



Study Protocol

P5-C1-005

DARWIN EU® - Sex differences in treatment patterns for primary hypertension in European countries

01/10/2026

Version 6.0

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Public

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Study title	DARWIN EU® - Sex differences in treatment patterns for primary hypertension in European countries
Protocol version	V6.0
Date	01/10/2026
EUPAS number	EUPAS1000001092
Active Substance	Antihypertensive drugs (ATC classes: C02, C03, C07, C08, C09)
Medicinal Product	Not applicable
Research question and objectives	<p><u>Research question:</u></p> <p>To what extent do treatment patterns for primary hypertension differ between men and women in clinical practice in European countries?</p> <p><u>Study objectives:</u></p> <ol style="list-style-type: none"> 1. To describe antihypertensive treatment initiation for primary hypertension in men and women 2. To describe drug utilisation of antihypertensive treatments, including initial treatment duration and initial dose, in men and women 3. To describe antihypertensive treatment switching patterns in men and women <p>Analyses will be conducted overall and stratified by age groups and pre-existing conditions.</p>
Countries of study	Denmark, Finland, Spain, the Netherlands, the United Kingdom
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LIST OF ABBREVIATIONS

Acronyms/terms	Description
ACEi	Angiotensin-converting enzyme inhibitor(s)
ARB	Angiotensin receptor blocker(s)
ATC	Anatomical Therapeutic Chemical [Classification]
BB	Beta-blocker(s)
CC	Coordinating centre
CCB	Calcium channel blocker(s)
CDM	Common Data Model
CPRD GOLD	Clinical Practice Research Datalink GOLD
CV	Cardiovascular
CVD	Cardiovascular disease
DARWIN EU®	Data Analysis and Real-World Interrogation Network
DK-DHR	Danish Data Health Registries
DKMA	Danish Medicines Agency
DPC	Descendant person-counts
DRE	Digital Research Environment
DTZ	Data Transfer Zone
EHR	Electronic Health Records
EMA	European Medicines Agency
EMC	Erasmus University Medical Center
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EUPAS	EU Post-Authorisation Studies Register
FinOMOP-THL	Finnish Care Register for Health Care
GDPR	General Data Protection Regulation
GP	General Practitioner
ICD	International Classification of Diseases
IDIAPJGol	Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina
IP	Inpatient
IPCI	Integrated Primary Care Information
IQR	Interquartile range
IRB	Institutional Review Board
LOINC	Logical Observation Identifiers Names and Codes
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
OP	Outpatient

Acronyms/terms	Description
Oxford NDORMS	University of Oxford - Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences
RAAS	Renin-angiotensin-aldosterone system
RxNorm	Medical prescription normalised
SIDIAP	The Information System for Research in Primary Care
SNOMED	Systemized Nomenclature of Medicine
WHO	World Health Organization

1. TITLE

DARWIN EU® - Sex differences in treatment patterns for primary hypertension in European countries

2. DESCRIPTION OF THE STUDY TEAM

Study team role	Names	Organisation
Principal Investigator	Ivan Lam	University of Oxford
	Annika Jodicke	University of Oxford
Data Scientist	Nuria Mercade Besora	University of Oxford
	Edward Burn	University of Oxford
Clinical Domain Expert	Albert Prats Uribe	University of Oxford
	Daniel Prieto-Alhambra	University of Oxford, Erasmus MC
Epidemiologist	Xintong Li	University of Oxford
	Amy Lam	University of Oxford
Study Manager	Natasha Yefimenko Nosova	Erasmus MC
Data source	Names	Data Partner Organisation*
Danish Data Health Registries (DK-DHR)	Elvira Bräuner	Danish Medicines Agency (DKMA)
	Susanne Bruun	
Finnish Care Register for Health Care (FinOMOP-THL)	Toni Lehtonen	FinOMOP
The Information System for Research in Primary Care (SIDIAP)	Elena Roel Herranz	Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol)
	Augustina Giuliadori Picco	
	Laura Granés	
	Talita Duarte Salles	
Integrated Primary Care Information (IPCI)	Katia Verhamme	Erasmus University Medical Center (EMC)
	Mees Mosseveld	
	Marcel de Wilde	
	Tineke de Ben	
Clinical Practice Research Datalink GOLD (CPRD GOLD)	Antonella Delmestri	University of Oxford - Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences (Oxford NDORMS)

*Data partners do not have an investigator role. Data partners execute code at their data source, review, and approve their results.

3. ABSTRACT

Title

DARWIN EU® - Sex differences in treatment patterns for primary hypertension in European countries

Rationale and background

Emerging evidence suggests that biological sex may influence the development and progression of hypertension. Although women may be at an increased cardiovascular risk at lower blood pressure levels and often experience poorer blood pressure control following menopause, evidence informing sex-specific management remains scarce. Given the fragmented nature of the existing literature and the lack of consistent, large-scale Real-World Evidence across European healthcare systems, there is a need to better characterise potential sex differences in the management of pharmacological treatment of hypertension.

By evaluating sex-specific patterns in the initiation of antihypertensive drug treatment and subsequent treatment patterns among individuals with primary hypertension, this study aims to identify actionable gaps in care that may inform clinical, regulatory, and public health decision-making.

Research question and objectives

Research question

To what extent do treatment patterns for primary hypertension differ between men and women in clinical practice in European countries?

Objectives

1. To describe antihypertensive treatment initiation for primary hypertension in men and women
2. To describe drug utilisation of antihypertensive treatments, including initial treatment duration and initial dose, in men and women
3. To describe antihypertensive treatment switching patterns in men and women

Analyses will be conducted overall and stratified by age groups and pre-existing conditions.

Methods

Study design

A (new user) cohort study will be conducted using routinely collected health data from 5 data sources from 5 countries across Europe.

Population

Objective 1 (Characterisation of antihypertensive drug treatment initiation)

Inclusion criterion

- First recorded diagnosis of primary hypertension during the recruitment period

Exclusion criteria

- Age <18 years at first recorded diagnosis of primary hypertension (index date)
- Less than 365 days of available history before the index date
- Record of primary hypertension before study start (01/01/2015)
- Record of secondary hypertension on or before the index date
- Record of antihypertensive drug prescription/dispensation before the index date

Objectives 2 and 3 (Drug utilisation of antihypertensive treatment and characterisation of treatment switching patterns)

Inclusion criteria

- First recorded diagnosis of primary hypertension during the recruitment period
- Initiation of antihypertensive drug treatment within 180 days after diagnosis (index date)

Exclusion criteria

- Age <18 years on the date of antihypertensive drug treatment initiation
- Less than 365 days of available history before the date of antihypertensive drug treatment initiation
- Record of primary hypertension before study start (01/01/2015)
- Record of secondary hypertension on the day of or before diagnosis of primary hypertension
- Record of antihypertensive drug prescription/dispensation before first diagnosis of primary hypertension

Variables

Exposure:

Exposure to antihypertensive drug treatment for primary hypertension will be identified as the first prescription or dispensing recorded for antihypertensive drug classes after or on the day of diagnosis of primary hypertension.

Classes of antihypertensive drugs include angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), beta-blockers (BB) excluding topical preparations, calcium channel blockers (CCB), thiazide/thiazide-like diuretics. Two additional groups comprise “other diuretics” and “other antihypertensives”, respectively.

Covariates:

Age, sex, baseline comorbidities (cardiovascular disease (i.e. coronary heart disease, peripheral arterial disease, stroke), heart failure, chronic kidney disease, risk factors for cardiovascular (CV) events (type 2 diabetes, hypercholesterolemia, obesity), and asthma.

Data sources

1. Denmark: Danish Data Health Registries (DK-DHR)
2. Finland: Finnish Care Register for Health Care (FinOMOP-THL)
3. Spain: The Information System for Research in Primary Care (SIDIAP)
4. The Netherlands: Integrated Primary Care Information (IPCI)
5. The United Kingdom: Clinical Practice Research Datalink GOLD (CPRD GOLD)

Study size

No sample size has been calculated, as this is an exploratory study which will not test a specific hypothesis.

Statistical analysis

Objective 1 (Characterisation of antihypertensive drug treatment initiation)

Among individuals with newly diagnosed primary hypertension, initiation of antihypertensive treatment within 180 days following diagnosis will be characterised. The distribution of 7 antihypertensive drug classes/groups, including monotherapy and their respective combination drug treatment, will be described and compared between men and women. The time between hypertension diagnosis and treatment initiation will be described.

Objective 2 (Drug utilisation of antihypertensive treatment)

Among individuals initiating antihypertensive treatment, initial dose and treatment duration will be described for 35 pre-selected ingredients.

Objective 3 (Characterisation of treatment switching patterns)

Treatment pathways following initiation of antihypertensive therapy (7 drug classes/groups and their respective combinations) will be characterised by evaluating changes in antihypertensive drug class throughout follow-up at day 180, 365, and 730 after the index date. Switching patterns and treatment sequences will be described and illustrated in Sankey diagrams and compared between men and women.

Analyses will be conducted overall and stratified by age groups and pre-existing conditions, respectively.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Study milestones and deliverables	Planned dates*
Final Study Protocol	July 2026
Creation of Analytical code	July 2026
Execution of Analytical Code on the data	August 2026
Draft Study Report	September 2026
Final Study Report	To be confirmed by EMA

*Planned dates are dependent on obtaining approvals from the internal review boards of the data sources and deliverables review rounds.

6. RATIONALE AND BACKGROUND

Hypertension is the leading modifiable risk factor for cardiovascular disease (CVD) and premature mortality worldwide, affecting approximately 30% of the adult population.[1, 2] Effective blood pressure control through antihypertensive therapy has been consistently associated with reductions in cardiovascular morbidity and mortality, causing antihypertensive agents to be among the most widely prescribed medications globally.

Antihypertensive drug treatments lower blood pressure through a variety of mechanisms targeting key physiological pathways involved in cardiovascular homeostasis, including the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system activity, vascular tone, cardiac output, and renal sodium handling. Major antihypertensive drug classes, such as angiotensin-converting enzyme inhibitor(s) (ACEi), angiotensin receptor blocker(s) (ARB), calcium channel blocker(s) (CCB), beta-blocker(s) (BB), and diuretics, differ in their mechanisms of action and may offer distinct clinical benefits depending on a patient's comorbidities and overall cardiovascular risk profile.[3] Consequently, treatment recommendations often vary according to clinical characteristics and coexisting conditions.

Emerging evidence suggests that biological sex may also influence the development and progression of hypertension.[4] There is a marked increase in hypertension prevalence in women after menopause, accompanied by accelerated vascular ageing and a rise in cardiovascular risk. Sex hormones, particularly oestrogen, interact with the RAAS and other vascular regulatory pathways, influencing endothelial function, arterial stiffness, inflammation, and target-organ damage.[5] These mechanisms may contribute to sex-specific differences in blood pressure regulation, cardiovascular risk, and, potentially, treatment response. However, despite growing recognition of these biological differences, current clinical guidelines generally provide similar treatment recommendations for men and women, largely due to the limited availability of robust evidence supporting sex-specific antihypertensive treatment strategies.

The 2023 Arterial Hypertension Guidelines of the European Society of Hypertension highlighted the persistent underrepresentation of women in both clinical trials and real-world studies.[6] Although women may be at increased cardiovascular risk at lower blood pressure levels (at all ages) and often experience poorer blood pressure control following menopause, evidence informing sex-specific management remains scarce. As a result, important questions remain regarding whether treatment patterns differ between men and women in routine clinical practice and whether such differences may contribute to disparities in outcomes.

Given the fragmented nature of the existing literature and the lack of consistent, large-scale Real-World Evidence across European healthcare systems, there is a need to better characterise potential sex differences in hypertension management.

As part of the broader European Medicines Agency's (EMA) Women's Health Initiative, the current study aims to evaluate sex-specific patterns in the initiation of antihypertensive drug treatment and subsequent treatment patterns among individuals with primary hypertension, to identify actionable gaps in care that may inform clinical, regulatory, and public health decision-making.

7. RESEARCH QUESTION AND OBJECTIVES

Research questions

To what extent do treatment patterns for primary hypertension differ between men and women in clinical practice in European countries?

Research objectives

1. To describe antihypertensive treatment initiation for primary hypertension in men and women
2. To describe drug utilisation of antihypertensive treatments, including initial treatment duration and initial dose, in men and women
3. To describe antihypertensive treatment switching patterns in men and women

Analyses will be conducted overall and stratified by age groups and pre-existing conditions.

8. RESEARCH METHODS

8.1. Study design

A (new user) cohort study will be conducted using routinely collected health data from 5 data sources from 5 countries across Europe to:

- describe antihypertensive drug treatment initiation at drug class level (7 drug classes/groups and their respective combinations) for primary hypertension in men and women (Objective 1).
- describe the initial duration and initial dose of use of the five most commonly used antihypertensives for each drug class (35 pre-selected ingredients) (Objective 2).
- describe antihypertensive drug treatment switching patterns at drug class level (7 drug classes/groups and their respective combinations) (Objective 3).

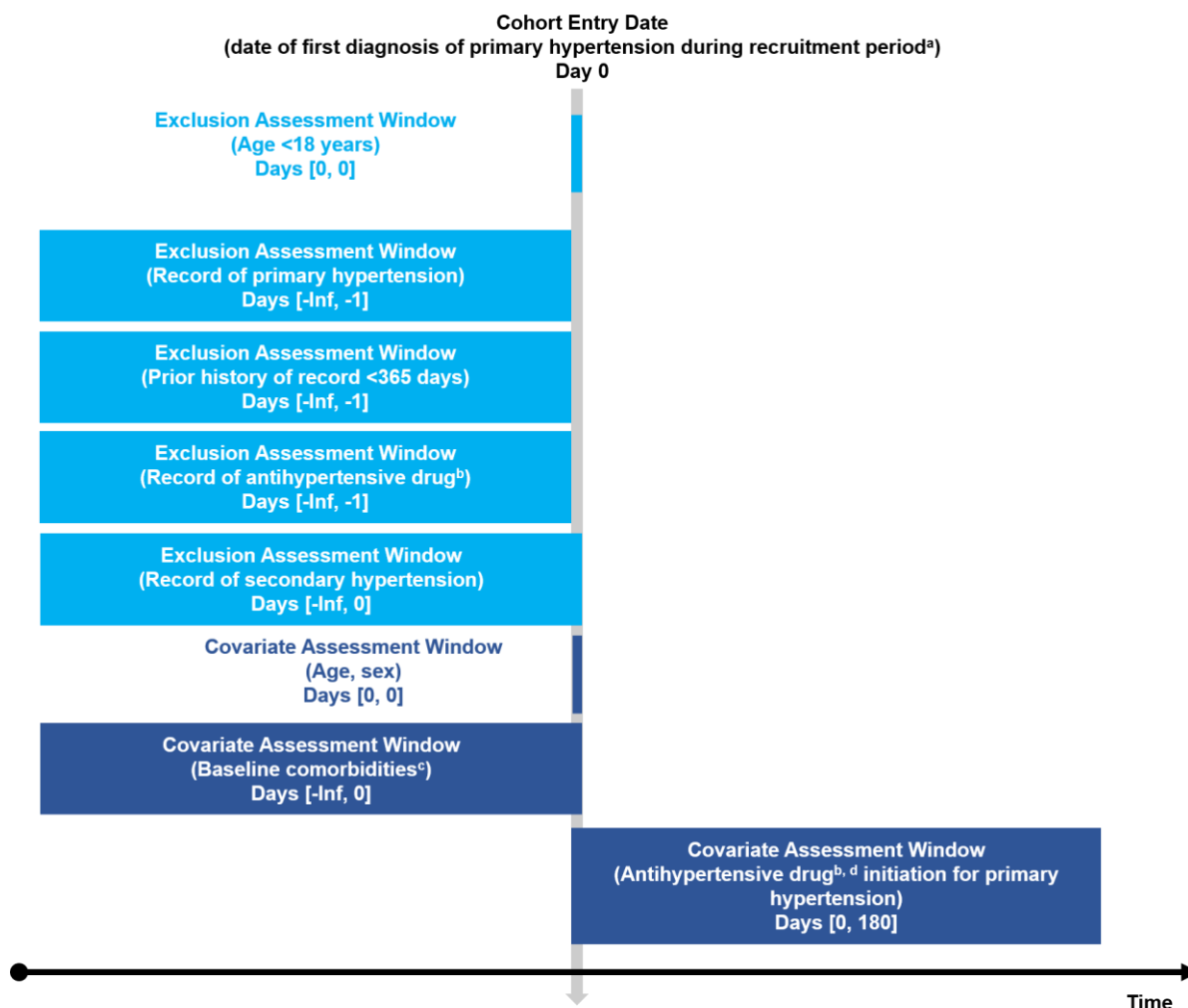


Figure 1. Graphical depiction of the study design of Objective 1.

- a. Recruitment period will be from 01/01/2015 to the earliest of 180 days before the end of the data source observation period or 180 days before the end of study period.
- b. Antihypertensive drugs include ACEi, ARB, BB, CCB, thiazide/thiazide-like diuretics, other diuretics, and other antihypertensives.
- c. Baseline comorbidities for characterisation include cardiovascular disease, coronary heart disease, peripheral arterial disease, aortic disease, stroke, heart failure, chronic kidney disease, asthma, type 2 diabetes, obesity, and hypercholesterolemia. Baseline comorbidities for stratification include cardiovascular disease, heart failure, chronic kidney disease, asthma, and type 2 diabetes/hypercholesterolemia/obesity.
- d. Antihypertensive drugs will be assessed at class level. Monotherapy and combination regimen will be treated as mutually exclusive treatment options.

ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; BB = beta-blockers; CCB = calcium channel blockers.

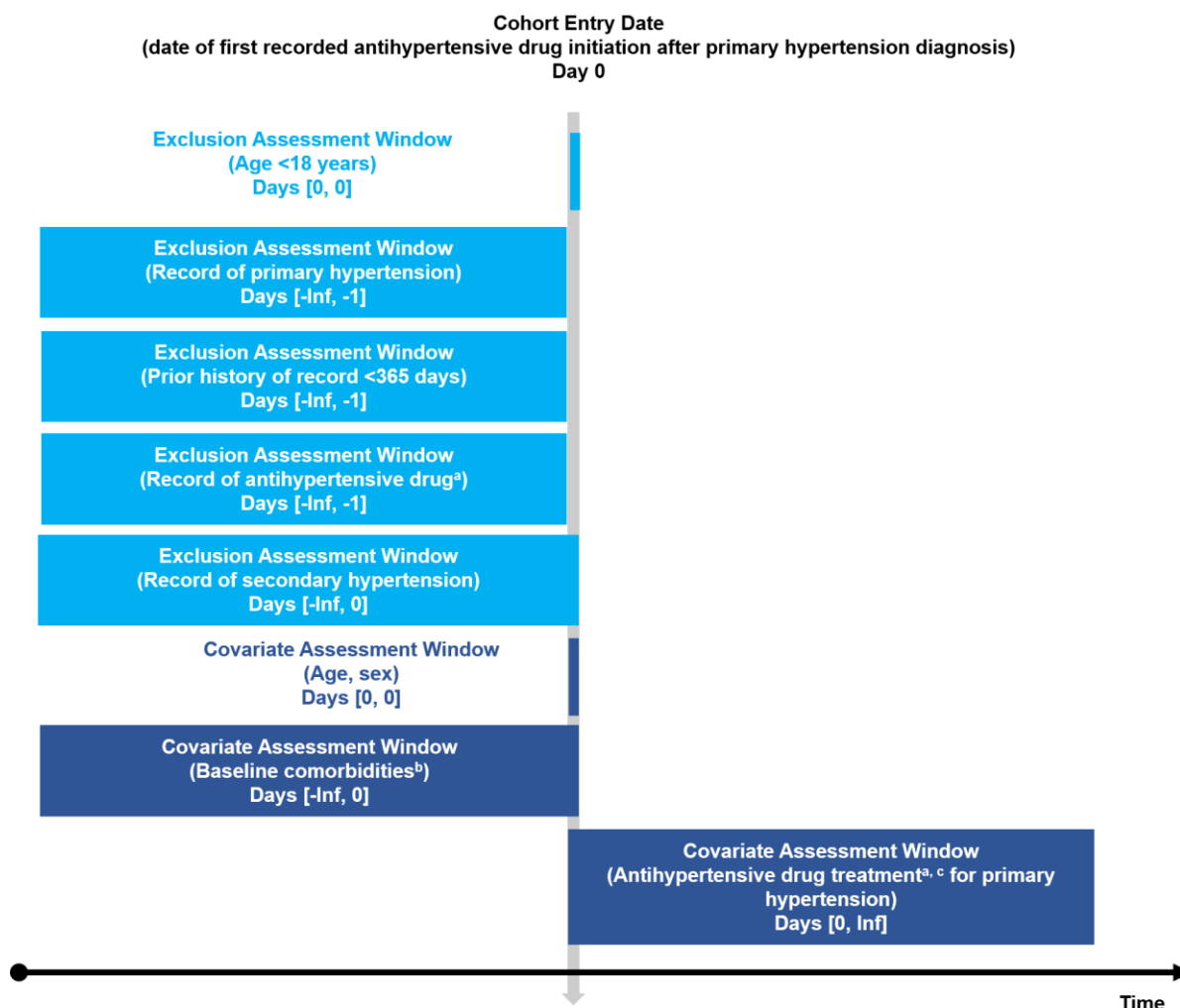


Figure 2. Graphical depiction of the study design of Objective 2.

- a. Antihypertensive drugs include ACEi, ARB, BB, CCB, thiazide/thiazide-like diuretics, other diuretics, and other antihypertensives.
- b. Baseline comorbidities for characterisation include cardiovascular disease, coronary heart disease, peripheral arterial disease, aortic disease, stroke, heart failure, chronic kidney disease, asthma, type 2 diabetes, obesity, and hypercholesterolemia. Baseline comorbidities for stratification include cardiovascular disease, heart failure, chronic kidney disease, asthma, and type 2 diabetes/hypercholesterolemia/obesity.
- c. Treatment duration of first drug era (with gap era of 90 days) and initial dose of first drug exposure record will be assessed at ingredient level for the most common antihypertensives per drug class/group.

ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; BB = beta-blockers; CCB = calcium channel blockers.

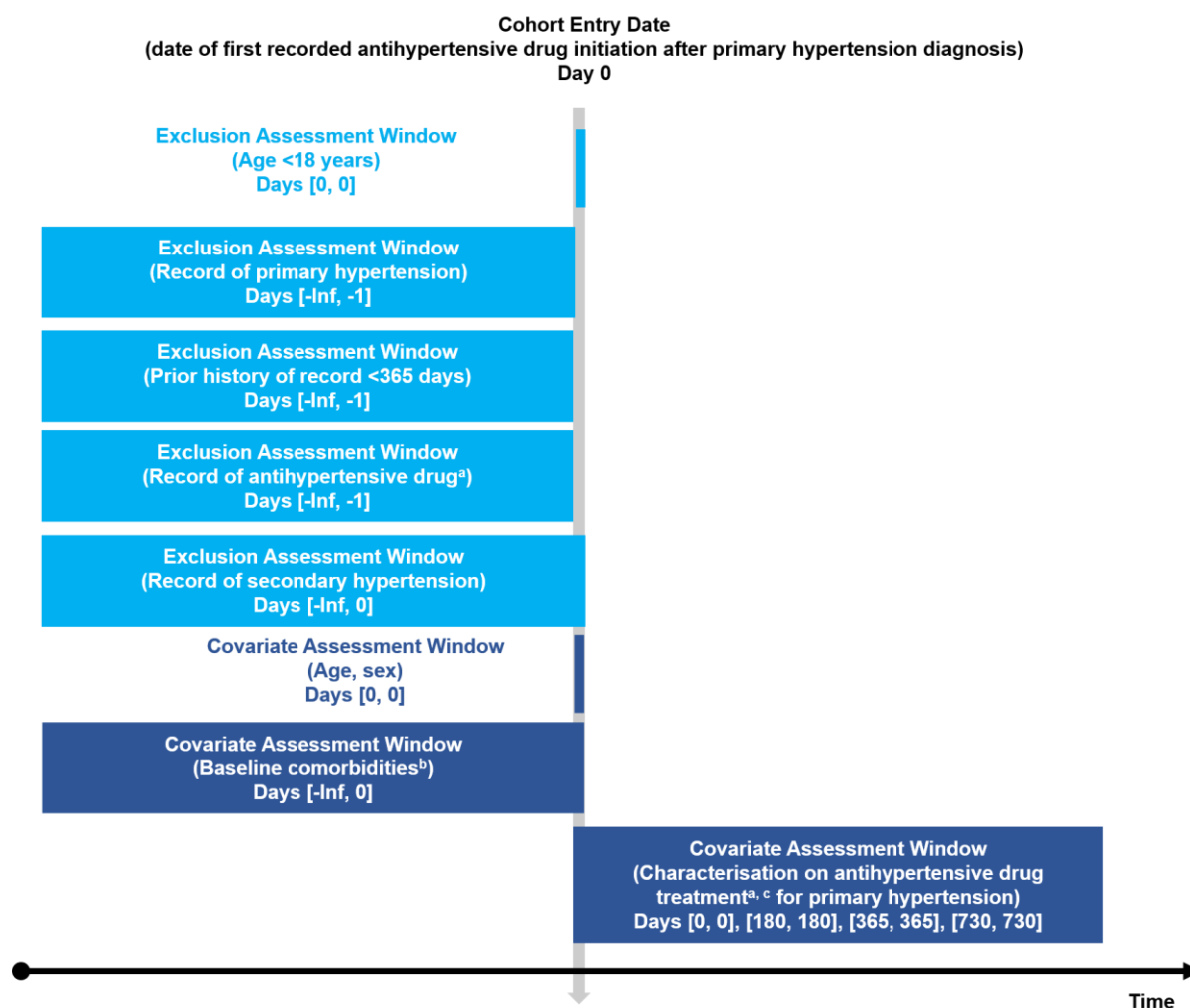


Figure 3. Graphical depiction of the study design of Objective 3.

- Antihypertensive drugs include ACEi, ARB, BB, CCB, thiazide/thiazide-like diuretics, other diuretics, and other antihypertensives.
- Baseline comorbidities for characterisation include cardiovascular disease, coronary heart disease, peripheral arterial disease, aortic disease, stroke, heart failure, chronic kidney disease, asthma, type 2 diabetes, obesity, and hypercholesterolemia. Baseline comorbidities for stratification include cardiovascular disease, heart failure, chronic kidney disease, asthma, and type 2 diabetes/hypercholesterolemia/obesity.
- Characterisation of antihypertensive drug treatment for primary hypertension will be conducted at class level (ACEi, ARB, BB (excluding topical preparations), CCB, thiazide/thiazide-like diuretics, other diuretics, or other antihypertensives). Each single-class or combination regimen will be treated as a mutually exclusive treatment option.

ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; BB = beta-blockers; CCB = calcium channel blockers.

8.2. Follow-up

Specific follow-up for Objectives 1–3:

Objective 1: Follow-up will start on the date of first diagnosis of primary hypertension (index date) recorded after the study start in 01/2015. Follow-up will end on the earliest of loss to follow-up, death, end of the observation period (the latest available data), the study end date (31/12/2025), or 180 days after the index date. A 180-day assessment window was selected to ensure that antihypertensive treatment initiation is associated with the diagnosis of primary hypertension while allowing sufficient time to capture individuals who initially undergo lifestyle modification before initiating pharmacological treatment.

Objective 2: For analyses describing initial dose and duration, follow-up will start on the date of antihypertensive drug treatment initiation (index date). Follow-up will end on the earliest of loss to follow-up, death, end of the observation period (the latest available data), or the study end date (31/12/2025).

Objective 3: For the characterisation of antihypertensive treatment switching patterns between drug classes/groups and their respective combinations, follow-up will start on the date of antihypertensive drug treatment initiation (index date). Follow-up will end on the earliest of loss to follow-up, death, end of the observation period (the latest available data), the study end date (31/12/2025), or 730 days after the index date.

8.3. Study population with inclusion and exclusion criteria

Objective 1 (Characterisation of antihypertensive drug treatment initiation)

Inclusion criterion: First recorded diagnosis of primary hypertension during the recruitment period

Exclusion criteria

- Age <18 years at first recorded diagnosis of primary hypertension (index date)
- Less than 365 days of available history before the index date
- Record of primary hypertension before study start (01/01/2015)
- Record of secondary hypertension on or before the index date
- Record of antihypertensive drug prescription/dispensation before the index date

Objectives 2 and 3 (Drug utilisation of treatment and characterisation of treatment switching patterns)

Inclusion criteria

- First recorded diagnosis of primary hypertension during the recruitment period
- Initiation of antihypertensive drug treatment within 180 days after diagnosis (index date)

Exclusion criteria

- Age <18 years on the date of antihypertensive drug treatment initiation
- Less than 365 days of available history before the date of antihypertensive drug treatment initiation
- Record of primary hypertension before study start (01/01/2015)
- Record of secondary hypertension on the day of or before diagnosis of primary hypertension
- Record of antihypertensive drug prescription/dispensation before the first diagnosis of primary hypertension

8.4. Study setting and data sources

This study will be conducted using routinely collected data from five primary and secondary care data sources in the DARWIN EU® Network of Data Partners from five European countries. All data were *a priori* mapped to the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM).

Table 1. Data sources.

Country	Name of Data source	Health Care setting	Type of Data	Number of active individuals	Calendar period covered by each data source
Denmark	Danish Data Health Registries (DK-DHR)	Community pharmacies, secondary care — specialists, hospital inpatient care	Registries	6.0M	1st January 2015 to 31st December 2025
Finland	Finnish Care Register for Health Care (FinOMOP-THL)	Primary care, secondary care — specialists (ambulatory or hospital OP care), hospital IP care	EHR, Registries	6.2M	1st January 2015 to 31st December 2025
Spain	The Information System for Research in Primary Care (SIDIAP)	Primary care data source + linkage to hospital data	EHR	6.1M	1st January 2015 to 31st December 2024
The Netherlands	Integrated Primary Care Information (IPCI)	Primary care	EHR	1.3M	1st January 2015 to 31st December 2025
The United Kingdom	Clinical Practice Research Datalink (CPRD GOLD)	Primary care	EHR	2.4M	1st January 2015 to 1st December 2025

EHR = electronic health record; IP = inpatient; M = million; OP = outpatient.

Data sources selection

These data sources fulfil the criteria required in terms of data quality, completeness, timeliness, availability to conduct the study within the required timelines, and representativeness for patient-level drug utilisation study while covering different regions of Europe ([Annex II](#)).

8.5. Study period

The study period is from 01/01/2015 to 31/12/2025 or the date of the most recent data available for each contributing data source.

The study recruitment period is from 01/01/2015 to the earliest of 180 days before the end of the data source observation period or 180 days before the end of the study period.

8.6. Variables

8.6.1. Exposure

Diagnosis of primary hypertension

All individuals with an incident (first recorded) diagnosis of primary hypertension recorded during the study period will be selected. Primary hypertension will be defined as:

(i) Condition or observation of primary/essential hypertension, or (ii) Measurement of systolic blood pressure equal to or over 140mmHg or diastolic blood pressure equal to or over 90mmHg, on at least two different days within one year (if blood pressure measurements are available in the respective data source). A "narrow" definition of primary hypertension will be included as sensitivity analysis.

Individuals with a specific diagnosis of secondary hypertension recorded on the same day of the incident (primary) hypertension diagnosis or any time before (assessment window [-Inf, 0] days) will be excluded.

Antihypertensive drugs and drug classes

Exposure to antihypertensive drug treatment for primary hypertension will be identified as the first recorded prescription or dispensing for an antihypertensive drug (ingredient) or a combination of antihypertensive drugs (ingredients) after or on the day of diagnosis of incident primary hypertension. For DK-DHR, CPRD GOLD, IPCI, and SIDIAP, prescription records will be used, whereas for FinOMOP-THL, dispensation records will be used.

For each ingredient or concomitantly prescribed or dispensed ingredients, treatment episodes of sequential prescription or dispensation records (i.e. drug era) of the same single ingredient or concomitantly prescribed or dispensed ingredients will be generated. A maximum of 90 days between the end date of one prescription or dispensation record (based on the prescription/dispensation end date recorded) and the start date of the next prescription or dispensation record (i.e. definition of gap) will be allowed for them to be combined to continuous treatment eras.

By concatenating individual drug exposure records into a combined drug era, the drug era represents the duration during which the individual is likely to be using the corresponding antihypertensive drugs (ingredients).

Antihypertensive drug classes comprise ACEi, ARB, BB, CCB, thiazide/thiazide-like diuretics, and two additional groups were defined to comprise "other diuretics (e.g. high-ceiling diuretics)", and "other antihypertensives (e.g. aliskiren)". Antihypertensive drug classes/groups and respective ingredients include the following:

- ACEi: benazepril, captopril, cilazapril, enalapril, fosinopril, imidapril, lisinopril, moexipril, perindopril, quinapril, ramipril, spirapril, temocapril, trandolapril, zofenopril
- ARB: azilsartan, candesartan, eprosartan, fimasartan, irbesartan, losartan, olmesartan, telmisartan, valsartan
- BB (excluding topical preparations): acebutolol, alprenolol, atenolol, betaxolol, bevantolol, bisoprolol, bopindolol, bupranolol, carteolol, carvedilol, celiprolol, esmolol, labetalol, landiolol, mepindolol, metipranolol, metoprolol, nadolol, nebivolol, oxprenolol, penbutolol, pindolol, practolol, propranolol, sotalol, talinolol, tertatolol, timolol
- CCB: amlodipine, benidipine, bepridil, cilnidipine, clevidipine, diltiazem, felodipine, fendiline, gallopamil, isradipine, lercanidipine, levamlodipine, lidoflazine, manidipine, mepirodipine, mibefradil, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, perhexiline, verapamil
- Thiazides/thiazide-like diuretics: althiazide, bendroflumethiazide, buthiazide, chlorothiazide, chlorthalidone, clopamide, cyclopenthiazide, cyclothiazide, epithiazide, hydrochlorothiazide, hydroflumethiazide, indapamide, mebutizide, mefruside, methyclothiazide, meticrane, metolazone, polythiazide, quinethazone, trichlormethiazide, xipamide
- "Other diuretics": amiloride, bumetanide, canrenoate, canrenone, cicletanine, clofenamide, clorexolone, conivaptan, eplerenone, ethacrynate, etozolin, finerenone, furosemide, mersalyl, muzolimine, pirtanide, spironolactone, theobromine, tienilic acid, tolvaptan, torsemide, triamterene, rilmenidine, trimazosin, trimethaphan, urapidil

- “Other antihypertensives”: aliskiren, ambrisentan, aprocitentan, bethanidine, bieteaserpine, bosentan, cadralazine, clonidine, debrisoquin, delapril hydrochloride, deserpidine, diazoxide, dihydralazine, doxazosin, guanabenz, guanethidine, guanfacine, guanoxan, hydralazine, indoramin, ketanserin, macitentan, mecamlamine, methoserpidine, methyl dopa, metyrosine, minoxidil, moxonidine, nitroprusside, pargyline, picodralazine, pinacidil, prazosin, rescinnamine, reserpine, rilmenidine, riociguat, sitaxentan, trimazosin, trimethaphan, urapidil

The preliminary concept sets used for the identification of primary hypertension are described in [Annex IV](#). These codes will be refined during the study execution, following the standard DARWIN EU® phenotyping processes, which involve the review of code lists by clinical experts and the review of phenotypes after their execution in the participating data sources. For instance, based on results from diagnostics, it might be necessary to restrict the definition of “primary hypertension” to using recorded hypertension diagnoses without blood pressure measurements. Concept sets for antihypertensive drugs are also available in [Annex IV](#).

Due to the large number of antihypertensive ingredients, the following ingredients have been prioritised for estimation of the initial dose and duration in Objective 2. Feasibility person-counts in the five contributing data sources for all antihypertensive ingredients have been generated to select the five most commonly used antihypertensive ingredients per drug class/group (presented in descending order):

- ACEi: enalapril, ramipril, lisinopril, perindopril, captopril
- ARB: losartan, candesartan, valsartan, telmisartan, irbesartan
- BB (excluding topical preparations): bisoprolol, propranolol, metoprolol, atenolol, timolol
- CCB: amlodipine, lercanidipine, nifedipine, felodipine, diltiazem
- Thiazides/thiazide-like diuretics: hydrochlorothiazide, bendroflumethiazide, indapamide, chlorthalidone, metolazone
- “Other diuretics”: furosemide, spironolactone, amiloride, bumetanide, torsemide
- “Other antihypertensives”: doxazosin, clonidine, moxonidine, minoxidil, prazosin

Complete feasibility person-counts are available in [Annex V](#).

8.6.2. Covariates, including confounders, effect modifiers, and other variables

All analyses will be conducted separately for men and women.

Objective 1 (Characterisation of antihypertensive drug treatment initiation)

The following covariates will be characterised on the date of first diagnosis of primary hypertension (index date), with selected covariates being used for stratification (i.e. age groups, 5 pre-defined comorbidities, as shown below)

- Age at the index date (median, interquartile range (IQR))
- Age groups at index date (N, %)
 - 18 – 29
 - 30 – 49
 - 50 – 64 years
 - 65+ years
- Comorbidities, with assessment window [-Inf, 0] days relative to the index date (N, %)

- cardiovascular disease (including coronary heart disease, peripheral arterial disease, stroke)
- heart failure
- chronic kidney disease
- elevated cardiovascular (CV) risk (including type 2 diabetes, hypercholesterolemia, obesity)
- asthma
- Measurements, with assessment window [-365, 0] days relative to the index date (median, IQR)
 - systolic blood pressure
 - diastolic blood pressure
- Time from the index date to treatment initiation (median, IQR)

Objectives 2 and 3 (Drug utilisation of treatment and characterisation of treatment switching patterns)

The following covariates, identified on the date of initiation of antihypertensive drug treatment (index date), will be used for stratification:

- Age groups at the index date
 - 18 – 29
 - 30 – 49
 - 50 – 64 years
 - 65+ years
- Comorbidities, with assessment window [-Inf, 0] days relative to the index date
 - cardiovascular disease (including coronary heart disease, peripheral arterial disease, stroke)
 - heart failure
 - chronic kidney disease
 - elevated CV risk (including type 2 diabetes, hypercholesterolemia, obesity)
 - asthma

The preliminary concept sets used for the identification of covariates are described in [Annex IV](#). Codes for identifying covariates will be reviewed and finalised through the on-going DARWIN EU® - Population demographics and disease frequency across the DARWIN EU® Network study ([EUPAS1000000962](#)).

8.7. Study size

No sample size has been calculated, as this study will not test a specific hypothesis. In addition, already collected available data will be used to estimate patient characteristics, treatment characteristics, and treatment switching patterns. Thus, the sample size is driven by the availability of data for individuals with exposure of antihypertensive drugs in the participating data sources. Preliminary feasibility person-counts for the included antihypertensive drugs are available in [Annex V](#).

8.8. Analysis

8.8.1. Federated network analyses

All analyses will be conducted separately for each data source and will be carried out in a federated manner, allowing analyses to be run locally without sharing individuals-level data.

Before sharing the study package, test runs of the analytics will be performed on a subset of the data sources, and quality control checks will be performed. After all the tests are passed (see [Annex III](#)), the final package will be released in a version-controlled study repository for execution against all the participating data sources.

8.8.2. Data privacy protection

The data partners will locally execute the analytics against the OMOP CDM in R Studio and review and approve the default aggregated results. They will then be made available to the Principal Investigators and study team in a secure online repository of the Data Transfer Zone (DTZ). All results will be locked and timestamped for reproducibility and transparency. The study results of all data sources will be checked, after which they are made available to the team, and the Study Dissemination Phase can start. All analyses will be conducted separately for each data source, and will be carried out in a federated manner, allowing analyses to be run locally without sharing patient-level data. Cell counts <5 will be suppressed when reporting results to comply with the data source's privacy protection regulations.

8.8.3. Statistical model specification and assumptions of the analytical approach considered

All analyses will be conducted separately for men and women and will subsequently be stratified by age group and pre-defined comorbidities ([Section 8.6.2](#)).

Objective 1 (Characterisation of antihypertensive drug treatment initiation)

Characterisation of antihypertensive drug treatment initiation for primary hypertension will be conducted based on OMOP CDM mapped data using the R package *CohortCharacteristics*, developed by DARWIN EU[®]. [7]

The index date will be defined as the date of first diagnosis of primary hypertension. Incident treatment will be assessed with the assessment window [0, 180] days relative to the index date. The first-ever record of antihypertensive drug after diagnosis of primary hypertension will be considered as the initial antihypertensive drug treatment. Combinations of multiple classes of antihypertensive drug treatments, e.g. the prescription or dispensation of ingredients belonging to different drug classes/groups on the same date, which is the date of antihypertensive drug treatment initiation, will be allowed. Single antihypertensive drug classes (e.g. ACEi, BB, CCB) and combinations of drug classes (e.g. ACEi + BB, ACEi + CCB) will be reported as mutually exclusive groups, i.e. an individual with a first prescription of ACEi + BB will only be included in the ACEi + BB group, and not in the single antihypertensive drug classes for ACEi and BB, respectively.

The number and proportion of individuals who initiated antihypertensive drug treatments, at drug class/group level (single or combination, mutually exclusive groups), among those diagnosed with primary hypertension, will be reported. The median (IQR) time between the index date (incident hypertension diagnosis) and treatment initiation will be reported. Age will be reported as median (IQR). Baseline comorbidities will be assessed with the assessment window [-Inf, 0] relative to the index date and will be reported as number and proportion.

Objective 2 (Drug utilisation of antihypertensive treatment)

Drug utilisation analyses for antihypertensive drug treatment for primary hypertension will be conducted based on OMOP CDM mapped data using the R package *DrugUtilisation*, developed by DARWIN EU[®].

The index date will be defined as the date of initiation of antihypertensive treatment for primary hypertension. Initial dose and initial treatment duration will be described at the drug ingredient level, for the five most commonly used ingredients per antihypertensive drug class/group and for monotherapy only.

Initial dose will be determined by the daily dose prescribed/dispensed on the index date. Treatment episodes of sequential prescriptions (i.e. drug era) of the same drug ingredient that have a maximum of 90 days between the end date of one prescription and the start date of the next prescription (i.e. definition of gap), will be generated. Initial treatment duration will be determined by the duration of the first drug era. Initial dose and initial treatment duration will be reported as median (IQR).

Objective 3 (Characterisation of treatment switching patterns)

Characterisation of treatment switching patterns in individuals who started antihypertensive treatment will be conducted based on OMOP CDM mapped data using the R package *PatientProfiles*, developed by DARWIN EU®.

The index date will be the date of initiation of the antihypertensive drug treatment for primary hypertension. Analyses of treatment switching patterns will be conducted at drug class level. Drug eras will be computed, allowing for 90 days between subsequent prescription of ingredients of the same drug class. Antihypertensive drug treatment for primary hypertension will be determined on day 0 (index date), day 180, day 365, and day 730. Similar to Objective 1, combinations of ingredients belonging to different antihypertensive drug classes as treatment on the index date will be allowed. Number and proportion of individuals receiving each treatment option will be reported at each assessment time point. Sankey diagrams will be used to illustrate switching patterns.

8.8.4. Output

Study output will include the following:

A PDF report, including an executive summary and the following tables and figures.

- Table 1. Characteristics of baseline covariates and antihypertensive treatment in individuals with primary hypertension, separately for men and women.
- Table 2. Characteristics of baseline covariates and antihypertensive treatment in individuals with primary hypertension, separately for men and women, and stratified by age group.
- Table 3. Drug utilisation for antihypertensive treatments for primary hypertension, separately for men and women.
- Figure 1–5. Sankey plot for treatment switching patterns in men, per data source.
- Figure 6–10. Sankey plot for treatment switching patterns in women, per data source.

Mock tables and figures are available in [Annex VI](#).

Analyses stratified by baseline comorbidities will be available in the Shiny app. An interactive dashboard will be generated by incorporating all the results (tables and figures) included in the PDF report mentioned above.

8.9. Evidence synthesis

Results from analyses described in [Section 8.8.3](#) will be presented separately for each data source. No meta-analysis of results will be conducted.

9. STRENGTHS AND LIMITATIONS

The study will be informed by routinely collected health care data, and so, data quality issues must be considered.

Initial dose and duration of exposure will be assessed for selected drug ingredients. Heterogeneity in drug data recording might affect the consistency of drug exposure duration and dose information across data sources. Therefore, careful diagnostic procedures to inspect drug records within each data source will be essential to ensure accurate and reliable results.

Due to the large number of antihypertensive ingredients, only the five most commonly used antihypertensive drug ingredients were selected from each drug class. Selection was based on the number of individuals (person-counts) with a prescription of an antihypertensive ingredient in each data source: For each ingredient, the person-counts were then summed across the five contributing data sources. This approach might lead to data sources with larger populations dominating the number and choice of selected antihypertensive ingredients. However, when comparing the five most commonly used drug ingredients across all data sources with the five most commonly used drug ingredients within each individual data source, the currently selected antihypertensive ingredients in each class include at least three of the five most commonly used antihypertensive drug ingredients in every data source, indicating that the selected ingredients are representative of their respective drug classes. Moreover, this selection is based on preliminary feasibility person-counts without considering treatment indication or dosage form. Therefore, these feasibility counts may have included users who received prescriptions for indications different from hypertension. Baseline characterisation of conditions such as heart failure, cardiovascular disease, or renal impairment, for which selected antihypertensives are included in the respective treatment guidelines, will illustrate (potentially) overlapping indications and allow for the assessment of differences in comorbidities in men and women treated with antihypertensives.

Several of the antihypertensive treatments included for this study are also indicated for the treatment of other cardiovascular conditions. While this study requires a diagnosis of hypertension within the last 6 months to identify a prescription as new antihypertensive treatment and will conduct stratified analyses to assess the impact of comorbidities on treatment choice, the actual indication for a prescription is not well recorded in most data sources. Therefore, it cannot be ruled out that antihypertensives were initiated for additional reasons/indications on top of blood pressure lowering effects.

The documentation of comorbidities required for population characterisation may vary across data sources. To ensure consistent definitions of comorbidities, a careful phenotyping process will be conducted for the selected comorbidities, using the DARWIN EU® - Population demographics and disease frequency across the DARWIN EU® Network study ([EUPAS1000000962](#)). To ensure complete capture of primary hypertension diagnoses, both condition records for primary hypertension/essential hypertension and blood pressure measurement records will be used.

Additionally, the results estimated from this study will only reflect the populations represented in the included data sources. Electronic health records have inherent limitations because they are collected for clinical purposes rather than primarily for research. Consequently, the use of five primary care or national linked registries data sources from Denmark, Finland, Spain, the Netherlands, and the United Kingdom limits the generalisability of the findings to these countries.

10. REFERENCES

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7. Du M, Prats-Urbe A, Mercade-Besora N, Lopez-Guell K, Guo Y, Alcalde-Herraiz M, et al. CohortCharacteristics: an R package for population characterisation in observational studies using the OMOP common data model. *Eur J Epidemiol*. 2026.

11. ANNEXES

ANNEX I. Description of data sources

Denmark: Danish Data Health Registries (DK-DHR)

#	Section	Description
1	Data source identification and country	DK-DHR (Danish Data Health Registries) Denmark
2	Data partner information section	Danish Medicines Agency (DKMA) Data & Data Analysis (DAD)
3	Coverage and timespan	Data collection since: 1995 Extent: Nation-wide. The data is representative of the entire Danish population.
4	Healthcare setting / type of data	Community pharmacists, and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care. The following data elements are collected: diagnosis (including rare diseases and pregnancy data), hospital admissions, discharge and ICU data, Cause of death, Drug prescriptions, dispensing, vaccination and contraception, Procedures (surgical and non-surgical hospital), and Sociodemographic information (sex and age only).
5	Data collection process	Outpatient electronic health records, and Inpatient hospital electronic health records, and Registries, and Other. All causes of deaths, all retrieved drug prescriptions, all records of vaccinations, all hospital inpatient and outpatients contacts including disease diagnoses and hospital surgical and non-surgical procedures, histologically confirmed incident cancers, laboratory test results for the entire Danish population from 1/1/1995 onwards.
6	General representativeness	The data is representative of the entire Danish population. Healthcare is free in Denmark, so we do not expect any bias in data collection based on socio-economic status.
7	Data content / source coding	Diagnoses and causes of death are collected using the ICD-10 vocabulary. ATC and RxNorm are used for Drugs. SNOMED codes are used for Procedures.
8	Data Harmonisation	The data has been mapped to the OMOP CDM v5 and the OMOP standard vocabularies. The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. Patients have unique identifiers used to link datasets.
9	Quality control (data source specific)	The data we have received relating to nationwide Danish Health Data registries offer an opportunity for large-scale, population-based studies with several advantages 1) Their large size improves the precision of estimates and enables the study of rare exposures and outcomes with long-term latency, 2) Inclusion of nearly all individuals in the target population ensures that the data reflect routine clinical care and all clinical segments of the source population, 3) Data are collected independently of each research study, thus minimising certain types of bias, e.g., non-response, and the influence from attention to the research question on the diagnostic process. Before the source data is sent to us, the Danish Health Data Authority runs and does comprehensive checks of the registry table data validity of the variables, breaks in data, changes in variable coding, missingness, etc. We perform checks of missingness/completeness in relation to requested variables. In essence, we are receiving a dump of a mirror of the data that is controlled by the SDS. The documentation performed by SDS is available online, in Danish primarily https://www.esundhed.dk/Dokumentation (all variables), but also in English https://sundhedsdatastyrelsen.dk/da/english/health_data_and_registers/national_health_registers
10	Linkage	There is no linkage in this data source.
11	Vital status	The Cause of Death registry (DAR) is used, the cause of death is collected using ICD-10 codes.

#	Section	Description
12	Limitations	<ul style="list-style-type: none"> - Lifestyle factors (such as smoking status and weight) are only complete for pregnant women. - Stillborn children will not have any records in our CDM. This means that e.g. birth weight and birth length of stillborns is not recorded. - There is no information on key socio-economic status (SES) factors, such as occupation, education, and income. - Patient contacts in primary care (visits to the GP) are not included. Consequently, the incidence of chronic diseases like Type 2 Diabetes (T2D) and asthma must be determined using drug prescriptions as a proxy.
13	Main references	Schmidt M, Schmidt SAJ, Adelborg K, Sundbøll J, Laugesen K, Ehrenstein V, Sørensen HT "The Danish health care system and epidemiological research: from health care contacts to database records." Clinical epidemiology (2019): 31372058
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111217 Website: https://sundhedsdatastyrelsen.dk/da/english/health_data_and_registers/healthdatadenmark

Finland: Finnish Care Register for Health Care (FinOMOP-THL)

#	Section	Description
1	Data source identification and country	FinOMOP-THL (Finnish Care Register for Health Care) Finland
2	Data partner information section	FinOMOP (FinOMOP) The Department of Data and Analytics
3	Coverage and timespan	Data collection since: 1998 Extent: Nation-wide. The current CDM population comprises all persons having been alive and residing in Finland since the beginning of 2011.
4	Healthcare setting / type of data	<p>Primary care – General Practitioner, and primary care specialists (e.g. paediatricians), and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care, and other (specify).</p> <p>THL maintains health registers that cover both public and private, primary, and specialised inpatient, urgent and outpatient health care encounters in Finland, starting from 2011. The entire public sector and private inpatient encounters have been included since 2011, while private outpatient encounters, including occupational care, are included since 2020.</p> <p>Since 1998, the Care Register for Health Care (TerveysHilmo) has covered both public outpatient and inpatient specialized care and private inpatient care. Since 2009, the Finnish National Vaccination Register has covered all vaccinations from the public sector and from a large part of private vaccination providers, with the data coverage from both sections being very good to complete from 2020 onwards.</p> <p>Since 2011, the Register of Primary Health Care Visits (AvoHilmo) has covered public primary care. Since 2020, the register has also covered private outpatient care and occupational care.</p> <p>In addition, the CDM also contains positive COVID-19 test results from the Finnish National Infectious Diseases Register. The register itself covers all laboratory confirmations for around 70 specific microbes from 1995 onwards, but only COVID-19 has currently been mapped to the CDM.</p> <p>The CDM also includes prescription records from multiple different sources. Both Care Register for Health Care and Register of Primary Health Care Visits contain very basic prescription data recorded during health care encounters that include just the ATC-code and trade name of medication. More comprehensive prescription data from Kanta Prescription Centre, maintained by Social Insurance Institution of Finland (Kela), has been integrated into the CDM since its 2024 release. The Kanta Prescription records are based electronic prescriptions, which were adopted by most public health care providers in 2010 and by most private providers by 2017.</p>
5	Data collection process	Outpatient electronic health records, and Inpatient hospital electronic health records, and Registries. Data is entered by clinicians upon healthcare contact and processed by THL (Kela in the case of Kanta Prescription Centre).

#	Section	Description
6	General representativeness	The THL data has national coverage and is therefore well representative of the Finnish population. Using the complete population as a basis for the person table also serves to facilitate calculations on a population level, e.g. incidence rates.
7	Data content / source coding	The following coding systems have been OMOP-mapped, typically to a good level of completeness: ICD10fi Finnish Extension, ICPC-2, ATC, Toimenpideluokitus (procedure classification adapted from the Nordic Classification of Surgical Procedures (NCSP)), Terveystieteiden tutkimuskeskusten erikoissalat (Hilmo specific provider speciality), Rokotustapa (AR/YDIN National classification for vaccine administration), Tupakointistatus (AR/YDIN National classification for smoking status). Vaccinations are identified on product level based on batch number, trade name, vaccine title, and ATC-code. This is mapped on brand and type in the OMOP CDM.
8	Data Harmonisation	The data has been mapped to the OMOP CDM v5 and the OMOP standard vocabularies. The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. Each patient in THL has a unique identifier.
9	Quality control (data source specific)	The source data collection undergoes a structural and semantic validation before entry into the source database. Additionally, some coded variables undergo quality assessment against the respective code systems post entry into the database. The source registers are also assessed for completeness and coverage, with the aim of improving future collection in the areas where data is lacking.
10	Linkage	THL is already a linkage of multiple Finnish registries (see above).
11	Vital status	The National Population registry data forms the basis for forming the patient population. This ensures an up-to-date location (municipality of residence) of patients, as well as complete death occurrences (although not the cause of death).
12	Limitations	<p>All drug records in the CDM are currently based on prescriptions. Kanta Prescription Centre also includes information on drug dispensings, but these have not currently been converted into OMOP CDM. Depending on the type of the medication, a single prescription can be for up to two years dosage of the drug. This means a patient can have up to two-year breaks between observations while actively using the drug. Observation of a prescription also does not mean that the patient necessarily bought or used the medication.</p> <p>The CDM does not currently have meaningful end dates or days of supply for drug exposure. This information is not available for Care Register for Health Care or Register of Primary Health Care Visits, and for Kanta Prescription Centre it is only available in unstructured, free-form format that has not been converted into OMOP CDM. The source system for prescription drug data is only available to the DP until Dec-2023, therefore drug_exposure records from this source are only available in that time range.</p> <p>Some vital signs, like height and weight measurements, are recorded even if the person has not been actually measured, just that the measurement is deemed relevant to the condition or it's treatment. This may lead to duplicate measurements as the value from previous visit might be taken. Not all private health care records are covered for the CDM's entire follow-up time from 2011 onwards. For Register of Primary Health Care Visits and Finnish National Vaccination Register, records from private health care have been available from 2020 onwards. For Kanta Prescription Centre, the coverage of private health care records has been good from 2017 onwards. The inclusion of private health care mainly presents itself as an increase in the number of observations, meaning that it has to be accounted for when interpreting any time series data from the CDM.</p>
13	Main references	Häkkinen, Pirjo; Mölläri, Kaisa; Saukkonen, Sanna-Mari; Väyrynen, Riikka; Mielikäinen, Lasse; Järvelin, Jutta "Hilmo - Sosiaali- ja terveydenhuollon hoitoilmoitus 2020 : Määrittelyt ja ohjeistus : Voimassa 1.1.2020 alkaen" Terveystieteiden tutkimuskeskusten erikoissalat (2019):
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111187 ; https://catalogues.ema.europa.eu/data-source/1111191 Website: https://thl.fi/en/statistics-and-data/data-and-services/register-descriptions ; https://www.kanta.fi/en/research-and-knowledge-management

Spain: The Information System for Research in Primary Care (SIDIAP)

#	Section	Description
1	Data source identification and country	SIDIAP (The Information System for Research in Primary Care) Catalunya, Spain
2	Data partner information section	Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol)
3	Coverage and timespan	Data collection since: 2006 Extent: Regional. SIDIAP is a database of primary care electronic health records of the population of Catalonia, North-East Spain. It contains pseudo-anonymised records of more than 8 million people, of which 6.1 million are active as of 2022, representing around 76% of the Catalan population.
4	Healthcare setting / type of data	Primary care – General Practitioner, and hospital inpatient care. SIDIAP captured data includes routine visits, socio-demographics, diagnoses, laboratory tests, drugs (prescribed and dispensed), referrals, sick leaves and lifestyle information.
5	Data collection process	Outpatient electronic health records, and Inpatient hospital electronic health records. Data is entered by primary care physicians upon healthcare contact, supplemented with hospital discharge records. The Institut Català de la Salut (Catalan Health Institute) is the data controller.
6	General representativeness	It was previously shown that the captured SIDIAP population is highly representative of the entire Catalan region in terms of geographic, age, and sex distributions.
7	Data content / source coding	SIDIAP data covers all services that occur at the Primary Care Centres, as well as support services, such as sexual and reproductive health or home end-of-life care. Drugs are coded in ATC-WHO terminology in the source data. Health outcomes are captured in ICD-10CM codes. The SIDIAP contains all laboratory tests and results performed in primary health centres. Demographics, geographical, as well as socio-economic factors are recorded for each patient.
8	Data Harmonisation	The data has been mapped to the OMOP CDM v5 and the OMOP standard vocabularies. The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. A patient has a unique id, also upon changing practice or re-registration.
9	Quality control (data source specific)	Internal and external validation processes are carried out to determine the data quality of the SIDIAP information at each data update. These include stratifying the data by geographical regions and year in order to identify differences in data collection that need to be harmonized (e.g. recording of specific information under different codes). The measurement units of variables measuring one characteristic are also homogenized (e.g. transformation of the data from every laboratory that measures haemoglobin to grams per decilitre). Visual inspection of all data included in the database by week is also conducted, allowing one to see temporal patterns in the registry of a certain variable. With this information, the SIDIAP team can issue recommendations to researchers about the most common variable(s) where certain information is recorded (e.g., there are several variables with information concerning the women's menopausal status and with these visual inspection tools the SIDIAP team can inform the researchers about which related variables have the largest number of records and could be more helpful to capture menopause). Data availability (longitudinally and reliability), plausibility (range checks and unusual values), and consistency are inspected through visualisation tools. In addition, before accessing the data for a requested project, research teams have access to a quality-control report. This document contains counts, years, percentiles, maximums and minimums, incidences, and prevalence of the data requested for the project, allowing detection of inconsistencies in the data extraction prior to data delivery. External validation processes of the SIDIAP database mainly include assessing the data recorded in SIDIAP through linkage to external gold standard data sources, by analysing free text, or by sending questionnaires to health professionals.

#	Section	Description
10	Linkage	SIDIAP is linked to a hospital discharge database, pharmacy dispensation, and primary care laboratories. It can also be linked to other registries in Catalonia on a project by project basis.
11	Vital status	Mortality is fully captured in SIDIAP. The cause of death is not available, but can be linked to the Spanish death registry on a project by project basis.
12	Limitations	The SIDIAP data is not representative of individuals not using public primary care, and conditions that are usually followed by specialist care might not be properly captured. In addition, there is limited information on lifestyle variables. Patients are followed until Death or when transferring to another primary health care centre that does not contribute to SIDIAP.
13	Main references	Recalde M, Rodríguez C, Burn E, Far M, García D, Carrere-Molina J, Benítez M, Moleras A, Pistillo A, Bolívar B, Aragón M, Duarte-Salles T "Data Resource Profile: The Information System for Research in Primary Care (SIDIAP)." International journal of epidemiology (2022): 35415748
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/50190 Website: https://www.sidiap.org/index.php/en

The Netherlands: Integrated Primary Care Information (IPCI)

#	Section	Description
1	Data source identification and country	IPCI (Integrated Primary Care Information) the Netherlands
2	Data partner information section	Erasmus University Medical Center (EMC) Department of Medical Informatics
3	Coverage and timespan	Data collection since: 2006 Extent: Nation-wide. IPCI is a Dutch database that contains patient records from 2006 onwards. However, it mainly covers the central part of the country, including the most densely populated area (the 'Randstad') and non-urban areas. IPCI contains information on all patients registered with GPs responsible for non-emergency care and referrals. A patient is registered at birth or at first encounter with the GP.
4	Healthcare setting / type of data	Primary care – General Practitioner. Data is collected from primary care EHR. This includes demographic information, complaints and symptoms, diagnoses, laboratory test results, lifestyle factors (in limited amount), and correspondence with secondary care, such as referral and discharge letters.
5	Data collection process	Outpatient electronic health records. Data is entered into the EHR system by the GPs, during or after the visit. The patient dossiers are collected by Erasmus MC data managers and combined in one harmonized database. Several checks are done on this database to ensure correct data processing. Persons can have dossiers at multiple GPs.
6	General representativeness	More than 99% of the Dutch population has health insurance, and almost all citizens are registered with a general practitioner. Over 12 months, around 78% of the population has at least one contact with their GP. IPCI included around 350 GP practices out of around 5000 in the country (~ 7%). The demographic composition of the IPCI population mirrors that of the general Dutch population in terms of age and sex.
7	Data content / source coding	Dutch GPs use mainly Dutch standard codes, like ICPC-1 and Diagnostische Bepalingen maintained by NHG. And for therapy the G-Standard is used, maintained by ZIndex.
8	Data Harmonisation	The data has been mapped to the OMOP CDM v5 and the OMOP standard vocabularies. The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. Patients can be registered under different IDs, but since a patient can only be registered at one GP at a time, the observations periods will not overlap.

#	Section	Description
9	Quality control (data source specific)	<p>Prior to each data release, extensive quality control steps are performed, e.g., comparison of patient characteristics between practices, and checks to identify abnormal temporal data patterns in practices. For each practice, around 200 quality indicators are obtained. Of these indicators, a quarter refer to population characteristics, e.g. number of birth and mortalities relative to practice size, temporal consistency. The other indicators are based on medical data, e.g. distribution of measurement values, frequencies of diagnoses and procedures relative to age, completeness of data. The indicators are combined in a couple of quality scores for each practice. For these scores, cut-off values for acceptable quality have been defined. Practices with a score below a cut-off are excluded for research. This approach has shown to be very important, for example to check if data from practices that just joined the database are at an acceptable level of quality. The details of the approach, like the cut-off values for acceptance, are based on years of experience. In addition, trends are compared with the previous database release.</p> <p>Extensive quality control steps are performed before each data release. These include comparing patient characteristics between practices and checks to identify abnormal temporal data patterns in practices. Additional checks include over 200 indicators related to population characteristics (e.g., reliability of birth and mortality rates) and medical data (e.g., availability of durations of prescriptions and completeness of laboratory results). Records of low quality are excluded from the database.</p>
10	Linkage	Linkage requires additional approval steps and needs to be assessed on a case-by-case basis. IPCI is not routinely linked with other databases.
11	Vital status	Vital status (death date and cause) is collected based on GP records.
12	Limitations	<p>The main limitation comes with the fact that IPCI is limited to GP records, and although it contains information on referrals and discharge letters, it may not fully capture specific hospital information.</p> <p>Capture of oral contraceptives in IPCI is incomplete. The first prescription is recorded within the patient's medical file but not the subsequent prescriptions. If you want to use IPCI data for research questions on oral contraceptives, you can do that but then you need to select those GPs that use MEDICOM as software system (where you have prescribing and dispensing). However, of hormone substitution therapy, the information on prescribing is COMPLETE. IPCI does not include coded/detailed data about medications/procedures/test results from the hospital or other care-providers.</p>
13	Main references	de Ridder MAJ, de Wilde M, de Ben C, Leyba AR, Mosseveld BMT, Verhamme KMC, van der Lei J, Rijnbeek PR "Data Resource Profile: The Integrated Primary Care Information (IPCI) database, The Netherlands." International journal of epidemiology (2022): 35182144
14	Link to HMA-EMA catalogue and data source webpage	<p>HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/42618</p> <p>Website: http://www.ipci.nl</p>

The United Kingdom: Clinical Practice Research Datalink GOLD (CPRD GOLD)

#	Section	Description
1	Data source identification and country	CPRD GOLD (Clinical Practice Research Datalink GOLD) the United Kingdom
2	Data partner information section	University of Oxford - Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences (Oxford NDORMS) NDORMS
3	Coverage and timespan	<p>Data collection since: 1987</p> <p>Extent: Nation-wide.</p> <p>CPRD GOLD consists of patients in contributing practices using Vision software. Historically this covered the whole of the UK, but the number of contributing practices in the England is dropping. In January 2025 only 3 practices from England were a part of CPRD GOLD, while historical patient data were from the whole of the UK, and will continue to be so. In the future,</p>

#	Section	Description
		no practices from England will be present, only practices from Scotland, Wales, and Northern Ireland.
4	Healthcare setting / type of data	Primary care – General Practitioner, and primary care specialists (e.g. paediatricians), and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care. CPRD GOLD data include patient demographics, biological measurements, clinical symptoms and diagnoses, referrals to specialist/hospital and their outcome, laboratory tests/results, and prescribed medications.
5	Data collection process	Outpatient electronic health records. Data are entered by clinicians into the EHR. Data is processed by CPRD that provides data releases for research.
6	General representativeness	In the last 10 years, the CPRD GOLD regional distribution of currently contributing general practitioner (GP) practices has significantly shifted, resulting in many new practices joining from Scotland, Wales, and Northern Ireland, and fewer participating from England. These changes have affected the CPRD GOLD population size, regional coverage, and eligibility for data linkages. CPRD GOLD January 2024 contains >21.3 million historical and current patients (12.9 in England, 3.1 in Wales, 4.7 in Scotland, 0.7 in Northern Ireland). Of these, nearly 3 million are currently registered in a GP practice and represent ~4.3% of the estimated current UK population (0.1% in England, 32.3% in Wales, 28.6% in Scotland, 16.2% in Northern Ireland). Patients currently registered in CPRD GOLD January 2024 are broadly representative of the UK population with respect to age and sex. Reference: https://doi.org/10.1093/ije/dyaf077
7	Data content / source coding	Gemscript, Read, dm+d
8	Data Harmonisation	The data has been mapped to the OMOP CDM v5 and the OMOP standard vocabularies. The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. In GOLD, a patient can be registered under different ID numbers upon changing practice or re-registration. Researchers are not able to identify these patients, as the data are anonymised. However, GOLD covers less than 5% of the current UK GP practices and it is unlikely that an individual who does change GP practice ends up in another GP practice which uses the Vision software and accepts the CPRD data collection agreement. The very small number of duplicated IDs will have different observation periods and should not have an impact on the data analyses.
9	Quality control (data source specific)	CPRD GOLD only includes practices whose data quality is assessed to be up-to-standard (UTS). Each practice is associated to an UTS date set when the data quality standards become satisfactory, and CPRD recommend using only longitudinal data starting from this UTS date. Every time CPRD collect the EHR from a practice, checks are run for the data quality standards, and if they are not adequate, the EHR is not accepted. When the data quality becomes acceptable again, CPRD updates the practice UTS date. CPRD also checks data quality standards at the patient level, and associates each patient with a flag, reporting if its data are acceptable for clinical research. Only patients with acceptable data quality are included in the population to be mapped to CDM.
10	Linkage	CPRD GOLD can be linked to several sources, however our Oxford OMOP CDM is only linked to the CPRD GOLD Ethnicity Record and to the CPRD Townsend Deprivation Index at the Practice Level.
11	Vital status	The date of death in CPRD GOLD has been validated against the Population registry (ONS) mortality data. Reference: https://doi.org/10.1002/pds.4747
12	Limitations	The main limitation is due to the fact that CPRD GOLD is limited to GP records, and although it contains information on referrals and discharge letters, it may not fully capture specific hospital information. Events from hospital and specialist care are not covered.
13	Main references	Sanchez-Santos MT, Axson EL, Dedman D, Delmestri A "Data Resource Profile Update: CPRD GOLD." International journal of epidemiology (2025): 40499193

#	Section	Description
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111113 Website: https://www.cprd.com/data/primary-care-data/cprd-gold

ANNEX II. Fitness for use assessment

Danish Data Health Registries (DK-DHR)

DK-DHR will be included in this study because it is a registry data source that provides relevant information on prescription records of antihypertensives in the general adult population.

Moreover, data availability and follow-up in DK-DHR is sufficient, as data availability starts in 1995, and the date of the most recent data extraction is 4th June 2026, which aligns with the study period.

There are no study specific limitations present in DK-DHR.

Lastly, DK-DHR has blanket Institutional Review Board (IRB) approval, which makes the execution of this study feasible within the current study timelines.

Finnish Care Register for Health Care (FinOMOP-THL)

FinOMOP-THL will be included in this study because it is a primary and secondary care data source that provides relevant information on prescription records of antihypertensives in the general adult population.

Moreover, data availability and follow-up in FinOMOP-THL is sufficient, as data availability starts in 1998, and the date of the most recent data extraction is 14th April 2026, which aligns with the study period.

There are no study specific limitations present in FinOMOP-THL.

Lastly, IRB approval for FinOMOP-THL is estimated to take 1–3 months, which makes the execution of this study feasible within the current study timelines.

The Information System for Research in Primary Care (SIDIAP)

SIDIAP will be included in this study because it is a primary and secondary care data source that provides relevant information on prescription records of antihypertensives in the general adult population.

Moreover, data availability and follow-up in SIDIAP is sufficient, as data availability starts in 2006, and the date of the most recent data extraction is 31st December 2024, which aligns with the study period.

There are some study specific limitations present in SIDIAP, namely the absence of data from 31st December 2024 onward.

Lastly, IRB approval for SIDIAP is estimated to take 1–3 months, which makes the execution of this study feasible within the current study timelines.

Integrated Primary Care Information (IPCI)

IPCI will be included in this study because it is a primary care data source that provides relevant information on prescription records of antihypertensives in the general adult population.

Moreover, data availability and follow-up in IPCI is sufficient, as data availability starts in 2006, and the date of the most recent data extraction is 19th April 2026, which aligns with the study period. The median follow-up of the first observation period in IPCI is 1,830 days.

There are no study specific limitations present in IPCI.

Lastly, IPCI has blanket IRB approval, which makes the execution of this study feasible within the current study timelines.

Clinical Practice Research Datalink GOLD (CPRD GOLD)

CPRD GOLD will be included in this study because it is a primary care data source that provides relevant information on prescription records of antihypertensives in the general adult population.

Moreover, data availability and follow-up in CPRD GOLD is sufficient, as data availability starts in 1987, and the date of the most recent data extraction is 1st December 2025, which aligns with the study period.

There are some study specific limitations present in CPRD GOLD, namely the absence of data from 1st December 2025 onward.

Lastly, CPRD GOLD has blanket IRB approval, which makes the execution of this study feasible within the current study timelines.

ANNEX III. Operational and reporting considerations

DATA MANAGEMENT

Data management

All data sources 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 standardised analytics wherever possible. Each data partner will execute the study code against their data source 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.

Data storage and protection

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

All data sources used in this study are already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses will be run, which generate non-identifiable aggregate summary results.

The output files are stored in the DARWIN EU® Digital Research Environment (DRE). These output files do not contain any data that allow identification of subjects included in the study. The DRE implements further security measures to ensure a high level of stored data protection to comply with the local implementation of the General Data Protection Regulation (GDPR) (EU) 679/2016 in the various member states.

QUALITY CONTROL

Data source quality control

When defining drug cohorts, non-systemic products will be excluded from the list of included codes summarised on the ingredient level.

When defining cohorts for indications, a systematic search of possible codes for inclusion will be identified using the *CodelistGenerator* R package (<https://github.com/darwin-eu/CodelistGenerator>). This package allows the user to define a search strategy and will use this to query the vocabulary tables of the OMOP common data model so as to find potentially relevant codes. In addition, the *PhenotypeR* (<https://github.com/OHDSI/phenotypeR>) and *DrugExposureDiagnostics* (<https://cran.r-project.org/web/packages/DrugExposureDiagnostics/index.html>) R packages will be run, if needed, to assess the use of different codes across the data sources contributing to the study and identify any codes potentially omitted in error. The *DrugExposureDiagnostics* package evaluates ingredient-specific attributes and patterns in drug exposure records.

The study code will be based on DARWIN EU® R packages: *DrugUtilisation* (<https://github.com/darwin-eu/DrugUtilisation/>) to characterise the drug use, and *CohortCharacteristics* (<https://github.com/darwin-eu/CohortCharacteristics/>) and *PatientProfiles* (<https://github.com/darwin-eu/PatientProfiles/>) to characterise the cohort. These packages will include numerous automated unit tests to ensure the validity

of the codes, alongside software peer review and user testing. The R package will be made publicly available via GitHub.

PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A PDF report including an executive summary, and the specified tables and/or figures will be submitted to EMA by the DARWIN EU® CC upon completion of the study.

An interactive dashboard incorporating all the results (tables and figures) will be provided alongside the PDF report. The full set of underlying aggregated data used in the dashboard will also be made available, if requested.

ANNEX IV. List of concepts

Table S1. Preliminary list of concept IDs on conditions for defining primary and secondary hypertension.

Concept ID	Concept Name	Vocabulary
Hypertension (Broad)		
193493	Benign hypertensive renal disease	SNOMED
195556	Hypertensive heart AND renal disease	SNOMED
201313	Hypertensive renal disease	SNOMED
312648	Benign essential hypertension	SNOMED
312938	Hypertensive encephalopathy	SNOMED
313502	Benign hypertensive heart disease without congestive heart failure	SNOMED
314369	Malignant hypertensive heart disease without congestive heart failure	SNOMED
314378	Hypertensive heart disease with congestive heart failure	SNOMED
316866	Hypertensive disorder	SNOMED
316994	Malignant hypertensive heart disease with congestive heart failure	SNOMED
317895	Renovascular hypertension	SNOMED
317898	Malignant essential hypertension	SNOMED
319034	Hypertensive heart disease without congestive heart failure	SNOMED
320128	Essential hypertension	SNOMED
376965	Hypertensive retinopathy	SNOMED
377551	Blind hypertensive eye	SNOMED
439694	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure	SNOMED
439695	Hypertensive heart and renal disease with renal failure	SNOMED
439696	Hypertensive heart and renal disease with (congestive) heart failure	SNOMED
439698	Benign hypertensive heart disease with congestive cardiac failure	SNOMED
442603	Malignant hypertensive heart AND renal disease	SNOMED
442604	Hypertensive heart disease	SNOMED
442626	Benign hypertensive heart AND renal disease	SNOMED
442766	Malignant hypertensive renal disease	SNOMED
443919	Hypertensive renal failure	SNOMED
444101	Hypertensive heart failure	SNOMED
764011	Benign hypertensive heart disease and chronic renal disease	SNOMED
1340364	Exacerbation of hypertensive disorder	OMOP Extension
3174555	Hypertensive cerebrovascular disease	Nebraska Lexicon
4028741	Benign hypertension	SNOMED
4032952	Renal sclerosis with hypertension	SNOMED
4033353	Hypertensive leg ulcer	SNOMED
4049389	Paroxysmal hypertension	SNOMED
4058987	High-renin essential hypertension	SNOMED

Concept ID	Concept Name	Vocabulary
Hypertension (Broad)		
4108213	Hypertension secondary to drug	SNOMED
4159755	Labile essential hypertension	SNOMED
4167358	Diastolic hypertension	SNOMED
4173820	Cardiomegaly due to hypertension	SNOMED
4180283	Systolic essential hypertension	SNOMED
4183981	Malignant hypertensive heart disease	SNOMED
4209293	Systolic hypertension	SNOMED
4227517	Hypertensive choroidopathy	SNOMED
4228419	Hypertensive optic neuropathy	SNOMED
4242878	Sustained diastolic hypertension	SNOMED
4262182	Hypertension with albuminuria	SNOMED
4263067	Low-renin essential hypertension	SNOMED
4263504	Benign hypertensive heart disease	SNOMED
4276511	Labile diastolic hypertension	SNOMED
4289933	Malignant hypertension	SNOMED
4302748	Chronic hypertensive uremia	SNOMED
4317265	Ischemic ulcer of skin due to arterial hypertension	SNOMED
36684653	Hypertension with disorder of right retina	SNOMED
36684718	Hypertension with disorder of left retina	SNOMED
36684780	Bilateral hypertension with disorder of retinas	SNOMED
36712757	Cardiomyopathy due to hypertension	SNOMED
36713024	Labile systemic arterial hypertension	SNOMED
37208172	Resistant hypertensive disorder	SNOMED
37208293	Multiple drug intolerant hypertension	SNOMED
40481896	Hypertensive urgency	SNOMED
42538697	Diastolic hypertension and systolic hypertension	SNOMED
42599748	Cardiac hypertrophy secondary to systemic hypertension	SNOMED Veterinary
42709887	Hypertensive complication	SNOMED
43020424	Hypertensive emergency	SNOMED
43021748	Hypertensive nephrosclerosis	SNOMED
43021852	Malignant hypertensive chronic kidney disease	SNOMED
44782429	Chronic kidney disease due to hypertension	SNOMED
44782728	Hypertensive heart AND chronic kidney disease with congestive heart failure	SNOMED
44783643	Intermittent hypertension	SNOMED
44784439	Benign hypertensive renal disease with renal failure	SNOMED
44784621	Hypertensive heart and chronic kidney disease	SNOMED

Concept ID	Concept Name	Vocabulary
Hypertension (Broad)		
44784637	Hypertensive heart AND chronic kidney disease on dialysis	SNOMED
44809026	Stage 1 hypertension (NICE - National Institute for Health and Clinical Excellence 2011)	SNOMED
44809027	Severe hypertension (NICE - National Institute for Health and Clinical Excellence 2011)	SNOMED
44809548	Hypertension resistant to drug therapy	SNOMED
44809569	Stage 2 hypertension (NICE - National Institute for Health and Clinical Excellence 2011)	SNOMED
44811110	Nocturnal hypertension	SNOMED
44811932	Stage 1 hypertension (NICE 2011) without evidence of end organ damage	SNOMED
44811933	Stage 1 hypertension (NICE 2011) with evidence of end organ damage	SNOMED
45757787	Postpartum pre-existing essential hypertension	SNOMED
45768449	Hypertensive crisis	SNOMED
46270353	Chronic kidney disease due to benign hypertension	SNOMED
Hypertension (Narrow)		
193493	Benign hypertensive renal disease	SNOMED
195556	Hypertensive heart AND renal disease	SNOMED
201313	Hypertensive renal disease	SNOMED
312648	Benign essential hypertension	SNOMED
312938	Hypertensive encephalopathy	SNOMED
313502	Benign hypertensive heart disease without congestive heart failure	SNOMED
314369	Malignant hypertensive heart disease without congestive heart failure	SNOMED
314378	Hypertensive heart disease with congestive heart failure	SNOMED
316866	Hypertensive disorder	SNOMED
316994	Malignant hypertensive heart disease with congestive heart failure	SNOMED
317895	Renovascular hypertension	SNOMED
317898	Malignant essential hypertension	SNOMED
319034	Hypertensive heart disease without congestive heart failure	SNOMED
320128	Essential hypertension	SNOMED
376965	Hypertensive retinopathy	SNOMED
377551	Blind hypertensive eye	SNOMED
439694	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure	SNOMED
439695	Hypertensive heart and renal disease with renal failure	SNOMED
439696	Hypertensive heart and renal disease with (congestive) heart failure	SNOMED
439698	Benign hypertensive heart disease with congestive cardiac failure	SNOMED
442603	Malignant hypertensive heart AND renal disease	SNOMED
442604	Hypertensive heart disease	SNOMED
442626	Benign hypertensive heart AND renal disease	SNOMED
442766	Malignant hypertensive renal disease	SNOMED

Concept ID	Concept Name	Vocabulary
Hypertension (Broad)		
443919	Hypertensive renal failure	SNOMED
444101	Hypertensive heart failure	SNOMED
764011	Benign hypertensive heart disease and chronic renal disease	SNOMED
1340364	Exacerbation of hypertensive disorder	OMOP Extension
3174555	Hypertensive cerebrovascular disease	Nebraska Lexicon
4028741	Benign hypertension	SNOMED
4032952	Renal sclerosis with hypertension	SNOMED
4033353	Hypertensive leg ulcer	SNOMED
4049389	Paroxysmal hypertension	SNOMED
4058987	High-renin essential hypertension	SNOMED
4108213	Hypertension secondary to drug	SNOMED
4159755	Labile essential hypertension	SNOMED
4167358	Diastolic hypertension	SNOMED
4173820	Cardiomegaly due to hypertension	SNOMED
4180283	Systolic essential hypertension	SNOMED
4183981	Malignant hypertensive heart disease	SNOMED
4209293	Systolic hypertension	SNOMED
4227517	Hypertensive choroidopathy	SNOMED
4228419	Hypertensive optic neuropathy	SNOMED
4242878	Sustained diastolic hypertension	SNOMED
4262182	Hypertension with albuminuria	SNOMED
4263067	Low-renin essential hypertension	SNOMED
4263504	Benign hypertensive heart disease	SNOMED
4276511	Labile diastolic hypertension	SNOMED
4289933	Malignant hypertension	SNOMED
4302748	Chronic hypertensive uremia	SNOMED
4317265	Ischemic ulcer of skin due to arterial hypertension	SNOMED
36684653	Hypertension with disorder of right retina	SNOMED
36684718	Hypertension with disorder of left retina	SNOMED
36684780	Bilateral hypertension with disorder of retinas	SNOMED
36712757	Cardiomyopathy due to hypertension	SNOMED
36713024	Labile systemic arterial hypertension	SNOMED
37208172	Resistant hypertensive disorder	SNOMED
37208293	Multiple drug intolerant hypertension	SNOMED
40481896	Hypertensive urgency	SNOMED
42538697	Diastolic hypertension and systolic hypertension	SNOMED

Concept ID	Concept Name	Vocabulary
Hypertension (Broad)		
42599748	Cardiac hypertrophy secondary to systemic hypertension	SNOMED Veterinary
42709887	Hypertensive complication	SNOMED
43020424	Hypertensive emergency	SNOMED
43021748	Hypertensive nephrosclerosis	SNOMED
43021852	Malignant hypertensive chronic kidney disease	SNOMED
44782429	Chronic kidney disease due to hypertension	SNOMED
44782728	Hypertensive heart AND chronic kidney disease with congestive heart failure	SNOMED
44783643	Intermittent hypertension	SNOMED
44784439	Benign hypertensive renal disease with renal failure	SNOMED
44784621	Hypertensive heart and chronic kidney disease	SNOMED
44784637	Hypertensive heart AND chronic kidney disease on dialysis	SNOMED
44809026	Stage 1 hypertension (NICE - National Institute for Health and Clinical Excellence 2011)	SNOMED
44809027	Severe hypertension (NICE - National Institute for Health and Clinical Excellence 2011)	SNOMED
44809548	Hypertension resistant to drug therapy	SNOMED
44809569	Stage 2 hypertension (NICE - National Institute for Health and Clinical Excellence 2011)	SNOMED
44811110	Nocturnal hypertension	SNOMED
44811932	Stage 1 hypertension (NICE 2011) without evidence of end organ damage	SNOMED
44811933	Stage 1 hypertension (NICE 2011) with evidence of end organ damage	SNOMED
45757787	Postpartum pre-existing essential hypertension	SNOMED
45768449	Hypertensive crisis	SNOMED
46270353	Chronic kidney disease due to benign hypertension	SNOMED
Secondary hypertension		
314958	Benign secondary hypertension	SNOMED
317895	Renovascular hypertension	SNOMED
318437	Malignant secondary hypertension	SNOMED
319826	Secondary hypertension	SNOMED
443771	Renal hypertension	SNOMED
3656115	Hypertension due to aortic arch obstruction	SNOMED
4048212	Goldblatt hypertension	SNOMED
4061667	Hypertension induced by oral contraceptive pill	SNOMED
4108213	Hypertension secondary to drug	SNOMED
4110947	Malignant secondary renovascular hypertension	SNOMED
4110948	Hypertension secondary to endocrine disorder	SNOMED
4178312	Hypertension secondary to kidney transplant	SNOMED
4212496	Parenchymal renal hypertension	SNOMED
4249016	Benign secondary renovascular hypertension	SNOMED

Concept ID	Concept Name	Vocabulary
Hypertension (Broad)		
4253928	Secondary diastolic hypertension	SNOMED
4305599	Renal arterial hypertension	SNOMED
4322735	Hypertension associated with transplantation	SNOMED
35624277	Hypertension due to gain-of-function mutation in mineralocorticoid receptor	SNOMED
45771064	Hypertension in chronic kidney disease due to type 2 diabetes mellitus	SNOMED

Table S2. Preliminary list of concept IDs on measurements on systolic blood pressure for defining hypertension.

Concept ID	Concept Name	Vocabulary
4152194	Systolic blood pressure	SNOMED
3004117	Brachial artery - left Systolic blood pressure	LOINC
3018822	Systolic blood pressure at First encounter	LOINC
3007295	Brachial artery - right Systolic blood pressure	LOINC
3004249	Systolic blood pressure	LOINC
21492239	Systolic blood pressure by Noninvasive	LOINC
3003205	Brachial artery Systolic blood pressure	LOINC
3018586	Systolic blood pressure--sitting	LOINC
3021627	Systolic blood pressure Brachial artery - right/Brachial artery	LOINC
37396683	Baseline systolic blood pressure	SNOMED
903118	Computed systolic blood pressure, mean of 2nd and 3rd measures	PPI
4161413	Systolic blood pressure on admission	SNOMED
4232915	Sitting systolic blood pressure	SNOMED

Table S3. Preliminary list of concept IDs on measurements on diastolic blood pressure for defining hypertension.

Concept ID	Concept Name	Vocabulary
903115	Computed diastolic blood pressure, mean of 2nd and 3rd measures	PPI
40486938	Diastolic blood pressure on admission	SNOMED
3002785	Brachial artery - left Diastolic blood pressure	LOINC
3018592	Diastolic blood pressure at First encounter	LOINC
3012888	Diastolic blood pressure	LOINC
37399010	Baseline diastolic blood pressure	SNOMED
4248524	Sitting diastolic blood pressure	SNOMED
21492240	Diastolic blood pressure by Noninvasive	LOINC
3001810	Brachial artery - right Diastolic blood pressure	LOINC
4154790	Diastolic blood pressure	SNOMED
3010404	Brachial artery Diastolic blood pressure	LOINC

Table S4. Preliminary list of antihypertensive drug definitions.

Ingredient concept ID	Concept name
ACEi	
1335471	Benazepril
1340128	Captopril
19050216	Cilazapril
1341927	Enalapril
1342001	Enalaprilat
1363749	Fosinopril
19122327	Imidapril
1308216	Lisinopril
1310756	Moexipril
1373225	Perindopril
1331235	Quinapril
1334456	Ramipril
19040051	Spirapril
43009010	Temocapril hydrochloride
1342439	Trandolapril
19102107	Zofenopril
ARB	
40235485	Azilsartan
1351557	Candesartan
1346686	Eprosartan
43009001	Fimasartan potassium
1347384	Irbesartan
1367500	Losartan
40226742	Olmesartan
1317640	Telmisartan
1308842	Valsartan
BB (excluding topical preparations)	
1319998	Acebutolol
19081284	Alprenolol
1314002	Atenolol
1322081	Betaxolol
43009042	Bevantolol hydrochloride
1338005	Bisoprolol
19018640	Bopindolol
19018489	Bupranolol

Ingredient concept ID	Concept name
950370	Carteolol
1346823	Carvedilol
19049145	Celiprolol
19063575	Esmolol
1386957	Labetalol
35197852	Landiolol hydrochloride
19072028	Mepindolol
905531	Metipranolol
1307046	Metoprolol
1313200	Nadolol
1314577	Nebivolol
19024904	Oxprenolol
1327978	Penbutolol
1345858	Pindolol
19135791	Practolol
1353766	Propranolol
1370109	Sotalol
19100435	Talinolol
19100451	Tertatolol
902427	Timolol
CCB	
1332418	Amlodipine
43009040	Benidipine hydrochloride
1319751	Bepridil
43009017	Cilnidipine
19089969	Clevidipine
1328165	Diltiazem
1353776	Felodipine
19053866	Fendiline
19057715	Gallopamil
1326012	Isradipine
19004539	Lacidipine
19015802	Lercanidipine
1146278	Levamlodipine
19124331	Lidoflazine
19071995	Manidipine
19102106	Mepirodipine

Ingredient concept ID	Concept name
1345141	Mibefradil
1318137	Nicardipine
1318853	Nifedipine
19113063	Nilvadipine
1319133	Nimodipine
1319880	Nisoldipine
19020061	Nitrendipine
19032359	Perhexiline
1307863	Verapamil
Thiazide/thiazide-like diuretics	
19018435	Althiazide
1316354	Bendroflumethiazide
19039770	Buthiazide
992590	Chlorothiazide
1395058	Chlorthalidone
19099181	Clopamide
19010015	Cyclopenthiazide
19082886	Cyclothiazide
37493796	Epithiazide
974166	Hydrochlorothiazide
1376289	Hydroflumethiazide
978555	Indapamide
40798952	Mebutizide
19000556	Mefruside
905273	Methyclothiazide
35198062	Meticrane
907013	Metolazone
948787	Polythiazide
19081320	Quinethazone
904639	Trichlormethiazide
19010493	Xipamide
Other diuretics	
991382	Amiloride
932745	Bumetanide
19123864	Canrenoate
19019698	Canrenone
19051444	Cicletanine

Ingredient concept ID	Concept name
40798722	Clofenamide
40798761	Clorexolone
19010927	Conivaptan
1309799	Eplerenone
987406	Ethacrynate
40798813	Etozolin
1537451	Finerenone
956874	Furosemide
19003070	Mersalyl
40798971	Muzolimine
19025498	Piretanide
970250	Spironolactone
19137056	Theobromine
40799172	Tienilic acid
19036797	Tolvaptan
942350	Torsemide
904542	Triamterene
Other antihypertensives	
1317967	Aliskiren
1337068	Ambrisentan
36859655	Aprocitentan
19022533	Bethanidine
36849057	Bietaserpine
1321636	Bosentan
43009081	Cadralazine
1398937	Clonidine
19011951	Debrisoquin
36878917	Delapril hydrochloride
1387219	Deserpidine
1523280	Diazoxide
19026448	Dihydralazine
1363053	Doxazosin
1366237	Guanabenz
1366279	Guanethidine
1344965	Guanfacine
40798853	Guanoxan
1373928	Hydralazine

Ingredient concept ID	Concept name
19078808	Indoramin
19085688	Ketanserlin
44507580	Macitentan
1394333	Mecamylamine
19055531	Methoserpidine
1305447	Methyldopa
1401581	Metyrosine
1309068	Minoxidil
19011021	Moxonidine
19020994	Nitroprusside
19027413	Pargyline
36860098	Picodralazine
19093166	Pinacidil
1350489	Prazosin
19062195	Rescinnamine
1362225	Reserpine
19115050	Rilmenidine
44506752	Riociguat
36878846	Sitaxentan
40799160	Trimazosin
19005658	Trimethaphan
19101849	Urapidil

Remarks: Alkaloids in herbal preparation are not included, including rauwolfia alkaloids from ATC class C02AA and veratrum alkaloids from ATC class C02KA.

ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; ATC = Anatomical Therapeutic Chemical [Classification]; BB = beta-blockers; CCB = calcium channel blockers.

ANNEX V. Preliminary feasibility person counts for antihypertensive drugs

Counts are given as descendant person-counts (DPC), which gives the number of unique persons with that concept or its descendant concepts. Antihypertensive drugs are arranged in descending order based on the DPC subtotal within each drug class.

Table S5. Preliminary feasibility person-counts for antihypertensive drugs.

Concept ID	Concept name	DPC CPRD GOLD	DPC DK-DHR	DPC FinOMOP-THL	DPC IPCI	DPC SIDIAP	DPC Subtotal
ACEi							
1341927	enalapril	136900	733800	234200	81400	1077900	2264200
1334456	ramipril	1002800	444900	399200	7600	235300	2089800
1308216	lisinopril	526700	95300	30900	63000	271100	987000
1373225	perindopril	273900	92600	73500	89200	28100	557300
1340128	captopril	40700	43100	100	3600	53900	141400
1342439	trandolapril	9700	79000		100	5600	94400
1331235	quinapril	8300	6400	1400	2300	9100	27500
1363749	fosinopril	8900	4300		6400	4800	24400
19122327	imidapril	1300				14500	15800
19050216	cilazapril	1600			100	1600	3300
1335471	benazepril		2100		100	700	2900
1310756	moexipril	100	700				800
19102107	zofenopril				500		500
ARB							
1367500	losartan	291300	1032700	568500	72600	415600	2380700
1351557	candesartan	222200	214200	542000	24800	74000	1077200
1308842	valsartan	81500	72800	202600	45200	247300	649400
1317640	telmisartan	23600	35400	118800	14500	58400	250700
1347384	irbesartan	100000	52200		34100	59400	245700
40226742	olmesartan	22800	8100	14200	5000	135300	185400
1346686	eprosartan	8400	10300	6000	400	22400	47500
40235485	azilsartan	100			100		200
BB							
1338005	bisoprolol	666800	112300	1056300	43700	529000	2408100
1353766	propranolol	895900	348500	604800	53000	145200	2047400
1307046	metoprolol	54600	1003800	227900	212800	10600	1509700
1314002	atenolol	714900	145700	24200	14800	174700	1074300
902427	timolol	130400	182400	123100	29200	183500	648600
1346823	carvedilol	31900	133900	38900	5300	92800	302800
1314577	nebivolol	29800	19700	33800	8100	50500	141900

Concept ID	Concept name	DPC CPRD GOLD	DPC DK-DHR	DPC FinOMOP-THL	DPC IPCI	DPC SIDIAP	DPC Subtotal
1370109	sotalol	45800	49600	7300	28500	6200	137400
1386957	labetalol	29700	27700	29300	3300	12900	102900
1322081	betaxolol	13600	11600	11000	600	2600	39400
950370	carteolol	8200	700		600	18300	27800
1345858	pindolol	1600	13700	1600	200		17100
1313200	nadolol	2600				12500	15100
19049145	celiprolol	6900		6900	1000	300	15100
19024904	oxprenolol	8300	800		100	200	9400
1319998	acebutolol	2400	1900	3300	300		7900
19081284	alprenolol	1300	700				2000
905531	metipranolol	600	100		200		900
19100451	tertatolol		100				100
CCB							
1332418	amlodipine	1156900	1175300	894700	166000	618300	4011200
19015802	lercanidipine	91300	249700	240700	9600	53700	645000
1318853	nifedipine	265800	78300	39400	42500	54800	480800
1353776	felodipine	220200	139300	98600	2400	7100	467600
1328165	diltiazem	201900	105200	17400	36500	79800	440800
1307863	verapamil	64400	157800	24600	17800	31500	296100
19071995	manidipine					86700	86700
19004539	lacidipine	22500	7300		100	4700	34600
19102106	mepirodipine				14900	17700	32600
1319133	nimodipine	700	1000	1100	200	19000	22000
19020061	nitrendipine		3800		200	11700	15700
1326012	isradipine	600	9200	2200	600		12600
19113063	nilvadipine		800	10700			11500
1318137	nicardipine	5300	500		100	5300	11200
1319880	nisoldipine	300		1500		500	2300
1345141	mibefradil	400	1400				1800
19032359	perhexiline	100					100
Thiazides/thiazide-like diuretics							
974166	hydrochlorotiazide	113200	709800	664400	183700	1060200	2731300
1316354	bendroflumetiazide	1021500	1369900				2391400
978555	indapamide	207000	46600	31900	11900	75600	373000

Concept ID	Concept name	DPC CPRD GOLD	DPC DK-DHR	DPC FinOMOP-THL	DPC IPCI	DPC SIDIAP	DPC Subtotal
1395058	chlorthalidone	51700	13700		14800	36000	116200
907013	metolazone	14800	1100	6700			22600
1376289	hydroflumethiazide	2500	20100				22600
19010015	cyclopenthiiazide	17000					17000
19099181	clopamide	600	11100		100		11800
19010493	xipamide	1500				2800	4300
904639	trichlormethiazide			2500			2500
37493796	Epithiazide				2200		2200
19000556	mefruside	300	1400				1700
992590	chlorothiazide	1000	100		100		1200
948787	polythiazide	400	300				700
Other diuretics							
956874	furosemide	1113300	1222000	578600	105000	595100	3614000
970250	spironolactone	216100	401700	199800	48100	159900	1025600
991382	amiloride	227200	164300	83200	3900	57600	536200
932745	bumetanide	138700	58700	100	31700	1300	230500
942350	torsemide	2600				200400	203000
1309799	eplerenone	28700	29500	700	4700	44700	108300
904542	triamterene	26500		15300	9000	5600	56400
1537451	finerenone	200	1900	1500	100		3700
19025498	piretanide	200				500	700
19036797	tolvaptan	100	200	200	100		600
19123864	canrenoate		100				100
987406	ethacrynate	100					100
Other antihypertensives							
1363053	doxazosin	305900	83800	100	12400	122800	525000
1398937	clonidine	118700	101800	18900	12400	1700	253500
19011021	moxonidine	23400	38600	45400	500	2700	110600
1309068	minoxidil	8000	10000	12000	5200	18100	53300
1350489	prazosin	14800	9800	25500	100	1000	51200
1373928	hydralazine	10200	1300		300	30600	42400
1305447	methyldopa	17700	9200		3100	4000	34000

Concept ID	Concept name	DPC CPRD GOLD	DPC DK-DHR	DPC FinOMOP-THL	DPC IPCI	DPC SIDIAP	DPC Subtotal
1317967	aliskiren	2300	7700	200	1800	11000	23000
1344965	guanfacine	2000	6700	4700	400	4300	18100
19078808	indoramin	18100					18100
19020994	nitroprusside		9100	100			9200
36878917	delapril hydrochloride					3700	3700
1366279	guanethidine	1100	600				1700
19093166	pinacidil		1200				1200
1321636	bosentan	200		300	200		700
44507580	macitentan	100		500	100		700
1523280	diazoxide	300		200	100		600
19085688	ketanserin				500		500
44506752	riociguat			200	100		300
19101849	urapidil		100	100	100		300
1337068	ambrisentan	100		100	100		300
19011951	debrisoquin	300					300
19026448	dihydralazine			100			100
1362225	reserpine	100					100
19022533	bethanidine	100					100
19055531	methoserpidine	100					100

ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; BB = beta-blockers; CCB = calcium channel blockers; CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; DPC = Descendant person-counts; FinOMOP-THL = Finnish Care Register for Health Care; IPCI = Integrated Primary Care Information; SIDIAP = The Information System for Research in Primary Care.

ANNEX VI. Mock tables and figures

The mock tables and figures provided below are for illustrative purposes only and do not contain any results. They are presented as table and figure shells.

Mock Table 1. Characteristics of baseline covariates, and antihypertensive treatment in individuals with primary hypertension, separately for men and women.

Variable name	Variable level	Estimate name	Data sources				
			DK-DHR	FinOMO P-THL	SIDIAP	IPCI	CPRD GOLD
Women							
Number subjects	–	N					
Age	–	Median (IQR)					
Age group	18 – 29	N (%)					
	30 – 49	N (%)					
	50 – 64	N (%)					
	65+	N (%)					
Antihypertensive treatment	Untreated	N (%)					
	CCB	N (%)					
	Other diuretics;thiazide diuretics	N (%)					
History of comorbidities, [-Inf, 0]	Hypercholesterolemia	N (%)					
	Stroke	N (%)					
	Chronic kidney disease	N (%)					
	Heart failure	N (%)					
	Coronary heart disease	N (%)					
	Type 2 diabetes	N (%)					
	Peripheral arterial disease	N (%)					
	Cardiovascular disease	N (%)					
	Asthma	N (%)					
	Obesity	N (%)					
Measurements [-365, 0]	Systolic blood pressure	Median (IQR)					
	Diastolic blood pressure	Median (IQR)					
Time to treatment initiation	–	Median (IQR)					
Men							
Number subjects	–	N					
Age	–	Median (IQR)					
Age group	18 – 29	N (%)					

Variable name	Variable level	Estimate name	Data sources				
			DK-DHR	FinOMO P-THL	SIDIAP	IPCI	CPRD GOLD
	30 – 49	N (%)					
	50 – 64	N (%)					
	65+	N (%)					
Antihypertensive treatment	Untreated	N (%)					
	ARB	N (%)					
	CCB	N (%)					
	Other antihypertensives	N (%)					
History of comorbidities, [-Inf, 0]	Hypercholesterolemia	N (%)					
	Stroke	N (%)					
	Chronic kidney disease	N (%)					
	Heart failure	N (%)					
	Coronary heart disease	N (%)					
	Type 2 diabetes	N (%)					
	Peripheral arterial disease	N (%)					
	Cardiovascular disease	N (%)					
	Asthma	N (%)					
	Obesity	N (%)					
Measurements [-365, 0]	Systolic blood pressure	Median (IQR)					
	Diastolic blood pressure	Median (IQR)					
Time to treatment initiation	–	Median (IQR)					

ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; BB = beta-blockers; CCB = calcium channel blockers; CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; FinOMOP-THL = Finnish Care Register for Health Care; IPCI = Integrated Primary Care Information; IQR = interquartile range; SIDIAP = The Information System for Research in Primary Care.

Mock Table 2. Characteristics of baseline covariates, and antihypertensive treatment in individuals with primary hypertension, separately for men and women, and stratified by age group.

Variable name	Variable level	Estimate name	Data source				
			DK-DHR	FinOMO P-THL	SIDIAP	IPCI	CPRD GOLD
Women; 18 to 29 years							
Number subjects	–	N					
Age	–	Median (IQR)					
Antihypertensive treatment	Untreated	N (%)					
	CCB	N (%)					

Variable name	Variable level	Estimate name	Data source				
			DK-DHR	FinOMO P-THL	SIDIAP	IPCI	CPRD GOLD
	Other diuretics;thiazide diuretics	N (%)					
History of comorbidities, [-Inf, 0]	Hypercholesterolemia	N (%)					
	Stroke	N (%)					
	Chronic kidney disease	N (%)					
	Heart failure	N (%)					
	Coronary heart disease	N (%)					
	Type 2 diabetes	N (%)					
	Peripheral arterial disease	N (%)					
	Cardiovascular disease	N (%)					
	Asthma	N (%)					
	Obesity	N (%)					
Measurements [-365, 0]	Systolic blood pressure	Median (IQR)					
	Diastolic blood pressure	Median (IQR)					
Time to treatment initiation	–	Median (IQR)					
Men; 18 to 29 years							
Number subjects	–	N					
Age	–	Median (IQR)					
Antihypertensive treatment	Untreated	N (%)					
	ARB	N (%)					
	CCB	N (%)					
	Other antihypertensives	N (%)					
History of comorbidities, [-Inf, 0]	Hypercholesterolemia	N (%)					
	Stroke	N (%)					
	Chronic kidney disease	N (%)					
	Heart failure	N (%)					
	Coronary heart disease	N (%)					
	Type 2 diabetes	N (%)					

Variable name	Variable level	Estimate name	Data source				
			DK-DHR	FinOMO P-THL	SIDIAP	IPCI	CPRD GOLD
	Peripheral arterial disease	N (%)					
	Cardiovascular disease	N (%)					
	Asthma	N (%)					
	Obesity	N (%)					
Measurements [-365, 0]	Systolic blood pressure	Median (IQR)					
	Diastolic blood pressure	Median (IQR)					
Time to treatment initiation	–	Median (IQR)					
Women; 30 to 49 years							
Number subjects	–	N					
Age	–	Median (IQR)					
Antihypertensive treatment	Untreated	N (%)					
	CCB	N (%)					
	Other diuretics;thiazide diuretics	N (%)					
History of comorbidities, [-Inf, 0]	Hypercholesterolemia	N (%)					
	Stroke	N (%)					
	Chronic kidney disease	N (%)					
	Heart failure	N (%)					
	Coronary heart disease	N (%)					
	Type 2 diabetes	N (%)					
	Peripheral arterial disease	N (%)					
	Cardiovascular disease	N (%)					
	Asthma	N (%)					
	Obesity	N (%)					
Measurements [-365, 0]	Systolic blood pressure	Median (IQR)					
	Diastolic blood pressure	Median (IQR)					
Time to treatment initiation	–	Median (IQR)					
Men; 30 to 49 years							
Number subjects	–	N					

Variable name	Variable level	Estimate name	Data source				
			DK-DHR	FinOMO P-THL	SIDIAP	IPCI	CPRD GOLD
Age	–	Median (IQR)					
Antihypertensive treatment	Untreated	N (%)					
	ARB	N (%)					
	CCB	N (%)					
	Other antihypertensives	N (%)					
History of comorbidities, [-Inf, 0]	Hypercholesterolemia	N (%)					
	Stroke	N (%)					
	Chronic kidney disease	N (%)					
	Heart failure	N (%)					
	Coronary heart disease	N (%)					
	Type 2 diabetes	N (%)					
	Peripheral arterial disease	N (%)					
	Cardiovascular disease	N (%)					
	Asthma	N (%)					
	Obesity	N (%)					
Measurements [-365, 0]	Systolic blood pressure	Median (IQR)					
	Diastolic blood pressure	Median (IQR)					
Time to treatment initiation	–	Median (IQR)					

ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; BB = beta-blockers; CCB = calcium channel blockers; CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; FinOMOP-THL = Finnish Care Register for Health Care; IPCI = Integrated Primary Care Information; IQR = interquartile range; SIDIAP = The Information System for Research in Primary Care.

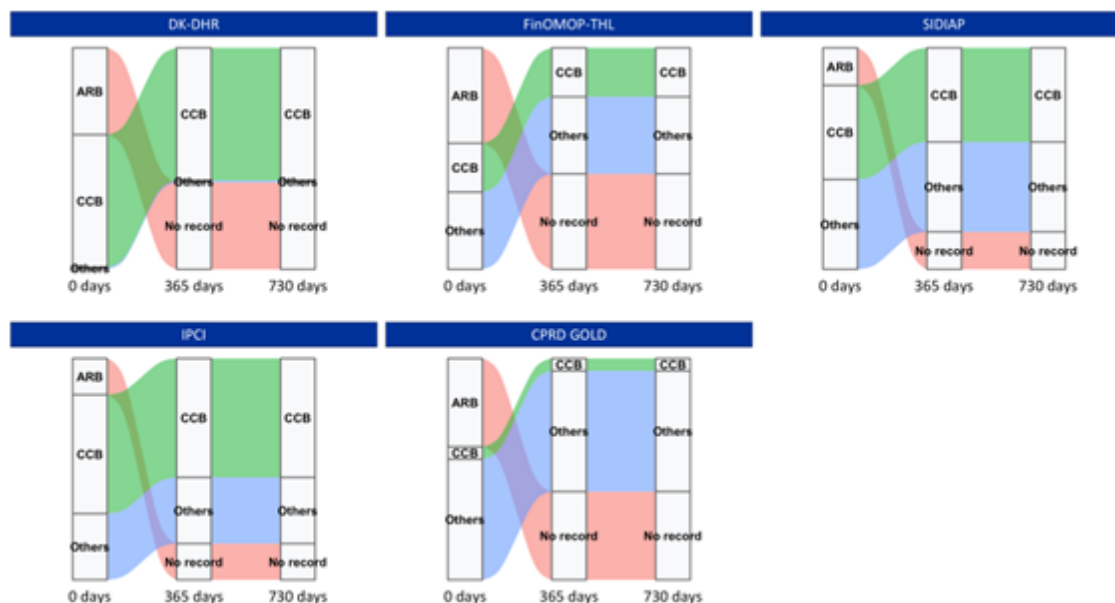
Mock Table 3. Drug utilisation for antihypertensive treatments for primary hypertension, separately for men and women.

Ingredient	Estimate name	Data source									
		DK-DHR		FinOMOP-THL		SIDIAP		IPCI		CPRD GOLD	
		Variable name									
		Initial exposure duration	Initial daily dose (milligram)	Initial exposure duration	Initial daily dose (milligram)	Initial exposure duration	Initial daily dose (milligram)	Initial exposure duration	Initial daily dose (milligram)	Initial exposure duration	Initial daily dose (milligram)
Drug class 1; Women											
ingredient 1	Median (IQR)										
ingredient 2	Median (IQR)										
ingredient 3	Median (IQR)										
ingredient 4	Median (IQR)										
Drug class 1; Men											
ingredient 1	Median (IQR)										
ingredient 2	Median (IQR)										
ingredient 3	Median (IQR)										
ingredient 4	Median (IQR)										
Drug class 2; Women											
ingredient 1	Median (IQR)										

Ingredient	Estimate name	Data source									
		DK-DHR		FinOMOP-THL		SIDIAP		IPCI		CPRD GOLD	
		Variable name									
		Initial exposure duration	Initial daily dose (milligram)	Initial exposure duration	Initial daily dose (milligram)	Initial exposure duration	Initial daily dose (milligram)	Initial exposure duration	Initial daily dose (milligram)	Initial exposure duration	Initial daily dose (milligram)
ingredient 2	Median (IQR)										
ingredient 3	Median (IQR)										
ingredient 4	Median (IQR)										
Drug class 2; Men											
ingredient 1	Median (IQR)										
ingredient 2	Median (IQR)										
ingredient 3	Median (IQR)										
ingredient 4	Median (IQR)										
Drug class 3; Women											
ingredient 1	Median (IQR)										
ingredient 2	Median (IQR)										
ingredient 3	Median (IQR)										

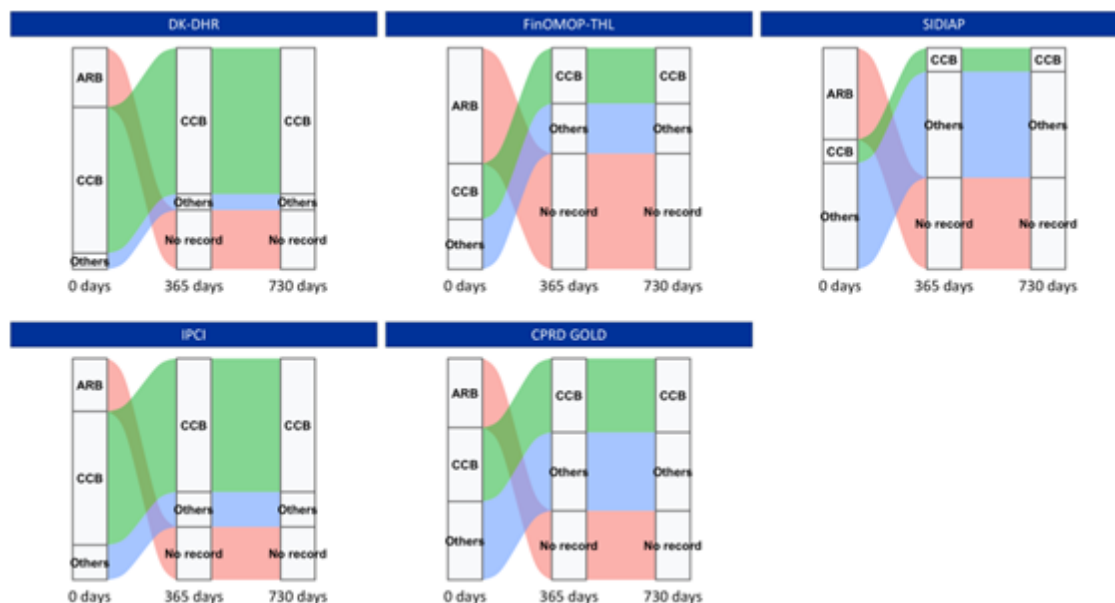
Ingredient	Estimate name	Data source									
		DK-DHR		FinOMOP-THL		SIDIAP		IPCI		CPRD GOLD	
		Variable name									
		Initial exposure duration	Initial daily dose (milligram)	Initial exposure duration	Initial daily dose (milligram)	Initial exposure duration	Initial daily dose (milligram)	Initial exposure duration	Initial daily dose (milligram)	Initial exposure duration	Initial daily dose (milligram)
ingredient 4	Median (IQR)										
Drug class 3; Men											
ingredient 1	Median (IQR)										
ingredient 2	Median (IQR)										
ingredient 3	Median (IQR)										
ingredient 4	Median (IQR)										

ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; BB = beta-blockers; CCB = calcium channel blockers; CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; FinOMOP-THL = Finnish Care Register for Health Care; IPCI = Integrated Primary Care Information; IQR = interquartile range; SIDIAP = The Information System for Research in Primary Care.



Mock Figure 1–5. Sankey plot for treatment switching patterns in men, per data source.

ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; BB = beta-blockers; CCB = calcium channel blockers; CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; FinOMOP-THL = Finnish Care Register for Health Care; IPCI = Integrated Primary Care Information; IQR = interquartile range; SIDIAP = The Information System for Research in Primary Care.



Mock Figure 6–10. Sankey plot for treatment switching patterns in women, per data source.

ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; BB = beta-blockers; CCB = calcium channel blockers; CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; FinOMOP-THL = Finnish Care Register for Health Care; IPCI = Integrated Primary Care Information; IQR = interquartile range; SIDIAP = The Information System for Research in Primary Care.

ANNEX VII. ENCePP checklist for study protocols

ENCePP Checklist for Study Protocols (Revision 4)

Study title: DARWIN EU® - Sex differences in treatment patterns for primary hypertension in European countries

EU PAS Register® number: EUPAS1000001092
Study reference number (if applicable): P5-C1-005

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				5
1.1.1 Start of data collection ¹	☒	☐	☐	
1.1.2 End of data collection ²	☒	☐	☐	
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.	☒	☐	☐	

Comments:

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	6, 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)	☒	☐	☐	
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no <i>a priori</i> hypothesis?	☒	☐	☐	

Comments:

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.

<u>Section 3: Study design</u>		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?	☒	☐	☐	8.4
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.6, 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))	☐	☐	☒	
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:

<u>Section 4: Source and study populations</u>		Yes	No	N/A	Section Number
4.1	Is the source population described?	☒	☐	☐	8.4
4.2	Is the planned study population defined in terms of:				
4.2.1	Study time period	☒	☐	☐	8.5
4.2.2	Age and sex	☒	☐	☐	8.3
4.2.3	Country of origin	☒	☐	☐	8.4
4.2.4	Disease/indication	☐	☐	☒	
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)	☒	☐	☐	8.3

Comments:

<u>Section 5: Exposure definition and measurement</u>		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)	☒	☐	☐	8.6.1
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?	☐	☐	☒	

<u>Section 5: Exposure definition and measurement</u>	Yes	No	N/A	Section Number
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	8.6.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

<u>Section 6: Outcome definition and measurement</u>	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☐	☐	☒	
6.2 Does the protocol describe how the outcomes are defined and measured?	☐	☐	☒	
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:

<u>Section 7: Bias</u>	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
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)	☐	☐	☒	

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)	☐	☐	☒	

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:	☒	☐	☐	Annex I, II
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	Annex I, II
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	Annex I, II
9.1.3 Covariates and other characteristics?				
9.2 Does the protocol describe the information available from the data source(s) on:	☒	☐	☐	Annex I, II
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	Annex I, II
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	Annex I, II
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)				
9.3 Is a coding system described for:	☒	☐	☐	Annex IV
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	Annex IV
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	Annex I, II

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?	☒	☐	☐	8.8
10.3 Are descriptive analyses included?	☒	☐	☐	8.8

<u>Section 10: Analysis plan</u>	Yes	No	N/A	Section Number
10.4 Are stratified analyses included?	☒	☐	☐	8.8
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	8.8
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

<u>Section 11: Data management and quality control</u>	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)	☒	☐	☐	Annex III
11.2 Are methods of quality assurance described?	☒	☐	☐	Annex III
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

<u>Section 12: Limitations</u>	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9
12.1.2 Information bias?	☒	☐	☐	9
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)	☒	☐	☐	Annex II, V

Comments:

<u>Section 13: Ethical/data protection issues</u>	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	Annex II

<u>Section 13: Ethical/data protection issues</u>	Yes	No	N/A	Section Number
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	Annex III

Comments:

<u>Section 14: Amendments and deviations</u>	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	4

Comments:

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

Comments:

Name of the main author of the protocol: Amy Lam

Date: 30/06/2026

Signature: A. Lam

ANNEX VIII. Glossary

Additional definitions are available in the EMA Glossary of terms <https://www.ema.europa.eu/en/about-us/glossaries>.

Aggregated Data

Data collected and combined from multiple sources to generate summary information, typically anonymised.

Benefit-Risk Assessment

Evaluation of the positive therapeutic effects of a medicine compared to its risks (e.g. side effects).

Common Data Model (CDM)

A standardised data structure that enables data from multiple sources to be harmonised, making analysis consistent and reproducible. DARWIN EU® utilises the OMOP CDM maintained by the OHDSI community.

Complex Studies (C3)

Studies requiring the development or customisation of specific study designs, protocols, and Statistical Analysis Plans (SAPs), with extensive collection or extraction of data. Examples include etiological studies measuring the strength and determinants of an association between an exposure and the occurrence of a health outcome in a defined population considering sources of bias, potential confounding factors, and effect modifiers.

Coordination Centre (CC)

The central hub responsible for managing and overseeing the activities within DARWIN EU®. It is based at Erasmus University Medical Center in Rotterdam, the Netherlands.

Data Access

The process of obtaining permission to use specific datasets for regulatory or scientific studies.

Data Quality Framework

A set of standards and procedures to ensure accuracy, completeness, timeliness, and consistency of data used in DARWIN EU®.

Data Source

A data source or repository of structured health-related data, such as electronic health records (EHRs), insurance claims, or registries.

DARWIN EU®

The European Medicines Agency's (EMA) federated network of real-world data sources designed to generate evidence to support regulatory decision-making.

EMA (European Medicines Agency)

The regulatory body responsible for the evaluation and supervision of medicinal products in the EU, overseeing DARWIN EU®.

Evidence Generation

The process of analysing real-world data to produce scientific information that can inform healthcare or regulatory decisions.

Federated Network

A data infrastructure where data remain at their original location but can be analysed in a harmonised way across multiple partners using a common model and tools.

GDPR (General Data Protection Regulation)

The EU regulation governing the protection of personal data and privacy, crucial to how DARWIN EU® handles health data.

Health Technology Assessment (HTA)

A systematic evaluation of properties and impacts of health technology, often using DARWIN EU® data to support assessments.

Metadata

Descriptive information about a data source (e.g. its content, quality, and structure), essential for identifying relevant data sources in DARWIN EU® studies.

Off-the-Shelf Studies (OTS)

Studies for which a standard protocol per study/analysis type and standardised analytics may be developed and applied or adapted, typically relating to a descriptive research question. This includes studies on disease epidemiology, for example, the estimation of the prevalence or incidence of health outcomes in defined time periods and population groups, or drug utilisation studies at the population or patient level.

OHDSI (Observational Health Data Sciences and Informatics)

An open-science collaborative community that develops tools and standards (including the OMOP CDM) to enable large-scale analytics of observational health data. OHDSI provides the technical and scientific foundation for DARWIN EU®'s analytical ecosystem.

Patient-Level Data

Data related to individuals, de-identified, used for longitudinal or detailed analyses.

OMOP (Observational Medical Outcomes Partnership)

A common data model (CDM) that standardises the structure and content of observational healthcare data, enabling systematic analysis across disparate datasets. DARWIN EU® uses the OMOP CDM to ensure interoperability and consistency in real-world evidence generation.

Real-World Data (RWD)

Data relating to individual health status or healthcare delivery that is collected from routine clinical practice rather than from randomised controlled trials.

Real-World Evidence (RWE)

Clinical evidence derived from the analysis of RWD, used to inform decisions by regulators, payers, or clinicians.

Regulatory Decision-Making

The process by which authorities like EMA assess data to authorise, monitor, or modify the use of medicines in the EU.

Routine Repeated Studies (RR)

Studies that are either Off-the-Shelf or Complex studies repeated on a regular basis, following the same protocol and study code, but with updated data and/or different data partners.

Study Protocol

A detailed plan describing how a specific real-world study will be conducted, including objectives, design, data sources, and analyses.

Very Complex Studies (C4)

Studies which cannot rely only on electronic health care data sources, or which would require complex methodological work, for example, due to the occurrence of events that cannot be defined by existing diagnosis codes, including events that do not yet have a diagnosis code, where it may be necessary to combine a diagnosis code with other data such as results of laboratory investigations. These studies might require the collection of data prospectively, or the inclusion of new (not previously onboarded) data sources.