Isotretinoin and the effectiveness of the pregnancy prevention programme in Europe

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1. Background / rationale

Isotretinoin is an effective pharmacological treatment for severe nodular acne vulgaris that is unresponsive to other, first-line therapies. However, it is highly teratogenic when used during the first trimester of pregnancy. Therefore, pregnancy prevention programs (PPPs) are in place across Europe, committing female isotretinoin users of childbearing potential to use at least two effective means of contraception just before, during, and immediately after isotretinoin use. Despite these PPPs, 'breakthrough' pregnancies still occur in females using isotretinoin.[1]

Research indicates that often, females are unaware of the requirement to use contraceptive measures when using isotretinoin[2] and the question arises as to why this should be the case. Thus far, no clear indications exist to suggest certain populations in Europe are at higher risk of failure to adhere to contraceptive advice given with isotretinoin prescriptions. One study from the Netherlands identified better adherence to the PPP when isotretinoin was prescribed by GPs than by dermatologists,[3] whereas another Dutch study suggested the opposite.[4] There was no indication of real differences in adherence between different age groups.[4]

This phenomenon observed with isotretinoin highlights the possibility that PPPs for other products may not be as effective as required. For PPPs in place with cancer treatments it could be argued the issue is less pressing than for acne treatment. However, more products with indications other than cancer are being introduced on the market that are teratogenic and for which PPPs will be introduced; a recent example being alitretinoin for severe chronic hand eczema refractory to corticosteroids.[5] To ensure efficacy of the PPPs, therefore, the question needs to be addressed as to what makes PPPs fail and what can be done to improve adherence to pregnancy prevention guidelines in users of teratogenic products who are of childbearing potential.

2. Aims and objectives

2.1 Aims

1. To determine the prevalence of isotretinoin use in females of childbearing age.
2. To characterise female users of isotretinoin in terms of demographic and clinical characteristics.
3. To estimate the risk of occurrence of pregnancies in females of childbearing age using isotretinoin and of factors associated with this risk.
4. To evaluate the main limiting and/or facilitating factors associated with the effectiveness of the PPP.
5. To provide practical recommendations for improving the effectiveness of PPPs in Europe.

2.2 Objectives

1. To use data from population-based healthcare databases in the United Kingdom, Italy and Norway (data from the Netherlands have already been published) to determine the prevalence of isotretinoin use in females of childbearing age.
2. To use the databases to identify characteristics of female isotretinoin users in terms of age, comorbidity, socio-economic status, smoking status, alcohol use, body mass index, parity, gravidity and contraceptive history (oral as well as depot contraceptive preparations, emergency contraception, intra uterine devices, sterilisation, vasectomy of husband) where known as well as duration of use and the frequency of visits to their GP and to their dermatologist.
3. To use data from population-based healthcare databases to calculate the incidence (with 95% CI) of pregnancy among women of childbearing age using oral isotretinoin.
4. To identify, within these databases, factors associated with a higher or lower likelihood of pregnancy occurrence such as age, socio-economic status,

smoking status, alcohol use, pre-pregnancy body mass index, parity, gravidity, and contraceptive history (as above) as well as the frequency of visits to their GP and to their dermatologist where known.

5. To update the literature review by Crijns *et al.* (2011)[1] on Compliance with pregnancy prevention programmes of isotretinoin in Europe.
6. To conduct interviews with dermatologists, pharmacists, and females experiencing 'breakthrough pregnancies' (identified by the Netherlands Teratology Information Centres as well as other participating countries where feasible) to provide an insight on the main limiting and or facilitating factors associated with the effectiveness of the PPP.
7. To evaluate information provided via the interviews with females experiencing 'breakthrough pregnancies' regarding the need for avoiding pregnancy as well as any influence of religious beliefs on any decisions (not) to adhere to the contraceptive advice associated with isotretinoin use.
8. To develop further the PPP failure model in light of a workshop with a committee constituting representatives from across Europe of stakeholders from dermatology, hospital and community pharmacy, general practice, fertility specialists, teratology information services as well as female user representatives of childbearing potential.

3. Study design and data sources

The study consists of three main components

a. A drug utilisation study of isotretinoin use in women of childbearing age.
b. A study to identify factors associated with a higher or lower likelihood of pregnancy occurrence in women of childbearing age and predictive of PPP failure.
c. A qualitative consultation exercise to obtain additional information regarding these risk factors and to create a PPP failure model.

The first two components will use data from five population-based healthcare databases. These are summarised below and outlined in Table 1.

The United Kingdom's General Practice Research Database (GPRD)

The GPRD contains longitudinal medical records collected within UK primary care as part of the clinical management of patients. At present there are 69.5 million person years of data available and data is actively being collected on around 5.3 million patients.[6] Within the GPRD, data is available on medical diagnoses and symptoms (including those relating to pregnancy), tests and referrals to specialists, prescriptions issued by GPs and information on lifestyles variables including smoking status and alcohol intake.[7]

The Secure Anonymised Information Databank (SAIL) in Wales, UK

The SAIL databank contains a range of routinely collected anonymised administrative and clinical data and covers 1.8 million individuals, approximately half of the Welsh population. The data captured by SAIL includes medical diagnoses, diagnostic tests and prescriptions issued by GPs in primary care as well as secondary care hospital in-patient data.[8] Within the SAIL databank the National Community Child Health Database is used to identify live and stillbirths and the Patient Episode Data for Wales allows the identification of pregnancies which require hospital interventions. Where recorded by the GP, information on lifestyles variables including smoking status and alcohol intake is also available.

Region Emilia-Romagna (RER) and Tuscany databases

The RER and Tuscany healthcare databases are population based databases containing linkable data from a range of healthcare settings. At present data is being captured on around 4.2 million and 3.7 patients in Region Emilia-Romagna and Tuscany respectively. The Certificate of Delivery Assistance database contains information on all pregnancies that result in a delivery and take place in a hospital (~99% of all births) within the region. Diagnosis and procedure code data is available in relation to hospital discharge events, as are the dates of admission and discharge. Administrative prescription claims data is also available for all drugs that are reimbursed under the Italian National Health Service.[9,10]

Norwegian Medical Birth Register and the Norwegian Prescription Database

The Norwegian Prescription Database contains all prescriptions dispensed in Norway since January 2004, regardless of reimbursement, and covers the entire Norwegian population of approximately 4.9 million inhabitants.[11] The Norwegian Medical Birth Register contains data on all births that take place in Norway. Within the medical birth register data is available on smoking and links can be made to data on socio-economic status.

Qualitative data sources

The third component of the study is qualitative in nature. This will involve conducting interviews with dermatologists and pharmacists as well as females identified from the Netherlands Teratology Information Services who experienced a 'breakthrough pregnancy' whilst taking isotretinoin. The results of the drug utilisation study will be used to develop the topic guide for the interviews. The interviews will be analysed using thematic and content analysis;[12] the results of the interviews and the database drug utilisation study will be presented at a workshop with key stakeholders and representatives from dermatology, hospital and community pharmacy, general practice, fertility specialists, teratology information services and female users of childbearing potential. The information gathered from the workshop will feed into the PPP failure model. We will publish the PPP failure model recommendations for multi-stakeholder European structured consultation on the internet before being modified and finalised.

Table 1. Inventory of databases that will contribute

Country	**Norway**	**Italy**	**Italy**	**England, Scotland and N. Ireland**	**Wales**
Database	***Medical Birth Register & the Norwegian Prescription Database***	***Emilia-Romagna***	***Tuscany***	***GPRD***	***SAIL***
Population base (resident at any one time)	4.8M	4.2M	3.7M	5.3M	1.8M
Pregnancies	575,000	350,000	300,000	1M	500,000
Date of last menstrual period known	yes	estimated	estimated	yes for 60%, estimated for 40%	estimated
Calendar time	1999 onwards	2003 onwards	2003 onwards	1992 onwards	1990 onwards
Setting	administrative database	administrative database	administrative database	GP prescribing	GP prescribing
Medical codes	ICD-10	ICD-9 and ICD-10	ICD-9	Read	Read
Induced terminations of pregnancy	yes if at >12 weeks completed gestation	no	no	yes	yes
Spontaneous abortions	yes if at >12 weeks completed gestation[1]	no	no	yes	yes
% of pregnancies resulting in a pregnancy loss	25%	22%	22%	28%	18%
Congenital malformations	yes	yes	yes	yes	yes
Stillbirths	yes	yes	yes	yes	yes
Data source for drug use info	pharmacy	pharmacy	pharmacy	GP	GP
Outpatient prescribing	yes	yes	yes	yes	yes
Inpatient prescribing	yes	yes	no	some	some
Date of prescription issue	no	no	no	yes	yes

[1] Incomplete recording if occurred between 12 and 16 weeks gestation

Database	***Medical Birth Register & the Norwegian Prescription Database***	***Emilia-Romagna***	***Tuscany***	***GPRD***	***SAIL***
Date of prescription dispensing	yes	yes	yes	no	yes
Low dose folic acid	some	no	no	occasionally	occasionally
High dose folic acid	some	yes	yes	yes	yes
Smoking	yes[2]	yes	no	yes	yes
Alcohol	no	no	no	some	some
Pre-pregnancy BMI	no	no	no	yes	yes
A measure of socioeconomic status	yes	yes	yes	yes	yes
HbA1c	no	no	no	for approx. 20%	for approx. 20%
Historic pregnancy outcomes	yes	yes	yes	yes	yes
Co-morbidity	yes	yes	yes	yes	yes
Verification against charts possible	yes	no	no	yes	no
Questionnaires possible	no	no	no	yes	yes

[2] Only available for pregnant females as information is recorded in the Medical Birth Register

4. Sample size and power considerations

Based on data available thus far we anticipate we will have exposure information on around 30,000 females of childbearing age using isotretinoin from across Europe. Given that the study is descriptive in nature, no power calculation for risk assessment has been carried out.

5. Source population and study populations

5.1 Source population

The source population will be all individuals who have contributed data to one of the five databases, for a minimum time period of 12 consecutive months, between 1 January 2004 and 31 December 2010. Patients within the GPRD who are registered with a GP practice in Wales will be excluded from the study population to avoid duplication of patients captured in the SAIL database.

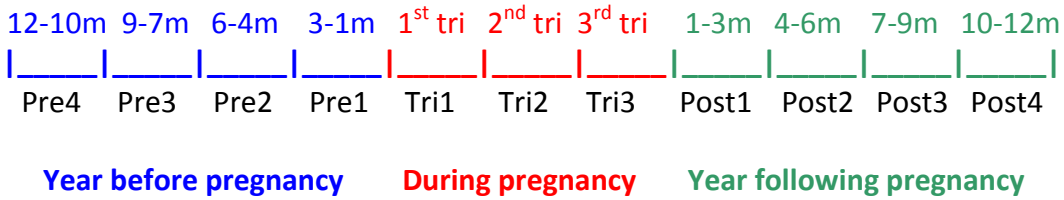
5.2 Study populations

- For the drug utilisation study the study population will be all eligible females who have received ≥1 prescription for an oral isotretinoin product at anytime during the study period.
- For the factors predictive of PPP failure study the study population will be all females of child bearing age (11-50 years) who have received ≥1 prescription for isotretinoin.

6. Exposure definition and measurement

The exposure of interest will be isotretinoin for oral administration (i.e. excluding topical applications) and will be defined as a record for ≥1 prescription (issued/dispensed – depending on the data source) for isotretinoin capsules or tablets recorded in the relevant databases during the time period of interest.

For females who became pregnant we will determine isotretinoin exposure during the year before pregnancy, each of the pregnancy trimesters and the year after pregnancy as outlined below in 3-month time periods.



Exposure during each of the 3-month time periods will be determined by mapping the prescriptions issued to ensure that females who receive a prescription in one time period with a sufficient number of day's supply to run into the next period will be captured. Prescription duration will be calculated based on the number of tablets/capsules dispensed and the prescribed daily dose. Where a female receives a new prescription before the expected end date of a previous prescription the duration of the prescriptions will be concatenated with the assumption made that one prescription cannot start until there has been sufficient time for a previous prescription to have been finished. Where there is insufficient information to determine the prescription duration the mode duration within the study population will be imputed.

In the UK oral isotretinoin can only be prescribed by a specialist and this may result in some prescriptions not being captured in GP records. Preliminary review of a sample of anonymised medical records demonstrated that there are instances where the GP enters the first visit to a dermatology clinic and the issue of an isotretinoin prescription but for subsequent monthly visits the GP only records the dermatology visit and not the issue of a prescription. From this it is not clear whether the patient is receiving further isotretinoin prescriptions or not. To take this into account, dermatology clinic visits that fall under the scenario above will be taken as 'possible isotretinoin prescriptions' and sensitivity analyses will be carried out that include 'possible isotretinoin prescriptions' identified in this manner.

7. Outcome definition and measurement

For the factors predictive of PPP failure component of the study, the main outcome of interest will be evidence of a pregnancy whilst taking oral isotretinoin or in the five weeks following the end of the last oral isotretinoin prescription. Owing to the differences between databases, the methods of pregnancy identification will be country and database specific. A summary of these is provided in Table 2.

For the United Kingdom all types of pregnancy outcome will be identified (live births, stillbirths, spontaneous abortions and induced terminations). In Italy and Norway only pregnancies resulting in a live birth or stillbirth will be captured.

Table 2 Summary of the methods used for pregnancy identification

	Norway	Italy Emilia Romagna	Italy Tuscany	England, Scotland and N. Ireland	Wales
Name of database(s) that pregnancies will be identified from	Norwegian Medical Birth Registry	Certificate of delivery assistance database	Certificate of delivery assistance database	General Practice Research Database	National Community Child Health Database and the Patient Episode Data for Wales
Source of information recorded within the database (e.g. GP records, hospital discharge, Registration of births)	Mandatory notification of all births in Norway and pregnancy losses at >12 weeks gestation	Registration of births that took place in a hospital	Registration of births that took place in a hospital	General Practitioner records from primary care	General practice data and hospital admissions
Method used to determine pregnancy end dates	Date of delivery	Date of delivery	Date of delivery	An algorithm which incorporates all medical codes relating to a pregnancy outcome in a woman's medical record is used to derive the estimated date of delivery / pregnancy loss	Deliveries - Record of the child's week of birth Pregnancy losses – administration date of an ICD-10 pregnancy loss code
Method used to determine pregnancy start dates	Calculated based on the gestational age at birth which is based on ultrasound	Date of LMP reported by the woman - where this is not available it will be estimated from ecographic data or gestational age at delivery	Date of conception or date of LMP reported by the woman - where this is not available it will be estimated from ecographic data	Determined based on the following in order of priority: Estimated date of delivery, date of LMP, records of gestational age / ultrasound, defaulted to 280 days before delivery or 70 days for pregnancy losses	Calculated based on gestational age at delivery where available (81.3%) and defaulted to 280 days before delivery for the remainder. For pregnancy losses the LMP is defaulted to 70 days before the date of pregnancy loss

For all PPP failures identified, we will establish whether they resulted in a spontaneous pregnancy loss, a termination of pregnancy or a delivery and whether they resulted in congenital malformations.

8. Covariate definitions and measurement

Where available, information will be collected on the following

- Age on date of first oral isotretinoin prescription (Rx)
- Likely indication for isotretinoin prescribing – diagnosis of any of the indications listed below in the 12 months straddling the date of the first Rx

Acne
Psoriasis
Ichthyosis
Hidradenitis suppurativa
Xeroderma pigmentosum
Other chronic skin disorders
Neuroblastoma
Other cancer

- Socio-economic status quintile
- Smoking status (non-smoker, smoker, ex-smoker, unknown)
- Alcohol use (teetotal, drinks alcohol, heavy/problem drinker, ex-drinker, unknown)
- BMI (≤19, 20-24, 25-29, 30-34, ≥35, unknown)
- Parity
- Gravidity
- Contraceptive history (record of prescriptions for oral as well as depot contraceptive preparations, emergency contraception, intra uterine devices) where known as well as duration of use
- Fertility – record in medical record of sterilisation or vasectomy of husband
- Frequency of visits to their GP in the 12 months straddling the first isotretinoin prescription
- Frequency of visits to their dermatologist in the 12 months straddling the first isotretinoin prescription

- Diagnosis of depression in the 12 months straddling the first isotretinoin prescription

9. Analysis plan

1. As part of objective 1, the prevalence (with 95% CI) of oral isotretinoin use in women of childbearing age will be calculated separately for each of the five data sources and if appropriate for the two UK data sources combined and two Italian data sources combined.
2. For objective 2, the characteristics of oral isotretinoin users will be described in terms of age, comorbidity, socio-economic status, smoking status, alcohol use, body mass index, parity, gravidity and contraceptive history (oral as well as depot contraceptive preparations, emergency contraception, intra uterine devices, sterilisation, vasectomy of husband) where known as well as duration of use and the frequency of visits to their GP and to their dermatologist.
3. For objective 3, the incidence (with 95% CI) of pregnancy among women of childbearing age using oral isotretinoin will be calculated for the five data sources separately and, if appropriate, for countries combined and all data sources combined.
4. For objective 4, characteristics of oral isotretinoin users who become pregnant will be compared with those who do not in order to identify factors associated with a higher or lower likelihood of pregnancy. Differences in proportions will be tested using X^2 tests, differences in means will be tested using student's t-tests, and predictors of the risk of becoming pregnant in the isotretinoin user population will be identified using logistic regression. Variables will be entered into the stepwise models if they are statistically significant at the level of $p<0.2$ in the univariate analyses and retained in the final model if they are statistically significant at the level of $p<0.05$ or if they result in changes of >10% in the odds ratio of other relevant covariates. We will test for interaction between variables. Stability of the model will be tested using the Hosmer-Lemeshow statistic.

5. For objective 5 the literature review by Crijns *et al.* (2011) on Compliance with pregnancy prevention programmes of isotretinoin in Europe will be updated. The literature will be searched for publications that have been published since 1st January 2009 and will involve using the same search strategy as was reported in the Crijns paper.[1] In Medline this will involve using the Medical Subject Headings (MeSH) 'isotretinoin, pregnancy, Europe' and 'isotretinoin, pregnancy'. In Embase the search will involve the terms 'isotretinoin, pregnancy'. Articles will be restricted to those reporting on oral isotretinoin and isotretinoin use in humans and those published in English, French, German or Dutch. Publications will also be restricted to those that are full studies or case reports. The search will be supplemented with manual analyses of the reference lists in the leading publications and all identified European publications reporting on systemic use of isotretinoin and birth defects.
6. For objective 6, the transcripts of interviews with dermatologists, pharmacists, and females experiencing 'breakthrough pregnancies' will be reviewed and information relating to the main limiting and or facilitating factors associated with the effectiveness of the PPP will be summarised.
7. For objective 7, the transcripts of interviews with females experiencing 'breakthrough pregnancies' will be reviewed to determine attitudes regarding the need for avoiding pregnancy as well as any influence of religious beliefs on any decisions (not) to adhere to the contraceptive advice associated with isotretinoin use.
8. For objective 8, the key findings from the workshop with representatives from dermatology, hospital and community pharmacy, general practice, fertility specialists, teratology information services and female users of childbearing potential will be used to aid the further development of a PPP failure model. We will publish these recommendations for multi-stakeholder European structured consultation on the internet before being modified and finalised.

10. Study limitations

- **Selection bias**

The contributing data sources are population based, however, given that isotretinoin prescribing is accompanied by a PPP it often is prescribed by dermatologists rather than by general practitioners. This will mean that not all prescribing will be captured in automated healthcare databases and may result in an underestimate of exposure frequency as well as the incidence of pregnancy amongst users. Where possible, however, attempts will be made to identify likely isotretinoin prescribing (e.g. where the female has a record of an oral isotretinoin prescription on the same date as a visit to a dermatologist and then monthly repeat visits to the dermatologist with no record of a prescription). Sensitivity analyses will be carried out that include 'possible isotretinoin' prescriptions identified in this manner.

- **Information bias**

Information on some of the covariates of interest (e.g. smoking status, alcohol intake) will not be recorded for some patients, however, this is likely to be missing at random and therefore is not thought to have a large impact on the risk estimates for predictors of 'breakthrough pregnancy'.

Pregnancies that result in an early loss, before the pregnancy was clinically recognised, will not be captured by any of the databases.

- **Confounders**

None anticipated

- **Effect modifiers**

The extent to which PPP failure occurs may differ by country and the recording of pregnancies and pregnancy losses also varies by country. We therefore intend to only combine study results from the different data sources where appropriate as demonstrated by the data. This will result in stratified analyses by country which

should account for any effect modification. We do not anticipate any other effect modifiers.

- **Other limitations**

The database analyses will be based on the issue or dispensing of a prescription and it will not be possible to know whether the product was actually consumed or the exact dates which it was taken.

It will not be possible to identify pregnancies that result in a termination of pregnancy in the Italian data sources. We are confident, however, that pregnancies have been identified appropriately and the algorithms have been verified against external sources. The identification of pregnancy losses on the GPRD has been verified and found to be accurate for 95% of pregnancy losses identified. Specificity of pregnancy loss is expected to be not as high.

The views of females who are identified via the Teratology Information Service as having a 'breakthrough pregnancy' may not be representative of all women who experience a pregnancy whilst exposed to isotretinoin. The Teratology Information Service is, however, the most pragmatic method of identifying these women and the information will be informative even if it cannot be generalised to the entire population of women who become pregnant whilst taking isotretinoin.

11. Ethical issues

Ethical approval will be sought in each of the participating countries. In all aspects of the study steps will be taken to ensure that all participating individuals remain anonymous and cannot be identified. Pregnancy loss is not captured in Italy for ethical reasons. In the GPRD, SAIL and the Norwegian Medical Birth Register it will be captured but data will be presented in an aggregated format to ensure study participants cannot be identified from the study publications. This will be the same for reporting information on congenital malformations.

From the data sources there is no information on the identity of prescribers and we will ensure the opinions of all interview participants and those involved in the consultation workshop remain anonymous. We do not envisage any other ethical concerns associated with this study.

12. Data storage

All data will be anonymised and stored on secure servers with restricted access and in accordance with national and European data protection legislation. Data and all log files will be will be available for audit purposes. Raw data will remain with the local providers; output files and any other data collected as well as interview and workshop transcripts will be stored on a secure server at the University of Bath in the research environment for epidemiology in the following directory: \Projects\EMA isotretinoin and will be available for audit and data sharing on site.

13. Quality assurance

Code identification for drug and medical codes will be undertaken by two people independently. Discrepancies will be identified and agreement will be reached by consensus. Where this is difficult, expert opinion will be consulted. Clinicians and pharmacists will be involved in this process to ensure all correct codes have been identified.

Where pragmatically feasible, double-programming will be undertaken by two people independently. Where this is not feasible, one person will identify the study population using a computer algorithm, the underlying principles of which will have been designed and agreed upon by at least two people. A person other than the person who wrote the extraction program will assess the code used for the extraction procedure.

14. Plans for disseminating and communicating study results

The results of the study will be written up and shared with the European Medicines Agency. They will also be submitted for publication in peer reviewed journals and

submitted for presentation at the annual conference of the International Society for Pharmacoepidemiology.

15. Study timelines

The Gantt chart below illustrates the proposed work schedule

		Months after start of project																
Task	**Task Summary**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
1	Protocols agreed and submitted to EMA																		
2	Protocols submitted for ethics, IRB, ENCePP																		
3	Data generated at all centres																		
4	Central data cleaning and verification																		
5	Central analysis																		
6	Interview women with 'breakthrough pregnancies'																		
7	Write report on user characteristics																		
8	Write report on risk factors																		
9	Write final report on database studies for EMA																		
10	Write manuscript on database studies																		
11	Update literature review by Crijns *et al.*																		
12	Workshop with stakeholders																		
13	Structured consultation of recommendations																		
14	Assimilate information from above tasks																		
15	Write manuscript with final recommendations																		

16. Amendments and deviations

Any amendments or deviations from the protocol will be documented here.

17. References

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