Blurred vision	RCD	X75bT	Hazy vision	
Blurred vision	RCD	XE16K	Blurred vision NOS	
Cataract	ICD10	H26.9	Cataract, unspecified	
Cataract	ICD10CM	H26.9	Unspecified cataract	
Cataract	ICD9CM	366	Cataract	
Cataract	ICD9CM	366.9	Unspecified cataract	
Cataract	ICPC	F92	Cataract	
Cataract	ICPC2P	F92001	Cataract	
Cataract	RCD	F46..	Cataract	

Cataract	RCD	F46z.	Cataract NOS	
Cataract	RCD	X75kX	Cataract form	
Cerebrovascular accident	ICD10	I64	Stroke, not specified as haemorrhage or infarction	
Cerebrovascular accident	ICD10CM	I63.9	Stroke NOS	
Cerebrovascular accident	ICPC	K90	Stroke/cerebrovasc accident	
Cerebrovascular accident	ICPC2P	K90002	Cerebrovascular accident	
Cerebrovascular accident	ICPC2P	K90017	Stroke	
Cerebrovascular accident	ICPC2P	K90024	Apoplexy	
Cerebrovascular accident	RCD	X00D1	Stroke	
Cerebrovascular accident	RCD	XaEGq	Stroke NOS	
Cerebrovascular accident	RCD	XE2aB	Stroke and cerebrovascular accident unspecified	
Depression motion	RCD	X78x6	Depression - motion	
Drug Allergy	ICD10CM	T88.7	Drug hypersensitivity NOS	
Drug Allergy	ICPC2P	A85004	Allergic reaction;drug(s)	
Drug Allergy	RCD	Xa1pS	Allergic reaction to drug	
Drug Allergy	RCD	XE1os	Drug hypersensitivity NOS	
Feeling suicidal (finding)	ICD9CM	V62.84	Suicidal ideation	
Feeling suicidal (finding)	ICPC2P	P77002	Feeling;suicidal	
Feeling suicidal (finding)	RCD	1BD1.	Suicidal thoughts	
Feeling suicidal (finding)	RCD	Ua1XF	Feeling suicidal	
Hypersensitivity	ICD10	T78.4	Allergy, unspecified	
Hypersensitivity	ICD10CM	T78.40	Allergy, unspecified	
Hypersensitivity	ICPC	A12	Allergy/allergic reaction NOS	

Hypersensitivity	ICPC2P	A12007	Allergic reaction
Hypersensitivity	ICPC2P	A12009	Allergy
Hypersensitivity	ICPC2P	A92007	Allergic reaction
Hypersensitivity	ICPC2P	A92008	Allergy
Hypersensitivity	RCD	SN530	Allergic reaction
Hypersensitivity	RCD	X79pp	Allergy
Hypersensitivity	RCD	X79pv	Hypersensitivity
Hypersensitivity	RCD	Xa1pQ	Allergic disorder
Hypersensitivity	RCD	Xa1zh	Allergic reaction to substance
Hypersensitivity	RCD	XE1ot	Allergy, unspecified
Hypersensitivity	RCD	XM0xz	Allergic reaction NOS
Inflammatory Bowel Diseases	ICPC2P	D94009	Disease;inflammatory bowel
Inflammatory Bowel Diseases	RCD	XE0ae	Inflammatory bowel disease
Physical aggression	ICD10CM	R45.6	Violent behavior
Physical aggression	RCD	X7659	Physical aggression
Pseudotumor Cerebri	ICD10	G93.2	Benign intracranial hypertension
Pseudotumor Cerebri	ICD10CM	G93.2	Benign intracranial hypertension
Pseudotumor Cerebri	ICD9CM	348.2	Benign intracranial hypertension
Pseudotumor Cerebri	RCD	F282.	Idiopathic intracranial hypertension
Psychotic Disorders	ICD9CM	290-299.99	PSYCHOSES
Psychotic Disorders	ICD9CM	298.9	Unspecified psychosis
Psychotic Disorders	ICPC2P	P98003	Psychotic
Psychotic Disorders	ICPC2P	P98004	Psychosis
Psychotic Disorders	RCD	X00S6	Psychotic disorder

Vasculitis	ICPC2P	K99016	Vasculitis	
Vasculitis	RCD	G76B.	Vasculitis	

ISOTRETINOIN ADRS

Concept name	Coding system	Code	Code name
Aggressive behavior	ICPC2P	P80001	Aggression
Aggressive behavior	RCD	X7651	Aggressive behaviour
Aggressive behavior	RCD	X78wl	Aggressive
Agranulocytosis	ICD10	D70	Agranulocytosis
Agranulocytosis	ICD10CM	D70	agranulocytosis
Agranulocytosis	ICPC2P	B84001	Agranulocytosis
Agranulocytosis	RCD	D400z	Agranulocytosis NOS
anaphylaxis	ICD10	T78.2	Anaphylactic shock, unspecified
anaphylaxis	ICD10CM	T78.2	Allergic shock
anaphylaxis	ICPC2P	A12004	Shock;anaphylactic
anaphylaxis	ICPC2P	A92005	Shock;anaphylactic
anaphylaxis	RCD	SN50.	Systemic anaphylaxis
Bronchial Spasm	ICPC2P	R03001	Bronchospasm
Bronchial Spasm	RCD	Xa0Ns	Bronchospasm
Cerebrovascular accident	ICD10	I64	Stroke, not specified as haemorrhage or infarction
Cerebrovascular accident	ICD10CM	I63.9	Stroke NOS
Cerebrovascular accident	ICPC	K90	Stroke/cerebrovasc accident
Cerebrovascular accident	ICPC2P	K90002	Cerebrovascular accident
Cerebrovascular accident	ICPC2P	K90017	Stroke

Cerebrovascular accident	ICPC2P	K90024	Apoplexy
Cerebrovascular accident	RCD	X00D1	Stroke
Cerebrovascular accident	RCD	XaEGq	Stroke NOS
Cerebrovascular accident	RCD	XE2aB	Stroke and cerebrovascular accident unspecified
Deafness	ICD10CM	H91.9	Deafness NOS
Deafness	ICPC	H86	Deafness all degrees NOS
Deafness	ICPC2P	H86003	Deafness
Deafness	RCD	XE0s9	Deafness
Deafness	RCD	XE17P	Deafness NOS
Drug Allergy	ICD10CM	T88.7	Drug hypersensitivity NOS
Drug Allergy	ICPC2P	A85004	Allergic reaction;drug(s)
Drug Allergy	RCD	Xa1pS	Allergic reaction to drug
Drug Allergy	RCD	XE1os	Drug hypersensitivity NOS
Feeling suicidal (finding)	ICD9CM	V62.84	Suicidal ideation
Feeling suicidal (finding)	ICPC2P	P77002	Feeling;suicidal
Feeling suicidal (finding)	RCD	1BD1.	Suicidal thoughts
Feeling suicidal (finding)	RCD	Ua1XF	Feeling suicidal
Gastrointestinal Hemorrhage	ICD10	K92.2	Gastrointestinal haemorrhage, unspecified
Gastrointestinal Hemorrhage	ICD10CM	K92.2	Gastrointestinal hemorrhage, unspecified
Gastrointestinal Hemorrhage	ICD9CM	578	Gastrointestinal hemorrhage
Gastrointestinal Hemorrhage	ICD9CM	578.9	Hemorrhage of gastrointestinal tract, unspecified
Gastrointestinal Hemorrhage	ICPC2P	D15001	Bleeding;gastrointestinal
Gastrointestinal Hemorrhage	RCD	J68..	Gastrointestinal haemorrhage

Gastrointestinal Hemorrhage	RCD	J68zz	Gastrointestinal tract haemorrhage NOS
Gastrointestinal Hemorrhage	RCD	XE0bJ	Gastrointestinal haemorrhage unspecified
hearing impairment	ICD10	H91.9	Hearing loss, unspecified
hearing impairment	ICD10CM	H91.9	Unspecified hearing loss
hearing impairment	ICD9CM	389	Hearing loss
hearing impairment	ICD9CM	389.9	Unspecified hearing loss
hearing impairment	ICPC2P	H02004	Loss (of);hearing
hearing impairment	ICPC2P	H28002	Impairment;hearing
hearing impairment	RCD	XE0s9	Hearing loss
Hearing Loss, Partial	RCD	1C132	Partial deafness
Hepatitis	ICD10	K75.9	Inflammatory liver disease, unspecified
Hepatitis	ICD10CM	K75.9	Inflammatory liver disease, unspecified
Hepatitis	ICD9CM	573.3	Hepatitis, unspecified
Hepatitis	ICPC2P	D72002	Hepatitis
Hepatitis	ICPC2P	D97008	Hepatitis
Hepatitis	RCD	J633.	Hepatitis unspecified
Hepatitis	RCD	J633z	Hepatitis unspecified NOS
Hepatitis	RCD	X306T	Inflammatory liver disease
Hypersensitivity	ICD10	T78.4	Allergy, unspecified
Hypersensitivity	ICD10CM	T78.40	Allergy, unspecified
Hypersensitivity	ICPC	A12	Allergy/allergic reaction NOS
Hypersensitivity	ICPC2P	A12007	Allergic reaction
Hypersensitivity	ICPC2P	A12009	Allergy
Hypersensitivity	ICPC2P	A92007	Allergic reaction

Hypersensitivity	ICPC2P	A92008	Allergy
Hypersensitivity	RCD	SN530	Allergic reaction
Hypersensitivity	RCD	X79pp	Allergy
Hypersensitivity	RCD	X79pv	Hypersensitivity
Hypersensitivity	RCD	Xa1pQ	Allergic disorder
Hypersensitivity	RCD	Xa1zh	Allergic reaction to substance
Hypersensitivity	RCD	XE1ot	Allergy, unspecified
Hypersensitivity	RCD	XM0xz	Allergic reaction NOS
Inflammatory Bowel Diseases	ICPC2P	D94009	Disease;inflammatory bowel
Inflammatory Bowel Diseases	RCD	XE0ae	Inflammatory bowel disease
Neutropenia	ICD10CM	D70	Neutropenia
Neutropenia	ICD10CM	D70.9	Neutropenia, unspecified
Neutropenia	ICD9CM	288.0	Neutropenia
Neutropenia	ICD9CM	288.00	Neutropenia, unspecified
Neutropenia	ICPC2P	B84008	Neutropenia
Neutropenia	RCD	Xa9E8	Neutropenic disorder
Optic Neuritis	ICD10	H46	Optic neuritis
Optic Neuritis	ICD10CM	H46	Optic neuritis
Optic Neuritis	ICD10CM	H46.9	Unspecified optic neuritis
Optic Neuritis	ICD9CM	377.3	Optic neuritis
Optic Neuritis	ICD9CM	377.30	Optic neuritis, unspecified
Optic Neuritis	ICPC2P	F99011	Neuritis;optic
Optic Neuritis	RCD	F4H3.	Optic neuritis
Optic Neuritis	RCD	F4H30	Unspecified optic neuritis

Optic Neuritis	RCD	F4H3z	Optic neuritis NOS
Pancreatitis	ICD10CM	K85.9	Pancreatitis NOS
Pancreatitis	ICPC2P	D99043	Pancreatitis
Pancreatitis	RCD	X308h	Pancreatitis
Physical aggression	ICD10CM	R45.6	Violent behavior
Physical aggression	RCD	X7659	Physical aggression
Pseudotumor Cerebri	ICD10	G93.2	Benign intracranial hypertension
Pseudotumor Cerebri	ICD10CM	G93.2	Benign intracranial hypertension
Pseudotumor Cerebri	ICD9CM	348.2	Benign intracranial hypertension
Pseudotumor Cerebri	RCD	F282.	Idiopathic intracranial hypertension
Psychotic Disorders	ICD9CM	290-299.99	PSYCHOSES
Psychotic Disorders	ICD9CM	298.9	Unspecified psychosis
Psychotic Disorders	ICPC2P	P98003	Psychotic
Psychotic Disorders	ICPC2P	P98004	Psychosis
Psychotic Disorders	RCD	X00S6	Psychotic disorder
Rhabdomyolysis	ICD10CM	M62.82	Rhabdomyolysis
Rhabdomyolysis	ICD9CM	728.88	Rhabdomyolysis
Rhabdomyolysis	RCD	X70AI	Rhabdomyolysis
Seizures	ICD10CM	R56.9	Unspecified convulsions
Seizures	ICD9CM	780.3	Convulsions
Seizures	ICPC2P	N07001	Convulsions
Seizures	ICPC2P	N07002	Fit(s)
Seizures	ICPC2P	N07003	Seizure
Seizures	RCD	R003.	[D]Convulsions

Seizures	RCD	R0032	[D]Fit
Seizures	RCD	R003z	[D]Convulsion NOS
Seizures	RCD	XaDbE	Fit - convulsion
Seizures	RCD	XaEHz	Seizure
Seizures	RCD	XaEI2	Fits - convulsions
Stevens-Johnson Syndrome	ICD10	L51.1	Bullous erythema multiforme
Stevens-Johnson Syndrome	ICD10CM	L51.1	Stevens-Johnson syndrome
Stevens-Johnson Syndrome	ICD9CM	695.13	Stevens-Johnson syndrome
Stevens-Johnson Syndrome	ICPC2P	A12005	Stevens Johnson syndrome
Stevens-Johnson Syndrome	ICPC2P	S99032	Stevens Johnson syndrome
Stevens-Johnson Syndrome	RCD	M1517	Stevens-Johnson syndrome
Stevens-Johnson Syndrome	RCD	X50CE	Bullous erythema multiforme
Syncope	ICD10	R55	Syncope and collapse
Syncope	ICD10CM	R55	Syncope and collapse
Syncope	ICD9CM	780.2	Syncope and collapse
Syncope	ICPC	A06	Fainting/syncope
Syncope	ICPC2P	A06003	Attack(s);fainting
Syncope	ICPC2P	A06005	Fainting
Syncope	ICPC2P	A06009	Syncope
Syncope	ICPC2P	A06012	Swoon
Syncope	RCD	R002.	[D]Syncope
Syncope	RCD	R0021	[D]Fainting
Syncope	RCD	R002z	[D]Syncope and collapse NOS
Syncope	RCD	XaBua	Syncope and collapse

Syncope	RCD	XM010	Syncope
Syncope	RCD	XM06a	Fainting
Syncope	RCD	XM0CY	Syncope symptom
Thrombocytopenia	ICD10	D69.6	Thrombocytopenia, unspecified
Thrombocytopenia	ICD10CM	D69.6	Thrombocytopenia, unspecified
Thrombocytopenia	ICD9CM	287.5	Thrombocytopenia, unspecified
Thrombocytopenia	ICPC2P	B83012	Thrombocytopaenia
Thrombocytopenia	RCD	D315.	Thrombocytopenia NOS
Thrombocytopenia	RCD	Xa8Hh	Thrombocytopenic disorder
Thrombocytopenia	RCD	XE24o	Thrombocytopenia
Toxic Epidermal Necrolysis	ICD10	L51.2	Toxic epidermal necrolysis [Lyell]
Toxic Epidermal Necrolysis	ICD10CM	L51.2	Toxic epidermal necrolysis [Lyell]
Toxic Epidermal Necrolysis	ICD9CM	695.15	Toxic epidermal necrolysis
Toxic Epidermal Necrolysis	RCD	M1518	Toxic epidermal necrolysis
Vasculitis	ICPC2P	K99016	Vasculitis
Vasculitis	RCD	G76B.	Vasculitis
Visual disturbance	ICD10	H53	Visual disturbances
Visual disturbance	ICD10	H53.9	Visual disturbance, unspecified
Visual disturbance	ICD10CM	H53	Visual disturbances
Visual disturbance	ICD10CM	H53.9	Unspecified visual disturbance
Visual disturbance	ICD9CM	368	Visual disturbances
Visual disturbance	ICD9CM	368.9	Unspecified visual disturbance
Visual disturbance	RCD	F48..	Visual disturbance
Visual disturbance	RCD	F48z.	Visual disturbance NOS

ANNEX V. DATES OF IMPLEMENTATION OF PPP PER COUNTRY

Drug	Country	Minimum		Maximum	
		Date	Date Type	Date	Date Type
Acitretin	The Netherlands	NA: Partly implemented	Updated SmPC	NA: Nearly to be launched	Pharmacist Checklist
	Denmark	24 AUG 2018	First Updated SmPC, Updated PIL	12 APR 2019	Last Updated SmPC, Updated PIL
	Spain	DEC 2018	Updated SmPC, Updated PIL	FEB 2019	Boxed warning
	Italy	03 SEP 2018	Patient reminder card, Prescriber checklist, Pharmacist checklist	13 JAN 2019	Prescription validity 7 days
Isotretinoin	The Netherlands	NA: Partly implemented	Updated SmPC	NA: Nearly to be launched	Pharmacist Checklist
	Denmark	24 AUG 2018	First Updated SmPC, Updated PIL, Boxed warning	12 APR 2019	Last Updated SmPC, Updated PIL, Boxed warning
	Spain	OCT 2018	Boxed warning	MAR 2019	Updated SmPC
	Italy	03 SEP 2018	Patient reminder card,	19 NOV 2018	DHCP letter

			Prescriber checklist, Pharmacist checklist		
Alitretinoin	The Netherlands	NA: Partly implemented	Updated SmPC	NA: Nearly to be launched	Pharmacist Checklist
	Denmark	24 AUG 2018	First Updated SmPC, Updated PIL, Boxed warning	12 APR 2019	Last Updated SmPC, Updated PIL, Boxed warning
	Spain	JUL 2018	Updated PIL	FEB 2019	Updated SmPC
	Italy	03 SEP 2018	Patient reminder card, Prescriber checklist, Pharmacist checklist	19 NOV 2018	DHCP letter