PASS information

Title	Study of utilisation of combined hormonal contraceptives in Europe
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Marketing authorisation holder(s)	Not applicable
Joint PASS	No

Research question and objectives	Was there a change in CHC prescribing patterns between the periods January 2012 – January 2014 and February 2014 – December 2015 and, if so, was there a subsequent change in the incidence rate of VTE? **Objectives** 1. To investigate trends in new user (initiators) prescribing patterns in the two years preceding the relevant Commission Decision (January 2012 – January 2014) and in a similar period following the decision (February 2014– December 2015). 2. To investigate switching patterns between products among prevalent users including reasons for changes (e.g., reimbursement or regulatory and clinical guidance). 3. Within Objectives 1 and 2, to examine any changes in utilisation in groups defined by patient's clinical and demographic risk factors for VTE as detailed in the warnings and contraindications in the European Union Summary of Product Characteristics (SmPC). 4. To examine any differences in the incidence rates of VTE between the two periods specified and, in light of the results for Objective 1-3, to investigate any measurable association between the observed changes in CHC use and changes in the VTE incidence rates.
Country(-ies) of study	The Netherlands, Denmark, United Kingdom
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Contents

1. Marketing authorisation holder(s)

Marketing authorisation holder(s)	Not applicable
MAH contact person	Not applicable

2. List of abbreviations

CHC	Combined hormonal contraceptives
VTE	Venous thromboembolism
EMA	European Medicines Agency
WP	Work Packages
SFK	Dutch Foundation for Pharmaceutical Statistics
CBS	Central Bureau of Statistics
DOAC	Direct oral anticoagulant
THIN	The Health Improvement Network
BMI	Body mass index

3. Responsible parties

Name	Role	Tasks
Dr Astrid van Hylckama Vlieg	Lead academic	Protocol development, oversee the management of the project, directly supervise the Dutch researcher, ensure correct ethics and governance consents, oversee supervision of researchers located outside of The Netherlands, ensure timely dissemination in relation to reports and publications
Ms D. Khialani	PhD student	Under the supervision of the lead researcher; provide the template and conduct the Analysis of WP1 and WP4.
Dr Anne Staub Rasmussen	MD, PhD-student, epidemiologist	Denmark projects (WP2 and 5)
TBA	A statistician at MSc or PhD level from the staff of the Department of Clinical Epidemiology	Data requests Data linkage, management, coding, analysis
Dr Vera Ehrenstein	Lead contact for the consortium, supervise Danish analyses	Overall communication, oversee the budget
Dr Irene Petersen	PhD, Reader in Epidemiology and Statistics	Oversee the conduct of the UK projects (WP3 and 6), write protocol for scientific review, by data providers
TBA	Statistician/ Epidemiologist	Under the supervision of IP; provide the template and conduct the Analysis of WP3 and WP6

4. Abstract

Title

Study of utilisation of combined hormonal contraceptives in Europe

Version 1.1

drs. Deeksha Khialani, Department of Clinical Epidemiology, Leiden University Medical Center (LUMC), Netherlands

Rationale and background:

Many studies have shown that combined hormonal contraceptive (CHC) use is associated with an increased risk of venous thromboembolism (VTE). A review in 2013 by the European Medicines Agency (EMA) showed that the risk varies by the type of progesterone in the CHC (see table below). After the publication of the review by the EMA, the European Commission adopted, on 16 January 2014, a legally binding decision to update the product information of all CHC throughout the European Union. This information included information to patients: awareness of factors that increase the risk of VTE and information to health care professionals: the type of CHC with the lowest VTE risk (levonorgestrel, norethisterone, or norgestimate)(1).
It is unknown whether the publication of the review has led to a change in prescribing patterns and a subsequent change in the incidence of VTE. Therefore, we want to investigate the CHC prescribing patterns among women in three European Union Member states (the Netherlands, Denmark and the United Kingdom) in a time period including the completion of the 2013 review and implementation of the resulting recommendations and to estimate any changes in the incidence of VTE between the two periods specified.

Risk of developing a blood clot (VTE) in a year	
Women **not using** a combined hormonal pill/patch/ring and are not pregnant	About 2 out of 10,000 women
Women using a CHC containing **levonorgestrel, norethisterone or norgestimate**	About 5-7 out of 10,000 women
Women using a CHC containing **etonogestrel or norelgestromin**	About 6-12 out of 10,000 women
Women using a CHC containing **drospirenone, gestodene or desogestrel**	About 9-12 out of 10,000 women
Women using a CHC containing **chlormadinone, dienogest or nomegestrol**	Not yet known[1]

[1] Further studies are ongoing or planned to collect sufficient data to estimate the risk for these products.

Research question

Was there a change in CHC prescribing patterns between the periods January 2012 – January 2014 and February 2014 – December 2015 and, if so, was there a subsequent change in the incidence rate of VTE?

Objectives

1. To investigate trends in new user (initiators) prescribing patterns in the two years preceding the relevant Commission Decision (January 2012 – January 2014) and in a similar period following the decision (February 2014 – December 2015).

2. To investigate switching patterns between products among prevalent users including reasons for changes (e.g., reimbursement or regulatory and clinical guidance).

3. Within Objectives 1 and 2, to examine any changes in utilisation in groups defined by patient's clinical and demographic risk factors for VTE as detailed in the warnings and contraindications in the European Union Summary of Product Characteristics (SmPC)(2).

4. To examine any differences in the incidence rates of VTE between the two periods

specified and, in light of the results for Objective 1-3, to investigate any measurable association between the observed changes in CHC use and changes in the VTE incidence rates.

Study design:

Using data retrieved from electronic health records (see below: Data sources) from three European Union member states, i.e. the Netherlands, Denmark, and United Kingdom, we will adress the study objectives in

1. A drug utilization study into prescribing patterns including new use of CHCs and calender-period specific changes in switching of CHCs
2. A cohort study for incidences of VTE

Population, Variables and Data sources:

For the Dutch drug utilization study and cohort study, we will make use of de-identified data obtained through The Dutch Foundation for Pharmaceutical Statistics (SFK), which gathers its data from >95% of community pharmacies in the Netherlands (https://www.sfk.nl/english). All women between the ages of 18-49 years with at least one prescription of combined oral contraceptive use in the period from January 2012 through December 2015 will be included, i.e., both new users as well as prevalent users. New users are defined as women who do not have a prescription of CHC in the two years before starting. We will also obtain information on prevalent users of CHC and thereby we can assess all individual changes (switches) in CHC. Prevalent users of CHC are defined as women who used at least one cycle of CHC. Age at initiation and 4 digit postcodes is also available in the SFK database which allows further characterization of CHC users by age and socioeconomic status. The latter information will be retrieved by using information from the Central Bureau of Statistics (CBS), the Netherlands, which keeps record of socioeconomic status by use of 4-digit postcodes. Although SFK does not indicate if women had venous thrombotic disease for which they need to receive anticoagulant treatment, it can be approximated by the first dose of oral anticoagulant (direct oral anticoagulant (DOAC)) or duration of anticoagulant (vitamin K antagonist), which is specific for VTE.

For the Danish drug utilization and cohort study, data will be linked from the following databases: The Danish Civil Registration System (contains data on age, sex, vital status and migration), the Danish National Prescription Registry (outpatient dispenations of CHC and other

medications), and data on income and education at Statistics Denmark. Women between the ages 18-49 years in the period January 2012- December 2015 will be included, i.e. both new and prevalent users.

For the UK drug utilization and cohort study, we will make use of anonymised primary care data. In the period January 2012- December 2015, women between the ages 18-49 years who have been registered for at least two years prior with one of the general practices that contributed data to The Health Improvement Network (THIN) primary care database will be included. New and prevalent users will be identified. In addition, information is available on social deprivation, body mass index (BMI) and smoking status which can be used to stratify patients on the risk of VTE.

Study size:

In 2014, approximately 1.4 million women between 15-50 years used oral contraceptives in the Netherlands, of whom ~1.3 million are registered in the SFK. In women between 15-25 years, the majority of oral contraceptive users will be starters (the new users in our study will include these starters as well as women who have used CHC in the past, but not in the previous two years). Data from the CBS indicated, that in 2014, there were 1 011 127 women between 15-25 years, of whom ~59% were using oral contraceptives (n=596 565). From unpublished data from the department of Clinical Epidemiology, Leiden University, we estimate that in 2-year period, approximately 16% of premenopausal women switch from one oral contraceptive agent to another. With 1.3 million oral contraceptive users, this indicates ~212 000 switches per 2-year period.

As mentioned above, the number of women between 15-25 years using CHCs in 2014 is 596 565. This number will vary in the other years of the study period. From literature it is known that the risk of VTE is increased 8-fold among starters in the first year of use (in the first three months, the risk is increased 13x) (3). However, this risk differs for the different types of CHCs. Also the proportion of each generation of CHC will differ in each observation window. Therefore, it is difficult to estimate the number of cases of VTE in new users of CHC in the study period January 2012- December 2015.

In Denmark, annually more than 330 000 women receive CHC (https://laegemiddelstyrelsen.dk/da/udgivelser/2016/~/media/CD29697BD25C4642968D9386979472A9.ashx; http://medstat.dk/). The annual incidence rate of VTE is about 4 per 10 000 for women of reproductive age not using oral contraceptives. Thus, a conservative estimate for 4 years of follow-up assuming the size of the study population of 300 000, is at least 480 cases of

VTE (4).

A previous UK primary care database study estimated the crude incidence rate of VTE cases per 10 000 women years was 5.9 (95% confidence interval 5.7-6.0) in CPRD and 6.1 (6.0- 6.3) in QResearch (5). In UK around 28% use oral contraceptives and CHC form a substantial proportion of these.

Data analysis:

In order to assess the effects of the review on initiation (new use) as well as on switching of treatment (between January 2012- January 2014 and between February 2014- December 2015), we will perform segmented regression analyses.

For the Dutch part of study, we will calculate the incidence of VTE among the new users of CHC within each calendar window (January 2012- January 2014 and February 2014- December 2015). From segmented regression analysis, we will obtain information on a potential change in the proportion of different types of oral contraceptives in new users separately and grouped according to generation of CHC after the European commission decision (January 2014). Since we have information about the prescription patterns among new users, we can assess whether the changes observed in the proportions of use of each generation is associated with changes in the incidence rate of VTE in women initiating oral contraceptive use. Furthermore, we will study the changes in the incidence of VTE within users of different types (and generations) of CHCs. A change in this incidence over time, may indicate that certain preparations are prescribed to low/high risk individuals. We will stratify analyses on age and socioeconomic status (risk factors of VTE) of the women.

For the Danish and UK part of the study, estimates on the incidence of VTE will be calculated. Overall estimates as well as estimates stratified by risk factors such as age, socio-economic status, BMI (UK only), smoking status (UK only) will be provided. For the Danish and UK data we will compare the age-standardised incidence rates of VTE against the age standardised initiations of oral contraceptives in order to evaluate whether overall changes in CHC use is associated with overall changes in incidence of VTE.

Milestones:

Task	Month
Data extraction and analysis	10
Writing study results for the EMA	3
Writing manuscript for submission to peer-reviewed journal	3

5. Amendments and updates

None

6. Milestones

Milestone	Planned date
Start of data collection (extraction)	31-03-2017
End of data collection (extraction)	31-12-2017
Final report of study results	01-05-2018
Delivery of manuscript	01-05-2018

7. Rationale and background

Venous thromboembolism (VTE) in young women is rare, with an annual incidence of approximately 2-5 per 10 000 women (6). An increased risk of VTE associated with oral contraceptive use has long been established and while the absolute risk of VTE in young women is low, the fact that millions of women worldwide are using oral contraceptives indicates that these preparations are responsible for a large number of cases of VTE

(3, 7-11). Several large studies including a review in 2013 by the European Medicines Agency (EMA) concluded that the risk of VTE associated with hormonal contraceptive preparations which contained gestodene, desogestrel, or drospirenone was increased compared with hormonal contraceptive preparations containing levonorgestrel (1, 5, 12, 13).

After the publication of the review by the EMA, the European Commission adopted on 16 2014, a legally binding decision to update the product information of all combined hormonal contraceptives (CHC) throughout the European Union. This included information to patients: awareness of factors that increase the risk of VTE and information to health care professionals: the type of CHC with the lowest VTE risk (levonorgestrel, norethisterone, or norgestimate) and the fact that CHC are contraindicated in the presence of one serious or multiple risk factors for VTE. It is currently unknown whether the publication of this review led to a change in prescription patterns and a subsequent change in the incidence of VTE in young women.

The aim of this study is therefore to investigate the CHC utilisation and prescribing patterns in a sample of Three European Union Member states (Denmark, United Kingdom, and the Netherlands) in a time period including the completion of the 2013 review and implementation of the resulting recommendations and to estimate any changes in the incidence of VTE between the two periods specified.

This study will provide evidence regarding the necessity of the recommendation to use safer oral contraceptive preparations, as it will show whether the implementation of the recommendation was successful and whether it actually affected the incidence of VTE in the target population.

8. Research question and objectives

Was there a change in CHC prescribing patterns between the periods January 2012 – January 2014 and February 2014 – December 2015 and, if so, was there a subsequent change in the incidence rate of VTE?

1. To investigate trends in new user (initiators) prescribing patterns in the two years preceding the relevant Commission Decision (January 2012 – January 2014) and in a similar period following the decision (February 2014– December 2015).
2. To investigate switching patterns between products among prevalent users including reasons for changes (e.g., reimbursement or regulatory and clinical guidance).
3. Within Objectives 1 and 2, to examine any changes in utilisation in groups defined by patient's clinical and demographic risk factors for VTE as detailed in the warnings and contraindications in the European Union Summary of Product Characteristics (SmPC).
4. To examine any differences in the incidence rates of VTE between the two periods specified and, in light of the results for Objective 1-3, to investigate any measurable association between the observed changes in CHC use and changes in the VTE incidence rates.

9. Research methods

9.1 Study design

Drug utilisation study and epidemiological cohort study using data retrieved from electronic health records from three EU member states, i.e., the Netherlands, Denmark, and the United Kingdom. The study will comprise of seven work packages (WP).

WP1 The Netherlands. Drug utilisation study into prescribing patterns including new use as well as switching between products in the periods before and after implementation of the decision of the European Commission, i.e. January 2012 to January 2014 and February 2014 to December 2015 by using de-identified data obtained through The Dutch Foundation for Pharmaceutical Statistics (SFK), which gathers its data from >95% of community pharmacies in the Netherlands (https://www.sfk.nl/english). The drug utilization study described in this WP is descriptive in nature. The outcome will be the number and proportion of women (within each calendar window) initiating different types of oral contraceptives or per switching pattern.

WP2 Denmark. Drug utilisation study into prescribing patterns including new use as well as switching between products in the periods before and after implementation of the decision of the European Commission, i.e. January 2012 to January 2014 and February 2014 to December 2015 by linking data from the following databases: The Danish Civil Registration System (14) (personal identifier, migrations, vital status); and the Danish National Prescription Registry (15) (outpatient dispensations, including date, ATC code, defined daily dose, amount dispensed).

WP3 United Kingdom. Drug utilisation study into prescribing patterns including new use as well as switching between products in the periods before and after implementation of the decision of the European Commission, i.e. January 2012 to January 2014 and February 2014 to December 2015 by using anonymised prescribing data from UK primary care which can be linked to the British National formulary and also to ATC codes.

WP4 The Netherlands. For the calculation of the incidence rate of VTE between the two periods specified, i.e, January 2012 to January 2014 and February 2014 to December 2015, we will analyse new users of CHCs (within each calender window) and assess whether they will develop VTE within one year of CHC initiation. From the analysis of WP1, we will obtain information on a potential change in the proportion of initiators of each generation of CHC between January 2012-January 2014 and February 2014- December 2015. Since we have information about the prescription patterns among new users, we can assess whether the changes observed in the proportions of each generation is associated with changes in the incidence rate of VTE in women initiating oral contraceptive use. Furthermore, we can study the changes in the incidence of VTE within users of different types (and generations) of oral contraceptives. A change in this incidence over time, may indicate that certain preparations are prescribed to low/high risk individuals. Because we have information about the age and socioeconomic status (risk factors of VTE) of these women, we can stratify analyses on these factors.

WP5 Denmark. Incidence rate of VTE will be estimated from the routinely recorded data based on validated algorithms. VTE will be measured using discharge diagnoses recorded in the Danish National Patient Registry.

WP6 United Kingdom. Incidence rates of VTE will be estimated from the routinely recorded data. VTE will be measured by using diagnoses entered into the electronic primary care records by Read codes. It is a hierarchical classification system, linked to the International Classification of Diseases (ICD 10), but more comprehensive.

WP7 Combining findings from WP1-6 to report on trends in oral contraceptive use in the periods before and after the publication of the 2013 EMA review, i.e., January 2012 – January 2014 and February 2014 – December 2015, and the associated changes in the incidence of VTE in the two periods. These results will be combined in the final report for the EMA and in the manuscript for submission for publication.

9.2 Data collection and analysis

WP1

Objectives

To obtain the number and proportion of women (within each calendar window) initiating different types of oral contraceptives or per switching pattern using data from the SFK.

Methods

Study population

For the Dutch drug utilization study, we will make use of de-identified data obtained through The SFK, which gathers its data from >95% of community pharmacies in the Netherlands (https://www.sfk.nl/english). All women who had one or more prescription of CHC in the period from January 2012 through December 2015 will be included, i.e., both new users as well as prevalent users. Age at initiation and 4 digit postcodes is also available in the SFK database which allows further characterization of CHC users by age and socioeconomic status. The latter information will be retrieved by using information from the Central Bureau of Statistics (CBS), the Netherlands, which keeps record of socioeconomic status by use of 4-digit postcodes. Although SFK does not indicate if women had venous thrombotic disease for which they need to receive anticoagulant treatment, it can be approximated by the first dose of oral anticoagulant (direct oral anticoagulant (DOAC)) or duration of anticoagulant (vitamin K antagonist), which is specific for VTE.

Per calendar year of the study period (1 January 2012 to 31 December 2015), we will identify new users of CHC use. New users will be defined as women between the ages of 18 to 49 years old who do not have a prior prescription of CHC in the two years before.

Furthermore, we will obtain information on prevalent users of CHC and thereby we can assess all individual changes (switches) in CHC in the study period (1 January 2012 to 31 December 2015). Prevalent users of CHC are defined as women who used at least one cycle of oral contraceptives.

Oral contraceptives

We will consider CHCs. According to the EMA review, the CHCs which contain levonorgestrel, norgestimate and norethisterone show the lowest risk of VTE (1). Therefore, additional to the analysis of individual types of combined oral contraceptives, in our analysis, we will group CHC

together according to generation (i.e., the ‘second’ generation containing levonorgestrel, norgestimate and norethisterone; third generation containing gestodene, desogestrel; and the newer generations containing drospirenone, norelgestromin and cyproterone acetate).

Analysis

For each calendar year, we provide estimates of the number and proportion of new users of each oral contraceptive type and the number and proportion of switchers (from one type to another or to a different dose) overall and stratified by age at initiation of oral contraceptives (18-24, 25-29, 30-34, 35-39, 40-44 and 45-49 years) and socioeconomic status.
In order to assess the effects of the review on initiation as well as on switching of treatment (between January 2012- January 2014 and between February 2014- December 2015), we will perform segmented regression analysis (16).

For our analysis we will use SPSS for Windows, release 23.0.

WP2

Objectives

To obtain the number and proportion of women (within each calendar window) initiating different types of oral contraceptives or per switching pattern using data from the Danish Civil Registration System and the Danish National Prescription Registry.

Methods

Study population

For the Danish drug utilization study, we will obtain information on use of oral contraceptives from the Danish National Prescription Registry, demographic information (age, sex, vital status and migration) from the Danish Civil Registration System and data on income and education at Statistics Denmark in the study period (1 January 2012 to 31 December 2015). Women with no oral contraceptives prescription prior to study start date (from 2010 onwards) will be followed up until they receive their first oral contraceptive dispensation, become 50 years of age, 31 December 2015, or they emigrate or die. The new users are defined as women with no prior prescription of CHC in the two years before.

To investigate switching patterns among prevalent users, individuals will be defined as prevalent users if they had at least one dispensation for an oral contraceptive between 1 July 2011 and 1 August 2015. Prevalent users will be followed from the date of the study start/entry until switch of treatment (defined as prescription of a new type of CHC before expiration of the days supplied of the previous drug), becoming 50 years of age, December 31st 2015, death or emigration, whichever comes first.

Oral contraceptives

We will consider each CHC individually and, additional to the analysis of individual types of combined oral contraceptives, in our analysis, we will group CHC together according to generation (i.e., the second generation containing levonorgestrel/norgestimate and ethinylestradiol, the third generation containing gestodene/desogestrel and ethinylestradiol and the newer generations containing drospirenone and ethinylestradiol).

Analysis

For each calendar year, we provide estimates of the proportion of each oral contraceptive type and the number of switchers (from one type to another or to a different pill strength) overall and stratified by age at initiation of CHC (18-24, 25-29, 30-34, 35-39, 40-44 and 45-49 years).
We will stimate incidence rates of initiating CHC use per 1000 person years at risk including 95% confidence intervals for each calendar year using incident dispensation as the indicator if CHC initiation. Similarly, we will provide estimates of incidence rates of switching per 1000 person years at risk including 95% confidence intervals for each calendar year of the study period.
In order to assess the effects of the review on initiation as well as on switching of treatment (between January 2012- January 2014 and between February 2014- December 2015), we will perform segmented regression analysis, taking the two time periods into account.

For our analyses we will be using SAS version 9.2 or higher.

WP3

Objectives

To obtain the number and proportion of women initiating different types of oral contraceptives in UK between January 2012 to December 2015 and to investigate switching pattern using data from The Health Improvement Network (THIN) primary care database.

Methods

Study population

For the UK drug utilization study, we will make use of anonymised primary care data from when women consult their general practice to obtain oral contraceptives. For each calendar year of the study period (1 January 2012 to 31 December 2015) we will identify women who were between 18 and 49 years and have been registered for at least two years prior with one of the general practices that contributed data to THIN. Individuals with no oral contraceptives prescription prior to study entry (from 2010 onwards) will be followed up until they receive their first oral contraceptive prescription, they become 50 years of age, 31 December 2015, or leave the practice . The new users are defined as women with no prior prescription of CHC in the two years before.

To investigate switching patterns among prevalent users, individuals will be defined as prevalent users if they had at least one prescription of oral contraceptives between 1 July 2011 and 1 August 2015. Prevalent users will be followed until switch of treatment, six months after last prescription, becoming 50 years of age, December 31st 2015, leave the practiceor death, whichever comes first.

Oral contraceptives

We will consider each CHC individually and, additional to the analysis of individual types of combined oral contraceptives, in our analysis, we will group CHC together according to generation (i.e., the second generation containing levonorgestrel/norgestimate and ethinylestradiol, the third generation containing gestodene/desogestrel and ethinylestradiol and the newer generations containing drospirenone and ethinylestradiol).

Analysis

For each calendar year, we provide estimates of the number of initiators of each oral contraceptive type and the number of switchers (from one type to another or to a different dose) overall and stratified by age at initiation of CHC (18-24, 25-29, 30-34, 35-39, 40-44 and 45-49 years), social deprivation (Quintiles of Townsend Deprivation scores), body mass index (BMI) and smoking status.

We will tabulate the estimates of new users by 1000 person years at risk including 95% confidence intervals for each calendar year. Similarly, we will provide estimates of switchers by 1000 person years at risk including 95% confidence intervals for each calendar year of the study period.

In order to assess the effects of the review on initiation as well as on switching of treatment (between January 2012- January 2014 and between February 2014- December 2015), we will perform segmented regression analysis.

For our analyses we will be using Stata version 14 or higher.

WP4

Objectives

To assess changes in the incidence rate of VTE among women using CHCs of reproductive age in the Netherlands between January 2012- January 2014 and February 2014- December 2015 and to investigate any measurable association between these changes and the observed changes in CHC use.

Methods

Study population

Medication use in the SFK database will be used to approximate the occurrence of VTE by using the first dose of oral anticoagulant, which, in case of DOAC use is specific for VTE or the duration of treatment with Vitamin K antagonists. Incidence of VTE is calculated by following the new users of CHC within each calendar window until they experience a VTE, or up to one year.
We will calculate the incidence among the new users of oral contraceptives in general and per type of oral contraceptive (different types and grouped by generation (second, third and newer generations)).

Analysis

We will tabulate the estimates of the annual incidence of VTE including 95% confidence intervals for each calender window of the study period.
From segmented regression analysis (WP1), we will obtain information on a potential change in the proportion of initiators of each generation of CHC between January 2012-January 2014 and February 2014- December 2015. Since we have information about the prescription patterns among new users, we can assess whether the changes observed in the proportions of each generation is associated with changes in the incidence rate of VTE in women initiating oral contraceptive use.
Furthermore, we can study the changes in the incidence of VTE within users of different types (and generations) of oral contraceptives. A change in this incidence over time, may indicate that certain preparations are prescribed to low/high risk individuals.
Because we have information about the age and socioeconomic status (risk factors of VTE) of these women, we can stratify analyses on these factors.

For our analysis we will use SPSS for Windows, release 23.0.

WP5

Objectives

To assess changes in the incidence rates of VTE among women of reproductive age overall and by CHC-initiation/switching in Denmark between January 2012-January 2014 and February 2014-December 2015.

Study population

For each calendar year of the study period (1 January 2012 to 31 December 2015) we will identify women who were between 18 and 49 years old. Individuals with no previous record of VTE prior to study entry (from 2002 onwards) will be followed until they are recorded with a VTE, become 50 years of age, 31st of December 2015 or they migrate.

Analysis

We will estimate the incidence rates of VTE by 10 000 person years at risk in CHC-initiators/switchers before and after the EMA recommendation, including 95% confidence intervals for each calendar year of the study period. We provide overall estimates as well as estimates stratified by age at CHC initiation in oral contraceptive initiators.
For each observation window period (January 2012- January 2014 and between February 2014-December 2015) we will compare the age-standardised incidence rates of VTE against the age standardized VTE incidence rates among initiatiators/switchers of oral contraceptives in order to evaluate whether overall changes in CHC use is associated with overall changes in incidence of VTE.

Analyses will be performed using SAS version 9.2 or higher.

WP6

Objectives

To assess the incidence rate of VTE among women of reproductive age overall and by initated CHC in United Kingdom between January 2012- December 2015.

Study population

For the estimate of incidence of VTE in CHC users in UK we will make use of anonymized primary care data. For each calendar year of the study period (1 January 2012 to 31 December 2015) we will identify women who were between 18 and 49 years and have been registered for at least two years prior with one of the general practices that contributed data to THIN. Individuals initiated on CHC with no previous record of VTE prior to study entry (from 2002 onwards) will be followed up until they have their first record of VTE, they become 50 years of age, 31 December 2015 or they de-register with the general practice, which ever comes first.

Analysis

We will tabulate the estimates of incident VTE by 10 000 person years at risk including 95% confidence intervals for each calendar year of the study period among women using CHCs of reproductive age in UK. We provide overall estimates as well as estimates stratified by age, social deprivation (Quintiles of Townsend Deprivation scores), BMI and smoking status.
For each observation window period (January 2012- January 2014 and between February 2014- December 2015) we will calculate the incidence among the new users of oral contraceptives in general and per type of oral contraceptive (different types and grouped by generation (second, third and newer generations)).

From segmented regression analysis (WP3), we will obtain information on a potential change in the proportion of initiators of each generation of CHC between January 2012-January 2014 and February 2014- December 2015. Since we have information about the prescription patterns among new users, we can assess whether the changes observed in the proportions of each generation is associated with changes in the incidence rate of VTE in women initiating oral contraceptive use.
Furthermore, we can study the changes in the incidence of VTE within users of different types

(and generations) of oral contraceptives. A change in this incidence over time, may indicate that certain preparations are prescribed to low/high risk individuals.

Analysis will performed using Stata version 14 or higher.

WP7

Outline for the study report

The study report will combine the findings from all 6 work packages. Data from three countries will be used to report on the trends in first ever user prescribing in the two years preceding the relevant Commission Decision January 2012 – January 2014 and the period following the decision February 2014 – December 2015 . Furthermore, using different research strategies, we will report on the changes in the incidences of VTE in the different observation windows, separately for each country. The report will provide evidence regarding the necessity of the recommendation to use safer oral contraceptive preparations as it will show whether the implementation of the recommendation was successful and whether it actually affected the incidence of VTE in the target population.

9.3 Data management

Each institution will ensure the necessary compliance with local data protection, storage and archiving, and patient privacy laws and regulations and will obtain all permission necessary to conduct this study. In the Netherlands, completely anonymised data will be obtained from the Dutch Foundation for Pharmaceutical Statistics (SFK) for which no separate ethical approval is necessary.
In Denmark no ethical approval is needed since the study is purely registry based. Permission from our Data Protection Agency will be obtained.

9.4 Quality control

The drafts of the study plan and protocol and final versions will be overseen by the lead researcher. There will be administrative support to ensure smooth running of the project and five steering group meetings, roughly spaced throughout the project.
The lead researcher is experienced in supervising as well as experienced in the proposed

methodology, specific methods and topic of decision making. The wider consortium have previously worked together successfully on tenders for the EMA.

9.5 Limitations of the research methods

Women in the SFK who receive an anticoagulant treatment (DOAC or VKA) are women who survived a thrombosis. Women who died (with a worse prognosis) will not have a treatment prescription and are therefore not identified as cases in this study.
Because we are relying on the anticoagulant treatment as a proxy for women having a VTE, the cases are not confirmed cases, since the real diagnostic criteria for Deep vein Thrombosis (Doppler ultrasonography) and Pulmonary Embolism (ventilation perfusion lung scan, spiral computed tomography, or angiogram) is not assessed.
In Denmark all executed prescriptions are registered in the Danish National Prescription Registry. Combined oral contraceptives are prescription medications and the registration is an automated process, so the data validity is considered high. Regarding VTE occurance data is obtained from the National Registry of Patients. This registry is automatically updated with all diagnosis codes from Danish Hospital contacts, so as for the Netherlands VTEs that might miss in this project are those with fatal disease that do not attend hospital.

10. Protection of human subjects

No ethical approval is needed.

11. Plans for disseminating and communicating study results

Results from WP1-6 will be combined for the final report for the EMA and in the manuscript for submission for publication in an academic journal.
The abstract of the paper can be submitted for conferences.

12. References

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Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

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

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

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

Study title: Study of utilization of combined hormonal contraceptives in Europe

Study reference number: EMA/49122/2016

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6.milestones
1.1.2 End of data collection[2]	☒	☐	☐	6.milestones
1.1.3 Study progress report(s)	☐	☒	☐	
1.1.4 Interim progress report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS register	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	6.milestones

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

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	4
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	7
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.2 (methods per WP)
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.2 (WP 1-3)
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	9.2 (WP 4-6)
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Ad 3.5 We will make use of existing data registries

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2 (study pop. per WP)
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9.2
4.2.2 Age and sex?	☒	☐	☐	9.2
4.2.3 Country of origin?	☒	☐	☐	9.2

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.4 Disease/indication?	☒	☐	☐	9.2
4.2.5 Duration of follow-up?	☒	☐	☐	9.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.2 (analysis per WP)
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	Page 9 (population)
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.2

Comments:

Ad 5.2 exposure is registered in existing databases

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.2 (specified per WP)
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.2 (analysis per WP)
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.2 (stratification)
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:	☐	☐	☐	
7.2.1. Selection biases (e.g. healthy user bias)	☐	☐	☒	
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.5
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	9.5

Comments:

Ad 7.1 This is a descriptive analysis

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

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.2 (per WP)
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.2 (per WP)
9.1.3 Covariates?	☒	☐	☐	9.2 (per WP)
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☒	☐	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☒	☐	
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.2 (per WP)
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.1

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.3 Covariates?	☒	☐	☐	9.2 (per WP)
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.2 (per WP)
10.2 Are descriptive analyses included?	☒	☐	☐	9.2 (per WP)
10.3 Are stratified analyses included?	☒	☐	☐	9.2 (per WP)
10.4 Does the plan describe methods for adjusting for confounding?	☐	☒	☐	
10.5 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	Page 10 (study size)

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	
11.2 Are methods of quality assurance described?	☒	☐	☐	9.4
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	
12.1.2 Information bias?	☐	☐	☒	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☒	☐	

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	Page 10

Comments:

This study uses large pharmacy databases, civil registration systems, and primary care data.

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9.3

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	11
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11

Comments:

Name of the main author of the protocol: Astrid van Hylckama Vlieg

Date: 09/10/2017

Signature: