Study Protocol

P3-C3-008

DARWIN EU® - Association of venous thromboembolism with non-steroidal anti-inflammatory drug use in women 15-49 years using hormonal contraceptives

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Version 4.0

Contents

Study title	DARWIN EU® - Association of venous thromboembolism with non-steroidal anti-inflammatory drug use in women 15-49 years using hormonal contraceptives
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Research question and objectives	The study aims to answer the question: Is there an an association with VTE during concomitant use of NSAIDs prescribed to women hormonal contraceptive users aged 15-49 years old? Specific objectives: 1. To characterise the use of oral NSAIDs among women aged 15-49 using hormonal contraceptives. 2. To measure the association of any oral NSAID use and the incidence of VTE among 15-49 years old women on high, medium, and low risk hormonal contraceptives. 3. To measure the association of ibuprofen, diclofenac and naproxen use on the incidence of VTE among 15-49 years old women on high, medium, and low risk hormonal contraceptives.
Country(ies) of study	UK, Spain, Norway, Denmark
Author(s)	Xintong Li, Daniel Prieto-Alhambra

LIST OF ABBREVIATIONS

Abbreviation	Name
NSAID	Non-steroidal anti-inflammatory drugs
VTE	Venous thromboembolism
CDM	Common Data Model
EHR	Electronic Health Record
SNOMED	Systematized Nomenclature of Medicine
IRR	Incidence rate ratio
ATC	Anatomical Therapeutic Chemical (ATC)

1. TITLE

DARWIN EU® - Association of venous thromboembolism with non-steroidal anti-inflammatory drug use in women 15-49 years using hormonal contraceptives

2. RESPONSIBLE PARTIES – STUDY TEAM

Study team role	Names	Organisation
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Clinical Domain Expert	Albert Prats-Uribe Daniel Prieto-Alhambra	University of Oxford University of Oxford, Erasmus MC
Data Partner*	**Names**	**Organisation**
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DK-DHR	Claus Møldrup Elvira Bräuner Susanne Bruun	Danish Medicines Agency
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*Data partners' role is only to execute code at their data source, review and approve their results. They do not have an investigator role. Data analysts/programmers do not have an investigator role and thus declaration of interests (DOI) for them is not needed.

3. ABSTRACT

Title

DARWIN EU® – Association of venous thromboembolism with non-steroidal anti-inflammatory drug use in women 15-49 years using hormonal contraceptives

Rationale and background

Multiple studies have showed that oral combined hormonal contraception is associated with an increased risk of venous thromboembolism (VTE), especially for high dose combined oral contraception.

Recently, a nationwide study from Denmark reported that NSAIDs use was associated with increased VTE risk in women 15-49 years old, especially among those with concomitant use of high/medium risk hormonal contraception. More data on the association of venous thromboembolism with NSAIDs in women of reproductive age has been requested by medicines regulators to see if such associations are seen in other databases, including data on women using hormonal contraception.

Research question and objectives

The study aims to answer the question of: Is there an association with VTE during concomitant use of NSAIDs prescribed to women taking hormonal contraceptive users aged 15-49 years old?

Specific objectives:

1. To characterise the use of oral NSAIDs among women aged 15-49 using hormonal contraceptives.
2. To measure the association of any oral NSAID use and the incidence of VTE among 15-49 years old women on high, medium, and low risk hormonal contraceptives.
3. To measure the association of ibuprofen, diclofenac and naproxen use on the incidence of VTE among 15-49 years old women on high, medium, and low risk hormonal contraceptives.

Methods

Study design

Objective 1 will be a drug utilisation study where new users of oral NSAIDs during the use of hormonal contraceptives will be characterised.

Objectives 2 and 3 will use a self-controlled case series (SCCS) design, nested within a cohort of hormonal contraceptive users.

Data source

This study will be conducted using routinely collected health data (also known as 'real world data') from 4 databases in 4 European countries. All databases were previously mapped to the OMOP CDM.

1. Clinical Practice Research Datalink (CPRD GOLD), United Kingdom
2. Danish Data Health Registries (DK-DHR), Denmark
3. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
4. Norwegian Linked Health Registry data (NLHR), Norway

Population

In Objective 1, the study population will be women aged 15-49 who initiate oral NSAIDs (ibuprofen, diclofenac, and naproxen) during the use of hormonal contraceptives, defined using a 90-day washout window.

In objective 2, study population will include women aged 15-49, included when they start treatment with hormonal contraceptives, and with no history of venous or arterial thromboembolism, cancer (except non-melanoma skin cancer), thrombophilia, hysterectomy, bilateral oophorectomy, sterilisation, or infertility treatment. For the SCCS analysis, only women who used NSAIDs as well as having VTE events during the hormonal contraceptive use will be included.

Variables

Hormonal contraceptives will be classified into three groups based on the risk of VTE.

The exposures will be any NSAIDs, and Ibuprofen, diclofenac, and naproxen separately. Ibuprofen, diclofenac, naproxen are most used NSAIDs in Europe. The primary outcome of interest is incident VTE, deep vein thrombosis and pulmonary embolism will be assessed combined and individually.

Other variables include the risk factors of VTE and indications of NSAIDs: recent surgery, trauma/ fracture, cancer, and hospitalisation.

Statistical analysis

Objective 1: Drug utilisation of oral NSAIDs (ibuprofen, diclofenac, and naproxen) among women aged 15-49 using hormonal contraceptives.

Among women using hormonal contraceptives who initiate concomitant oral ibuprofen, diclofenac and naproxen, the initial dose and cumulative dose will be assessed at ingredient level for the initial medication. A grace period of 30 days will be used to define the treatment episode. For each drug exposure record in the database, the start date is the dispensing or prescription date, and the end date is defined either by duration or days' supply, or quantity divided by daily dose. A 90-days washout window will be used to define NSAIDs initiation.

Duration of the treatment episode will be summarised providing the minimum, p25, median, p75, and maximum treatment duration. Number of prescriptions within the treatment episode will be reported. We will also assess the potential indication of NSAIDs during the 7- and 30- days before initiation. Analysis will be conducted for ibuprofen, diclofenac, and naproxen separately.

Objectives 2 and 3: Incidence rate ratio of VTE

For the descriptive analysis, we will conduct large-scale characterisation as well as pre-specified patient-level characteristics of the study population at: i. cohort entry for each contraceptive group (start of hormonal contraceptive); ii. start of NSAIDs exposure (First treatment episode) during hormonal contraceptive use; and iii. time of VTE diagnosis. We will report number and percentage of people who developed conditions that might increase the risk of VTE during each follow-up period.

We will then conduct the self-controlled case series analysis, which compares the incidence rate of events during time exposed to NSAIDs with the rate during all other observed time periods using hormonal contraceptives within individual. We will allocate person-time exposed to hormonal contraceptive into four intervals: Baseline period, defined as on treatment with hormonal contraceptive but not exposed to a NSAIDs; NSAIDs exposure risk period, defined by concomitant use of hormonal contraceptives and NSAIDs; Pre-exposure period: 2-week period before starting NSAIDs (while on hormonal contraceptives); and post-exposure period: 30-day period after stopping using NSAIDs (while still on hormonal contraceptives).

Firstly, we will perform diagnostics to test the assumptions of SCCS analysis, including event-dependent exposures, and event-dependent observation periods.

The SCCS model will be fitted using conditional Poisson regression with an offset of the length of risk periods. Incidence rate ratios (IRR) and 95% confidence intervals of events will be estimated for the pre-exposure period and the risk periods. Age, and development of health conditions that are risk factors of VTE will be adjusted for as they are time-varying confounders.

All analyses will be conducted for each hormonal contraceptive groups (high, medium, low). In objective 2, we will define the exposure as any NSAIDs. In objective 3, ibuprofen, diclofenac and naproxen will be analysed separately. We will use paracetamol both with or without codeine as a negative control exposure.

Three sensitivity analyses will be performed. In SCCS analysis, if an event increases the probability of death, the assumption of "occurrence of the outcome event does not affect an individual's time observed" might be violated. Therefore, we will conduct a sensitivity analysis by excluding cases who died within 90 days of VTE outcome. To assess the impact of confounding by indication, that NSAIDs were prescribed to treat conditions which are also risk factors of VTE, we will exclude VTE recorded recorded in the 6 months after cancer, trauma, cancer, or hospitalisation records. We will also conduct a sensitivity analysis by restricting to the first hormonal contraceptives use episode of individuals.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Study milestones and deliverables	Planned dates
Draft Study Protocol	October 2024
Final Study Protocol	January 2024
Creation of Analytical code	January - March 2024
Execution of Analytical Code on the data	March - April 2025
Draft Study Report	End of April 2025
Final Study Report	End of May 2025

6. RATIONALE AND BACKGROUND

Venous thromboembolism (VTE) refers to the formation of a blood clot in a deep vein and is a rare but potentially preventable cause of death in women of reproductive age. Multiple studies have showed that oral combined hormonal contraception is associated with an increased risk of VTE, especially high-dose combined oral contraception (>=50 µg ethinyl estradiol and progestins).[1]

Additionally, the use of non-steroidal anti-inflammatory drugs (NSAIDs) has also been linked to increased VTE risk. Meta-analyses and observational studies have suggested an increased risk of VTE among NSAIDs users.[2,3]

Recently, a nationwide study from Denmark found that NSAIDs use is associated with increased VTE risk in women 15-49 years old, especially among those with concomitant use of high/medium risk hormonal contraception. [4] This study was fraught with limitations, particularly as the study design did not satisfactorily account for confounding.

More data on the association of venous thromboembolism with NSAIDs in women of reproductive age has been requested by medicines regulators to see if such associations are seen in other databases, including data on women using hormonal contraception.

7. RESEARCH QUESTION AND OBJECTIVES

Study question: Is there an association with VTE during concomitant use of NSAIDs prescribed to women hormonal contraceptive users aged 15-49 years old?

Specific objectives:

1. To characterise the use of NSAIDs among women aged 15-49.
2. To measure the association of any NSAID use and the incidence of VTE among 15-49 years old women on high, medium, and low risk hormonal contraceptives.
3. To measure the association of ibuprofen, diclofenac and naproxen use on the incidence of VTE among 15-49 years old women on high, medium, and low risk hormonal contraceptives.

Table 1. Primary and secondary research questions and objective.

A. Primary research question and objective.

Objective:	1. To characterise the use of NSAIDs among women aged 15-49 using hormonal contraceptives. 2. To measure the association of any NSAID use and the incidence of VTE among 15-49 years old women on high, medium, and low risk hormonal contraceptives.
Hypothesis:	Objective 1 is descriptive analysis of drug utilisation. Objective 2's hypothesis is that the incidence rate of VTE may be different with NSAIDS (versus no NSAIDS) use among women aged 15-49 with contraceptives
Population *(mention key inclusion-exclusion criteria):*	In Objective 1, the study population will be women aged 15-49 who initiate ibuprofen, diclofenac, and naproxen during hormonal contraceptives, defined using a 9090-day washout window. In Objective 2, study population will include women aged 15-49, included when they start treatment with hormonal contraceptives, and with no history of venous or arterial thromboembolism, cancer (except non-melanoma skin cancer), thrombophilia, hysterectomy, bilateral oophorectomy, sterilisation, or infertility treatment. For the self-controlled case series analysis, only women who used NSAIDs as well as having VTE events during the hormonal contraceptive use will be included.
Exposure:	Any NSAIDS use.
Comparator:	Self-controlled design, time when not using NSAIDS.
Outcome:	VTE, including deep vein thrombosis and pulmonary embolism.
Time *(when follow up begins and ends):*	Follow-up time will start from the 1st of January 2014 or initiation of hormonal contraceptives and will end when the individual stops the use of hormonal contraceptives or end of study period.
Setting:	Primary and secondary care
Main measure of effect:	In the SCCS analysis, Incidence rate ratios (IRR) and 95% confidence intervals will be estimated

B. Secondary research question 1 and objective.

Objective:	To measure the association of ibuprofen, diclofenac and naproxen use and the incidence of VTE among 15-49 years old women on high, medium, and low-risk hormonal contraceptives.
Hypothesis:	Analysis of the secondary research question (objective 3) will be the same as objective 2, with the exposures focus on ibuprofen, diclofenac, and naproxen.
Exposure:	Ibuprofen, diclofenac, and naproxen.

8. RESEARCH METHODS

8.1 Study type and study design

Table 2. Description of potential study types and related study designs.

Study type	Study design	Study classification
Drug/Vaccine Safety Studies	Self-controlled case series (SCCS)	Complex
Patient-level DUS	Drug utilisation study	Complex

8.2 Study setting and data sources

This study will be conducted using routinely collected data from 4 databases in 4 European countries. All databases were previously mapped to the OMOP CDM.

- Clinical Practice Research Datalink (CPRD GOLD), United Kingdom
- Danish Data Health Registries (DK-DHR), Denmark
- Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
- Norwegian Linked Health Registry data (NLHR), Norway

Rationale of data partners selection

For this study, we are interested in databases that cover primary care and outpatient settings to identify the study population as hormonal contraceptive users and the key exposure NSAIDs, both prescribed by outpatient specialists and general practitioners. The study outcome (VTE) is typically well recorded in GP records for those countries where the GPS are the "Gate keeper" in the healthcare system, and in secondary care, as shown by previous validation studies. Therefore, all four proposed databases cover primary care and outpatient settings to identify the exposure and outcomes of interests.

While it is possible that not all NSAIDs and contraceptives use will be captured in the data, the SCCS design will only include people with records of contraceptives, NSAIDs, and VTE, hence minimising the impact of misclassification of unexposed time. Finally, regarding outcome/s, VTE has been phenotyped and used as study outcomes in three of the four suggested databases as part of previous studies.

Information on data source(s) to be used with a justification for their choice in terms of ability to capture the relevant data is described in a **Table 3**.

Table 3. Description of the selected data sources.

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Feasibility count of exposure	Feasibility count of disease (unique patient)	Data lock for the last update
United Kingdom	Clinical Practice Research Datalink (CPRD) GOLD	Population level EHR with hormonal contraception recorded.	primary care	EHR	2.89m	ibuprofen: 3777100 diclofenac: 2911200 naproxen: 2220100	Pulmonary embolism: 78400 deep venous thrombosis: 127100	2024-07-01
Spain	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP)	Population level EHR with hormonal contraception recorded.	primary care + hospital	EHR	5.95m	ibuprofen: 4377200 diclofenac: 2102900 naproxen: 1563900	Pulmonary embolism: 52000 deep venous thrombosis: 82800	2023-06-30
Denmark	Danish Data Health Registries (DK-DHR)	National wide health registries	community pharmacists, secondary care.	EHR	5.96m	ibuprofen: 2412100 diclofenac: 1299700 naproxen: 454000	Pulmonary embolism: 91200 deep venous thrombosis: 42100	2024-5-21
Norway	Norwegian Linked Health Registry data (NLHR)	Population level EHR with hormonal contraception recorded.	primary care, specialists, and hospital data	Registries	5.67m	diclofenac: 863600 naproxen: 731600 ibuprofen: 613900	Pulmonary embolism: 79100 deep venous thrombosis: 37300	2024-06-30

8.3 Study period

From 2014 or the earliest data available to end of 2023 or the latest data availability of the participating database. The study period was suggested by EMA based on a possible change in prescribing of diclofenac after a referral in 2013. In the NLHR (Norway) data, study period will start on 2018 as secondary care data were available from 2018 onwards in that data source.

8.4 Follow-up

In objectives 2 and 3, we will conduct SCCS analyses nested in a cohort of hormonal contraceptive users.

Firstly, we will construct hormonal contraceptives use episode within each hormonal contraceptives category defined by VTE risk (detailed in section 8.6.1 Exposures). For oral hormonal contraceptives, a 30-day gap (grace period) will be used to define episodes of use. Treatment will be assumed to be continuous if the time between stopping of the previous and starting of the next oral contraceptive prescription is 30 days or less. For implants and intrauterine devices, follow-up will end when either there is a record of removal, or based on the suggested period as per usual practice. For example, for the Mirena (levonorgestrel-releasing intrauterine system) a 5-year period will be used to define end of hormonal contraceptive use unless a code of removal was identified. For Nexplanon (Etonogestrel implant), a 3-year period will be used.

For each hormonal contraceptive episode, if the episode started after 2014, the follow-up would start from the initiation of the hormonal contraceptive episode (Scenario A, **Figure 1**). If the episode started before 2014, the follow-up time will start from 1st January 2014 (Scenario B, **Figure 1**).

If individuals switch (start a new hormonal contraceptive before the previous episode ends or start within 30 days after the previous ends) to a different contraceptive within the same VTE risk group (including change of route, e.g. oral to IUD), we will keep following them up. If individuals switch to contraceptive in a different group, the follow-up will stop at time of switching, and the participant will participate in the newly initiated hormonal contraceptive cohort (Scenario C, **Figure 1**).

For each hormonal contraceptive use episode, the follow-up time will end when the individual stops the use of hormonal contraceptives, defined as having a more than 30 days gap in prescription records. That is, at the end date of a prescription record (usually calculated by days of supply), if we do not identify the next prescription within 30 days, we define that the current hormonal contraceptive use episode discontinued.

Therefore, times that an individual is not using a hormonal contraceptive (e.g. period between discontinuation and re-start) will not be included in the SCCS analysis. The follow-up will also end if individual turn to age 50, or at time of pregnancy.

Within the follow-up of each episode of hormonal contraceptive use, we will allocate the person-time into four intervals based on the concomitant exposure of NSAIDs: (**Figure 1**):

(i) Baseline period, defined as not exposed to a NSAIDs.
(ii) NSAIDs exposure risk period. The risk period will be further divided into the first 7 days on NSAIDs, and days after.
(iii) Pre-exposure period: 2-week period before starting NSAIDs.
(iv) Post-exposure period: 30-day period immediately after discontinuation of NSAIDs. The post-exposure period was introduced to allow the risk to return to baseline.[5]

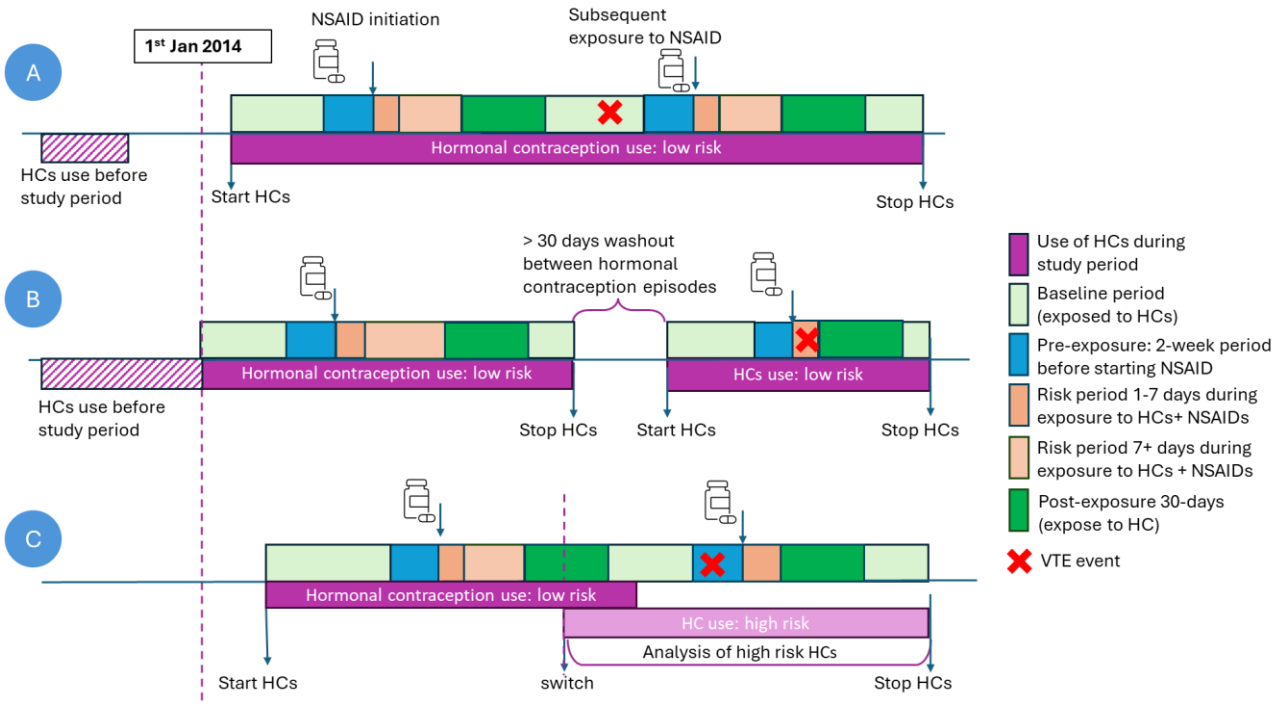


Figure 1. Pictorial representation of study design. (A. Multiple NSAIDs exposure within one HCs episode; B. HCs use started before study period of 2014 and multiple HCs episodes; C. Switch between HCs categories.)

Table 4 describes the follow-up of individuals within the study based on study specific criteria with regard to time of inclusion and time of exclusion within the study.

Table 4. Operational definition of time 0 (index date) and other primary time anchors.

Study population name(s)	Time Anchor Description (e.g. time 0)	Number of entries	Type of entry	Washout window	Care Setting[1]	Code Type[2]	Diagnosis position	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
Obj1: NSAID user	Time of NSAID initiation	multi	Incident	90d	OP	RxNorm	n/a	n/a	n/a	n/a
Obj2, 3: Hormonal contraceptive user	Hormonal contraceptive use	multi	incident	30d	OP	RxNorm, SNOMED	n/a	n/a	n/a	n/a

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

The table below further describes the operational definitions with regard to the follow-up start and the follow-up end of hormonal contraceptive use episode.

Follow up start	Day 0: Initiation of hormonal contraceptive or 1st Jan 2014	
Follow up end[1]	**Select all that apply**	**Specify**
Date of outcome		
Date of death	yes	Censor
End of observation in data	yes	Censor
Day X following index date *(specify day)*		
End of study period (specify date)	yes	End of 2023
End of exposure *(specify operational details, e.g. stockpiling algorithm, grace period)*	yes	Discontinuation of hormonal contraceptive, defined using a 30-day grace period.
Date of add to/switch from exposure *(specify algorithm)*	yes	Individual switch to a hormonal contraceptives of a different VTE risk category, e.g. from high to low.
Other date *(specify)*	yes	Age of 50, start of pregnancy.

[1] Follow up ends at the first occurrence of any of the selected criteria that end follow up.

8.5 Study population with inclusion and exclusion criteria

Objective 1: Drug utilisation of NSAIDs.

The study population will be women aged 15-49 who initiate oral NSAIDs of ibuprofen, diclofenac, and naproxen on or after 2014 while using hormonal contraceptives, defined using a 90-day washout window. We will require at least 365 days of data availability before NSAIDs use.

Objective 2 and 3: Incidence of VTE

The source population will be women of reproductive age using hormonal contraceptives or therapies. We will not limit to medication with contraceptive as indication, but also medications as a combination of estrogen and progestin for other indications. For example, the DIANE®-35, which contains ethinylestradiol and cyproterone acetate, is a treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhoea) and/or hirsutism in women of reproductive age, will be included in this study.

The study population will include women aged 15-49, using hormonal contraceptives, and with no history of venous or arterial thromboembolism, cancer (except non-melanoma skin cancer), thrombophilia, hysterectomy, bilateral oophorectomy, sterilisation, or infertility treatment.

We will require at least 365 days of data availability before hormonal contraception use in the respective database. This will enable us to characterise the comorbidities of individuals and assess the inclusion/ exclusion criteria.

We will exclude women who had any NSAIDs use during the 90-day time before starting the hormonal contraceptives.

Among those, people with a VTE during the hormonal contraceptive usage will be included in the SCCS analysis.

The operational definitions of the inclusion and exclusion criteria are presented by means **of Table 5** and **Table 6**, respectively. Index day refers to the date of hormonal contraceptive initiation.

Table 5. Operational definitions of inclusion criteria.

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position[2]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Women	Sex female	before	[0,0]	n/a	n/a	n/a	n/a	n/a	n/a
Age	Age 15 - 49	before	[0,0]	n/a	n/a	n/a	n/a	n/a	n/a
Hormonal contraceptive	Use of hormonal contraceptive of interest by VTE risk group during the study period	before	n.a.	n/a	n/a	n/a	n/a	n/a	n/a
Observation period of 365day prior entry	Study participants will be required to have 365 days prior history observed before contributing observation time	before	[-365,0]	n/a	n/a	n/a	n/a	n/a	n/a
Have VTE during HCs (for SCCS)	Experience VTE during the use of hormonal contraceptive	after	[1, discontinue of HCs]	n/a	n/a	n/a	n/a	n/a	n/a

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

Table 6. Operational definitions of exclusion criteria.

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position[2]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
History of condition	No history of venous or arterial thromboembolism, cancer (except non-melanoma skin cancer), thrombophilia, hysterectomy, bilateral oophorectomy, sterilisation, or infertility treatment	after	[-Inf,0]	OP, IP	SNOMED, RxNorm	n/a	n/a	n/a	n/a
Previous NSAIDs use	No recorded use of NSAIDs during the 90-dayday time before starting the hormonal contraceptives	after	[-90,0]	OP, IP	RxNorm	n/a	n/a	n/a	n/a

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

8.6 Variables

8.6.1 Exposure/s

Hormonal contraceptives will be classified into three groups by VTE risk. The ATC codes to identify hormonal contraception are available in the appendix.

In objective 1, the exposures will be oral ibuprofen, diclofenac, and naproxen.

In Objective 2, the exposures will be any oral NSAIDs, including ibuprofen, diclofenac, and naproxen during the use of hormonal contraceptives. We will use a grace period of 30 days to define the treatment episode of NSAIDs. Exposure to NSAIDs will then be classified into two periods: the first 7 days on NSAIDs, and days after. For example, if individual received one prescription of ibuprofen for 28 days, the 1-7 days will contribute to risk period one, and 8-28 days will contribute to risk period two. If individual received less than 7 days of NSAID, only risk period one will be contributed.

In objective 3, Ibuprofen, Diclofenac, and Naproxen use will be identified separately. ATC codes for identifying the medication are available in the appendix (**Table 7**).

We will also include a negative control exposure to assess potential residual confounding. In this study, we will use paracetamol with or without codeine as the negative control. Paracetamol has been previously used as active comparators for NSAIDs in other studies [6]. Given the possibility that paracetamol is co-prescribed with NSAIDs, we will only include individuals who initiate paracetamol without NSAIDs use during the 30 days prior to paracetamol.

Table 7. Operational definitions of exposure.

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting[1]	Code Type	Diagnosis position[2]	Applied to study populations	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
NSAIDs	Initiation of NSAIDs, with 90 days washout	[-90,-1]	After HCs initiation	OP	RxNorm	n/a	n/a	n/a	n/a	n/a
Ibuprofen, diclofenac, or naproxen	Initiation of ibuprofen, diclofenac, or naproxen, with 90 days washout	[-90,-1]	After HCs initiation	OP	RxNorm	n/a	n/a	n/a	n/a	n/a
Paracetamol with or without codeine	Initiation of paracetamol with or without codeine	[-90,-1]	After HCs initiation	OP	RxNorm	n/a	n/a	n/a	n/a	n/a

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

8.6.2 Outcome/s

The primary outcome of interest is incident VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE). Only the first-ever VTE event will be included.

We will also include DVT and PE are individual outcomes.

The computational phenotypes for the study outcomes have been developed during another DARWIN EU study (P3-C3-001) and are available in the DARWIN EU library of phenotypes. Preliminary code lists for the study outcomes are available in the appendix.

The operational definition of the outcomes is presented in the **Table 8**.

Table 8. Operational definitions of outcome.

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations	Measurement characteristics/ validation	Source of algorithm
Venous thromboembolism	Incident VTE, including deep vein thrombosis and pulmonary embolism	primary	binary	Inf	IP, OP	SNOMED	n/a	Hormonal contraceptive user	n/a	n/a
Deep vein thrombosis		primary	binary	Inf	IP, OP	SNOMED	n/a	Hormonal contraceptive user	n/a	n/a
Pulmonary embolism		primary	binary	Inf	IP, OP	SNOMED	n/a	Hormonal contraceptive user	n/a	n/a

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

8.6.3 Other covariates, including confounders, effect modifiers and other variables

Health conditions that are risk factors of VTE (for descriptive characteristics and time-varying cofounder)[7]:

- Edema of lower leg
- Inflammatory bowel disease
- Behcet's syndrome
- Lupus erythematosus
- Rheumatoid arthritis
- Cancer (except non-melanoma skin cancer)
- Major trauma/ Fracture
- Surgery
- Hospitalisation
- Reduced mobility, wheelchair use
- Smoking
- BMI

Condition/ treatment for exclusion criteria (before start contributing to follow-up of HCs):

- Venous thromboembolism
- Arterial thromboembolism: ischemic stroke or myocardial infraction
- Cancer (except non-melanoma skin cancer)
- Inherited blood clotting disorders: Haemophilia, acquired or familial thrombophilia, hereditary antithrombin III deficiency, Factor V Leiden.
- Hysterectomy
- Bilateral oophorectomy
- Sterilisation
- Infertility treatment.

Conditions/procedure for end of follow up:

- Pregnancy

Conditions for exclusion of eligible VTE event (Risk factors that temporarily raise the likelihood of VTE, also indication of NSAIDs, for sensitivity analysis):

- Cancer (except non-melanoma skin cancer)
- Major trauma/ Fracture
- Surgery
- Hospitalisation

For conditions/procedures/medications where phenotypes from previous studies are available, the phenotypes will be used. This applies to venous and arterial thromboembolism, and cancer. For other conditions/procedures/medications, we will use the major concept with descendants.

The study covariates are described conceptually, and the context or rationale for the choices are provided in this section. The operational definition of the covariates is described in the **Table 9**.

Table 9. Operational definitions of covariates.

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations	Measurement characteristics/ validation	Source for algorithm
Health conditions that are risk factors of VTE	These variables will be treated as time-varying variables in the SCCS model Edema of lower leg • Inflammatory bowel disease • Behcet's syndrome • Lupus erythematosus • Rheumatoid arthritis • Cancer (except non-melanoma skin cancer) • Major trauma/ Fracture • Surgery • Hospitalisation • Reduced mobility, wheelchair use • Smoking • BMI	*Binary, numeric (BMI)*	[0, end of HCs]	OP, IP	SNOMED	n/a	n/a	n/a	n/a
Condition/ treatment for exclusion criteria	• Venous thromboembolism • Arterial thromboembolism: ischemic stroke or myocardial infraction • Vancer (except non-melanoma skin cancer) • Inherited blood clotting disorders: Hemophilia, acquired or familial thrombophilia, hereditary antithrombin III deficiency, Factor V Leiden. • Hysterectomy • Bilateral ophorectomy • Sterilisation • Infertility treatment.	*binary*	*[-Inf, -1]*	OP, IP	*SNOMED*	n/a	n/a	n/a	n/a
Conditions/procedure for censoring of follow up or exclusion of eligible VTE event	• cancer (except non-melanoma skin cancer) • major trauma/ fracture • surgery • Hospitalisation	*binary*	[0, end of HCs]	OP, IP	*SNOMED*	n/a	n/a	n/a	n/a

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

8.7 Study size

The self-controlled case series analysis will include individuals with both the exposure and the study outcomes. We are not able to estimate the number of people who will fulfil the inclusion criteria at this stage. However, we calculated the sample size needed based on prior knowledge. Based on an exposure time of 30 days NSAIDs within a year of hormonal contraceptive use, and level of significance of 0.05, and 80% power, a sample size of 246 people is needed to detect a relative risk ratio of 1.8 (based on a previous meta-analysis on NSAIDs and VTE risk) [2,8].

In the Meaidi et.al's study, a much larger effect size was reported, with an adjusted incidence rate ratio of VTE of 7.2. The sample size needed is 19 people under this scenario.

Sample size calculation/s or statistical power will be estimated according to study objectives, and provided in this section, with a focus on primary study objective. In descriptive studies (Disease Epidemiology or Drug Utilisation Study/ies), this will be based on the desired/available precision for the metric/s of interest. In hypothesis testing ones (e.g. Comparative Safety or Self-Controlled designs), size/power will be estimated based on assumed values for the expected/available outcome rate/s and effect size.

8.8 Analysis

Objective 1: Drug utilisation of NSAIDs among women aged 15-49 using hormonal contraceptives.

Among individuals who initiate oral ibuprofen, diclofenac, and naproxen during use of hormonal contraceptives in 2014-2023, the initial dose and cumulative dose will be assessed at ingredient level for the initial medication. Duration of the treatment episode will be reported. A 90-days washout period will be used to define NSAIDs initiation. That is, if the there was no NSAIDs use in the 90 days prior to a NSAID prescription, that prescription will be considered as an incident use.

As explained in the previous section, a grace period of 30 days will be used to define the treatment episode. Treatment duration will be summarized providing the minimum, p25, median, p75, and maximum treatment duration. Number of prescriptions within the treatment episode will be reported.

We will also assess the potential indication of NSAIDs during the 7- and 30- days before initiation.

Analysis will be conducted for ibuprofen, diclofenac, and naproxen separately.

Objectives 2 and 3: Association with incidence of VTE.

Descriptive statistics:

For women with contraceptive use, we will conduct large-scale characterisation as well as pre-specified patient-level characteristics of the study population at the following time point:

- Using index date of the cohort entry for each contraceptive group (start of hormonal contraceptive or 1st Jan 2014, 2018, for NLHR data);
- Using index date of the start of NSAIDs exposure (First episode) during hormonal contraceptive use (regardless of whether have VTE during the hormonal contraceptives use);
- People with VTE during hormonal contraceptives use at time of diagnosis (regardless of whether have NSAIDs use during the hormonal contraceptives use).

For objective 2 and 3, variables will include but not be limited to age, obesity status, smoking status, comorbidities (diabetes mellitus, arterial thrombosis, lupus erythematosus and antiphospholipid syndrome), medication use(vitamin K antagonists or other oral anticoagulants, low molecular weight

heparin, antifibrinolytic agents, 2nd generation antipsychotics), and other important risk factors for VTE, and length and current episode of contraceptive use.

We will report number and percentage of people who developed conditions that might increase the risk of VTE during each follow-up period, as listed in section 3.6.

Incidence:

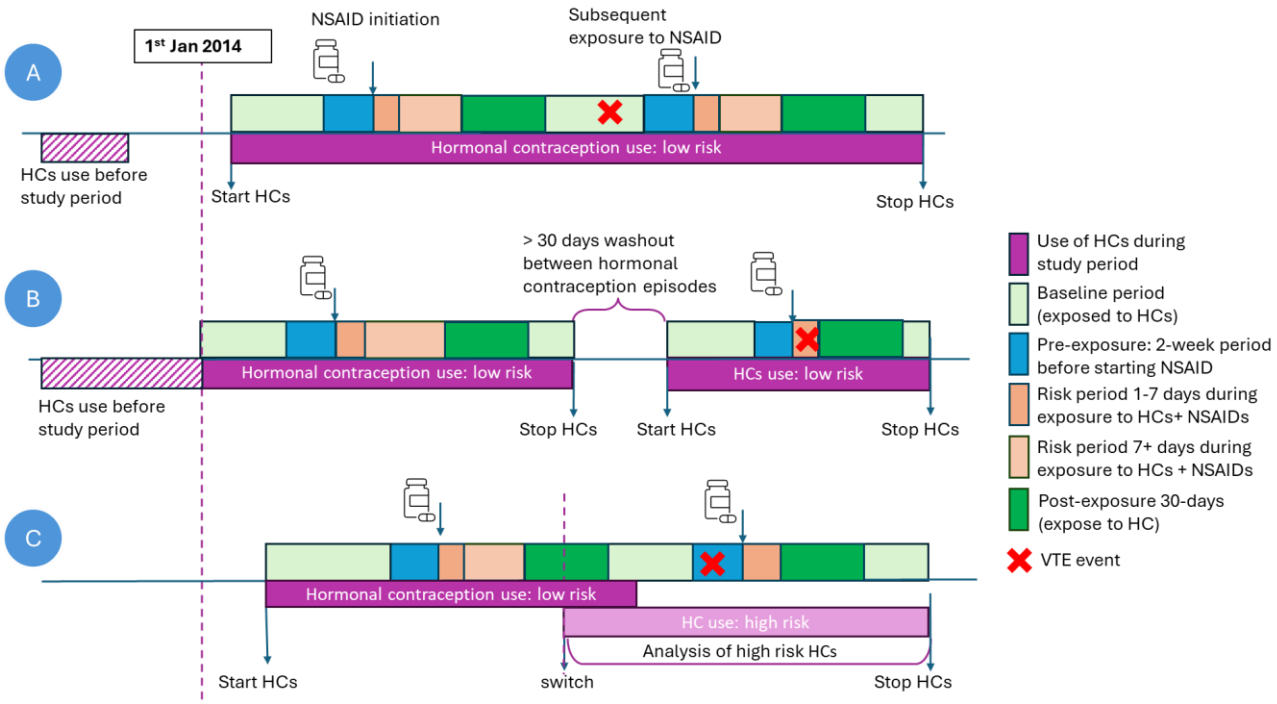
We will report the number, proportion, and incidence rates of VTE after the initiation of hormonal contraceptive, e.g. rates within 1 year of contraceptive or over 1 year use of hormonal contraceptives. We will plot the incident VTE since the start of hormonal contraceptive.

SCCS:

We will conduct a self-controlled case series analysis[9], which compares the rate of events during exposed periods of time with the rate during all other observed time periods within individual.

Firstly, we will perform diagnostics to test the assumptions of SCCS analysis, these includes:

- Event-dependent exposures[10]
    - A key assumption is that subsequent exposures should not appreciably be affected by previous events. One way to correct for this bias is to include a "pre-exposure period" just before an exposure. This can be examined by plotting the distribution of the interval between exposure and event time. If a peak or trough in events prior to exposure is apparent, the presence of short-term event-dependent exposures is indicated.
    - In this study, we will include a 2-week pre-exposure period before the starts of NSAIDs.
- Event-dependent observation periods
    - If the event increases the probability of death, then there is a chance that observation periods could be cut short as a direct result of the event.
    - This can be examinate by histograms of the times from event to end of observation, for those whose observation times are censored, and those are not separately. If a spike is apparent close to zero in the censored data histogram, the presence of event-dependent observation periods is indicated.
    - In this study, we will conduct the analysis for both all first VTE and exclude people who die within 90 days after VTE. Cause of death is not available in the proposed databases.



Recap of **Figure 1.**

In the SCCS analysis, we will include hormonal contraceptive episodes with both exposure to NSAIDs and an VTE event. In Figure 1, individual A has two exposures to NSAIDs during the use of hormonal contraceptive, and experienced a VTE event, will be included. Individual B experienced the event during the second episode of hormonal contraceptive, which will be included in the SCCS analysis. Individual C experienced the event after switching to the high hormonal contraceptives, therefore will contribute to the analysis of the high risk hormonal contraceptive category, and will not contribute to the SCCS for the low risk analysis.

The SCCS model will be fitted using conditional Poisson regression model with an offset of the length of risk periods. Incidence rate ratios (IRR) and 95% confidence intervals of events will be estimated for the pre-exposure period and the risk periods. Age will be adjusted for as they are time-varying confounders. Health conditions that are risk factors of VTE (Section 8.6.3) will be included as time-varying variable as well. If we observe higher incidence of VTE during the first year of hormonal contraceptive use, we will include variable of time on hormonal contraceptive (<1 year, >=1 year) into the model.

Stratification/ subpopulation:

All analysis will be conducted for in each hormonal contraceptive VTE groups (high, medium, low). In objective 2, we will define the exposure as any NSAIDs. In objective 3, ibuprofen, diclofenac and naproxen will be analysed separately.

Sensitivity analysis:

Three sensitivity analyses will be performed.

In SCCS analysis, if an event increases the probability of death, the assumption of "occurrence of the outcome event does not affect an individual's time observed" might be violated. We will conduct sensitivity analysis to assess the robustness of results to assumptions such as that the occurrence of an outcome

event did not influence the subsequent observation period, excluding those who died from the outcome within 90 days.

To assess the impact of confounding by indication, that NSAIDs were prescribed to some events which are also risk factors of VTE, we will exclude VTE cases happened within 6 months after cancer, trauma/fracture, surgery, or hospitalisation.

We will also conduct a sensitivity analysis by restricting to the first hormonal contraceptives use episode of each risk category of individuals.

Table 10. Primary, secondary, and subgroup analysis specification.

A. Primary analysis

Hypothesis:	Use of NSAIDs during usage of hormonal contraceptive impact on the association with incidence of VTE
Exposure contrast:	Use of NSAIDs
Outcome:	VTE
Analytic software:	R
Model(s): ***(provide details or code)***	Conditional Poisson regression model with an offset of the length of risk periods. Incidence rate ratio = incidence rate in risk period/ incidence rate in the baseline period, adjust for age and seasonality.
Confounding adjustment method	Self-controlled design, thus time-invariant variables are controlled by design. We will include age and seasonality as time-varying variables into the model.
Missing data methods	We will only include individuals with age and sex information available. No imputation will be conducted for missing data.
Subgroup Analyses	Low, mid, and high VTE risk hormonal contraceptive.

Table 11. Sensitivity analyses – rationale, strengths, and limitations.

	What is being varied? How?	Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary	Limitations of the sensitivity analysis compared to the primary
Test of event-dependent observation period	Exclude cases who died within 90 days after VTE event.	If VTE increases mortality, then there is a chance that observation periods could be cut short as a direct result of the event.	To test the assumption of SCCS	n/a
Test of confounding by indication	Exclude VTE cases with a recent history of classic risk factors in the previous 6 months: cancer, major trauma/ fracture, surgery, or hospitalisation.	Indications like cancer, trauma, and surgery are also risk factors of VTE	To test if confounding by indication impact on the study results	Could reduce the study size thus reduce the power of analysis
Restrict to first hormonal contraceptives	Restrict analysis to the first treatment episode of each risk category within individual	People with multiple episodes may have different risk profiles	Reduce the potential impact of tolerance to hormonal contraceptives	Could reduce sample size thus reduce the power

8.9 Evidence synthesis

Due to the heterogeneity in data sources, completeness of contraceptive captures, and differences in clinical practice, we will not synthesis the results across databases. All results will be presented for each database separately.

9. DATA MANAGEMENT

All databases have previously mapped their data to the OMOP common data model. This enables the use of standardised analytics and using DARWIN EU tools across the network since the structure of the data and the terminology system is harmonised. The OMOP CDM was developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org

The analytic code for this study will be written in R and will use standardized analytics wherever possible. Each data partner will execute the study code against their database containing patient-level data, and then

return the results (csv files) which will only contain aggregated data. The results from each of the contributing data sites will then be combined in tables and figures for the study report.

10. QUALITY CONTROL

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org/DataQuality.html). In particular, data partners will have run the OHDSI Data Quality Dashboard tool (https://github.com/OHDSI/DataQualityDashboard). This tool provides numerous checks relating to the conformance, completeness, and plausibility of the mapped data. Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality is solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values. Each of these categories has one or more subcategories and are evaluated in two contexts: validation and verification. Validation relates to how well data align with external benchmarks with expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

11. LIMITATIONS OF THE RESEARCH METHODS

Misclassification in exposures of both NSAIDS and hormonal contraception is the major limitation of this study. NSAIDs like ibuprofen are commonly purchased as over-the-counter (OTC) in many countries. We will not be able to capture these medication use, which may lead to misclassification of the expose/unexposed period.

Prescriptions and/or purchases of hormonal contraception differs from countries. In Denmark and Norway, hormonal contraceptives are only available through prescription.

In the UK, over-the-counter progestogen-only contraceptive pills only became available since July 2021, which falls into the low VTE contraceptive category. Apart from OTC use, contraceptives can also be prescribed in Sexual Health Clinics, therefore we might not be able to capture this information in GP data. In the latest NHS report of Sexual and Reproductive Health Services (Contraception), [11] the number of female using contraception service through the Sexual and Reproductive Health Services (SRH) decreased by half during 2014 to 2023. While no explanation were provided in the reports, the impact of decreased use through SRH could lead by either increased use through GP, or OTCs. In a previous study used the UK CPRD data to estimate the risk of VTE and oral contraceptives, the authors reported a similar age standardised rates of exposure to any oral contraceptive as compared to survey data from Office for National Statistics. [12] Since we defined HCs use by prescriptions, there are uncertainty on the actual use the HCs, that women might not start or stop using HCs as suggested on the prescriptions.

IIn Spain, only specific type of hormonal contraceptives is included in the universal healthcare, while others are purchased as OTC. For example, only since 2023, the long-acting reversible contraceptives for women and people who can get pregnant up to the age of 29 were included in the universal health care. Before that, hormonal contraceptives are only reimbursed (and therefore seen in the data) in Spain for women with additional indications, e.g. hyper- or dys-menorrhoea, hirsutism, polycystic ovaries, etc. In theory, a doctor's prescription is required for hormonal birth control. However, the practice may differ between pharmacies.

The incompleteness of contraception records could result in selection bias and reduce the generalisability of the study findings, especially when women with recorded use of contraception differ from women with contraception from sources not recorded in the data source.

Lacking information in OTC low-dose NSAIDs use is a general concern in observational studies using routinely collected health data. Misclassification of the NSAIDs exposure exists that during the "baseline" period, women could potentially expose to low-dose NSAIDs, which would bias the effect estimates towards the null.

Hormonal contraceptives are classified into three categories based on the risk of VTE, whiles combined oral contraceptives were defined as high HCs if contained 50 µg or more ethinyl oestradiol. However, previous studies suggested that the risk of VTE may differ between type of progestogen/ progestin as well.[12] The current study will not provide further stratification on each progestin type.

The definition of study outcome is subject to restricted granularity. In most of the participated databases, DVT was recorded without specification on which vein. For example, we will not be able to distinguish between sural thrombosis from the rest (popliteal/femoral/else).

In this study, we will include only event of DVT will be studied. While this approach could solve the potential violation of the recurrences of an event are not independent assumption, we will not be able to estimate the risk of recurrent DVT after NSAIDs.

With the SCCS design, we assume that apart from the effect of age and seasonality, the baseline risk of DVT during the usage of hormonal contraceptive is the same. However, previous studies on oral contraceptive use and VTE showed that the risk of VTE was higher at the early stage after initiation, and decreased over time.[13,14] We will plot the incidence rate of VTE since the initiation of hormonal contraceptive, to virtually explore if there the risk profile different on hormonal contraceptive duration.

With a different study design, this study aims to assess whether an association is seen in other databases than the initial study from Denmark, and the association may or may not be a causal association. However, thought we can control for time-fixed confounders with the SCCS design, the analysis could suffer from confounding by indications and/or protopathic bias, and results should be interpreted with caution.

12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events/adverse reactions will not be collected or analysed as part of this evaluation. The nature of this non-interventional evaluation, through the use of secondary data, does not fulfil the criteria for reporting adverse events, according to module VI, VI.C.1.2.1.2 of the Good Pharmacovigilance Practices (https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf).

Only in case of prospective data collection, there is a need to describe the procedures for the collection, management, and reporting of individual cases of adverse events/adverse reactions.

13. GOVERNANCE BOARD ASPECTS

IRB approved will be needed for all the databases. SIDIAP, DK-DHR, and CPRD GOLD will require ethical approvals from their local Institutional Review Boards to perform this study. This study has been approved in NLHR.

This process can start after the approval of the protocol. However, we need to take into account that the timeline may be delayed subject to the end of the year.

14. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Dissemination activities to be undertaken will include, although not exclusively, the creation of a final report, scientific publications, and presentations at conferences.

15. OTHER ASPECTS

None.

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17. ANNEXES

Appendix I: List of Stand-Alone documents (e.g. lists with concept definitions (conditions & drugs), validation procedures, questionnaires etc.)

Appendix II: ENCePP checklist for study protocols

Appendix III: Additional Information

Appendix I: Preliminary code list

Hormonal contraceptives

	ATC	Name	Form	Note
High VTE risk	G03AA13	norelgestromin and ethinylestradiol	transdermal patch	Brand name: Evra OMOP concept id: 21078393
	G02BB01	vaginal ring with progestogen and estrogen	vaginal ring	Brand name: NuvaRing (3 weeks + 1)
	G03AA09	desogestrel and ethinylestradiol	oral	
	G03AA10	gestodene and ethinylestradiol	oral	
	G03AA12	drospirenone and ethinylestradiol	oral	
	G03AB05	desogestrel and ethinylestradiol	oral	
	G03AB06	gestodene and ethinylestradiol	oral	
	G03HB01	cyproterone and estrogen	oral	
	G03AA01	etynodiol and ethinylestradiol	oral	tablets containing 50 µg ethinyl oestradiol (selected on the basis of the ethinyl oestradiol dose from WHO ATC code G03A)
	G03AA02	quingestanol and ethinylestradiol	oral	
	G03AA03	lynestrenol and ethinylestradiol	oral	
	G03AA04	megestrol and ethinylestradiol	oral	
	G03AA05	norethisterone and ethinylestradiol	oral	
	G03AA06	norgestrel and ethinylestradiol	oral	
	G03AA07	levonorgestrel and ethinylestradiol	oral	
	G03AA08	medroxyprogesterone and ethinylestradiol	oral	
	G03AA11	norgestimate and ethinylestradiol	oral	
	G03AA13	norelgestromin and ethinylestradiol	oral	
	G03AA15	chlormadinone and ethinylestradiol	oral	
	G03AA16	dienogest and ethinylestradiol	oral	
	G03AB01	megestrol and ethinylestradiol	oral	
	G03AB02	lynestrenol and ethinylestradiol	oral	
	G03AB03	levonorgestrel and ethinylestradiol	oral	
	G03AB04	norethisterone and ethinylestradiol	oral	
	G03AB07	chlormadinone and ethinylestradiol	oral	
	G03AB09	norgestimate and ethinylestradiol	oral	
Medium VTE risk	G03AA01	etynodiol and ethinylestradiol	oral	less than 50 ug ethinyl oestradiol or estradiol in combination with the progestins etynodiol, quingestanol, lynestrenol, megestrol, norethisterone,norgestrel,levonorgestrel,medroxyprogesterone,norgestimate,norelgestromin,nomegestrol,
	G03AA02	quingestanol and ethinylestradiol	oral	
	G03AA03	lynestrenol and ethinylestradiol	oral	
	G03AA04	megestrol and ethinylestradiol	oral	
	G03AA05	norethisterone and ethinylestradiol	oral	
	G03AA06	norgestrel and ethinylestradiol	oral	
	G03AA07	levonorgestrel and ethinylestradiol	oral	
	G03AA08	medroxyprogesterone and ethinylestradiol	oral	
	G03AA11	norgestimate and ethinylestradiol	oral	
	G03AA14	nomegestrol and estradiol	oral	

	G03AA15	chlormadinone and ethinylestradiol	oral	chlormadinone or dienogest
	G03AA16	dienogest and ethinylestradiol	oral	
	G03AA17	medroxyprogesterone and estradiol	oral	
	G03AB01	megestrol and ethinylestradiol	oral	
	G03AB02	lynestrenol and ethinylestradiol	oral	
	G03AB03	levonorgestrel and ethinylestradiol	oral	
	G03AB04	norethisterone and ethinylestradiol	oral	
	G03AB07	chlormadinone and ethinylestradiol	oral	
	G03AB08	dienogest and estradiol	oral	
	G03AB09	norgestimate and ethinylestradiol	oral	
	G03AC06	medroxyprogesterone	injection	Brand name: Depo-Provera (12 weeks interval), Sayana Press (13 week interval)
Low VTE risk	G02BB02	vaginal ring with progestogen	Vaginal ring	
	G03AC01	norethisterone	oral	
	G03AC02	lynestrenol	oral	
	G03AC03	levonorgestrel	oral	
	G03AC04	quingestanol	oral	
	G03AC05	megestrol	oral	
	G03AC06	medroxyprogesterone	oral	Exclude injection
	G03AC07	norgestrienone	oral	
	G03AC08	etonogestrel	implant	Depend on product
	G03AC09	desogestrel	oral	
	G03AC10	drospirenone	oral	
	G02BA03	plastic IUD with progestogen	Intrauterine device	Depend on product

Non-steroidal anti-inflammatory drugs (NSAIDs)

Generic name	WHO ATC codes	Generic name	WHO ATC codes
Acemetacin	M01AB11	Nabumetone	M01AX01
Aceclofenac	M01AB16	Naproxcinod	M01AE18
Alclofenac	M01AB06	Naproxen	M01AE02,M01AE52, M01AE56,M01AE57
Alminoprofen	M01AE16	Niflumic acid	M01AX02
Azapropazone	M01AX04	Nimesulide	M01AX17
Benoxaprofen	M01AE06	Orgotein	M01AX14
Benzydamine	M01AX07	Oxaceprol	M01AX24
Bufexamac	M01AB17	Oxametacin	M01AB13
Bumadizone	M01AB07	Oxaprozin	M01AE12
Celecoxib	M01AH01	Oxyphenbutazone	M01AA03
Clofezone	M01AA05	Parecoxib	M01AH04
Diacerein	M01AX21	Phenylbutazone	M01AA01

Difenpiramide	M01AB12	Piroxicam	M01AC01
Dexibuprofen	M01AE14	Pirprofen	M01AE08
Dexketoprofen	M01AE17	Polmacoxib	M01AH07
Diclofenac	M01AB05, M01AB55	Proglumetacin	M01AB14
Droxicam	M01AC04	Proquazone	M01AX13
Etodolac	M01AB08	Rofecoxib	M01AH02
Etoricoxib	M01AH05	Sulindac	M01AB02
Fenbufen	M01AE05	Suprofen	M01AE07
Fenoprofen	M01AE04	Tenidap	M01AX23
Fentiazac	M01AB10	Tenoxicam	M01AC02
Feprazone	M01AX18,M01AX68	Tiaprofenic acid	M01AE11
Flufenamic acid	M01AG03	Tolfenamic acid	M01AG02
Flunoxaprofen	M01AE15	Tolmetin	M01AB03
Flurbiprofen	M01AE09	Valdecoxib	M01AH03
Ibuprofen	M01AE01, M01AE51	Zomepirac	M01AB04
Ibuproxam	M01AE13	Ketoprofen	M01AE53
Indomethacin	M01AB01,M01AB51	Paracetamol	N02BE01
Indoprofen	M01AE10	Codeine and paracetamol	N02AJ06
Kebuzone	M01AA06		
Ketoprofen	M01AE03		
Ketorolac	M01AB15		
Lonazolac	M01AB09		
Lornoxicam	M01AC05		
Lumiracoxib	M01AH06		
Meclofenamic acid	M01AG04		
Mefenamic acid	M01AG01		
Meloxicam	M01AC06,M01AC56		
Mofebutazone	M01AA02		
Morniflumate	M01AX22		

VTE

Concept id	Concept name	domain	vocabulary
Deep vein thrombosis			
762047	Acute bilateral thrombosis of subclavian veins	Condition	SNOMED
762148	Acute deep vein thrombosis of bilateral iliac veins	Condition	SNOMED
35616028	Acute deep vein thrombosis of left iliac vein	Condition	SNOMED
35615035	Acute deep vein thrombosis of left lower limb following procedure	Condition	SNOMED
35615031	Acute deep vein thrombosis of left upper limb following procedure	Condition	SNOMED
43531681	Acute deep vein thrombosis of lower limb	Condition	SNOMED
35616027	Acute deep vein thrombosis of right iliac vein	Condition	SNOMED
44782746	Acute deep venous thrombosis	Condition	SNOMED
44782751	Acute deep venous thrombosis of axillary vein	Condition	SNOMED
762008	Acute deep venous thrombosis of bilateral axillary veins	Condition	SNOMED

760875	Acute deep venous thrombosis of bilateral calves	Condition	SNOMED
765155	Acute deep venous thrombosis of bilateral ileofemoral veins	Condition	SNOMED
762017	Acute deep venous thrombosis of bilateral internal jugular veins	Condition	SNOMED
762417	Acute deep venous thrombosis of bilateral legs	Condition	SNOMED
762020	Acute deep venous thrombosis of bilateral popliteal veins	Condition	SNOMED
765546	Acute deep venous thrombosis of bilateral tibial veins	Condition	SNOMED
762004	Acute deep venous thrombosis of both upper extremities	Condition	SNOMED
44782742	Acute deep venous thrombosis of calf	Condition	SNOMED
44782747	Acute deep venous thrombosis of femoral vein	Condition	SNOMED
762015	Acute deep venous thrombosis of ileofemoral vein of left leg	Condition	SNOMED
765541	Acute deep venous thrombosis of ileofemoral vein of right lower extremity	Condition	SNOMED
44782748	Acute deep venous thrombosis of iliofemoral vein	Condition	SNOMED
44782752	Acute deep venous thrombosis of internal jugular vein	Condition	SNOMED
762009	Acute deep venous thrombosis of left axillary vein	Condition	SNOMED
760876	Acute deep venous thrombosis of left calf	Condition	SNOMED
765540	Acute deep venous thrombosis of left femoral vein	Condition	SNOMED
765922	Acute deep venous thrombosis of left internal jugular vein	Condition	SNOMED
762418	Acute deep venous thrombosis of left lower extremity	Condition	SNOMED
765537	Acute deep venous thrombosis of left upper extremity	Condition	SNOMED
762022	Acute deep venous thrombosis of politeal vein of right leg	Condition	SNOMED
44782743	Acute deep venous thrombosis of popliteal vein	Condition	SNOMED
762021	Acute deep venous thrombosis of popliteal vein of left leg	Condition	SNOMED
762010	Acute deep venous thrombosis of right axillary vein	Condition	SNOMED
760877	Acute deep venous thrombosis of right calf	Condition	SNOMED
762013	Acute deep venous thrombosis of right femoral vein	Condition	SNOMED
762018	Acute deep venous thrombosis of right internal jugular vein	Condition	SNOMED
762419	Acute deep venous thrombosis of right lower extremity	Condition	SNOMED
762005	Acute deep venous thrombosis of right upper extremity	Condition	SNOMED
44782745	Acute deep venous thrombosis of thigh	Condition	SNOMED
44782744	Acute deep venous thrombosis of tibial vein	Condition	SNOMED
762026	Acute deep venous thrombosis of tibial vein of left leg	Condition	SNOMED
765156	Acute deep venous thrombosis of tibial vein of right leg	Condition	SNOMED
44782421	Acute deep venous thrombosis of upper extremity	Condition	SNOMED
762048	Acute thrombosis of left subclavian vein	Condition	SNOMED
45757410	Acute thrombosis of mesenteric vein	Condition	SNOMED
762049	Acute thrombosis of right subclavian vein	Condition	SNOMED
36712892	Acute thrombosis of splenic vein	Condition	SNOMED
4179911	Axillary vein thrombosis	Condition	SNOMED
44782762	Acute thrombosis of subclavian vein	Condition	SNOMED
37109253	Bilateral acute deep vein thrombosis of femoral veins	Condition	SNOMED
40478951	Bilateral deep vein thrombosis of lower extremities	Condition	SNOMED
4042396	Deep thrombophlebitis	Condition	SNOMED
77310	Deep vein phlebitis and thrombophlebitis of the leg	Condition	SNOMED
4133004	Deep venous thrombosis	Condition	SNOMED
45773536	Deep venous thrombosis of femoropopliteal vein	Condition	SNOMED
763942	Deep venous thrombosis of left lower extremity	Condition	SNOMED
761980	Deep venous thrombosis of left upper extremity	Condition	SNOMED
443537	Deep venous thrombosis of lower extremity	Condition	SNOMED

4133975	Deep venous thrombosis of pelvic vein	Condition	SNOMED
40480555	Deep venous thrombosis of peroneal vein	Condition	SNOMED
4322565	Deep venous thrombosis of profunda femoris vein	Condition	SNOMED
763941	Deep venous thrombosis of right lower extremity	Condition	SNOMED
761928	Deep venous thrombosis of right upper extremity	Condition	SNOMED
4207899	Deep venous thrombosis of tibial vein	Condition	SNOMED
4028057	Deep venous thrombosis of upper extremity	Condition	SNOMED
435565	Embolism and thrombosis of the vena cava	Condition	SNOMED
40481089	Embolism from thrombosis of vein of lower extremity	Condition	SNOMED
4119760	Iliofemoral deep vein thrombosis	Condition	SNOMED
4124856	Inferior mesenteric vein thrombosis	Condition	SNOMED
4096099	Phlebitis of deep veins of lower extremity	Condition	SNOMED
4281689	Phlegmasia alba dolens	Condition	SNOMED
4284538	Phlegmasia cerulea dolens	Condition	SNOMED
46285905	Provoked deep vein thrombosis	Condition	SNOMED
46271900	Recurrent deep vein thrombosis	Condition	SNOMED
4033521	Splenic vein thrombosis	Condition	SNOMED
4055089	Superior mesenteric vein thrombosis	Condition	SNOMED
4230403	Thrombophlebitis of axillary vein	Condition	SNOMED
4069561	Thrombophlebitis of deep femoral vein	Condition	SNOMED
761831	Thrombophlebitis of deep vein of bilateral lower limbs	Condition	SNOMED
761830	Thrombophlebitis of deep vein of left lower limb	Condition	SNOMED
761808	Thrombophlebitis of deep vein of left upper limb	Condition	SNOMED
761832	Thrombophlebitis of deep vein of right lower limb	Condition	SNOMED
761809	Thrombophlebitis of deep vein of right upper limb	Condition	SNOMED
4221821	Thrombophlebitis of deep veins of lower extremity	Condition	SNOMED
440750	Thrombophlebitis of deep veins of upper extremities	Condition	SNOMED
4176614	Thrombophlebitis of iliac vein	Condition	SNOMED
761821	Thrombophlebitis of left deep femoral vein	Condition	SNOMED
761819	Thrombophlebitis of left femoral vein	Condition	SNOMED
761820	Thrombophlebitis of right deep femoral vein	Condition	SNOMED
761818	Thrombophlebitis of right femoral vein	Condition	SNOMED
4110339	Thrombophlebitis of the anterior tibial vein	Condition	SNOMED
4111868	Thrombophlebitis of the common iliac vein	Condition	SNOMED
4110343	Thrombophlebitis of the external iliac vein	Condition	SNOMED
439314	Thrombophlebitis of the femoral vein	Condition	SNOMED
4109877	Thrombophlebitis of the internal iliac vein	Condition	SNOMED
4112171	Thrombophlebitis of the popliteal vein	Condition	SNOMED
4112172	Thrombophlebitis of the posterior tibial vein	Condition	SNOMED
4250765	Thrombophlebitis of tibial vein	Condition	SNOMED
42538533	Thrombosis of iliac vein	Condition	SNOMED
44811347	Thrombosis of internal jugular vein	Condition	SNOMED
765049	Thrombosis of left peroneal vein	Condition	SNOMED
4317289	Thrombosis of mesenteric vein	Condition	SNOMED
4203836	Thrombosis of subclavian vein	Condition	SNOMED
4175649	Thrombosis of the popliteal vein	Condition	SNOMED
4149782	Thrombosis of vein of lower limb	Condition	SNOMED
46285904	Unprovoked deep vein thrombosis	Condition	SNOMED
199837	Portal vein thrombosis	Condition	SNOMED
193512	Embolism and thrombosis of the renal vein	Condition	SNOMED

4111861	Phlebitis of popliteal vein	Condition	SNOMED
440738	Phlebitis of the femoral vein	Condition	SNOMED
Pulmonary embolism			
43530605	Pulmonary embolism with pulmonary infarction	Condition	SNOMED
45768439	Acute pulmonary embolism	Condition	SNOMED
45768888	Acute pulmonary thromboembolism	Condition	SNOMED
440417	Pulmonary embolism	Condition	SNOMED
4120091	Acute massive pulmonary embolism	Condition	SNOMED
4121618	Pulmonary thromboembolism	Condition	SNOMED
37016922	Pulmonary embolism on long-term anticoagulation therapy	Condition	SNOMED
4253796	Pulmonary microemboli	Condition	SNOMED
35615055	Saddle embolus of pulmonary artery with acute cor pulmonale	Condition	SNOMED
40761384	Pulmonary embolism requiring hospitalization	Observation	LOINC
36713113	Saddle embolus of pulmonary artery	Condition	SNOMED
4119607	Subacute massive pulmonary embolism	Condition	SNOMED
762808	Infarction of lung due to embolus	Condition	SNOMED

Covariates (medication)

	ATC
antithrombotic agents	B01A
vitamin K antagonists	B01AA
Antifibrinolytic agents	B02A
2nd generation antipsychotics	N05AL05 N05AE04 N05AX08 N05AX11 N05AX12 N05AX13 N05AH02 N05AH03 N05AH04
low molecular weight heparin	B01AB04 B01AB05 B01AB06 B01AB07 B01AB08 B01AB09 B01AB10 B01AB11 B01AB12

Covariates (conditions)

Concept name	Concept id	**Domain**	**Vocabulary**	Include descendent
Health conditions that are risk factors of VTE				
Edema of lower leg	42709835	Condition	SNOMED	x

Inflammatory bowel disease	4074815	Condition	SNOMED	x
Arthropathy	73553	Condition	SNOMED	X
Behcet's syndrome	436642	Condition	SNOMED	X
Lupus erythematosus	255891	Condition	SNOMED	X
Rheumatoid arthritis	80809	Condition	SNOMED	X
Condition/ treatment for exclusion criteria:				
thrombophilia	4125650	Condition	SNOMED	X
Hysterectomy	4127886	Procedure	SNOMED	X
bilateral ophorectomy				X
Excision of bilateral ovaries	4297990	Procedure	SNOMED	X
sterilisation				
Female sterilization	4246185	Procedure	SNOMED	x
infertility treatment				x
Female infertility therapy	4079372	Procedure	SNOMED	x
Conditions/procedure for censoring of follow up or exclusion of eligible VTE event				
pregnancy	4299535	Observation	SNOMED	x
major trauma				
Traumatic or non-traumatic injury	432795			
Traumatic injury	440921	Condition		x
Fracture				
Fracture of bone	75053	Condition	SNOMED	x

Appendix II: ENCePP checklist for study protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

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

Study title:

DARWIN EU® - – Association of venous thromboembolism with non-steroidal anti-inflammatory drug use in women 15-49 years using hormonal contraceptives

EU PAS Register® number: EUPAS1000000443

Study reference number: P3-C3-008

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]	☒	☐	☐	8.3
1.1.2 End of data collection[2]	☒	☐	☐	8.3
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☐	☐	☒	
1.1.6 Final report of study results	☒	☐	☐	5

Comments:

Study will be registered on EUPAS once approved.				
Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**

[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.

2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6
2.1.2 The objective(s) of the study?	☒	☐	☐	7
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.5
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, other design)	☒	☐	☐	8.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.2
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.8
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	8.8
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)	☒	☐	☐	12

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	8.5
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	8.3
4.2.2 Age and sex	☒	☐	☐	8.5
4.2.3 Country of origin	☒	☐	☐	8.2
4.2.4 Disease/indication	☒	☐	☐	8.6
4.2.5 Duration of follow-up	☒	☐	☐	8.4
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.5

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)	☒	☐	☐	8.6
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☒	☐	☐	8.6.1, 8.8
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	8.6.1

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?	☒	☐	☐	8.8
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.8
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	8.8
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	8.8

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	8.6.3

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)	☐	☐	☒	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☐	☐	☒	
9.1.3 Covariates and other characteristics?	☐	☐	☒	
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.2
9.2.2 Outcomes? (e.g. date of occurrence, multiple events, severity measures related to event)	☒	☐	☐	8.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.2
9.3 Is a coding system described for:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	8.6.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.6.2
9.3.3 Covariates and other characteristics?	☒	☐	☐	8.6.3
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 Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.8
10.2 Is study size and/or statistical precision estimated?	☒	☐	☒	8.7
10.3 Are descriptive analyses included?	☒	☐	☐	8.8
10.4 Are stratified analyses included?	☒	☐	☐	8.8
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	8.8
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	8.8

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
11.2 Are methods of quality assurance described?	☒	☐	☐	10
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?	☒	☐	☐	11
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 uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	8.7

Comments:

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

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?	☐	☐	☒	

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)?	☒	☐	☐	14
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	

Comments:

Name of the main author of the protocol: Xintong Li

Date: dd/Month/year 31/10/2024

Signature: