PASS information

Title	Study of regulatory communication and risk awareness following the Article 31 referral of Combined Hormonal Contraceptives in relation to thromboembolism
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Joint PASS	No

Research question and objectives	Do women and prescribers consider the risks of venous thromboembolism when making decisions about the use of combined hormonal contraceptives and what sources of information inform their assessments? **Objectives** 1. To consider the extent to which women and health professionals are aware of the risks of venous thromboembolism (VTE) in users of combined hormonal contraceptives (CHC) 2. To document awareness, knowledge, attitudes and practices related to recommendations from regulatory authorities 3. To understand how advice from regulators concerning CHC, and specifically how the risks of VTE are perceived? Is advice clearly communicated? Is it seen as helpful? How could it be improved? 4. To document ways in which communications aimed at women and health care professionals from regulatory authorities could be improved in the future
Country(-ies) of study	UK, Denmark, Germany, Slovakia, Netherlands, Spain
Author	Dr Fiona Stevenson

Contents

1. Marketing authorisation holder(s)

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

2. List of abbreviations

VTE	venous thromboembolism
CHC	combined hormonal contraceptives
WP	work packages
DVT	deep vein thrombosis
PE	pulmonary embolism
EU-28	Twenty eight members of the European Union

3. Responsible parties

Name	Role	Tasks
Dr Fiona Stevenson	Lead academic	Protocol development, oversee the management of the project, directly supervise the UK researcher, ensure correct ethics and governance consents, oversee supervision of researchers located outside of the UK, ensure timely dissemination in relation to reports and publications
Paula Alves	Post-doctoral researcher	Under the supervision of the lead researcher; provide the template and conduct the internet search and analysis, conduct the interviews and analysis, design the survey and analysis, contribute to dissemination. Co-ordinate meetings of the steering group and advisory panel
Researchers from consortium member Departments	Casual researchers / students fluent in Danish, German, Dutch, Spanish, Slovak	Conduct interviews with women and health care professionals. Transcribe and translate interview and survey material
Ms Fiona Giles	Administration	Assist with ethics and governance and overall project management, manage the budget, co-ordinate steering group meetings and communication within the consortium
Dr Vera Ehrenstein	Lead contact for the consortium	Overall communication, oversee the budget

4. Abstract

Title

Study of regulatory communication and risk awareness following the Article 31 referral of Combined Hormonal Contraceptives in relation to thromboembolism

Version 1.1

Dr Fiona Stevenson, University College London, UK

Rationale and background:

Research has demonstrated an increased risk of venous thromboembolism (VTE) in women using combined hormonal contraceptives (CHC) compared with non-users who are not pregnant. A review from the European Medicines Agency (EMA) conducted in 2013 reported that the risk of VTE associated with the use of CHCs varies with the type of progesterone in the CHC. Despite the risks identified, the EMA Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of CHC in preventing unwanted pregnancy continue to outweigh their risks, and that these well-known risks are small.

The risks and the benefits associated with use of CHC have long been established. What is less clear is the extent to which this information is being used to give advice in practice. There is a gap in evidence in relation to awareness of the risk of VTE in users of CHC and understanding of information sources, both formal and informal, used by women and practitioners. We also need to know the perceived influence of different information sources on both prescribing and use of CHC.

Research question

Do women and prescribers consider the risks of venous thromboembolism when making decisions about the use of combined hormonal contraceptives and what sources of information inform their assessments?

Objectives

1. To consider the extent to which women and health professionals are aware of the risks of venous thromboembolism (VTE) in users of combined hormonal contraceptives (CHC)
2. To document awareness, knowledge, attitudes and practices related to recommendations from regulatory authorities
3. To understand how advice from regulators concerning CHC, and specifically how the risks of VTE are perceived? Is advice clearly communicated? Is it seen as helpful? How could it be improved?
4. To document ways in which communications aimed at women and health care professionals from regulatory authorities could be improved in the future

Study design:

The study involves (i) an internet search to establish the sources of information both medical practitioners and women can easily access about the risks of VTE associated with the use of CHC, (ii) interviews with medical practitioners and women to explore knowledge of VTE related to use of CHC and views of sources of about the risks of VTE associated with CHC and how this affects the choices in relation to prescribing and use of CHC and (iii) an online survey aimed at women of childbearing age and medical practitioners to understand the range of information accessed and consider how regulators can help to ensure access to the most up to date evidence for both prescribing and use of CHC.

Population, Variables and Data sources:

The internet search will be conducted across six European Union Member States (Denmark, Germany, UK, Slovakia, The Netherlands and Spain), interviews will be conducted with prescribers and women of childbearing age (between 16 and 49 years of age) in three European countries (UK, Denmark and either Slovakia or The Netherlands (to be confirmed)). The online survey will be conducted across six European Union Member States (Denmark, Germany, UK, Slovakia, The

Netherlands and Spain) with prescribers and women of childbearing age (between 16 and 49 years of age).

Study size:

The initial internet search will be conducted according to a strict protocol and use the 'google' search engine which is available in all six of our target countries in the native language. Interviews will be conducted with a total of 24 women and 24 prescribers comprising up to eight women and eight prescribers from each of the three target countries, with a lower limit of six and a higher limit of 10 in each country. Data will be collected in each country until we feel we have saturation however we believe this sample size will allow us to successfully sample a range of characteristics (specifically; age, social and economic status and ethnicity) in each country. The online survey will aim to recruit 100 women and 100 prescribers in each of the six countries involved; 600 women and 600 prescribers in total.

Data analysis:

The internet search will be analysed using content analysis involving counts and basic thematic analysis. Thematic analysis will be used to analyse the interviews with prescribers and women. The online survey will be analysed using absolute counts. We are not planning any formal assessment of variation between countries, merely descriptive statistics which will provide an element of comparison.

Milestones:

Task	**Month**
Literature and internet searches	7
Interviews and data analysis with women and prescribers	12
Survey of women and prescribers	14
Study report	16
Manuscript preparation and delivery	18

5. Amendments and updates

None

6. Milestones

Milestone	Planned date
Start of data collection	02 February 2017
End of data collection	02 October 2017
Final report of study results	02 January 2018
Delivery of manuscript	02 March 2018

7. Rationale and background

Combined hormonal contraceptives (CHC) contain both oestrogen and progesterone. Research has demonstrated an increased risk of venous thromboembolism (VTE) in women using CHC compared with non-users who are not pregnant. Vinogradova et al [1] conducted an analysis of prescribing practices in the UK to quantify the association between prescribing of CHC and the risk of VTE. They reported that preparations containing gestodene, desogestrol, drospirenone and cyproterone were associated with significantly higher risks of VTE than preparations containing either levonorgestrol or norgestimate. They estimated the number of extra VTE cases per year per 10 000 women prescribed CHC was lowest for levonorgestrol, norgestimate and highest for desogestrol and cyproterone. The findings from these recently conducted studies are in line with the review from the European Medicines Agency (EMA), conducted in 2013, which also reported that the risk of VTE associated with the use of CHC varies with the type of progesterone in a given CHC. In addition, the report identified a very low risk of arterial thromboembolism; although there was no evidence for a difference in the level of risk between products depending on the type of progesterone. Despite the risks identified, the EMA's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of CHC in preventing unwanted pregnancies continue to outweigh their risks, and that these well-known risks are small[2].

These findings led to updating of product information for CHC in January 2014[3] in an attempt to provide women and their health care providers with an unbiased and readily available source of information upon which to base choices about the use of CHC. As well as women being aware of the risks of VTE and able to identify relevant signs and symptoms, it is important that health care providers prescribing CHC are confident in their ability to take into account contraindications, and a woman's individual risk factors, as well as remain vigilant in relation to how risk factors may change over time.

The risks of CHC, as well as the benefits associated with use of CHC, have been established in large-scale epidemiologic studies. What is less clear is the extent to which the findings from these studies are implemented in practice. What is now needed is an investigation of awareness of the risks of VTE in users of CHC and the extent to which both research evidence, and in particular recommendations from regulatory authorities, influence advice about taking CHC and prescribing practices. Similarly, we need to know to what extent women judge they are able to consider their choice of contraception based on clear and up-to-date information provided by healthcare professionals as well as sources outside of the medical environment.

8. Research question and objectives

Do women and prescribers consider the risks of venous thromboembolism when making decisions about the use of combined hormonal contraceptives and what sources of information inform their assessments?

- To consider the extent to which women and health professionals are aware of the risks of venous thromboembolism (VTE) in users of combined hormonal contraceptives (CHC)
- To document awareness, knowledge, attitudes and practices related to recommendations from regulatory authorities
- To understand how advice from regulators concerning CHC, and specifically how the risks of VTE are perceived? Is advice clearly communicated? Is it seen as helpful? How could it be improved?
- To document ways in which communications aimed at women and health care professionals from regulatory authorities could be improved in the future

9. Research methods

9.1.Study design

The project will investigate awareness, perceptions and use of regulatory communication among doctors, users and potential users of combined hormonal contraceptives, with specific focus on the risks of venous thromboembolism. The study will take a mixed methods approach and comprise seven work packages (WP).

WP1 brief literature review designed by expert librarians and reviewed by consortium members to assess current research evidence relating to: (i) information sources used by women when making decisions about the use of CHC, (ii) information sources used by health care professionals when advising women and making prescribing decisions concerning CHC, (iii) awareness of the risk of VTE among prescribers, potential users and users of CHC.

WP2 internet search using the google search engine in Danish, German, Slovakian, Dutch, Spanish and English to assess the information available online concerning the risks of VTE associated with the use of CHC.

WP3 Semi-structured interview study with up to 24 women of reproductive age (between the ages of 16 and 49 years), to include users and non-users of CHC. Interviews will be conducted in the UK, Denmark, and either the Netherlands or Slovakia (to be confirmed). The interview schedules will be informed by WP1 and WP2 and will explore the decisions women make about contraceptive choice and the reasons for their choices. Women will be asked about the sources of information they use and how they assess the information they find. They will be asked specifically about their familiarity with information from regulators such as the EMA.

WP4 interview study with up to 24 health professionals (family doctors, sexual health doctors, gynaecologists, specialist nurses, primary care nurses). Interviews will be conducted in the UK, Denmark, and either the Netherlands or Slovakia. The interview schedules will be informed by WP1 and WP2 and will explore knowledge, attitudes and prescribing practices in relation to CHCs. They will be asked about the sources of information they utilise and specifically about their familiarity with information from regulators such as the EMA.

WP5 findings from WP 1-4 will be used to develop a survey in electronic format for women of childbearing age (between the ages of 16 and 49 years) to explore: (i) if they sought information when making decisions about CHC, and if so from where, (ii) perceptions of risk in response to short scenarios based on previously collected interview data, (iii) awareness of information from the regulators such as the EMA, (iv) what optimal communication from regulators would look like. The survey will be distributed via local organisations such as schools, colleges and youth centres in six European Union Member States (Denmark, Germany, UK, Slovakia, The Netherlands and Spain). Social media will be used to help with recruitment. Potential participants will be directed to information and consent forms prior to completing the survey.

WP6 findings from WP 1-4 will be used to develop a survey in electronic format for health practitioners to establish awareness of regulatory communication concerned with the risks of VTE associated with CHC and to test suggestions for improvements in communication by regulatory authorities presented in interviews (WP3 and 4). The survey will be distributed via our European Primary Care Networks across six European Union Member States (Denmark, Germany, UK, Slovakia, The Netherlands and Spain). Potential participants will be directed to information and consent forms prior to completing the survey.

WP7 combining findings from WP1-6 to establish awareness, perceptions and use of regulatory communication among doctors, users and potential users of combined hormonal contraceptives; with specific focus on the risks of venous thromboembolism (VTE). This will form the final report and manuscript for submission for publication.

9.2.Data collection and analysis

WP1

Aim of WP

The aim of the overall project is to investigate awareness, perceptions and use of regulatory communication among doctors, users and potential users of combined hormonal contraceptives. In particular, the project is concerned with the risks of VTE associated with use of CHC. We will define VTE in relation to the risks of deep vein thrombosis (DVT) – defined as a blood clot that forms in the veins of the leg; and pulmonary embolism (PE) – defined as a blood clot in the lungs.

The literature review will therefore focus on: (i) information sources used by women when making decisions about the use of CHC, (ii) information sources used by health care professionals when advising women and making prescribing decisions concerning CHC (iii) awareness of the risk of VTE among prescribers, potential users and users of CHC.

Search strategy

We will develop the search strategy with the librarian in the Royal Free Hospital in London, UK, who is an expert in conducting literature searches. The review will be systematic in approach, but care will be taken to narrow the focus so it is possible given the time constraints of the overall project. The results will be circulate the results across the main team as a check no key literature has been omitted. We anticipate searches are likely to use the following terms in various combinations:

combined hormonal contraceptives

venous thromboembolism

women

health care professionals

prescribers

awareness of risk venous thromboembolism

perceptions of risk venous thromboembolism

advice about risks of combined hormonal contraception

Sources of information

contraceptive choice

regulatory communications

Language will be restricted to English, Danish, German, Dutch, Slovakian and Spanish. The period of interest will be 2013-2016 to take account of the update to the product information for CHCs in January 2014 and any information and references available immediately prior to the launch.

Process

Titles and abstracts will be reviewed in relation to the research questions, with full text articles obtained and considered as necessary. Evidence relating to the risks of VTE from use of CHCs will be outside the scope of the review. This is a scoping, not a systematic, review so no meta-analysis will be conducted.

The findings will be used to provide the context for subsequent work packages.

WP2

Aim of WP

As of the beginning of 2015, nearly four fifths (79 %) of all individuals in the EU-28, aged between 16 and 74 years, used the internet at least once. At least nine out of every 10 individuals in Luxembourg, Denmark, the Netherlands, Finland, the United Kingdom and Sweden used the internet. By comparison, around two thirds of all individuals aged 16 to 74 used the internet in Poland, Greece and Italy, with the share falling to 57 % in Bulgaria and 56 % in

Romania. Data from Slovakia, reported 77 % of people said they used the internet on a daily basis [4]. This, together with a recent survey across the EU which reported that 41% of Europeans think the internet is a good way to get information about health; with the figure rising to 62% in Denmark and 61% the Netherlands [5], indicates that the internet is likely to be an important source of information for women and prescribers relating to the risks of VTE associated with CHC.

Search strategy

The search will use the google search engine on the risks of VTE from CHC. The search will be initially developed in English, then rolled out in Danish, German, Slovakian, Dutch, and Spanish.

Analysis

A content analysis involving counts and basic thematic analysis will be employed. Data will be collected and tabulated according to (i) name of host site, (ii) type of site; e.g. charity, medical, support group, (iii) brief description of the information provided, (iv) last update to the site.

WP3

Aim of WP

Up to 24 semi-structured interviews with women of reproductive age (between the ages of 16 and 49) to explore (i) the decisions women make about contraceptive choice, (ii) the reasons for their choices, (iii) the sources of information they use, (iv) how information is assessed and used, (iv) familiarity with information from regulators such as the EMA.

Sample

Up to 24 women of reproductive age (16 – 49 years of age) across three European Union Member States (UK, Denmark, Slovakia or the Netherlands). Women will be purposively sampled according to (1) whether or not they take CHC products, (2) age, (3) social class and (4) ethnicity, to ensure a range of groups and potential responses are captured.

Qualitative interview studies usually aim for between 20 and 30 participants to ensure saturation of themes from the data. We will aim for 8 participants from each of the three target countries, with a lower limit of 6 and a higher limit of 10 in each country. Data will be collected in each country until we feel we have saturation however we believe this sample size will allow us to

successfully sample a range of characteristics (specifically; age, social and economic status and ethnicity) in each country.

Recruitment

We will recruit from universities and schools as they employ a range of people from cleaners and domestic staff to teachers and lecturers, and a variety of ages. This will provide a variety of women from whom to sample. Youth centres will be particularly helpful in recruiting young women who may not wish to accept an invitation through their place of education.

Research Process

The interview schedule will be developed in the UK and then translated to ensure consistency of data collection. Interviews will be conducted either face-to-face, by telephone or skype according to the respondents' preference. Interviews will last 30 minutes and will be audio-recorded. They will be conducted in people's native language. Participants will be encouraged to discuss the issues raised in their own terms, with prompts from the researcher. Their sources of knowledge will be explored (with prompts including the influence of factors such as information from medical professionals, information from the internet and written information included in packs). They will also be asked about any recent changes in information and advice about CHCs. Interviews will also explore women's awareness of regulators as a source of information about CHCs. This will include consideration of if, and if so how, they became aware of advice from regulators concerning CHCs, how they perceived this information and the way in which it was communicated. The interviews will focus in particular on suggestions for improvement in communication from regulators. All women will receive a 20 euro voucher by way of thanks for their participation.

Analysis

Interviews will be conducted in people's native language, and then transcribed and translated in to English so all the analysis can be conducted by one site (UK) to ensure comparability of approach and rigour. Framework analysis will be employed to aid comparability across the sites. Once the interviews are transcribed, they will be read repeatedly and key themes will be identified and noted to produce a detailed understanding of how information about the risks of CHCs, specifically the risks of thromboembolism, is presented, where it appears and in what context. We will also consider women's suggestions for optimal communication about the risks of VTE associated with taking CHC. The data generated will be discussed with both the steering and advisory group.

WP4

Aim of WP

Semi-structured interviews will be conducted with up to 24 health professionals to explore (i) knowledge, (ii) attitudes and (ii) prescribing practices in relation to CHCs; with a specific focus on the risks of VTE.

Sample

Up to 24 health professionals involved in the prescription of CHC will be recruited. The place of recruitment will vary according to country. Qualitative interview studies usually aim for between 20 and 30 participants to ensure saturation of themes from the data. We will aim for 8 participants from each of the three target countries, with a lower limit of 6 and a higher limit of 10 in each country. Data will be collected in each country until we feel we have saturation however we believe this sample size will allow us to successfully sample a range of characteristics (specifically; age, type of practitioner (nurse, doctor), location of practice (rural, urban) in each country.

Research Process

Interviews will be conducted either face-to-face, by telephone or skype according to the respondents' preference. Interviews will last 30 minutes and will be audio-recorded. They will be conducted in the respondents' native language. Participants will be encouraged to discuss the issues raised in their own terms, with prompts from the researcher. Interviews will explore the sources of information health professionals utilise when advising women; likely prompts include colleagues, training, information provided in updates and continuing professional development. Practitioners will be asked specifically about their familiarity with information from regulators such as the EMA. They will also be asked specifically about updates to information, their awareness of updates, if they proactively seek them and how they fit into their clinical practice.

We are particularly interested in perceptions of advice about CHCs from regulators, for example if, and if so how, they have received advice from the regulators concerning CHCs and how they perceived this information and the manner of communication. After providing their views we will show them the advice provided following the review by the EMA and ask them how familiar they are with it. Ideas for improvement in communication from the regulator will be proactively sought. We will also explore the extent to which health professionals report using information from updates

in practice, particular in relation to renewing an existing prescription for CHCs; which provides the opportunity to reassess the suitability of the CHC for the woman concerned. All health practitioners will receive a 20 euro voucher by way of thanks for their participation.

Analysis

Interviews will be conducted in respondents' native language, transcribed and translated in to English so all the analysis can be conducted by one site (UK) to ensure comparability of approach and rigour. Framework analysis will be employed to aid comparability of data from different countries. Once the interviews are transcribed, they will be read repeatedly and key themes will be identified and noted to produce a detailed understanding of how information about the risks of CHCs, specifically the risks of thromboembolism, is discussed and in what context. We will also consider suggestions for optimal communication about the risks of VTE associated with taking CHC. The data generated will be discussed with the steering and advisory group.

WP5

Aim of WP

The findings from WP1-4 will be used to develop a survey in electronic format for women of childbearing age (16-49 years), to explore: (i) if they sought information when making decisions about CHC, and if so from where, (ii) perceptions of risk in response to short scenarios based on previously collected interview data, (iii) awareness of information from the EMA, (iv) what optimal communication from regulators would look like.

Sample

The survey will be distributed via local organisations such as schools, colleges and youth centres in up to six European Union Member States (Denmark, Germany, UK, Slovakia, The Netherlands and Spain). Educational institutions employ a range of people from cleaners and domestic staff to teachers and lecturers, and a variety of ages. This will provide a range of women from whom to sample. Youth centres will be particularly helpful in recruiting young women who may not wish to accept an invitation through their place of education.
Eligibility will be assessed via an initial filter page that will check potential participants are between the ages of 16 and 49 years. We will seek responses from 100 women in each country; with an aim to recruit 10% who have chosen to use an alternative to CHC.

Research process

Surveys presented online generally get a reasonable response rate as people can answer questions at a time that is convenient to them, in privacy and with minimal effort, a key aspect being they don't need to speak to a researcher or receive or return an item by post. This also makes them cost-effective. Recruitment will be done via links with local organisations such as schools, colleges and youth centres. We will aim to recruit up to 600 women (100 per country), with an aim to recruit 10% in each country who have chosen to use an alternative to CHC. The recruitment information will differ to recruit women taking and not taking CHC. If women are eligible and willing to take part they will formally consent to participation online and then be directed to the survey. One we have filled the quota for each country (100 women; 90 using CHCs and 10 not) the link to recruitment will be removed. Participation will be incentivised by offering entry into a draw for a voucher to the value of 50 euro or equivalent local currency
The survey will consider the extent to which the findings from the interviews from WP 3 are transferrable to other European Union Member States. The survey will collect sociodemographic information including age, ethnicity, education and occupation and a measure (scores from 1-10) of women's perceived risk of VTE associated with taking CHCs. This method has been used successfully elsewhere to capture people's assessments of risk [6]. An important aspect of this survey is to explore what optimal communication from regulators would look like. This will be achieved through the presentation of a range of possible scenarios for improving communication, drawn from the qualitative work conducted in WP3. The internet survey will be conducted using REDCap, (Research Electronic Data Capture) a secure web application for building and managing online surveys and databases. This service enables data to be automatically captured and retained in a 'safe haven', ensuring rigorous research governance and data protection standards in relation to the survey data collected. This approach also eliminates the need for resources for data entry.

Analysis

Analysis will comprise simple descriptive statistics to consider information seeking, awareness of formal sources of information, risk awareness and responses to scenarios relating to communication from regulators such as the EMA. We will use absolute counts and are not planning any formal assessment of variation between countries, merely descriptive statistics which will provide an element of comparison.

Differences in responses by country will be considered, in particular differences in views expressed relating to maximising future information flow about medicines.

WP6

Aim of WP

The findings from WP1-4 will be used to develop a survey, which will be administered via the internet, to consider awareness of regulatory communication among doctors concerned with the risks of VTE associated with CHC and to test among suggestions for improvements in communication by regulatory authorities presented in interviews (WP3 and 4)

Sample

Heath care practitioners across 6 European Union Member States (Denmark, Germany, The Netherlands, Slovakia, Spain, UK) recruited via primary care networks. We will aim to recruit up to 100 practitioners per country (600 in total across all countries).

Research process

Surveys presented online generally get a reasonable response rate as people can answer questions at a time that is convenient to them, in privacy and with minimal effort, a key aspect being they don't need to speak to a researcher or receive or return an item by post. This also makes them cost-effective. Eligibility will be assessed via an initial filter page that will check potential participants are involved in advising about, and / or prescribing CHCs. If they are eligible they will formally consent to participation online and then be directed to the survey. One we have filled the quota for each country the link will be removed. We will incentivise participation by offering entry into a draw for a voucher to the value of 50 euro or equivalent local currency, whenever allowed by local law. The survey will consider the extent to which the findings from the interviews from WP 4 are transferrable to other European Union Member States. The survey will be sent to health professionals via the European General Practice Research Network. An important aspect of this survey is to explore what optimal communication from regulators would look like. This will be achieved through the presentation of a range of possible scenarios for improving communication, drawn from the initial in-depth qualitative work. The survey will also collect sociodemographic information including age, ethnicity, occupation and a measure (scores from 1-10) of health professionals' views of perceived risk of VTE associated with taking CHCs. This method has been used successfully elsewhere to capture people's assessments of risk [7]. The internet survey will be conducted using REDCap, (Research Electronic Data Capture) a secure web application for building and managing online surveys and

databases. This service enables data to be automatically captured and retained in a 'safe haven', ensuring rigorous research governance and data protection standards in relation to the survey data collected. This also eliminates the need for resources for data entry.

Analysis

Analysis will comprise simple descriptive statistics to consider perceptions of risks of VTE associated with CHC from across the European Member States and suggestions for improvements in communication by regulatory authorities. We will use absolute counts and are not planning any formal assessment of variation between countries, merely descriptive statistics which will provide an element of comparison. Differences in responses by country will be considered, in particular differences in views expressed relating to maximising future information flow about medicines.

WP7

Outline for the study report

The study report will combine the findings from all 6 work packages. Existing literature relating to information sources used and awareness of risks of VTE from taking CHC will be combined with an analysis of information available on the internet in relation to the risks of VTE associated with CHCs. This work will inform the development of the interview and questionnaire studies. Data from interviews will present an understanding of the role of regulatory authorities in the provision of recommendations and a detailed understanding of knowledge, attitude and practices of users, potential users of CHCs and health professionals in relation to the risks of VTE associated with the use of CHCs. Interview data will be based on studies in three European Union Member States. These data will be complemented by data from a survey of health professionals and users of CHCs from across six European Union Member States which will primarily explore how communication to patients and health care professionals can be improved in the future. The report will conclude with recommendations for communication strategies for the dissemination of advice from regulatory authorities to ensure maximum impact in relation to both health professionals and users of prescribed medicines. The expectation is that the findings from this work will be transferable to the role of the regulator in the provision of information about medicines more generally. Publication will be sought in an open access journal to maximise impact.

9.3.Data management

Identifiable data from interviews will be stored on secure servers in the country in which the data are collected. Anonymised transcripts will be provided to the UK for the purposes of analysis. The internet survey will be conducted using REDCap, (Research Electronic Data Capture) a secure web application for building and managing online surveys and databases. This service enables data to be automatically captured and retained in a 'safe haven', ensuring rigorous research governance and data protection standards in relation to the survey data collected.

9.4.Quality control

Final versions of all documents will be overseen by the lead researcher. The lead researcher will also closely supervise the research associate for each of the work packages; in particular the preparation of search terms for the literature and internet search and topic guides for the interviews with users and non-users of CHCs and health professionals, data collection plans and all the analysis. The lead researcher will also oversee the requirements for governance and ethics, with advice from local researchers.

There will be administrative support to ensure smooth running of the project and five steering group meetings, roughly spaced throughout the project. There will be patient and public involvement representatives asked to comment at each stage of the research (four time points) to ensure the analysis and subsequent findings make sense to people who would use them in the future.

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

The project is a mixed methods study which will investigate awareness, perceptions and decisions about the use of regulatory communication concerned with the risks of venous thromboembolism among doctors, users and potential users of CHC. The data provided will be descriptive and explanatory. It will not be suited to statements of quantification across different European countries of awareness of the risks of VTE associated with use of CHC

and quantification of behaviours in relation to the prescription and use of CHC.

11.Protection of human subjects

Ethical approval will initially be obtained through the lead university (UCL), with associated linked approvals in Denmark, Germany, the Netherlands, Slovakia, and Spain.

12. Plans for disseminating and communicating study results

Summaries of the findings of the work will be offered to all participants. Abstracts will be submitted for conferences such as the European General Practice Research Network conference. The last deliverable is a paper for submission to an academic journal.

A project on women's choice of contraception is currently being conducted in the lead researcher's Department and the two projects will work together to share ideas and findings.

13. References

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Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1	1.1	21/12/17	Gantt Chart

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 regulatory communication and risk awareness following the Article 31 referral of Combined Hormonal Contraceptives in relation to thromboembolism

Study reference number:
EMA/602994/2015

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
1.1.2 End of data collection[2]	☒	☐	☐	6
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

[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)	☒	☐	☐	9
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
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?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☐	☐	☒	
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)	☐	☐	☒	
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:

The information required in 3.5 is provided in the REC Form approved by UCL (attached to this form).

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	10.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	Gantt Chart
4.2.2 Age and sex?	☒	☐	☐	9.2

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.3 Country of origin?	☒	☐	☐	9.2
4.2.4 Disease/indication?	☒	☐	☐	9.2
4.2.5 Duration of follow-up?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	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)	☐	☐	☒	
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)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

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
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.2
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)	☒	☐	☐	9.2
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?	☐	☐	☒	
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)	☐	☐	☒	
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	

Comments:

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
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
9.1.3 Covariates?	☐	☐	☒	
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)	☐	☐	☒	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates?	☐	☐	☒	

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
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
10.2 Are descriptive analyses included?	☒	☐	☐	9.2
10.3 Are stratified analyses included?	☐	☐	☒	
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?	☒	☐	☐	10.1

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)	☒	☐	☐	9.3
11.2 Are methods of quality assurance described?	☒	☐	☐	9.4
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.4

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)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.2

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	11
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	9.8
13.3 Have data protection requirements been described?	☒	☐	☐	9.3

Comments:

The information required in 13.2 and 13.3 is provided in the REC Form approved by UCL (attached to this form).

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

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)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Fiona Stevenson

Date: 04/Oct/2017

Signature: