Study Protocol

P4-C1-024

DARWIN EU® - Assessing the feasibility of conducting a causal study on the potential association between beta-blockers and breast cancer

26/06/2026

Version 4.0

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Public

CONTENTS

Study title	DARWIN EU® - Assessing the feasibility of conducting a causal study on the potential association between beta-blockers and breast cancer
Protocol version	V4.0
Date	26/06/2026
EUPAS number	EUPAS1000001013
Active Substance	B_1-selective beta-blockers (*Atenolol, Metoprolol, Bisoprolol, Nebivolol, Betaxolol, Acebutolol*) Non-selective beta-blockers (*Propranolol, Nadolol, Timolol, Pindolol, Carvedilol, Labetalol*) Angiotensin-converting enzyme (ACE) inhibitors (*Enalapril, Lisinopril, Perindopril, Ramipril, Captopril, Benazepril, Fosinopril, Trandolapril*) Angiotensin II receptor blockers (ARBs) (*Losartan, Valsartan, Candesartan, Irbesartan, Telmisartan, Olmesartan, Azilsartan*) Dihydropyridine Calcium channel blockers (CCBs) (*Amlodipine, Felodipine, Nifedipine, Lercanidipine, Nicardipine*) Non-dihydropyridine CCBs (*Verapamil, Diltiazem*)
Medicinal Product	n/a
Research question and objectives	Are selected data sources in the DARWIN EU® network fit for supporting a study to examine the causal association between beta-blockers and breast cancer? The specific objectives are: • To describe baseline demographic, clinical characteristics, the potential indications, as well as antihypertensive medication taken in female individuals newly initiating the following distinct antihypertensive classes: B_1-selective beta-blockers, non-selective beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), non-dihydropyridines calcium channel blockers (CCBs), and dihydropyridines CCBs • To describe the number, proportion, and time-to-event distribution of the following events among female individuals newly initiating B_1-selective beta-blockers, non-selective beta-blockers, ACE inhibitors, ARBs, non-dihydropyridines CCBs, and dihydropyridines CCBs during 5 and 10 years of follow-up: 1) all-cause death, 2) loss to follow-up, and 3) discontinuation of index treatment • To estimate the yearly incidence of primary breast cancer in the general adult (≥18 years) female population overall and by age group (18–40, 41–50, >50 years) • To assess whether the study size provides adequate precision to support a causal analysis
Countries of study	Denmark, Norway, Spain, Sweden, the United Kingdom
Authors	Yuqing Hu, y.hu@darwin-eu.org Marzyeh Amini, m.amini@darwin-eu.org Julieta Politi[1], j.politi@darwin-eu.org Adam Black, a.black@darwin-eu.org Ger Inberg, g.inberg@darwin-eu.org Arianna Alamshahi, a.alamshahi@darwin-eu.org Talita Duarte Salles, t.duarte@darwin-eu.org

[1]Involved in the study until 30/04/2026.

LIST OF ABBREVIATIONS

Acronyms/terms	Description
ACE	Angiotensin-converting enzyme
ATC	Anatomical Therapeutic Chemical
ARB	Angiotensin II receptor blocker
BRCA	Breast Cancer gene
CC	Coordination centre
CCB	Calcium Channel Blocker
CDM	Common Data Model
CI	Confidence Interval
CPRD GOLD	Clinical Practice Research Datalink GOLD
DARWIN EU®	Data Analysis and Real-World Interrogation Network
DDD	Defined Daily Dose
DK-DHR	Danish Data Health Registries
DRE	Digital Research Environment
DTZ	Data Transfer Zone
ED	Emergency Department
ETL	Extract, Transform, and Load
EHR	Electronic Health Records
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EUPAS	EU Post-Authorisation Studies Register
F	Precision
GDPR	General Data Protection Regulation
GP	General Practitioner
HI-SPEED	Health Impact - Swedish Population Evidence Enabling Data-linkage
HRT	Hormone Replacement Therapy
ICD	International Classification of Diseases
IQR	Interquartile Range
IRB	Institutional Review Board
NLHR	Norwegian Linked Health Registry data
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
PY	Person year
RxNorm	Medical prescription normalised
RR	Rate ratio

Acronyms/terms	Description
SD	Standard Deviation
SIDIAP	The Information System for Research in Primary Care
SNOMED	Systemised Nomenclature of Medicine
WHO	World Health Organisation

1. TITLE

DARWIN EU® - Assessing the feasibility of conducting a causal study on the potential association between beta-blockers and breast cancer

2. DESCRIPTION OF THE STUDY TEAM

Study team role	Names	Organisation
Principal Investigator	Yuqing Hu Marzyeh Amini	Erasmus MC
Co-principal Investigator	Talita Duarte-Salles Julieta Politi#	Erasmus MC
Data Scientist	Adam Black Ger Inberg Arianna Alamshahi^ Maarten van Kessel Cesar Barbosa Ross Williams	Erasmus MC
Study Manager	Natasha Yefimenko	Erasmus MC
Data source	**Names**	**Data Partner Organisation***
Clinical Practice Research Datalink GOLD (CPRD GOLD)	Marta Pineda Moncusí Mandickel Kamtengeni Antonella Delmestri Hezekiah Omulo	University of Oxford
Danish Data Health Registries (DK-DHR)	Elvira Bräuner Susanne Bruun	Danish Medicines Agency
Health Impact - Swedish Population Evidence Enabling Data-linkage (HI-SPEED)	Huiqi Li Fredrik Nyberg Ballin Marcel Talbäck Mats Rickard Ljung	Swedish Medical Products Agency - Gothenburg University
Norwegian Linked Health Registry data (NLHR)	Hedvig Marie Egeland Nordeng Saeed Hayati Petrica-Ioan Olteanu	University of Oslo
The Information System for Research in Primary Care (SIDIAP)	Elena Roel Herranz Laura Granés González Agustina Giuliodori Picco	L'Institut d'Investigació en Atenció Primària de Salut Jordi Gol

*Data partners do not have an investigator role. Data partners execute code at their data source, review, and approve their results.
#Involved in the study until 30/04/2026.
^Involved in the study from 29/06/2026.

3. ABSTRACT

Title

DARWIN EU® - Assessing the feasibility of conducting a causal study on the potential association between beta-blockers and breast cancer

Rationale and background

Hypertension is highly prevalent in adult women and commonly requires long-term use of antihypertensive medications. Long-term use of antihypertensive medications raises concerns about potential adverse effects, including cancer risk.

Beta-blockers have been used for decades to treat hypertension. Beyond cardiovascular effects, beta-adrenergic signalling may influence cancer-related processes, which could affect breast cancer development. However, prior observational evidence is inconsistent, likely due to confounding by indication and design differences. B_1-selective agents differ from non-selective agents, yet many studies have evaluated beta-blockers as a single class.

This feasibility study assesses whether selected data sources in the DARWIN EU® Data Network can support robust causal research on a comparative safety of beta-blockers in relation to incident breast cancer.

Research question and objectives

Research question

Are selected data sources in the DARWIN EU® network fit for supporting a study to examine the causal association between beta-blockers and breast cancer?

Objectives

This study aims to assess the feasibility of conducting a causal study to examine the potential association between beta-blockers and breast cancer.

The specific objectives of this study are:

1. To describe baseline demographic, clinical characteristics, the potential indications, as well as antihypertensive medication use in female individuals newly initiating the following distinct antihypertensive classes: B_1-selective beta-blockers, non-selective beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), non-dihydropyridines calcium channel blockers (CCBs), and dihydropyridines CCBs.
2. To describe the number, proportion, and time-to-event distribution of the following events among female individuals newly initiating B_1-selective beta-blockers, non-selective beta-blockers, ACE inhibitors, ARBs, non-dihydropyridines CCBs, and dihydropyridines CCBs during 5 and 10 years of follow-up: 1) all-cause death, 2) loss to follow-up, and 3) discontinuation of index treatment.
3. To estimate the yearly incidence of primary breast cancer in the general adult (≥18 years) female population overall and by age group (18–40, 41–50, >50 years).
4. To assess whether the study size provides adequate precision to support a causal analysis.

Methods

Study design

A retrospective and descriptive cohort study.

Population

Objectives 1 and 2: Female individuals aged ≥18 years with a hypertension diagnosis on or before the index date (treatment initiation) and ≥365 days of prior observation.

Objective 3: Female individuals aged ≥18 years with ≥365 days of prior observation.

Variables

Exposure:

B_1-selective beta-blockers, non-selective beta-blockers, ACE inhibitors, ARBs, non-dihydropyridines CCBs, dihydropyridines CCBs.

Events of interest:

- Incident breast cancer diagnosis
- Discontinuation of index treatment: discontinuation will be defined as a gap of >90 days without a subsequent prescription/dispensation of index treatment. Date of discontinuation will be the last prescription/dispensation + days of supply
- All-cause death
- Loss to follow-up

Relevant covariates:

Age, age group (18–40, 41–50, >50 years), and calendar year will be assessed at index date.

Potential indications for the index treatment and clinical characteristics will be assessed, including duration of hypertension, family history of breast cancer, comorbidities, and healthcare utilisation.

Prescription/dispensation of medications will be assessed, including all contraceptives, hormone replacement therapy (HRT), and other antihypertensive medications at both ingredient and class levels.

Data sources

1. Denmark: Danish Data Health Registries (DK-DHR)
2. Norway: Norwegian Linked Health Registry data (NLHR)
3. Spain: The Information System for Research on Primary Care (SIDIAP)
4. Sweden: Health Impact - Swedish Population Evidence Enabling Data-linkage (HI-SPEED)
5. The United Kingdom: Clinical Practice Research Datalink GOLD (CPRD GOLD)

Study size

For each data source, all individuals who satisfy the eligibility criteria for a study cohort will be included. A precision size calculation will be part of the study output.

Statistical analysis

Characterisation of antihypertensive drug users will be performed in Objective 1. Continuous variables will be summarised using the mean and standard deviation, as well as the median and interquartile range. Categorical variables will be summarised as counts and proportions.

For Objective 2, the number, proportion, and time-to-event distribution of the events of interest among treatment initiators will be estimated at 5 and 10 years of follow-up.

For Objective 3, yearly breast cancer incidence, together with 95% Poisson confidence intervals, will be reported.

In Objective 4, the relative precision will be calculated to assess whether the available data are sufficient to support a future causal association study.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Study milestones and deliverables	Planned dates*
Final Study Protocol	June 2026
Creation of Analytical code	June 2026 – July 2026
Execution of Analytical Code on the data	July 2026 – August 2026
Draft Study Report	Early September 2026
Final Study Report	September 2026

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

6. RATIONALE AND BACKGROUND

Hypertension is highly prevalent in women, resulting in long-term use of antihypertensive medications.[1] Long-term use of antihypertensive medications raises concerns about potential adverse effects, including cancer risk. As many women are exposed to these treatments for prolonged periods, even modest associations between commonly prescribed hypertensive drugs and cancer risk could have important public health implications.

Beta-blockers have been a routine treatment for patients with hypertension for several decades.[2] Beyond their cardiovascular effects, beta-adrenergic signalling has been implicated in several cancer-related biological processes, including tumour proliferation, angiogenesis, immune modulation, and metastasis. Consequently, beta-blockers have been hypothesised to influence cancer development.[3] However, epidemiological evidence on the association between beta-blockers and breast cancer incidence remains inconsistent, potentially due to differences in study design, exposure definitions, comparator selection, duration of follow-up, and residual confounding.[3-5]

Beta-blockers also represent a pharmacologically heterogeneous drug class. B_1-selective beta-blockers differ from non-selective beta-blockers in receptor affinity and pharmacodynamic properties,[6] which may result in differential effects relevant to cancer risk. Nevertheless, many existing studies have evaluated beta-blockers as a single class, limiting inference for individual agents.[3-5]

Before undertaking a causal analysis, it is essential to assess whether available real-world data are fit-for-purpose. The DARWIN EU® Data Network provides federated access to multiple European healthcare data sources mapped to a common data model, enabling evaluation of whether key elements required for such analysis, such as baseline patient characteristics, antihypertensive treatment, long-term follow-up, and breast cancer outcome capture, are adequately recorded across data sources. This feasibility study aims to determine whether selected data sources in the DARWIN EU® network can support future causal research on the potential association between beta-blockers and incident breast cancer.

7. RESEARCH QUESTION AND OBJECTIVES

Research question

Are selected data sources in the DARWIN EU® network fit for supporting a study to examine the causal association between beta-blockers and breast cancer?

Research objectives

This study aims to assess the feasibility of conducting a causal study to examine the potential association between beta-blockers and breast cancer.

The specific objectives of this study are:

1. To describe baseline demographic, clinical characteristics, the potential indications, as well as previous and baseline antihypertensive medication use in female individuals newly initiating the following distinct antihypertensive classes: B_1-selective beta-blockers, non-selective beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), non-dihydropyridines calcium channel blockers (CCBs), dihydropyridines CCBs.
2. To describe the number, proportion, and time-to-event distribution of the following events among female individuals newly initiating B_1-selective beta-blockers, non-selective beta-blockers, ACE inhibitors, ARBs, non-dihydropyridines CCBs, and dihydropyridines CCBs during 5 and 10 years of follow-up: 1) all-cause death, 2) loss to follow-up, and 3) discontinuation of index treatment.
3. To estimate the yearly incidence of primary breast cancer in the general adult (≥18 years) female population overall and by age group (18–40, 41–50, >50 years).
4. To assess whether the study size provides adequate precision to support a causal analysis.

8. RESEARCH METHODS

8.1. Study design

A cohort study will be conducted using routinely collected health data from 5 data sources from 5 countries across Europe and in 3 European Union (EU) member states. The study will comprise:

- Retrospective cohort analyses: To address objectives 1, 2, and 3
- Precision assessment (objective 4): To evaluate whether the study size provides adequate precision to support a future causal analysis

A graphical representation of the study design for objectives 1 and 2 is presented in **Figure 1**, and for objective 3 in **Figure 2**.

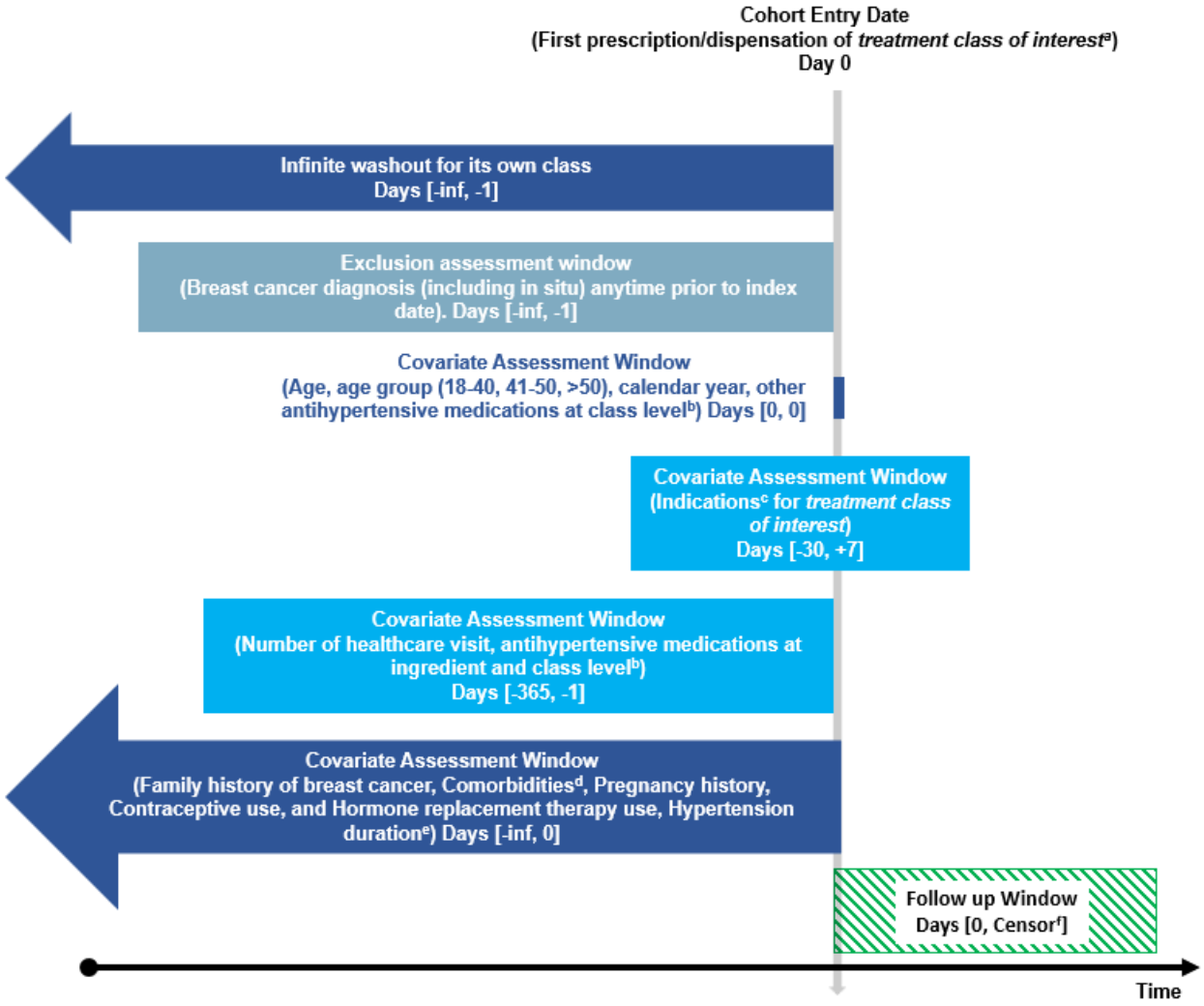

Figure 1. Graphical depiction of the study design for objectives 1 and 2.

a: First prescription/dispensation for a treatment of interest (i.e. index treatment), received between 01/01/2015 and 31/12/2024. Treatment of interest: B_1-selective beta-blockers; non-selective beta-blockers; angiotensin-converting enzyme (ACE) inhibitors; angiotensin II receptor blockers (ARBs); dihydropyridine calcium channel blockers (CCBs), and non-dihydropyridine CCBs.
b: Other antihypertensive medications: B_1-selective beta-blockers; non-selective beta-blockers; ACE inhibitors; ARBs; non-dihydropyridines CCBs; dihydropyridines CCBs; Diuretics.
c: Potential indications: arrhythmia, angina, myocardial infarction, coronary artery disease, and heart failure
d: Comorbidities of interest: diabetes mellitus, obesity and overweight, chronic obstructive pulmonary disease, infertility, endometriosis, polycystic ovary syndrome, hysterectomy, bilateral oophorectomy, ovarian cancer, endometrial cancer, osteoporosis
e: Defined as the time between the first recorded diagnosis of hypertension and the index date, classified as (<1, 1–5, and >5 years)
f: Earliest of: discontinuation of index treatment, all-cause death, disenrollment, end of the study period

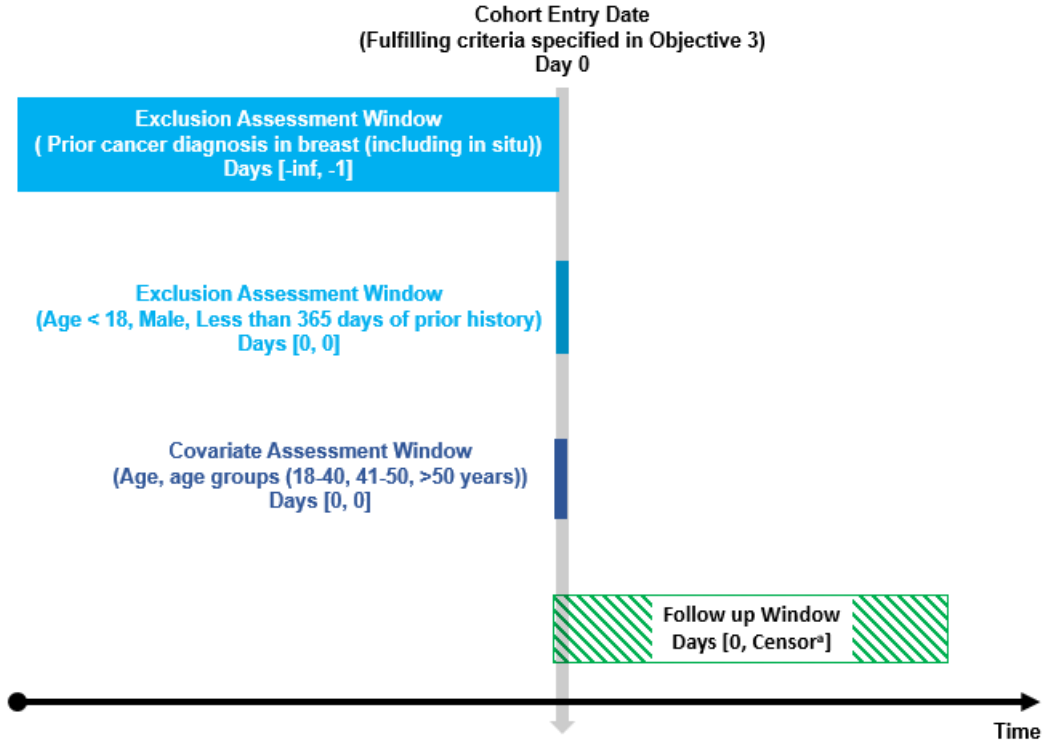

Figure 2. Graphical depiction of the study design for objective 3.

a: Earliest of: breast cancer diagnosis, all-cause death, disenrollment, end of the study period

8.2. Follow-up

Objectives 1 and 2: Follow-up will start on index date, defined as first prescription or dispensation of index treatment. When both are available in the data source, the prescription data will be preferred. Follow-up will end at the earliest of: discontinuation of index treatment, all-cause death, loss to follow-up, or study end date (31/12/2024).

Objective 3: For each calendar year during the study period, follow-up will start on the first of January or on the date eligibility criteria are first fulfilled within that year, whichever occurs later. Individuals may contribute person-time across multiple calendar years until the earliest of: incident breast cancer, all-cause death, loss to follow-up, or study end date (31/12/2024).

An example of entry into and exit from the denominator population for Objective 3 is shown in **Figure 3**. In this example, person ID 1 already fulfils eligibility criteria before the study start date, and the observation period ends after the study end date, so this individual will contribute person-time during the complete study period. Person IDs 2 and 4 only enter the study when they first fulfil eligibility criteria. Person ID 3 leaves when exiting the data source (the end of the observation period). Lastly, person ID 5 has two eligible observation periods in the data source and contributes person-time during both eligible periods. The first period contributes time from the study start until the end of the observation period. The second starts contributing time again once eligibility criteria are fulfilled and continues until the study end date.

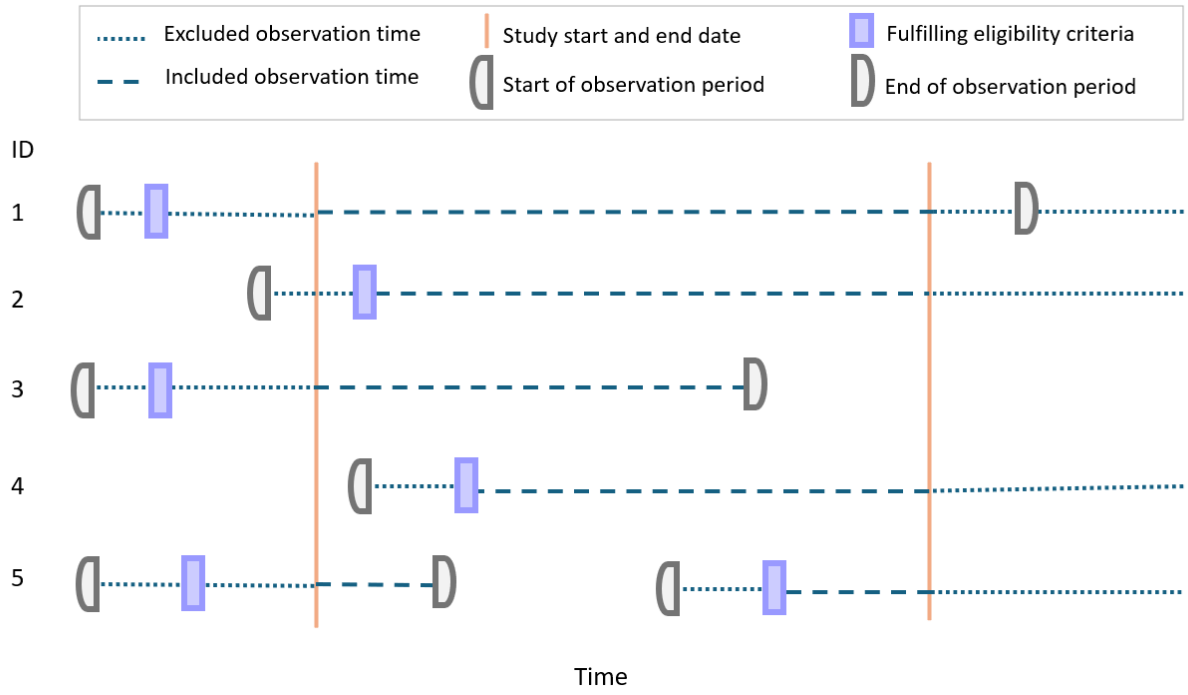

Figure 3. Included observation time for the denominator population.

8.3. Study population with inclusion and exclusion criteria

Study population:

Objectives 1, 2, and 4: Newly initiating an index treatment during the study period

Inclusion criteria

- Female individuals aged ≥18 years
- ≥365 days of prior observation
- Hypertension diagnosis on or before the index date

Exclusion criteria

- Breast cancer diagnosis (including in situ breast cancer) any time before the index date
- Infinite washout [-inf, -1] will be applied for prior use of the index treatment class. For any beta-blocker cohorts, washout will be applied across all beta-blockers. For any CCBs cohorts, washout will be applied across all CCBs

For objective 3, a different cohort (general female population) will be defined:

Inclusion criteria

- Female individuals aged ≥18 years
- ≥365 days of prior observation

Exclusion criteria

- Breast cancer diagnosis (including in situ) any time before index date.

8.4. Study setting and data sources

This study will be conducted using routinely collected data from five primary/secondary care data sources in the DARWIN EU® network of data partners from five European countries (**Table 1** and **ANNEX I**). All data were *a priori* mapped to the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM). Information on data sources included and a rationale for their inclusion in terms of ability to capture the relevant data is described in **ANNEX II.**

Table 1. Description of the selected data sources.

Country	Name of Data source	Health Care setting	Type of Data	Number of active individuals	Calendar period covered
The United Kingdom	CPRD GOLD	Primary care	EHR	2.63M	01/10/1987 – 01/04/2025
Denmark	DK-DHR	Secondary care	Nationwide Registry	5.98M	01/01/1995 – 30/11/2023
Sweden	HI-SPEED	Secondary care	Nationwide Registry	10.6M	01/01/2015 – 01/08/2025
Norway	NLHR	Primary and secondary care	Nationwide Registry	5.55M	01/01/2008 – 31/12/2023
Spain	SIDIAP	Primary care and hospital inpatient care *	EHR	6.07M	01/01/2006 – 01/12/2024

CPRD=Clinical Practice Research Datalink, DK-DHR=Danish Data Health Registries, HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage, NLHR=Norwegian Linked Health Registry data, SIDIAP=The Information System for Research in Primary Care.
M=millions, EHR=Electronic Health Records.
*In SIDIAP, for inpatient care, only diagnosis, procedures and duration of hospitalisation are available.

These data sources were preselected from DARWIN EU® network as they fulfil the criteria required in terms of data quality, completeness, timeliness, and representativeness for this study while covering different regions of Europe (**ANNEX I** and **ANNEX II**).

8.5. Study period

The study period is from 01/01/2015 to 31/12/2024 or the most recent data available for each contributing data source. It should be noted that, in HI-SPEED, accurate data are available from 01/01/2015 onward. Therefore, to satisfy the 365-day prior history requirement, the study period for HI-SPEED will start on 01/01/2016. In DK-DHR, cancer data are available through 30/11/2023. In NLHR and SIDIAP, data availability ends on 31/12/2023 and 01/12/2024, respectively.

8.6. Variables

8.6.1. Exposure

In Objectives 1, and 2:

- B_1-selective beta-blockers (*Atenolol, Metoprolol, Bisoprolol, Nebivolol, Betaxolol, Acebutolol*)
- Non-selective beta-blockers (*Propranolol, Nadolol, Timolol, Pindolol, Carvedilol, Labetalol*)

- ACE inhibitors (*Enalapril, Lisinopril, Perindopril, Ramipril, Captopril, Benazepril, Fosinopril, Trandolapril*)
- ARBs (*Losartan, Valsartan, Candesartan, Irbesartan, Telmisartan, Olmesartan, Azilsartan*)
- Non-dihydropyridines CCBs (*Verapamil, Diltiazem*)
- Dihydropyridines CCBs (*Amlodipine, Felodipine, Nifedipine, Lercanidipine, Nicardipine*)

Drug codes are available in RxNorm. Prescription or dispensation data will be used when available; when both are present in the data source, prescription records will be prioritised. The preliminary concept sets used for the identification of exposures are described in **Annex IV**. These codes will be refined during the study execution following the DARWIN EU® phenotyping standard processes, which involve the review of code lists by clinical experts and the review of phenotypes after their execution in the participating data sources.[7]

8.6.2. Outcome

Objective 1:

Not applicable.

Objective 2:

- Discontinuation of index treatment: discontinuation will be defined as a gap of >90 days without a subsequent prescription/dispensation of index treatment. The date of discontinuation will be the last prescription/dispensation + days of supply, where available. More detailed information about days of supply data and how the end of each prescription is estimated in each data source can be found in **Annex II**.
- All-cause death
- Loss to follow-up: defined as the end of an individual's observation period in the data source, which may reflect deregistration, disenrollment, or emigration.

Objective 3:

The outcome will be defined as the occurrence of incident breast cancer recorded in the data sources.

Breast cancer codes are available in SNOMED and ICDO3. The preliminary concept sets used for the identification of outcomes are described in **Annex IV**. These codes will be refined during the study execution following the DARWIN EU® phenotyping standard processes, which involve the review of code lists by clinical experts and the review of phenotypes after their execution in the participating data sources.[7]

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

Objective 1

Covariates assessed at index date [0, 0]:

- Age at index date will be determined, and age groups will be categorised (years), namely:
  - 18–40
  - 41–50
  - >50
- Index calendar year will be assessed

Clinical characteristics:

- Other potential indications for the index treatment (assessment window: [-30,+7 days]):
  - Coronary artery disease
  - Arrhythmia
  - Angina
  - Myocardial infarction
  - Heart failure
  - Other/unspecified
- Hypertension duration, defined as the time between the first recorded hypertension diagnosis and the index date ((assessment window: [-inf,0]), Categorised as:
  - <1 year
  - 1–5 years
  - >5 years
- Clinical comorbidities (assessment window: [-inf,0]):
  - Diabetes mellitus (Type I, Type II, Gestational)
  - Obesity or overweight (body mass index ≥25)
  - Infertility
  - Endometriosis
  - Polycystic ovary syndrome
  - Hysterectomy
  - Bilateral oophorectomy
  - Ovarian cancer
  - Endometrial cancer
  - Other malignancy except breast and non-melanoma skin cancer
  - Chronic obstructive pulmonary disease as a proxy for smoking
  - Osteoporosis, as a proxy for bone density and oestrogen-related breast cancer risk
- Family history of breast cancer (yes/no) (assessment window: [-inf,0])
- Number of healthcare visits (assessment window: [-365,-1]):
  - Outpatient visit
  - Inpatient visit
  - Emergency department

Medications:

- Prior and baseline antihypertensive medications at ingredient and class level (assessment windows (days): [-365,-1], [0,0])):
  - B_1-selective beta-blockers (*Atenolol, Metoprolol, Bisoprolol, Nebivolol, Betaxolol, Acebutolol*)

  - Non-selective beta-blockers (*Propranolol, Nadolol, Timolol, Pindolol, Carvedilol, Labetalol, Sotalol*)
  - ACE inhibitors (*Enalapril, Lisinopril, Perindopril, Ramipril, Captopril, Benazepril, Fosinopril, Trandolapril*)
  - ARBs (*Losartan, Valsartan, Candesartan, Irbesartan, Telmisartan, Olmesartan, Azilsartan*)
  - Non-dihydropyridines CCBs (*Verapamil, Diltiazem*)
  - Dihydropyridines CCBs (*Amlodipine, Felodipine, Nifedipine, Lercanidipine, Nicardipine*)
  - Diuretics (*Hydrochlorothiazide, Indapamide, Chlorthalidone, Bendroflumethiazide, Metolazone, Furosemide, Bumetanide, Torsemide, Ethacrynic acid*)
- Antihypertensive classes use at baseline (assessment window: [0,0]):
  - 1 class
  - 2–4 classes
  - 5–7 classes
- Contraceptive use (assessment window: [-inf,0]), Categorised as (days):
  - Current/recent use [-180,0] days
  - Past use [-infinite, -181] days
  - No recorded use [-infinite, 0] days
- Hormone replacement therapy (HRT) use (assessment window: [-inf,0]), Categorised as (days):
  - Current/recent use [-365,0] days
  - Past use [-inf, -366] days
  - No recorded use [-inf, 0] days

Covariates to be explored from large scale characterisation:

- Smoking
- Alcohol use
- Pregnancy history (assessment window: [-inf,0]) will be assessed where available. When sufficient information is available in the data source, categories may include:
  - Nulliparous
  - First pregnancy before age 35 years
  - First pregnancy at or after age 35 years
- Bilateral preventive mastectomy
- Preeclampsia
- Premature ovarian insufficiency

The preliminary concept sets used for the identification of covariates are described in **Annex IV**. These codes will be refined during the study execution following the DARWIN EU® phenotyping standard processes, which involve the review of code lists by clinical experts and the review of phenotypes after their execution in the participating data sources.[7] For covariates identified through large-scale

characterisation, this study will assess their availability, operational definitions, and completeness across data sources.

8.7. Study size

For each data source, all individuals who satisfy the eligibility criteria for a study cohort will be included. An estimation precision calculation will be part of the study output.

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' 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 secure online repository of DTZ (Data Transfer Zone). 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

<u>All objectives:</u>

We will use the R packages *PatientProfiles, CohortCharacteristics*, *CohortSurvival*, *DrugUtilisation*, and *IncidencePrevalence,* developed by DARWIN EU®, to describe patient-level characteristics and survival, and to estimate the incidence based on OMOP CDM mapped data.[8-12]

<u>Objective 1 (Characterisation in treatments of interest users)</u>

The *PatientProfiles* and *CohortCharacteristics* packages will be used to summarise baseline demographic, clinical characteristics, other potential indications, and antihypertensive medication taken at different time windows, as described in the **Section 8.6.3.**

Categorical variables (e.g. age group, calendar year at index date, number of antihypertensive medications, hypertension duration (categorised), potential indications, prior and baseline antihypertensive medications at ingredient and class level, clinical comorbidities, family history of breast cancer, pregnancy history, contraceptive and HRT use) will be described using counts and percentages.

Continuous variables (e.g. age, number of overall healthcare visits) will be described using means, standard deviations (SD), medians, and interquartile ranges (IQR).

Exploratory large-scale characterisation at different time windows [-365, -1], [-30, 7], and [0, 0] will also be conducted, and results will be available exclusively through the interactive Shiny application.

Objective 2 (Survival analysis)

Kaplan-Meier survival curves will be generated using the *CohortSurvival* and *DrugUtilisation* packages to describe the time-to-event distribution for events of interest over 5 and 10 years of follow-up. All-cause death and loss to follow-up will be analysed using the *CohortSurvival* package, while discontinuation of the index treatment will be analysed using the *DrugUtilisation* package. For each endpoint, we will report the estimated cumulative incidence at 5 and 10 years of follow-up, as well as the median time to event with IQR. In the analysis of each specific event, individuals who experience other events will be censored at the time those events occur.

Objective 3 (Incidence of breast cancer)

The *IncidencePrevalence* package will be used to estimate the yearly and overall incidence rate of breast cancer among the general adult female population in objective 3.

Yearly and overall incidence rates of breast cancer per 100,000 person-years will be estimated with the respective 95% confidence intervals. Estimates will be provided overall and stratified by age categories (18–40, 41–50, >50 years).

Eligible participants will contribute person-time from cohort entry until the earliest of the following: incident breast cancer diagnosis during the follow-up period, loss to follow-up, all-cause death, end of observation period (the latest available data), or study end date (31/12/2024). Participants without a breast cancer diagnosis will contribute time at risk until censoring, as described in **Section 8.2**. 95% confidence intervals will be based on a Poisson distribution.

Objective 4 (Precision calculation)

The precision will be assessed using the approach proposed by Rothman and Greenland.[13] Based on previous literature,[14] assumed rate ratios (RR) of 1.5, 2.0, and 2.5 will be evaluated as alternative scenarios. Relative precision (F) values of 5%, 10%, 20%, and 30% will be evaluated.

For each assumed RR and predefined F level, the expected 95% confidence interval (CI) around the assumed RR will be calculated as:

Lower 95%CI = RR / (1+F)

Upper 95%CI = RR * (1+F)

The required number of breast cancer events (D) to achieve each predefined level of relative precision will be calculated as:

$$D = \left(\frac{3.92}{log\ (1+F)}\right)^2$$

The incidence rate of breast cancer in the alternative antihypertensive treatment cohort will be estimated from Objective 3. Assuming RRs of 1.5, 2.0, and 2.5, the expected incidence rate in the beta- blockers cohorts will be estimated accordingly. The average incidence rate across both cohorts *p* will be calculated as:

$$p = \frac{p0 + p1}{2}$$

where *p*0 and *p*1 denote the incidence rate of breast cancer in the alternative antihypertensive treatment cohort and beta-blockers cohorts, respectively.

The required sample size (N) for each RR and F scenario will then be calculated as:

$$N = \frac{D}{p}$$

The predefined precision scenarios (5%, 10%, 20%, and 20%) will serve as a framework for interpreting the feasibility results. The observed cohort size and expected number of breast cancer events in each treatment pair will be mapped to these scenarios to identify the level of F that is likely to be achievable in a future comparative safety study. Results will be presented as the expected RR, corresponding to a 95% CI, required number of events, and required sample size for each predefined level of F. Based on the observed cohort size and expected number of events, a conclusion will be drawn regarding the level of precision that is expected to be achievable for the future comparative safety study.

8.8.4. Output

Output will include a PDF report, including an executive summary and the following tables and figures:

Objectives 1 and 2:

- Table 1. Study attrition of beta-blockers user cohorts across data sources.
- Table 2. Characteristics, covariates, and medication use in index treatment users across data sources.
- Table 3. Covariates to be explored from large scale characterisation across data sources.
- Figure 1. Time to index treatment discontinuation among index treatment users across data sources.
- Figure 2. Probability of all-cause death among index treatment users across data sources.
- Figure 3. Probability of loss to follow-up among index treatment users across data sources.
- Table 4. Follow-up outcomes at 5 and 10 years in index treatment cohorts across data sources.

Objective 3:

- Figure 4. Yearly breast cancer incidence rates per 100,000 PYs (95% CIs) among the general adult female population by data source.
- Figure 5. Yearly breast cancer incidence rates per 100,000 PYs (95% CIs) among the general adult female population stratified by age groups by data source.

Objective 4:

- Table 5. Relative precision assessment.

Table 1. Study attrition of beta-blockers user cohorts across data sources.

	CPRD GOLD N included	DK-DHR N included	HI-SPEED N included	NLHR N included	SIDIAP N included
Non-selective beta-blockers cohort					
Initiation of the index treatment class during the study period, with ≥365 days of prior observation					
Washout					
Age ≥18 years					
Female only					
Prior hypertension diagnosis					

	CPRD GOLD N included	DK-DHR N included	HI-SPEED N included	NLHR N included	SIDIAP N included
on/before index date					
No prior breast cancer diagnosis					
Final cohort included					
B_1-selective beta-blockers cohort					
Initiation of the index treatment class during the study period, with ≥365 days of prior observation					
Washout					
Age ≥18 years					
Female only					
Prior hypertension diagnosis on/before index date					
No prior breast cancer diagnosis					
Final cohort included					

N=Number, CPRD=Clinical Practice Research Datalink, DK-DHR=Danish Data Health Registries, HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage, NLHR=Norwegian Linked Health Registry data, SIDIAP=The Information System for Research in Primary Care.

Table 2. Characteristics, covariates, and medication use in index treatment users across data sources.

	B_1-selective beta-blockers	Non-selective beta-blockers	ACE inhibitors	ARBs	Non-dihydropyridine CCBs	Dihydropyridine CCBs
Characteristics						
Median age (IQR)						
Mean age (SD)						
Age group, in years						
18–40						
41–50						
>50						
Median index treatment initiation, calendar year (IQR)						
Other potential indications						
Angina						

	B_1-selective beta-blockers	Non-selective beta-blockers	ACE inhibitors	ARBs	Non-dihydropyridine CCBs	Dihydropyridine CCBs
Myocardial infarction						
Arrhythmia						
Coronary artery disease						
Heart failure						
Other/unspecified						
Hypertension duration, in years						
<1 year						
1–5 years						
>5 years						
Clinical comorbidities						
Type I Diabetes mellitus						
Type II Diabetes mellitus						
Gestational Diabetes mellitus						
Obesity or overweight						
Infertility						
Endometriosis						
Polycystic ovary syndrome						
Hysterectomy						
Bilateral oophorectomy						
Ovarian cancer						
Endometrial cancer						
All cancers except breast and non-melanoma skin cancer						
Chronic obstructive pulmonary disease						
Osteoporosis						
Family history of breast cancer						
Number of overall Healthcare visits						
Outpatient visit						
Inpatient visit						
Emergency department						
Prior antihypertensive medications						
B_1-selective beta-blockers						

	B_1-selective beta-blockers	Non-selective beta-blockers	ACE inhibitors	ARBs	Non-dihydropyridine CCBs	Dihydropyridine CCBs
Non-selective beta-blockers						
ACE inhibitors						
ARBs						
Non-dihydropyridines CCBs						
Dihydropyridines CCBs						
Diuretics						
Number of antihypertensive class use at baseline						
1 class						
2–3 classes						
4–7 classes						
Contraceptive use						
Current/recent use [-180,0] days						
Past use [-infinite, -181] days						
No recorded use [-infinite, 0] days						
HRT use						
Current/recent use [-365,0] days						
Past use [-inf, -366] days						
No recorded use [-inf, 0] days						

IQR=Interquartile Range, SD=Standard Deviation, ACE=Angiotensin-converting enzyme, ARBs=Angiotensin II receptor blockers, CCB=Calcium channel blockers, N=Number, CPRD=Clinical Practice Research Datalink, DK-DHR=Danish Data Health Registries, HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage, NLHR=Norwegian Linked Health Registry data, SIDIAP=The Information System for Research in Primary Care, HRT=Hormone replacement therapy.

Table 3. Covariates identified from large scale characterisation across data sources.

	CPRD GOLD	DK-DHR	HI-SPEED	NLHR	SIDIAP
Smoking					
Alcohol use					
Premature ovarian insufficiency					
Preeclampsia					
Pregnancy history					
Nulliparous					
First pregnancy before age 35 years					
First pregnancy at or after age 35 years					

CPRD=Clinical Practice Research Datalink, DK-DHR=Danish Data Health Registries, HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage, NLHR=Norwegian Linked Health Registry data, SIDIAP=The Information System for Research in Primary Care.

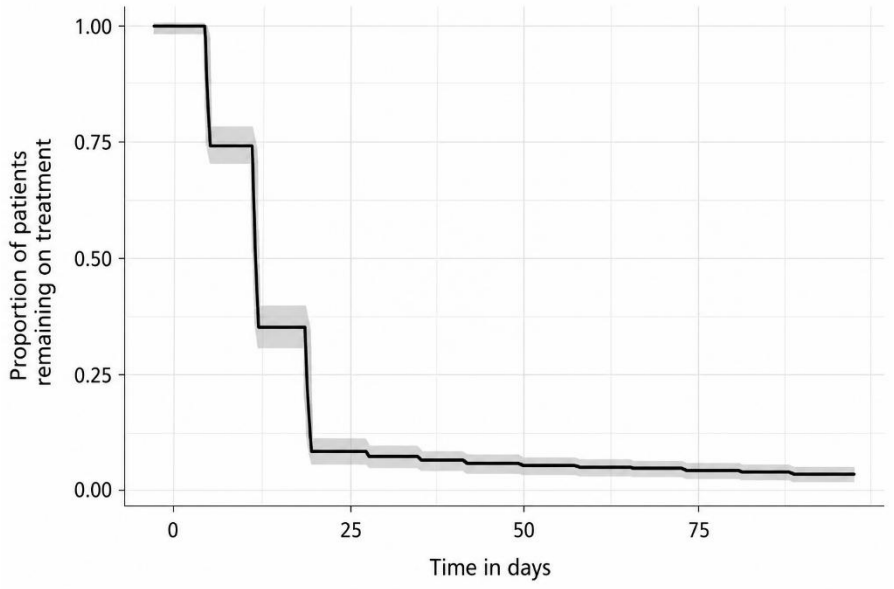

Figure 1. Time to index treatment discontinuation among index treatment users across data sources.

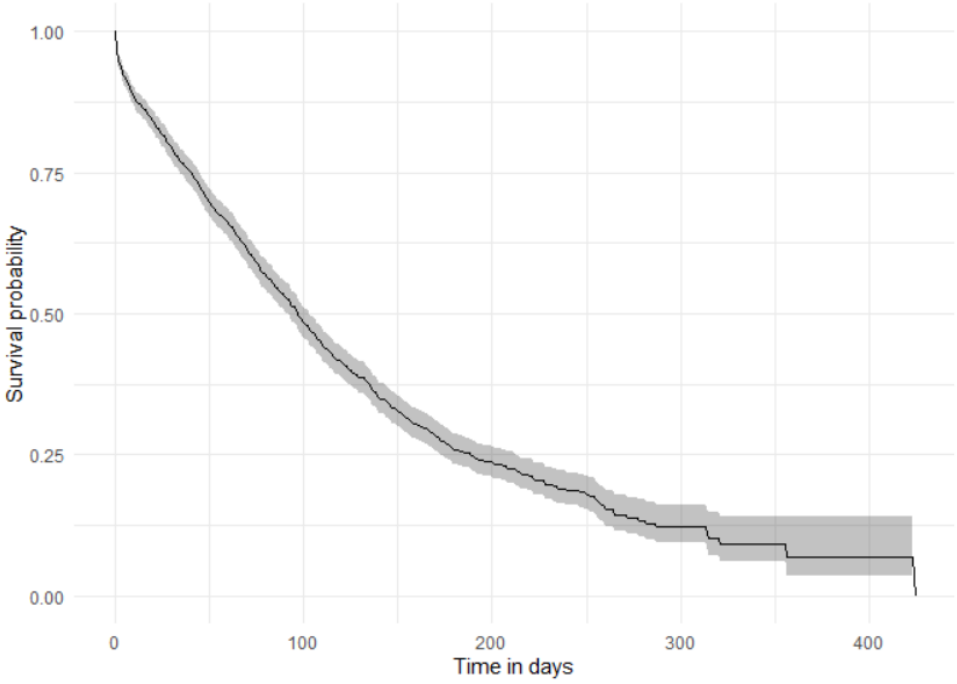

Figure 2. Probability of all-cause death among index treatment users across data sources.

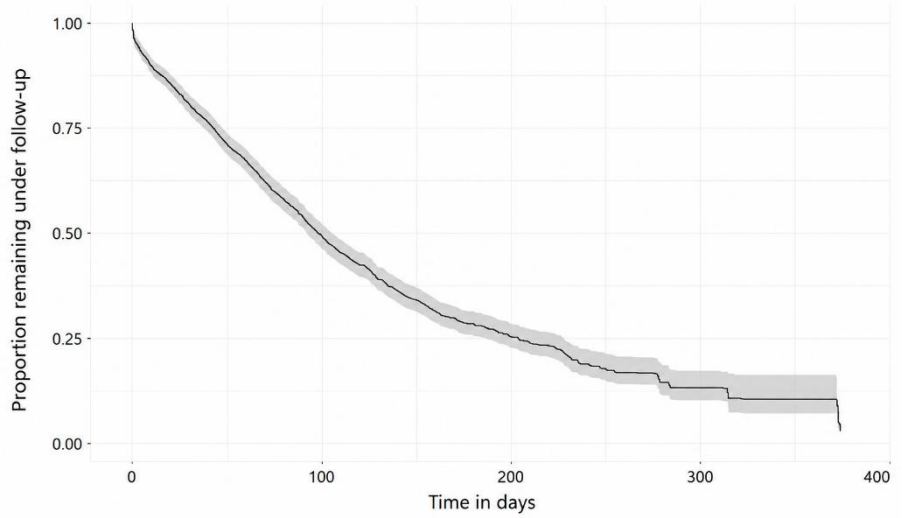

Figure 3. Probability of loss to follow-up among index treatment users across data sources.

Table 4. Follow-up outcomes at 5 and 10 years in index treatment cohorts across data sources.

Events of interest		B_1-selective beta-blockers	Non-selective beta-blockers	ACE inhibitors	ARBs	Non-dihydropyridine CCBs	Dihydropyridine CCBs
Assessed at 5 years of follow-up							
All-cause death	N (%)						
	Median time-to-event (IQR)						
Loss to follow-up for any reason	N (%)						
	Median time-to-event (IQR)						
Discontinuation of index treatment	N (%)						
	Median time-to-event (IQR)						
Assessed at 10 years of follow-up							
All-cause death	N (%)						
	Median time-to-event (IQR)						
Loss to follow-up for any reason	N (%)						
	Median time-to-event (IQR)						
Discontinuation of index treatment	N (%)						
	Median time-to-event (IQR)						

IQR=Interquartile Range, N=Number, CPRD=Clinical Practice Research Datalink, DK-DHR=Danish Data Health Registries, HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage, NLHR=Norwegian Linked Health Registry data, SIDIAP=The Information System for Research in Primary Care, ACE=Angiotensin-converting enzyme, ARBs=Angiotensin II receptor blockers, CCB=Calcium channel blockers.

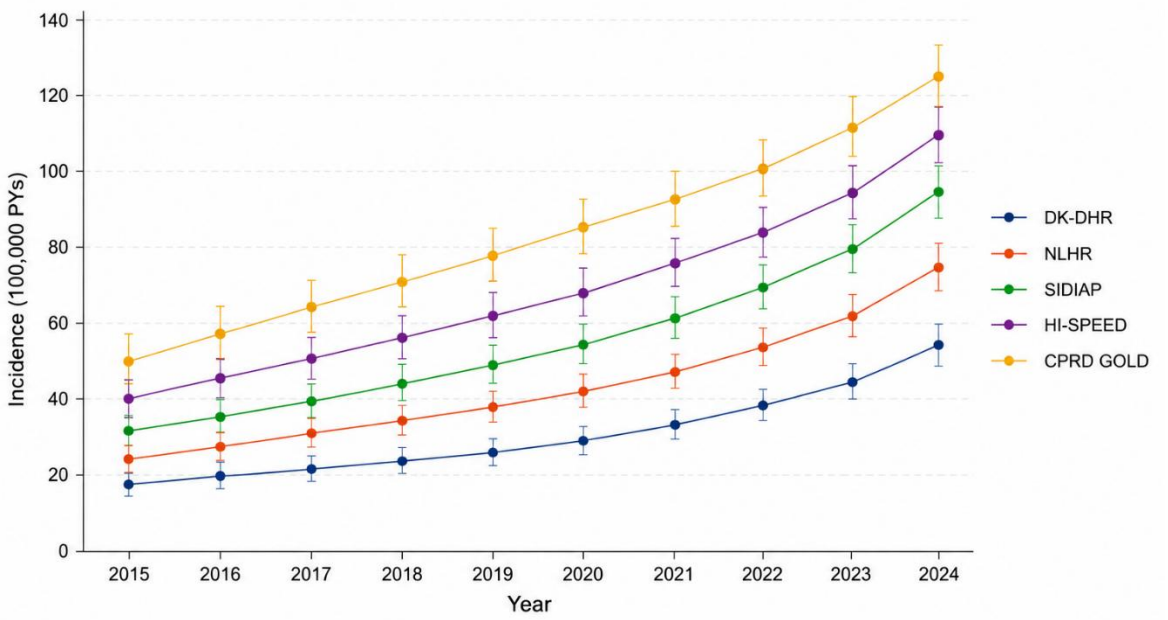

Figure 4. Yearly breast cancer incidence rates per 100,000 PYs (95% CIs) among the general adult female population by data source.

CPRD=Clinical Practice Research Datalink, DK-DHR=Danish Data Health Registries, HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage, NLHR=Norwegian Linked Health Registry data, SIDIAP=The Information System for Research in Primary Care, CI=Confidence Interval, PY=Person year.

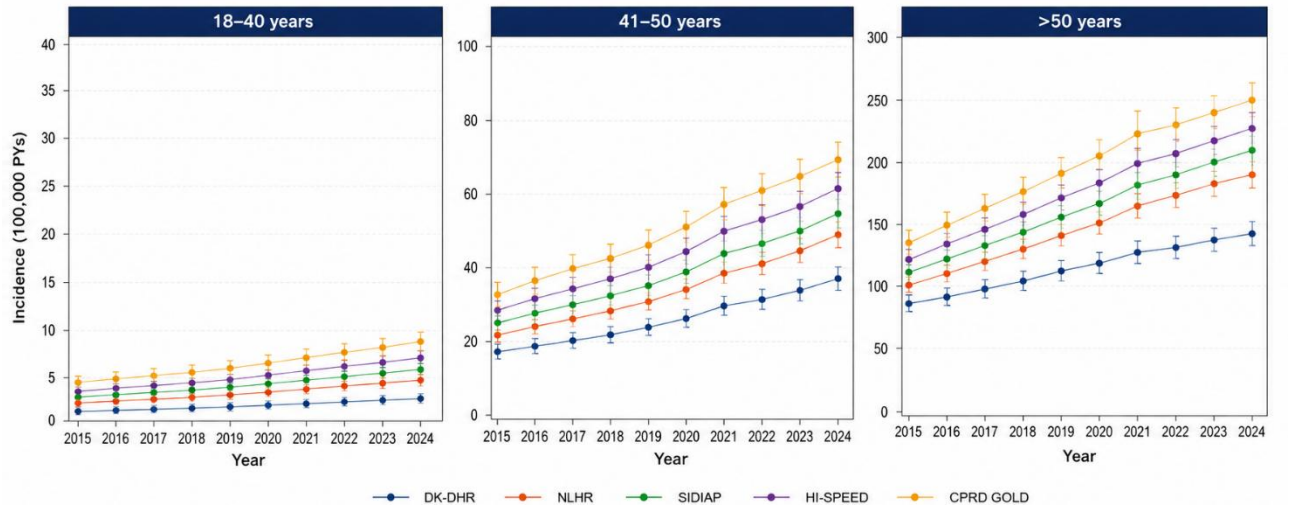

Figure 5. Yearly incidence rates per 100,000 PYs (95% CIs) of breast cancer among the general adult female population stratified by age groups by data source.

CPRD=Clinical Practice Research Datalink, DK-DHR=Danish Data Health Registries, HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage, NLHR=Norwegian Linked Health Registry data, SIDIAP=The Information System for Research in Primary Care, CI=Confidence Interval, PY=Person year.

Table 5. Relative precision assessment.

Expected RR	Incidence rate In alternative antihypertensive treatment cohorts	Estimated incidence rate In beta-blockers cohort	Relative precision (%)	95% CI	Events	Sample size
1.5			5			
1.5			10			
1.5			20			
1.5			30			
2.0			5			
2.0			10			
2.0			20			
2.0			30			
2.5			5			
2.5			10			
2.5			20			
2.5			30			

RR=Rate Ratio, CI=Confidence Interval

An interactive dashboard will be generated by incorporating all the results (tables and figures) included in the PDF report mentioned above.

The results of the large-scale characterisation will be made available exclusively through the interactive Shiny application.

8.9. Evidence synthesis

Results from analyses described in **Section 8.8** will be presented separately for each data source. No meta-analysis of results will be conducted.

9. STRENGTHS AND LIMITATIONS

At the design stage, harmonised cohort definitions and phenotyping procedures will be applied to ensure consistency across data sources and to support reproducibility. In addition, a broad set of relevant and available covariates will be systematically identified, considered, and characterised, thereby establishing a strong foundation for subsequent causal analyses.

However, as this study relies on routinely collected healthcare data, inherent data quality limitations must be considered. Several clinically relevant variables are not captured at all, such as genetic markers including Breast Cancer gene (BRCA) mutations and menopausal status. Pregnancy history cannot be ascertained in detail in most data sources especially in older women, and this will be further explored from the large scale characterisation results. Similarly, information on family history of breast cancer is not consistently available across all contributing data sources. In addition, some factors, such as smoking, alcohol use, and premature ovarian insufficiency, are not comprehensively captured across data sources, and even when available in certain data sources, their definitions, classification, and standardisation may vary. Therefore, their availability, recording, definitions, consistency, and potential usability will be further explored through the large-scale characterisation results in this study to assess whether they could be appropriately included in the subsequent causal study.[15]

Second, although the OMOP Common Data Model enables standardised mapping to established clinical vocabularies, such as SNOMED, inaccuracies, incompleteness, and inconsistencies in source-to-standard mapping may still occur across data sources. These issues may affect the validity and comparability of derived variables. Outcome misclassification is also possible because of limitations in coding practices and in the availability and granularity of diagnosis, which may in turn affect the sensitivity of outcome ascertainment. Furthermore, outcome data completeness may vary by data source type. More complete capture of cancer diagnoses is expected in registry-based data sources (e.g. DK-DHR, HI-SPEED, and NLHR), whereas in primary care-based data sources, such as CPRD GOLD, cancer diagnoses may be less completely recorded. To aid interpretation, incidence rates estimated across the different data sources in this study will be compared to one another and be benchmarked against estimates reported in external literature.

Third, exposure will be identified based on one prescription or dispensation record only, which may not fully reflect actual chronic medication use. Some individuals, such as those with less persistent or well-controlled hypertension, may discontinue treatment early or may not take the medication for prolonged periods. This may introduce uncertainty in the identification of sustained exposure. However, this issue will be partially evaluated through the analysis of discontinuation of index treatment, and the findings may help inform whether stricter exposure requirements should be considered in a future causal study. Discontinuation will be defined as a gap of more than 90 days without a subsequent prescription or dispensation of the index treatment, which may underestimate prescription durations longer than three months, although such prescribing patterns are uncommon in real-world practice.

In addition, because antihypertensive drugs are frequently prescribed in combination, it may be difficult to determine whether any potential risk is attributable to a single antihypertensive class or to concurrent use of multiple classes. To address this, this feasibility study will also assess co-antihypertensive medication use, which will help inform strategies for covariate adjustment in a future causal analysis.

Lastly, the estimates derived from this study will reflect only the populations represented in the included data sources.

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11. ANNEXES

ANNEX I. Description of data sources

Clinical Practice Research Datalink GOLD (CPRD GOLD)

#	Section	Description
1	Data source identification and country	CPRD GOLD (Clinical Practice Research Datalink GOLD) United Kingdom
2	Data partner information section	University of Oxford NDORMS
3	Coverage and timespan	Data collection since: 1987 Extent: Nation-wide. 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, 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). 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 v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). 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

#	Section	Description
		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
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

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	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 Institute Catala 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 v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). 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.

#	Section	Description
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.
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,Bolíbar 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

Norwegian Linked Health Registry data (NLHR)

#	Section	Description
1	Data source identification and country	NLHR (Norwegian Linked Health Registry data) Norway
2	Data partner information section	University of Oslo Faculty of Mathematics and Natural Science – Department of Pharmacy
3	Coverage and timespan	Data collection since: 2008 Extent: Nation-wide. Norway has a universal public health care system, consisting of primary and specialist health care services covering a population of approximately 5.4 million inhabitants.
4	Healthcare setting / type of data	Primary care – General Practioner, and primary care specialists (e.g. paediatricians), and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care. The following registries are included: the Medical Birth Registry of Norway (MBRN), the

#	Section	Description
		Norwegian Prescription Registry (NorPD), the Norwegian Patient Registry (NPR), Norway Control and Payment of Health Reimbursement (KUHR), the Norwegian Surveillance System for Communicable Diseases (MSIS), the Norwegian Immunisation Registry (SYSVAK), the National Death Registry, and the National Registry (NR).
5	Data collection process	Registries. Many population-based health registries were established in the 1960s, with use of unique personal identifiers facilitating linkage between registries. Data in these health registries are used for health analysis, health statistics, improving the quality of healthcare, research, administration, and emergency preparedness.
6	General representativeness	The NLHR data covers the full Norwegian population.
7	Data content /source coding	NPR: ICD-10 for diagnosis, ATC and some special codes for drug use, Norwegian codes for clinical procedures (surgery (NCSP), medicine (NCMP) and diagnostic imaging, image-guided intervention, and nuclear medicine (NCRP)). KUHR: ICD-10 and ICPC-2 and ICPC-2B for diagnosis/procedure. NorPD: ATC. SYSVAK and MSIS: national classifications. MBRN: custom classifications by questionnaires (incl. check box variables in Maternity health care card)
8	Data Harmonisation	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. Linkage between the registries was facilitated using project-specific person IDs generated from unique personal identification assigned at birth or immigration for all legal residents in Norway.
9	Quality control (data source specific)	In-house data quality checks of rates of common conditions, drug exposures, and outcomes. We compare obtained rates with official national statistics (e.g. birth statistics, yearly rates of drug dispensing, and diagnosis by age and gender). We also review missing data and outliers and inform registry holders of any unusual patterns.
10	Linkage	The NLHR is, by definition, a linkage of datasets. Helsedata.no is one central portal to apply for 11 national health registries, including all the registries that have been mapped to the OMOP CDM.
11	Vital status	The national death registry is linked.
12	Limitations	No database-specific limitations documented. General limitations for the data type applicable. (i) Diagnostic codes in the secondary care are limited to the comprehensive list requested from the registries. The list of codes will be revised annually with each data delivery. (ii) ICD-10 codes vary in granularity, ranging from 2-character to full-length codes. The granularity of data will be revised annually with each data delivery (iii) Drug dispensations to outpatients are included; however, over-the-counter (OTC) medications are not captured in the data. Only a few selected expensive drugs given in hospital, are included.
13	Main references	Trinh NT, Houghtaling J, Bernal FL, Hayati S, Maglanoc LA, Lupattelli A, Halvorsen L, Nordeng HM. Harmonizing Norwegian registries onto OMOP common data model: Mapping challenges and opportunities for pregnancy and COVID-19 research. Int J Med Inform. 2024 Nov;191:105602.
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1000000409 Website: https://www.mn.uio.no/farmasi/english/research/groups/pharma-safe/

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 Analytics Centre (DAC)
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 v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). 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.
12	Limitations	DK-DHR has the following limitations, which may be relevant confounders for certain complex Darwin EU studies: - We lack information on key socio-economic status (SES) factors, such as occupation, education, and income. These variables may be important for analysis in some studies. - We only have complete data on lifestyle factors (such as smoking status and weight) for pregnant women.

#	Section	Description
		- We have no information on patient contacts in primary care (visits to the GP). Consequently, the incidence of chronic diseases like Type 2 Diabetes (T2D) and asthma must be determined using drug prescriptions as a proxy. Stillborn children will not have any records in our CDM. This means that e.g. birth length of stillborns is not recorded.
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

Health Impact - Swedish Population Evidence Enabling Data-linkage (HI-SPEED)

#	Section	Description
1	Data source identification and country	HI-SPEED (Health Impact - Swedish Population Evidence Enabling Data-linkage) Sweden
2	Data partner information section	SMPA-GU, Läkemedelsverket, Box 26, 751 03 Uppsala, Sweden - Box 469, 405 30 Gothenburg, Sweden Pharmacoepidemiology and Analysis Department (FeA) - School of Public Health and Community Medicine, Institute of Medicine
3	Coverage and timespan	Data collection since: 2015 Extent: Nation-wide. The catchment area includes the whole of Sweden, covering the full population of approximately 11.7 million.
4	Healthcare setting / type of data	Primary care – General Practioner, and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care. Primary care (GPs) is available only for the 2 largest regions (~40% of national population) The following data elements are collected: Socio-demographics, dispensed drug prescriptions, cause of death, diagnoses and procedures from secondary (specialist) care and inpatient visits or clinical events, as well as from primary care visits (40%pop only).
5	Data collection process	Registries. The data is acquired from the relevant Swedish national and regional registries, only once all legislative, GDPR and ethical approvals have been granted. Therefore only relevant data is passed on, which will then be entered and processed by the study team. The data are updated several times annually.
6	General representativeness	The coverage includes all patients of all sociodemographic characteristics. Therefore it should mirror the source population to a very good extent.
7	Data content /source coding	Medicines are coded with ATC and NPLID (National Product ID), ICD10-SE is used for diagnoses and the Swedish procedure coding system (KVA) is used for clinical procedures.
8	Data Harmonisation	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. Patients have a uniquely id across datasets.
9	Quality control (data source specific)	The source data are obtained from the relevant Swedish National and Regional Registers. The registers perform some regular quality controls on their data. After receiving the data, we perform additional checks and cleaning. We also run regular quality checks on the data we manage.
10	Linkage	Data on specialist care is acquired from the National Patient Register, mortality information is provided by the Cause-Of-Death Registry. Drug data is provided by the Patient Drug Register. And similarly for other registers. Data are linked very accurately using the national personal ID

#	Section	Description
		number, and pseudonymized before delivery to HI-SPEED. All data are updated 2-4 times per year.
11	Vital status	Data on death and underlying + contributing causes-of-death are extracted from the Cause-of-Death registry (i.e. based on death certificates).
12	Limitations	General limitations for the data type applicable. This is a research project where all studies require ethics approval. Data collection since: 2015 for most data, except prescribed drug register (from 2018), and some COVID-related data (tests, vaccination) from 2020 Primary care is only available for a subset.
13	Main references	Nyberg F, Franzén S,Lindh M,Vanfleteren L,Hammar N,Wettermark B,Sundström J,Santosa A,Björck S,Gisslén M "Swedish Covid-19 Investigation for Future Insights - A Population Epidemiology Approach Using Register Linkage (SCIFI-PEARL)." Clinical epidemiology (2021): 34354377
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/node/4463/ Website: https://www.gu.se/en/research/scifi-pearl

ANNEX II. Fitness for use assessment

In this section we provide a justification for including the selected data sources. We also provide the expected number of persons counts based on a preliminary feasibility assessment. Please note that these numbers are approximate, rounded to the nearest multiple of 100, and correspond to the entire data source, with no restriction on age, sex, or study period. Therefore, the number of individuals who will be included in the study might differ to those reported in this section.

Data source	Coverage / population	Estimated breast cancer person count	Estimated atenolol use person count	Data availability & recency	Follow-up availability	IRB / ethics status	Drug exposure duration
DK-DHR	Entire Danish population; (~4.3 million female individuals)	~149,900	~144,900	Data available from 1995; latest extraction November 2023	Nationwide registry linkage enables follow-up from registry entry until death, emigration, or end of data availability. Median follow-up: 7,920 days.	Blanket IRB approval	Prescription data only; exposure duration is based on recorded prescription duration when available; otherwise, it is imputed during ETL using the most common product-specific duration or set to 1 day if unavailable.
CPRD GOLD	~8.6 million female individuals	~116,000	~714,000	Records from 01/01/1988; latest extraction March 2025	Longitudinal follow-up from GP registration until transfer out, death, or end of data availability. Median follow-up: 2,160 days.	Blanket IRB approval	Dispensing data only; exposure episodes are derived during ETL using dispensing characteristics, DDD, and other source variables.
SIDIAP	~76% of Catalan population (~4.5 million female individuals)	~161,700	~170,200	Data available since 2005; latest extraction December 2024	Longitudinal follow-up within the Catalan healthcare system until death, loss of coverage, or end of data availability. Median follow-up: 5,760 days.	IRB approval required; estimated 1–3 months	Prescription records are used for exposure assessment. Duration is based on recorded prescription start and end dates (days supply = end date − start date + 1)
HI-SPEED	Entire Swedish population (~6.0 million female individuals)	~106,700	~130,800	Data available from 2015; latest extraction August 2025	Nationwide registry linkage enables follow-up from registry entry until death or end of data availability.	IRB approval required; estimated <1 month	Dispensing records only. Exposure duration is estimated using a Swedish dosage-parsing algorithm; implausible durations (<1 or >181 days) are replaced by duration derived from the source variable fddd (dispensed quantity/DDD).

Data source	Coverage / population	Estimated breast cancer person count	Estimated atenolol use person count	Data availability & recency	Follow-up availability	IRB / ethics status	Drug exposure duration
					Median follow-up: 3,890 days.		
NLHR	Entire Norwegian population (~3.0 million female individuals)	~76,200	~29,900	Data available from 2008; latest extraction December 2025	Nationwide registry linkage enables follow-up from registry entry until death, emigration, or end of data availability. Median follow-up: 5,820 days.	Blanket IRB approval	Dispensing records only. Exposure duration is derived from dispensed quantity and DDD-based algorithms. A minimum duration of 1 day is assigned when the calculated duration is >0 but <1 day; if DDD is unavailable, a default duration of 30 days is assumed.

GP=General practitioner, CPRD=Clinical Practice Research Datalink, DK-DHR=Danish Data Health Registries, HI-SPEED=Health Impact - Swedish Population Evidence Enabling Data-linkage, NLHR=Norwegian Linked Health Registry data, SIDIAP=The Information System for Research in Primary Care, IRB=Institutional Review Board, ETL=Extract, transform, load, DDD=Defined Daily Dose.

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 standardized 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) 679/20161 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 *CohortDiagnostics* (https://github.com/OHDSI/CohortDiagnostics) 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: *IncidencePrevalence* to estimate Incidence and Prevalence, *DrugUtilisation* to characterise the drug use, and *CohortCharacteristics* to characterise the cohort by indication. 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 stand-alone documents

Table S1. Preliminary list of hypertension definitions.

Concept name (hypertension)	Concept ID (including descendants)	Vocabulary
Autosomal dominant progressive nephropathy with hypertension	45766198	SNOMED
Benign arteriolar nephrosclerosis	4268756	SNOMED
Benign essential hypertension	312648	SNOMED
Benign essential hypertension complicating AND/OR reason for care during childbirth	4215640	SNOMED
Benign essential hypertension complicating AND/OR reason for care during pregnancy	4034031	SNOMED
Benign essential hypertension complicating AND/OR reason for care during puerperium	4148205	SNOMED
Benign essential hypertension complicating pregnancy, childbirth and the puerperium	321638	SNOMED
Benign essential hypertension in obstetric context	4269358	SNOMED
Benign hypertension	4028741	SNOMED
Benign hypertensive heart AND renal disease	442626	SNOMED
Benign hypertensive heart disease	4263504	SNOMED
Benign hypertensive heart disease and chronic renal disease	764011	SNOMED
Benign hypertensive heart disease and chronic renal disease stage 1	765535	SNOMED
Benign hypertensive heart disease and chronic renal disease stage 2	762000	SNOMED
Benign hypertensive heart disease and chronic renal disease stage 3	762001	SNOMED
Benign hypertensive heart disease and chronic renal disease stage 4	765536	SNOMED
Benign hypertensive heart disease and chronic renal disease stage 5	760850	SNOMED
Benign hypertensive heart disease with congestive cardiac failure	439698	SNOMED
Benign hypertensive heart disease without congestive heart failure	313502	SNOMED
Benign hypertensive renal disease	193493	SNOMED
Benign hypertensive renal disease with renal failure	44784439	SNOMED
Benign secondary hypertension	314958	SNOMED
Benign secondary renovascular hypertension	4249016	SNOMED
Bilateral hypertension with disorder of retinas	36684780	SNOMED
Brachydactyly and arterial hypertension syndrome	36715087	SNOMED
Cardiomegaly due to hypertension	4173820	SNOMED
Cardiomyopathy due to hypertension	36712757	SNOMED
Cardiovascular renal disease	4135463	SNOMED
Chronic hypertension complicating AND/OR reason for care during childbirth	4304837	SNOMED
Chronic hypertension in obstetric context	4227607	SNOMED
Chronic hypertensive uremia	4302748	SNOMED
Chronic kidney disease due to benign hypertension	46270353	SNOMED
Chronic kidney disease due to hypertension	44782429	SNOMED

Concept name (hypertension)	Concept ID (including descendants)	Vocabulary
Chronic kidney disease stage 1 due to benign hypertension	46270354	SNOMED
Chronic kidney disease stage 1 due to hypertension	44782703	SNOMED
Chronic kidney disease stage 2 due to benign hypertension	46270355	SNOMED
Chronic kidney disease stage 2 due to hypertension	44782692	SNOMED
Chronic kidney disease stage 3 due to benign hypertension	46273636	SNOMED
Chronic kidney disease stage 3 due to hypertension	44782691	SNOMED
Chronic kidney disease stage 4 due to benign hypertension	46273514	SNOMED
Chronic kidney disease stage 4 due to hypertension	44782689	SNOMED
Chronic kidney disease stage 5 due to benign hypertension	46270356	SNOMED
Chronic kidney disease stage 5 due to hypertension	44782690	SNOMED
Coronary sinus hypertension as complication of procedure	43020833	SNOMED
Diastolic hypertension	4167358	SNOMED
Diastolic hypertension and systolic hypertension	42538697	SNOMED
Eclampsia added to pre-existing hypertension	4289142	SNOMED
Eclampsia with pre-existing hypertension in childbirth	45757119	SNOMED
End stage renal disease due to benign hypertension	46273164	SNOMED
End stage renal disease due to hypertension	37018886	SNOMED
End stage renal disease on dialysis due to hypertension	44782717	SNOMED
Essential hypertension	320128	SNOMED
Essential hypertension complicating AND/OR reason for care during childbirth	4083723	SNOMED
Essential hypertension complicating AND/OR reason for care during pregnancy	4302591	SNOMED
Essential hypertension complicating AND/OR reason for care during puerperium	4321603	SNOMED
Essential hypertension in obstetric context	4217486	SNOMED
Exacerbation of hypertensive disorder	1340364	OMOP Extension
Exertional hypertension	4179379	SNOMED
Fetal disorder due to maternal hypertension	604803	SNOMED
Fetal disorder due to maternal pre-eclampsia	604804	SNOMED
Goldblatt hypertension	4048212	SNOMED
Hemorrhagic cerebral infarction due to hypertension	37166871	SNOMED
High-renin essential hypertension	4058987	SNOMED
Hypertension associated with transplantation	4322735	SNOMED
Hypertension concurrent and due to end stage renal disease on dialysis	45772751	SNOMED
Hypertension concurrent and due to end stage renal disease on dialysis due to type 1 diabetes mellitus	45757393	SNOMED
Hypertension concurrent and due to end stage renal disease on dialysis due to type 2 diabetes mellitus	45757392	SNOMED

Concept name (hypertension)	Concept ID (including descendants)	Vocabulary
Hypertension due to aortic arch obstruction	3656115	SNOMED
Hypertension due to congenital adrenal hyperplasia	37163010	SNOMED
Hypertension due to gain-of-function mutation in mineralocorticoid receptor	35624277	SNOMED
Hypertension in chronic kidney disease due to type 1 diabetes mellitus	45771067	SNOMED
Hypertension in chronic kidney disease due to type 2 diabetes mellitus	45771064	SNOMED
Hypertension in chronic kidney disease stage 2 due to type 1 diabetes mellitus	1075903	SNOMED
Hypertension in chronic kidney disease stage 2 due to type 2 diabetes mellitus	45757447	SNOMED
Hypertension in chronic kidney disease stage 3 due to type 1 diabetes mellitus	1075888	SNOMED
Hypertension in chronic kidney disease stage 3 due to type 2 diabetes mellitus	45757446	SNOMED
Hypertension in chronic kidney disease stage 3A due to type 1 diabetes mellitus	1075887	SNOMED
Hypertension in chronic kidney disease stage 3A due to type 2 diabetes mellitus	1075905	SNOMED
Hypertension in chronic kidney disease stage 3B due to type 1 diabetes mellitus	1075886	SNOMED
Hypertension in chronic kidney disease stage 3B due to type 2 diabetes mellitus	1075904	SNOMED
Hypertension in chronic kidney disease stage 4 due to type 1 diabetes mellitus	1075907	SNOMED
Hypertension in chronic kidney disease stage 4 due to type 2 diabetes mellitus	45757445	SNOMED
Hypertension in chronic kidney disease stage 5 due to type 1 diabetes mellitus	1075906	SNOMED
Hypertension in chronic kidney disease stage 5 due to type 2 diabetes mellitus	45757444	SNOMED
Hypertension in the obstetric context	4279525	SNOMED
Hypertension induced by oral contraceptive pill	4061667	SNOMED
Hypertension resistant to drug therapy	44809548	SNOMED
Hypertension secondary to drug	4108213	SNOMED
Hypertension secondary to endocrine disorder	4110948	SNOMED
Hypertension secondary to renal disease complicating AND/OR reason for care during childbirth	4094374	SNOMED
Hypertension secondary to renal disease complicating AND/OR reason for care during puerperium	4219323	SNOMED
Hypertension secondary to renal disease in obstetric context	4006325	SNOMED
Hypertension with albuminuria	4262182	SNOMED
Hypertension with apparent mineralocorticoid excess	3169253	Nebraska Lexicon
Hypertension with disorder of left retina	36684718	SNOMED
Hypertension with disorder of right retina	36684653	SNOMED
Hypertension with hyperadrenergic findings	3191244	Nebraska Lexicon
Hypertensive cerebrovascular disease	3174555	Nebraska Lexicon
Hypertensive choroidopathy	4227517	SNOMED
Hypertensive complication	42709887	SNOMED

Concept name (hypertension)	Concept ID (including descendants)	Vocabulary
Hypertensive crisis	45768449	SNOMED
Hypertensive disorder	316866	SNOMED
Hypertensive emergency	43020424	SNOMED
Hypertensive encephalopathy	312938	SNOMED
Hypertensive heart and chronic kidney disease	44784621	SNOMED
Hypertensive heart AND chronic kidney disease on dialysis	44784637	SNOMED
Hypertensive heart AND chronic kidney disease stage 1	44784640	SNOMED
Hypertensive heart AND chronic kidney disease stage 2	43021836	SNOMED
Hypertensive heart AND chronic kidney disease stage 3	43021835	SNOMED
Hypertensive heart AND chronic kidney disease stage 4	44784639	SNOMED
Hypertensive heart AND chronic kidney disease stage 5	44784638	SNOMED
Hypertensive heart AND chronic kidney disease with congestive heart failure	44782728	SNOMED
Hypertensive heart AND renal disease	195556	SNOMED
Hypertensive heart AND renal disease complicating AND/OR reason for care during childbirth	4032790	SNOMED
Hypertensive heart AND renal disease complicating AND/OR reason for care during pregnancy	4046813	SNOMED
Hypertensive heart AND renal disease in obstetric context	4169751	SNOMED
Hypertensive heart and renal disease with (congestive) heart failure	439696	SNOMED
Hypertensive heart and renal disease with both (congestive) heart failure and renal failure	439694	SNOMED
Hypertensive heart and renal disease with renal failure	439695	SNOMED
Hypertensive heart disease	442604	SNOMED
Hypertensive heart disease complicating AND/OR reason for care during childbirth	4245279	SNOMED
Hypertensive heart disease complicating AND/OR reason for care during pregnancy	4049377	SNOMED
Hypertensive heart disease complicating AND/OR reason for care during puerperium	4145746	SNOMED
Hypertensive heart disease in obstetric context	4193900	SNOMED
Hypertensive heart disease with congestive heart failure	314378	SNOMED
Hypertensive heart disease without congestive heart failure	319034	SNOMED
Hypertensive heart failure	444101	SNOMED
Hypertensive left ventricular hypertrophy	4322893	SNOMED
Hypertensive nephrosclerosis	43021748	SNOMED
Hypertensive optic neuropathy	4228419	SNOMED
Hypertensive renal disease	201313	SNOMED
Hypertensive renal disease complicating AND/OR reason for care during childbirth	4169889	SNOMED
Hypertensive renal disease complicating AND/OR reason for care during pregnancy	4280382	SNOMED
Hypertensive renal disease complicating AND/OR reason for care during puerperium	4240080	SNOMED

Concept name (hypertension)	Concept ID (including descendants)	Vocabulary
Hypertensive renal disease in obstetric context	4218784	SNOMED
Hypertensive renal failure	443919	SNOMED
Hypertensive retinopathy	376965	SNOMED
Hypertensive urgency	40481896	SNOMED
Intermittent hypertension	44783643	SNOMED
Ischemic ulcer of skin due to arterial hypertension	4317265	SNOMED
Labile diastolic hypertension	4276511	SNOMED
Labile essential hypertension	4159755	SNOMED
Labile hypertension due to being in a clinical environment	44783644	SNOMED
Labile systemic arterial hypertension	36713024	SNOMED
Low-renin essential hypertension	4263067	SNOMED
Malignant arteriolar nephrosclerosis	4216685	SNOMED
Malignant essential hypertension	317898	SNOMED
Malignant hypertension	4289933	SNOMED
Malignant hypertension complicating AND/OR reason for care during childbirth	4023318	SNOMED
Malignant hypertension complicating AND/OR reason for care during pregnancy	4162306	SNOMED
Malignant hypertension complicating AND/OR reason for care during puerperium	4028951	SNOMED
Malignant hypertension in obstetric context	4218088	SNOMED
Malignant hypertensive chronic kidney disease	43021852	SNOMED
Malignant hypertensive chronic kidney disease stage 1	43021853	SNOMED
Malignant hypertensive chronic kidney disease stage 2	43021854	SNOMED
Malignant hypertensive chronic kidney disease stage 3	43020456	SNOMED
Malignant hypertensive chronic kidney disease stage 4	43020457	SNOMED
Malignant hypertensive chronic kidney disease stage 5	43020437	SNOMED
Malignant hypertensive end stage renal disease	43020455	SNOMED
Malignant hypertensive end stage renal disease on dialysis	43021864	SNOMED
Malignant hypertensive heart AND renal disease	442603	SNOMED
Malignant hypertensive heart disease	4183981	SNOMED
Malignant hypertensive heart disease and chronic renal disease stage 3	762033	SNOMED
Malignant hypertensive heart disease and chronic renal disease stage 4	762034	SNOMED
Malignant hypertensive heart disease with congestive heart failure	316994	SNOMED
Malignant hypertensive heart disease without congestive heart failure	314369	SNOMED
Malignant hypertensive renal disease	442766	SNOMED
Malignant secondary hypertension	318437	SNOMED
Malignant secondary renovascular hypertension	4110947	SNOMED
Martorell ulcer of lower leg	37164884	SNOMED

Concept name (hypertension)	Concept ID (including descendants)	Vocabulary
Martorell ulcer of lower limb	37164965	SNOMED
Multiple drug intolerant hypertension	37208293	SNOMED
Nephropathy following pre-eclampsia	42537547	SNOMED
Nocturnal hypertension	44811110	SNOMED
Page kidney	45757756	SNOMED
Parenchymal renal hypertension	4212496	SNOMED
Paroxysmal hypertension	4049389	SNOMED
Postpartum pre-existing essential hypertension	45757787	SNOMED
Pre-existing hypertension complicating AND/OR reason for care during childbirth	4146816	SNOMED
Pre-existing hypertension complicating AND/OR reason for care during pregnancy	4277110	SNOMED
Pre-existing hypertension complicating AND/OR reason for care during puerperium	4151903	SNOMED
Pre-existing hypertension in obstetric context	4311246	SNOMED
Pre-existing hypertensive chronic kidney disease in mother complicating pregnancy	45757356	SNOMED
Pre-existing secondary hypertension complicating pregnancy, childbirth and puerperium	4057979	SNOMED
Rebound hypertension	4221991	SNOMED
Renal arterial hypertension	4305599	SNOMED
Renal hypertension	443771	SNOMED
Renal hypertension complicating pregnancy, childbirth and the puerperium	197930	SNOMED
Renal sclerosis with hypertension	4032952	SNOMED
Renovascular hypertension	317895	SNOMED
Resistant hypertensive disorder	37208172	SNOMED
Secondary diastolic hypertension	4253928	SNOMED
Secondary hypertension	319826	SNOMED
Secondary hypertension due to congenital heart disorder	37163263	SNOMED
Secondary hypertension due to renal tubular disorder	37163257	SNOMED
Severe hypertension (NICE - National Institute for Health and Clinical Excellence 2011)	44809027	SNOMED
Stage 1 hypertension (NICE - National Institute for Health and Clinical Excellence 2011)	44809026	SNOMED
Stage 1 hypertension (NICE 2011) with evidence of end organ damage	44811933	SNOMED
Stage 1 hypertension (NICE 2011) without evidence of end organ damage	44811932	SNOMED
Stage 2 hypertension (NICE - National Institute for Health and Clinical Excellence 2011)	44809569	SNOMED
Supine hypertension	37016726	SNOMED
Sustained diastolic hypertension	4242878	SNOMED
Systolic essential hypertension	4180283	SNOMED
Systolic hypertension	4209293	SNOMED
Transient hypertension	4199306	SNOMED
Transient hypertension of pregnancy - not delivered	136760	SNOMED

Table S2. Preliminary list of index treatment definitions.

Phenotype	Phenotype class	Concept name	Concept ID (including descendants)	Vocabulary
Atenolol	B_1-selective beta-blockers	atenolol	1314002	RxNorm
Metoprolol	B_1-selective beta-blockers	metoprolol	1307046	RxNorm
Bisoprolol	B_1-selective beta- blockers	bisoprolol	1338005	RxNorm
Nebivolol	B_1-selective beta-blockers	nebivolol	1314577	RxNorm
Betaxolol	B_1-selective beta-blockers	betaxolol	1322081	RxNorm
Acebutolol	B_1-selective beta- blockers	acebutolol	1319998	RxNorm
Propranolol	Non-selective beta-blockers	propranolol	1353766	RxNorm
Nadolol	Non-selective beta-blockers	nadolol	1313200	RxNorm
Timolol	Non-selective beta- blockers	timolol	902427	RxNorm
Pindolol	Non-selective beta- blockers	pindolol	1345858	RxNorm
Carvedilol	Non-selective beta-blockers	carvedilol	1346823	RxNorm
Labetalol	Non-selective beta- blockers	labetalol	1386957	RxNorm
Sotalol	Non-selective beta-blockers	sotalol	1370109	RxNorm
Enalapril	Angiotensin-converting enzyme (ACE) inhibitors	enalapril	1341927	RxNorm
Lisinopril	ACE inhibitors	lisinopril	1308216	RxNorm
Perindopril	ACE inhibitors	perindopril	1373225	RxNorm
Ramipril	ACE inhibitors	ramipril	1334456	RxNorm
Captopril	ACE inhibitors	captopril	1340128	RxNorm
Benazepril	ACE inhibitors	benazepril	1335471	RxNorm
Fosinopril	ACE inhibitors	fosinopril	1363749	RxNorm
Trandolapril	ACE inhibitors	trandolapril	1342439	RxNorm
Losartan	Angiotensin II receptor blockers (ARBs)	losartan	1367500	RxNorm
Valsartan	ARBs	valsartan	1308842	RxNorm
Candesartan	ARBs	candesartan	1351557	RxNorm
Irbesartan	ARBs	irbesartan	1347384	RxNorm
Telmisartan	ARBs	telmisartan	1317640	RxNorm
Olmesartan	ARBs	olmesartan	40226742	RxNorm
Azilsartan	ARBs	azilsartan	40235485	RxNorm
Amlodipine	Dihydropyridines Calcium channel blockers (CCBs)	amlodipine	1332418	RxNorm
Felodipine	Dihydropyridines CCBs	felodipine	1353776	RxNorm
Nifedipine	Dihydropyridines CCBs	nifedipine	1318853	RxNorm
Lercanidipine	Dihydropyridines CCBs	lercanidipine	19015802	RxNorm
Nicardipine	Dihydropyridines CCBs	nicardipine	1318137	RxNorm

Phenotype	Phenotype class	Concept name	Concept ID (including descendants)	Vocabulary
Verapamil	Non-Dihydropyridines CCBs	verapamil	1307863	RxNorm
Diltiazem	Non-Dihydropyridines CCBs	diltiazem	1328165	RxNorm
Hydrochlorothiazide	Diuretics	hydrochlorothiazide	974166	RxNorm
Indapamide	Diuretics	indapamide	978555	RxNorm
Chlorthalidone	Diuretics	chlorthalidone	1395058	RxNorm
Bendroflumethiazide	Diuretics	bendroflumethiazide	1316354	RxNorm
Metolazone	Diuretics	metolazone	907013	RxNorm
Furosemide	Diuretics	furosemide	956874	RxNorm
Bumetanide	Diuretics	bumetanide	932745	RxNorm
Torsemide	Diuretics	torsemide	942350	RxNorm
Ethacrynic acid	Diuretics	ethacrynic acid	42707184	RxNorm
Hormone replacement therapy		Hormone replacement therapy	4141760	SNOMED
Ethinyl estradiol	Contraceptive use	ethinyl estradiol	1549786	RxNorm
Mestranol	Contraceptive use	mestranol	1503184	RxNorm
Estetrol	Contraceptive use	estetrol	36026931	RxNorm
Drospirenone	Contraceptive use	drospirenone	1512674	RxNorm
Norethindrone	Contraceptive use	norethindrone	1521369	RxNorm
Levonorgestrel	Contraceptive use	levonorgestrel	1589505	RxNorm
Desogestrel	Contraceptive use	desogestrel	1588000	RxNorm
Gestodene	Contraceptive use	gestodene	19097684	RxNorm
Norgestimate	Contraceptive use	norgestimate and ethinylestradiol; systemic	21602484	ATC
Etonogestrel	Contraceptive use	Etonogestrel	1519936	RxNorm
Norelgestromin	Contraceptive use	Norelgestromin	1518198	RxNorm

ACE=Angiotensin-converting enzyme, ARBs=Angiotensin II receptor blockers, CCB=Calcium channel blockers.

Table S3. Preliminary list of breast cancer definitions.

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Acinar cell carcinoma of axillary tail of breast	36560989	ICDO3
Acinar cell carcinoma of breast, NOS	44501094	ICDO3
Acinar cell carcinoma of central portion of breast	44502783	ICDO3
Acinar cell carcinoma of lower-inner quadrant of breast	36528296	ICDO3
Acinar cell carcinoma of lower-outer quadrant of breast	36553302	ICDO3
Acinar cell carcinoma of overlapping lesion of breast	36528268	ICDO3

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Acinar cell carcinoma of upper-inner quadrant of breast	36523946	ICDO3
Acinar cell carcinoma of upper-outer quadrant of breast	44500080	ICDO3
Acinar cell cystadenocarcinoma of axillary tail of breast	36517161	ICDO3
Acinar cell cystadenocarcinoma of breast, NOS	36524667	ICDO3
Acinar cell cystadenocarcinoma of central portion of breast	36559540	ICDO3
Acinar cell cystadenocarcinoma of lower-inner quadrant of breast	36535001	ICDO3
Acinar cell cystadenocarcinoma of lower-outer quadrant of breast	36547927	ICDO3
Acinar cell cystadenocarcinoma of overlapping lesion of breast	36540781	ICDO3
Acinar cell cystadenocarcinoma of upper-inner quadrant of breast	36528684	ICDO3
Acinar cell cystadenocarcinoma of upper-outer quadrant of breast	36533091	ICDO3
Adenocarcinoma in villous adenoma of axillary tail of breast	36534214	ICDO3
Adenocarcinoma in villous adenoma of breast, NOS	36530730	ICDO3
Adenocarcinoma in villous adenoma of central portion of breast	36548881	ICDO3
Adenocarcinoma in villous adenoma of lower-inner quadrant of breast	36534866	ICDO3
Adenocarcinoma in villous adenoma of lower-outer quadrant of breast	36520750	ICDO3
Adenocarcinoma in villous adenoma of nipple	36567217	ICDO3
Adenocarcinoma in villous adenoma of overlapping lesion of breast	36554325	ICDO3
Adenocarcinoma in villous adenoma of upper-inner quadrant of breast	36547352	ICDO3
Adenocarcinoma in villous adenoma of upper-outer quadrant of breast	36566738	ICDO3
Adenocarcinoma of breast	3655521	SNOMED
Adenocarcinoma with apocrine metaplasia of axillary tail of breast	36553114	ICDO3
Adenocarcinoma with apocrine metaplasia of breast, NOS	36567106	ICDO3
Adenocarcinoma with apocrine metaplasia of central portion of breast	36560612	ICDO3
Adenocarcinoma with apocrine metaplasia of lower-inner quadrant of breast	36562341	ICDO3
Adenocarcinoma with apocrine metaplasia of lower-outer quadrant of breast	36526872	ICDO3
Adenocarcinoma with apocrine metaplasia of nipple	36566773	ICDO3
Adenocarcinoma with apocrine metaplasia of overlapping lesion of breast	36551249	ICDO3
Adenocarcinoma with apocrine metaplasia of upper-inner quadrant of breast	36567711	ICDO3
Adenocarcinoma with apocrine metaplasia of upper-outer quadrant of breast	36526667	ICDO3

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Adenocarcinoma with cartilaginous and osseous metaplasia of axillary tail of breast	36533099	ICDO3
Adenocarcinoma with cartilaginous and osseous metaplasia of breast, NOS	36527204	ICDO3
Adenocarcinoma with cartilaginous and osseous metaplasia of central portion of breast	36533485	ICDO3
Adenocarcinoma with cartilaginous and osseous metaplasia of lower-inner quadrant of breast	36547578	ICDO3
Adenocarcinoma with cartilaginous and osseous metaplasia of lower-outer quadrant of breast	36520011	ICDO3
Adenocarcinoma with cartilaginous and osseous metaplasia of nipple	36557153	ICDO3
Adenocarcinoma with cartilaginous and osseous metaplasia of overlapping lesion of breast	36525405	ICDO3
Adenocarcinoma with cartilaginous and osseous metaplasia of upper-inner quadrant of breast	36545580	ICDO3
Adenocarcinoma with cartilaginous and osseous metaplasia of upper-outer quadrant of breast	36517511	ICDO3
Adenocarcinoma with mixed subtypes of axillary tail of breast	36530836	ICDO3
Adenocarcinoma with mixed subtypes of breast, NOS	44502281	ICDO3
Adenocarcinoma with mixed subtypes of central portion of breast	44501266	ICDO3
Adenocarcinoma with mixed subtypes of lower-inner quadrant of breast	36541548	ICDO3
Adenocarcinoma with mixed subtypes of lower-outer quadrant of breast	36551939	ICDO3
Adenocarcinoma with mixed subtypes of nipple	36551299	ICDO3
Adenocarcinoma with mixed subtypes of overlapping lesion of breast	36565039	ICDO3
Adenocarcinoma with mixed subtypes of upper-inner quadrant of breast	44502534	ICDO3
Adenocarcinoma with mixed subtypes of upper-outer quadrant of breast	44501345	ICDO3
Adenocarcinoma with neuroendocrine differentiation of axillary tail of breast	36562380	ICDO3
Adenocarcinoma with neuroendocrine differentiation of breast, NOS	44501025	ICDO3
Adenocarcinoma with neuroendocrine differentiation of central portion of breast	36527921	ICDO3
Adenocarcinoma with neuroendocrine differentiation of lower-inner quadrant of breast	36549156	ICDO3
Adenocarcinoma with neuroendocrine differentiation of lower-outer quadrant of breast	36550441	ICDO3
Adenocarcinoma with neuroendocrine differentiation of nipple	36551719	ICDO3

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Adenocarcinoma with neuroendocrine differentiation of overlapping lesion of breast	36544055	ICDO3
Adenocarcinoma with neuroendocrine differentiation of upper-inner quadrant of breast	36540326	ICDO3
Adenocarcinoma with neuroendocrine differentiation of upper-outer quadrant of breast	36564531	ICDO3
Adenocarcinoma with spindle cell metaplasia of axillary tail of breast	36559062	ICDO3
Adenocarcinoma with spindle cell metaplasia of breast, NOS	36542053	ICDO3
Adenocarcinoma with spindle cell metaplasia of central portion of breast	36550327	ICDO3
Adenocarcinoma with spindle cell metaplasia of lower-inner quadrant of breast	36564788	ICDO3
Adenocarcinoma with spindle cell metaplasia of lower-outer quadrant of breast	36563732	ICDO3
Adenocarcinoma with spindle cell metaplasia of nipple	36541792	ICDO3
Adenocarcinoma with spindle cell metaplasia of overlapping lesion of breast	36556994	ICDO3
Adenocarcinoma with spindle cell metaplasia of upper-inner quadrant of breast	36567559	ICDO3
Adenocarcinoma with spindle cell metaplasia of upper-outer quadrant of breast	36558786	ICDO3
Adenocarcinoma with squamous metaplasia of axillary tail of breast	36541767	ICDO3
Adenocarcinoma with squamous metaplasia of breast, NOS	36550405	ICDO3
Adenocarcinoma with squamous metaplasia of central portion of breast	36520568	ICDO3
Adenocarcinoma with squamous metaplasia of lower-inner quadrant of breast	36552975	ICDO3
Adenocarcinoma with squamous metaplasia of lower-outer quadrant of breast	36556660	ICDO3
Adenocarcinoma with squamous metaplasia of nipple	36553810	ICDO3
Adenocarcinoma with squamous metaplasia of overlapping lesion of breast	36521206	ICDO3
Adenocarcinoma with squamous metaplasia of upper-inner quadrant of breast	36546948	ICDO3
Adenocarcinoma with squamous metaplasia of upper-outer quadrant of breast	44502182	ICDO3
Adenocarcinoma, NOS, of axillary tail of breast	44499497	ICDO3
Adenocarcinoma, NOS, of breast, NOS	44501483	ICDO3
Adenocarcinoma, NOS, of central portion of breast	44501260	ICDO3
Adenocarcinoma, NOS, of lower-inner quadrant of breast	44501933	ICDO3
Adenocarcinoma, NOS, of lower-outer quadrant of breast	44500498	ICDO3
Adenocarcinoma, NOS, of nipple	44500439	ICDO3

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Adenocarcinoma, NOS, of overlapping lesion of breast	36545478	ICDO3
Adenocarcinoma, NOS, of upper-inner quadrant of breast	44500783	ICDO3
Adenocarcinoma, NOS, of upper-outer quadrant of breast	44501200	ICDO3
Adenoid cystic carcinoma of axillary tail of breast	36544230	ICDO3
Adenoid cystic carcinoma of breast, NOS	36528339	ICDO3
Adenoid cystic carcinoma of central portion of breast	44499435	ICDO3
Adenoid cystic carcinoma of lower-inner quadrant of breast	44503085	ICDO3
Adenoid cystic carcinoma of lower-outer quadrant of breast	44500016	ICDO3
Adenoid cystic carcinoma of nipple	36538949	ICDO3
Adenoid cystic carcinoma of overlapping lesion of breast	36524717	ICDO3
Adenoid cystic carcinoma of upper-inner quadrant of breast	44502387	ICDO3
Adenoid cystic carcinoma of upper-outer quadrant of breast	44500785	ICDO3
Adenomyoepithelioma with carcinoma of axillary tail of breast	42512701	ICDO3
Adenomyoepithelioma with carcinoma of breast, NOS	42512894	ICDO3
Adenomyoepithelioma with carcinoma of central portion of breast	42512546	ICDO3
Adenomyoepithelioma with carcinoma of lower-inner quadrant of breast	42511993	ICDO3
Adenomyoepithelioma with carcinoma of lower-outer quadrant of breast	42512278	ICDO3
Adenomyoepithelioma with carcinoma of overlapping lesion of breast	42512712	ICDO3
Adenomyoepithelioma with carcinoma of upper-inner quadrant of breast	42512919	ICDO3
Adenomyoepithelioma with carcinoma of upper-outer quadrant of breast	42512003	ICDO3
Adenosquamous carcinoma of axillary tail of breast	36559532	ICDO3
Adenosquamous carcinoma of breast, NOS	36529053	ICDO3
Adenosquamous carcinoma of central portion of breast	44502181	ICDO3
Adenosquamous carcinoma of lower-inner quadrant of breast	36538330	ICDO3
Adenosquamous carcinoma of lower-outer quadrant of breast	44501661	ICDO3
Adenosquamous carcinoma of nipple	36567537	ICDO3
Adenosquamous carcinoma of overlapping lesion of breast	36523999	ICDO3
Adenosquamous carcinoma of upper-inner quadrant of breast	36520290	ICDO3
Adenosquamous carcinoma of upper-outer quadrant of breast	36567556	ICDO3
Alveolar adenocarcinoma of axillary tail of breast	36533146	ICDO3
Alveolar adenocarcinoma of breast, NOS	36531301	ICDO3
Alveolar adenocarcinoma of central portion of breast	36520865	ICDO3
Alveolar adenocarcinoma of lower-inner quadrant of breast	36545416	ICDO3

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Alveolar adenocarcinoma of lower-outer quadrant of breast	36563347	ICDO3
Alveolar adenocarcinoma of nipple	36566941	ICDO3
Alveolar adenocarcinoma of overlapping lesion of breast	36553169	ICDO3
Alveolar adenocarcinoma of upper-inner quadrant of breast	36555646	ICDO3
Alveolar adenocarcinoma of upper-outer quadrant of breast	36517972	ICDO3
Apocrine adenocarcinoma of axillary tail of breast	36526963	ICDO3
Apocrine adenocarcinoma of breast, NOS	44499745	ICDO3
Apocrine adenocarcinoma of central portion of breast	44500300	ICDO3
Apocrine adenocarcinoma of lower-inner quadrant of breast	36547894	ICDO3
Apocrine adenocarcinoma of lower-outer quadrant of breast	44501085	ICDO3
Apocrine adenocarcinoma of nipple	36554533	ICDO3
Apocrine adenocarcinoma of overlapping lesion of breast	36559699	ICDO3
Apocrine adenocarcinoma of upper-inner quadrant of breast	44501647	ICDO3
Apocrine adenocarcinoma of upper-outer quadrant of breast	44502950	ICDO3
Atypical medullary carcinoma of axillary tail of breast	44502289	ICDO3
Atypical medullary carcinoma of breast, NOS	44501022	ICDO3
Atypical medullary carcinoma of central portion of breast	44501530	ICDO3
Atypical medullary carcinoma of lower-inner quadrant of breast	44501218	ICDO3
Atypical medullary carcinoma of lower-outer quadrant of breast	44501582	ICDO3
Atypical medullary carcinoma of overlapping lesion of breast	36531463	ICDO3
Atypical medullary carcinoma of upper-inner quadrant of breast	44500881	ICDO3
Atypical medullary carcinoma of upper-outer quadrant of breast	44501855	ICDO3
Basal cell adenocarcinoma of axillary tail of breast	36561242	ICDO3
Basal cell adenocarcinoma of breast, NOS	36549037	ICDO3
Basal cell adenocarcinoma of central portion of breast	36521879	ICDO3
Basal cell adenocarcinoma of lower-inner quadrant of breast	36524455	ICDO3
Basal cell adenocarcinoma of lower-outer quadrant of breast	36542579	ICDO3
Basal cell adenocarcinoma of nipple	36517996	ICDO3
Basal cell adenocarcinoma of overlapping lesion of breast	36560662	ICDO3
Basal cell adenocarcinoma of upper-inner quadrant of breast	36537242	ICDO3
Basal cell adenocarcinoma of upper-outer quadrant of breast	36517529	ICDO3
Basaloid carcinoma of breast, NOS	36531464	ICDO3
Basaloid carcinoma of overlapping lesion of breast	42511930	ICDO3
Basaloid carcinoma of upper-outer quadrant of breast	42512929	ICDO3
Carcinoma breast - lower, outer quadrant	4117852	SNOMED
Carcinoma ex pleomorphic adenoma of breast, NOS	42512266	ICDO3

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Carcinoma of breast	4116071	SNOMED
Carcinoma of breast - axillary tail	4113638	SNOMED
Carcinoma of breast - lower, inner quadrant	4113637	SNOMED
Carcinoma of breast - upper, inner quadrant	4117850	SNOMED
Carcinoma of central portion of breast	46270923	SNOMED
Carcinoma of salivary gland type of breast	37399542	SNOMED
Carcinoma of upper outer quadrant of breast	4117851	SNOMED
Carcinoma simplex of axillary tail of breast	36544715	ICDO3
Carcinoma simplex of breast, NOS	36564416	ICDO3
Carcinoma simplex of central portion of breast	36530779	ICDO3
Carcinoma simplex of lower-inner quadrant of breast	36518801	ICDO3
Carcinoma simplex of lower-outer quadrant of breast	36541559	ICDO3
Carcinoma simplex of nipple	36555657	ICDO3
Carcinoma simplex of overlapping lesion of breast	36535615	ICDO3
Carcinoma simplex of upper-inner quadrant of breast	36523044	ICDO3
Carcinoma simplex of upper-outer quadrant of breast	36543383	ICDO3
Carcinoma with osteoclast-like giant cells of axillary tail of breast	36534548	ICDO3
Carcinoma with osteoclast-like giant cells of breast, NOS	36565720	ICDO3
Carcinoma with osteoclast-like giant cells of central portion of breast	36567931	ICDO3
Carcinoma with osteoclast-like giant cells of lower-inner quadrant of breast	36523701	ICDO3
Carcinoma with osteoclast-like giant cells of lower-outer quadrant of breast	36560521	ICDO3
Carcinoma with osteoclast-like giant cells of nipple	36531354	ICDO3
Carcinoma with osteoclast-like giant cells of overlapping lesion of breast	36527755	ICDO3
Carcinoma with osteoclast-like giant cells of upper-inner quadrant of breast	36548065	ICDO3
Carcinoma with osteoclast-like giant cells of upper-outer quadrant of breast	36543673	ICDO3
Carcinoma, anaplastic, NOS, of axillary tail of breast	36540234	ICDO3
Carcinoma, anaplastic, NOS, of breast, NOS	44501699	ICDO3
Carcinoma, anaplastic, NOS, of central portion of breast	36531469	ICDO3
Carcinoma, anaplastic, NOS, of lower-inner quadrant of breast	36537809	ICDO3
Carcinoma, anaplastic, NOS, of lower-outer quadrant of breast	36558782	ICDO3
Carcinoma, anaplastic, NOS, of nipple	36553980	ICDO3
Carcinoma, anaplastic, NOS, of overlapping lesion of breast	36534751	ICDO3
Carcinoma, anaplastic, NOS, of upper-inner quadrant of breast	36536886	ICDO3

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Carcinoma, anaplastic, NOS, of upper-outer quadrant of breast	36548861	ICDO3
Carcinoma, diffuse type of breast, NOS	1553463	ICDO3
Carcinoma, NOS, of nipple	44499675	ICDO3
Carcinoma, NOS, of overlapping lesion of breast	36564496	ICDO3
Carcinoma, undifferentiated, NOS, of axillary tail of breast	36540630	ICDO3
Carcinoma, undifferentiated, NOS, of breast, NOS	44501060	ICDO3
Carcinoma, undifferentiated, NOS, of central portion of breast	36544307	ICDO3
Carcinoma, undifferentiated, NOS, of lower-inner quadrant of breast	36550782	ICDO3
Carcinoma, undifferentiated, NOS, of lower-outer quadrant of breast	36566265	ICDO3
Carcinoma, undifferentiated, NOS, of nipple	36547912	ICDO3
Carcinoma, undifferentiated, NOS, of overlapping lesion of breast	36535775	ICDO3
Carcinoma, undifferentiated, NOS, of upper-inner quadrant of breast	44502004	ICDO3
Carcinoma, undifferentiated, NOS, of upper-outer quadrant of breast	44500185	ICDO3
Carcinosarcoma, embryonal of axillary tail of breast	36559478	ICDO3
Carcinosarcoma, embryonal of breast, NOS	36559269	ICDO3
Carcinosarcoma, embryonal of central portion of breast	36567615	ICDO3
Carcinosarcoma, embryonal of lower-inner quadrant of breast	36548429	ICDO3
Carcinosarcoma, embryonal of lower-outer quadrant of breast	36521363	ICDO3
Carcinosarcoma, embryonal of overlapping lesion of breast	36547579	ICDO3
Carcinosarcoma, embryonal of upper-inner quadrant of breast	36522989	ICDO3
Carcinosarcoma, embryonal of upper-outer quadrant of breast	36519476	ICDO3
Carcinosarcoma, NOS, of axillary tail of breast	36549622	ICDO3
Carcinosarcoma, NOS, of breast, NOS	36524276	ICDO3
Carcinosarcoma, NOS, of central portion of breast	36519461	ICDO3
Carcinosarcoma, NOS, of lower-inner quadrant of breast	36560691	ICDO3
Carcinosarcoma, NOS, of lower-outer quadrant of breast	44502559	ICDO3
Carcinosarcoma, NOS, of overlapping lesion of breast	36560569	ICDO3
Carcinosarcoma, NOS, of upper-inner quadrant of breast	44499659	ICDO3
Carcinosarcoma, NOS, of upper-outer quadrant of breast	44500664	ICDO3
Clear cell adenocarcinoma, NOS, of axillary tail of breast	36549753	ICDO3
Clear cell adenocarcinoma, NOS, of breast, NOS	36518754	ICDO3
Clear cell adenocarcinoma, NOS, of central portion of breast	36551469	ICDO3
Clear cell adenocarcinoma, NOS, of lower-inner quadrant of breast	36529768	ICDO3
Clear cell adenocarcinoma, NOS, of lower-outer quadrant of breast	36521809	ICDO3
Clear cell adenocarcinoma, NOS, of nipple	36561381	ICDO3
Clear cell adenocarcinoma, NOS, of overlapping lesion of breast	36542307	ICDO3

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Clear cell adenocarcinoma, NOS, of upper-inner quadrant of breast	36530728	ICDO3
Clear cell adenocarcinoma, NOS, of upper-outer quadrant of breast	36540590	ICDO3
Comedocarcinoma, NOS, of axillary tail of breast	36536599	ICDO3
Comedocarcinoma, NOS, of breast, NOS	36568176	ICDO3
Comedocarcinoma, NOS, of central portion of breast	36566236	ICDO3
Comedocarcinoma, NOS, of lower-inner quadrant of breast	36549067	ICDO3
Comedocarcinoma, NOS, of lower-outer quadrant of breast	36533221	ICDO3
Comedocarcinoma, NOS, of overlapping lesion of breast	36544343	ICDO3
Comedocarcinoma, NOS, of upper-inner quadrant of breast	36521663	ICDO3
Comedocarcinoma, NOS, of upper-outer quadrant of breast	36548529	ICDO3
Cribriform carcinoma, NOS, of axillary tail of breast	44501262	ICDO3
Cribriform carcinoma, NOS, of breast, NOS	44500592	ICDO3
Cribriform carcinoma, NOS, of central portion of breast	44500862	ICDO3
Cribriform carcinoma, NOS, of lower-inner quadrant of breast	36557108	ICDO3
Cribriform carcinoma, NOS, of lower-outer quadrant of breast	44501848	ICDO3
Cribriform carcinoma, NOS, of nipple	44499538	ICDO3
Cribriform carcinoma, NOS, of overlapping lesion of breast	36531967	ICDO3
Cribriform carcinoma, NOS, of upper-inner quadrant of breast	44501792	ICDO3
Cribriform carcinoma, NOS, of upper-outer quadrant of breast	44500873	ICDO3
Cystadenocarcinoma, NOS, of axillary tail of breast	36552252	ICDO3
Cystadenocarcinoma, NOS, of breast, NOS	36561513	ICDO3
Cystadenocarcinoma, NOS, of central portion of breast	36549402	ICDO3
Cystadenocarcinoma, NOS, of lower-inner quadrant of breast	36542396	ICDO3
Cystadenocarcinoma, NOS, of lower-outer quadrant of breast	36551482	ICDO3
Cystadenocarcinoma, NOS, of nipple	36550109	ICDO3
Cystadenocarcinoma, NOS, of overlapping lesion of breast	36519532	ICDO3
Cystadenocarcinoma, NOS, of upper-inner quadrant of breast	36547095	ICDO3
Cystadenocarcinoma, NOS, of upper-outer quadrant of breast	36565077	ICDO3
Cystic hypersecretory carcinoma of nipple	36554874	ICDO3
Duct carcinoma, desmoplastic type of axillary tail of breast	36545391	ICDO3
Duct carcinoma, desmoplastic type of breast, NOS	36551694	ICDO3
Duct carcinoma, desmoplastic type of central portion of breast	36528580	ICDO3
Duct carcinoma, desmoplastic type of lower-inner quadrant of breast	36551404	ICDO3
Duct carcinoma, desmoplastic type of lower-outer quadrant of breast	36559774	ICDO3
Duct carcinoma, desmoplastic type of overlapping lesion of breast	36548379	ICDO3

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Duct carcinoma, desmoplastic type of upper-inner quadrant of breast	36524955	ICDO3
Duct carcinoma, desmoplastic type of upper-outer quadrant of breast	36556632	ICDO3
Encapsulated papillary carcinoma with invasion of axillary tail of breast	36564156	ICDO3
Encapsulated papillary carcinoma with invasion of breast, NOS	44501655	ICDO3
Encapsulated papillary carcinoma with invasion of central portion of breast	44500507	ICDO3
Encapsulated papillary carcinoma with invasion of lower-inner quadrant of breast	44500939	ICDO3
Encapsulated papillary carcinoma with invasion of lower-outer quadrant of breast	44502828	ICDO3
Encapsulated papillary carcinoma with invasion of overlapping lesion of breast	36520959	ICDO3
Encapsulated papillary carcinoma with invasion of upper-inner quadrant of breast	44502475	ICDO3
Encapsulated papillary carcinoma with invasion of upper-outer quadrant of breast	44502955	ICDO3
Epithelial-myoepithelial carcinoma of axillary tail of breast	36563169	ICDO3
Epithelial-myoepithelial carcinoma of breast, NOS	36518059	ICDO3
Epithelial-myoepithelial carcinoma of central portion of breast	44502830	ICDO3
Epithelial-myoepithelial carcinoma of lower-inner quadrant of breast	44502038	ICDO3
Epithelial-myoepithelial carcinoma of lower-outer quadrant of breast	36558395	ICDO3
Epithelial-myoepithelial carcinoma of nipple	36536105	ICDO3
Epithelial-myoepithelial carcinoma of overlapping lesion of breast	36534772	ICDO3
Epithelial-myoepithelial carcinoma of upper-inner quadrant of breast	36553182	ICDO3
Epithelial-myoepithelial carcinoma of upper-outer quadrant of breast	36532659	ICDO3
Epithelioid hemangioendothelioma, NOS, of axillary tail of breast	36520234	ICDO3
Epithelioid hemangioendothelioma, NOS, of breast, NOS	36532396	ICDO3
Epithelioid hemangioendothelioma, NOS, of central portion of breast	36542675	ICDO3
Epithelioid hemangioendothelioma, NOS, of lower-inner quadrant of breast	36536576	ICDO3
Epithelioid hemangioendothelioma, NOS, of lower-outer quadrant of breast	36559643	ICDO3
Epithelioid hemangioendothelioma, NOS, of overlapping lesion of breast	36546986	ICDO3
Epithelioid hemangioendothelioma, NOS, of upper-inner quadrant of breast	36565450	ICDO3

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Epithelioid hemangioendothelioma, NOS, of upper-outer quadrant of breast	36520108	ICDO3
Epithelioma, malignant of axillary tail of breast	36567892	ICDO3
Epithelioma, malignant of breast, NOS	36552908	ICDO3
Epithelioma, malignant of central portion of breast	36550208	ICDO3
Epithelioma, malignant of lower-inner quadrant of breast	36567185	ICDO3
Epithelioma, malignant of lower-outer quadrant of breast	36564823	ICDO3
Epithelioma, malignant of nipple	36544024	ICDO3
Epithelioma, malignant of overlapping lesion of breast	36542995	ICDO3
Epithelioma, malignant of upper-inner quadrant of breast	36525372	ICDO3
Epithelioma, malignant of upper-outer quadrant of breast	36527416	ICDO3
Estrogen receptor (ER) and progesterone receptor (PR) negative breast cancer (ONC)	2106968	CPT4
Estrogen receptor (ER) or progesterone receptor (PR) positive breast cancer (ONC)	2106967	CPT4
Giant cell and spindle cell carcinoma of axillary tail of breast	36528664	ICDO3
Giant cell and spindle cell carcinoma of breast, NOS	36548595	ICDO3
Giant cell and spindle cell carcinoma of central portion of breast	36541277	ICDO3
Giant cell and spindle cell carcinoma of lower-inner quadrant of breast	36531282	ICDO3
Giant cell and spindle cell carcinoma of lower-outer quadrant of breast	36553346	ICDO3
Giant cell and spindle cell carcinoma of nipple	36532695	ICDO3
Giant cell and spindle cell carcinoma of overlapping lesion of breast	36533026	ICDO3
Giant cell and spindle cell carcinoma of upper-inner quadrant of breast	36547953	ICDO3
Giant cell and spindle cell carcinoma of upper-outer quadrant of breast	44501468	ICDO3
Giant cell carcinoma of axillary tail of breast	36552843	ICDO3
Giant cell carcinoma of breast, NOS	36560382	ICDO3
Giant cell carcinoma of central portion of breast	36522493	ICDO3
Giant cell carcinoma of lower-inner quadrant of breast	36541774	ICDO3
Giant cell carcinoma of lower-outer quadrant of breast	36538685	ICDO3
Giant cell carcinoma of nipple	36542372	ICDO3
Giant cell carcinoma of overlapping lesion of breast	36520932	ICDO3
Giant cell carcinoma of upper-inner quadrant of breast	36559160	ICDO3
Giant cell carcinoma of upper-outer quadrant of breast	36523654	ICDO3
Glassy cell carcinoma of axillary tail of breast	36540058	ICDO3
Glassy cell carcinoma of breast, NOS	36524742	ICDO3

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Glassy cell carcinoma of central portion of breast	36533520	ICDO3
Glassy cell carcinoma of lower-inner quadrant of breast	36541577	ICDO3
Glassy cell carcinoma of lower-outer quadrant of breast	36558210	ICDO3
Glassy cell carcinoma of nipple	36530498	ICDO3
Glassy cell carcinoma of overlapping lesion of breast	36562136	ICDO3
Glassy cell carcinoma of upper-inner quadrant of breast	36551633	ICDO3
Glassy cell carcinoma of upper-outer quadrant of breast	36522382	ICDO3
Glycogen-rich carcinoma of axillary tail of breast	36520334	ICDO3
Glycogen-rich carcinoma of breast, NOS	36543982	ICDO3
Glycogen-rich carcinoma of central portion of breast	36533162	ICDO3
Glycogen-rich carcinoma of lower-inner quadrant of breast	36551971	ICDO3
Glycogen-rich carcinoma of lower-outer quadrant of breast	36551983	ICDO3
Glycogen-rich carcinoma of nipple	36564604	ICDO3
Glycogen-rich carcinoma of overlapping lesion of breast	36554044	ICDO3
Glycogen-rich carcinoma of upper-inner quadrant of breast	36567044	ICDO3
Glycogen-rich carcinoma of upper-outer quadrant of breast	36566227	ICDO3
Granular cell carcinoma of axillary tail of breast	36562515	ICDO3
Granular cell carcinoma of breast, NOS	36531629	ICDO3
Granular cell carcinoma of central portion of breast	36542024	ICDO3
Granular cell carcinoma of lower-inner quadrant of breast	36562723	ICDO3
Granular cell carcinoma of lower-outer quadrant of breast	36553245	ICDO3
Granular cell carcinoma of nipple	36563848	ICDO3
Granular cell carcinoma of overlapping lesion of breast	36549543	ICDO3
Granular cell carcinoma of upper-inner quadrant of breast	36550013	ICDO3
Granular cell carcinoma of upper-outer quadrant of breast	36567481	ICDO3
Granular cell tumor, malignant of axillary tail of breast	36525967	ICDO3
Granular cell tumor, malignant of breast, NOS	36521129	ICDO3
Granular cell tumor, malignant of central portion of breast	36527310	ICDO3
Granular cell tumor, malignant of lower-inner quadrant of breast	36523631	ICDO3
Granular cell tumor, malignant of lower-outer quadrant of breast	36536981	ICDO3
Granular cell tumor, malignant of overlapping lesion of breast	36531892	ICDO3
Granular cell tumor, malignant of upper-inner quadrant of breast	36550240	ICDO3
Granular cell tumor, malignant of upper-outer quadrant of breast	36541004	ICDO3
Hemangioendothelioma, malignant of axillary tail of breast	36526940	ICDO3
Hemangioendothelioma, malignant of breast, NOS	36543949	ICDO3
Hemangioendothelioma, malignant of central portion of breast	36534970	ICDO3

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Hemangioendothelioma, malignant of lower-inner quadrant of breast	36566966	ICDO3
Hemangioendothelioma, malignant of lower-outer quadrant of breast	36532078	ICDO3
Hemangioendothelioma, malignant of overlapping lesion of breast	36522831	ICDO3
Hemangioendothelioma, malignant of upper-inner quadrant of breast	36526309	ICDO3
Hemangioendothelioma, malignant of upper-outer quadrant of breast	36534268	ICDO3
HER2-positive carcinoma of breast	4142116	SNOMED
Hormone receptor positive malignant neoplasm of breast	4216891	SNOMED
Human epidermal growth factor 2 negative carcinoma of breast	4330242	SNOMED
Infiltrating duct and lobular carcinoma of axillary tail of breast	44499515	ICDO3
Infiltrating duct and lobular carcinoma of breast, NOS	44500508	ICDO3
Infiltrating duct and lobular carcinoma of central portion of breast	44499922	ICDO3
Infiltrating duct and lobular carcinoma of lower-inner quadrant of breast	44500306	ICDO3
Infiltrating duct and lobular carcinoma of lower-outer quadrant of breast	44502343	ICDO3
Infiltrating duct and lobular carcinoma of overlapping lesion of breast	36548839	ICDO3
Infiltrating duct and lobular carcinoma of upper-inner quadrant of breast	44500305	ICDO3
Infiltrating duct and lobular carcinoma of upper-outer quadrant of breast	44500259	ICDO3
Infiltrating duct carcinoma of axillary tail of breast	1075609	SNOMED
Infiltrating duct carcinoma of axillary tail of left breast	1075607	SNOMED
Infiltrating duct carcinoma of axillary tail of right breast	1075608	SNOMED
Infiltrating duct carcinoma of bilateral breasts	1077461	SNOMED
Infiltrating duct carcinoma of breast	4237178	SNOMED
Infiltrating duct carcinoma of central portion of breast	1075610	SNOMED
Infiltrating duct carcinoma of central portion of left breast	1075611	SNOMED
Infiltrating duct carcinoma of central portion of right breast	1075612	SNOMED
Infiltrating duct carcinoma of left breast	1075627	SNOMED
Infiltrating duct carcinoma of lower inner quadrant of breast	1075630	SNOMED
Infiltrating duct carcinoma of lower inner quadrant of left breast	1075632	SNOMED
Infiltrating duct carcinoma of lower inner quadrant of right breast	1075631	SNOMED
Infiltrating duct carcinoma of lower outer quadrant of breast	1075624	SNOMED
Infiltrating duct carcinoma of lower outer quadrant of left breast	1075626	SNOMED
Infiltrating duct carcinoma of lower outer quadrant of right breast	1075625	SNOMED

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Infiltrating duct carcinoma of right breast	1075628	SNOMED
Infiltrating duct carcinoma of upper inner quadrant of breast	1075620	SNOMED
Infiltrating duct carcinoma of upper inner quadrant of left breast	1075623	SNOMED
Infiltrating duct carcinoma of upper inner quadrant of right breast	1075622	SNOMED
Infiltrating duct carcinoma of upper outer quadrant of breast	1075619	SNOMED
Infiltrating duct carcinoma of upper outer quadrant of left breast	1075618	SNOMED
Infiltrating duct carcinoma of upper outer quadrant of right breast	1075617	SNOMED
Infiltrating duct carcinoma, NOS, of axillary tail of breast	44501150	ICDO3
Infiltrating duct carcinoma, NOS, of central portion of breast	44501944	ICDO3
Infiltrating duct carcinoma, NOS, of lower-inner quadrant of breast	44502447	ICDO3
Infiltrating duct carcinoma, NOS, of lower-outer quadrant of breast	44499818	ICDO3
Infiltrating duct carcinoma, NOS, of nipple	44500599	ICDO3
Infiltrating duct carcinoma, NOS, of overlapping lesion of breast	36564848	ICDO3
Infiltrating duct carcinoma, NOS, of upper-inner quadrant of breast	44499972	ICDO3
Infiltrating duct carcinoma, NOS, of upper-outer quadrant of breast	44502548	ICDO3
Infiltrating duct mixed with other types of carcinoma of axillary tail of breast	44501658	ICDO3
Infiltrating duct mixed with other types of carcinoma of breast, NOS	44501023	ICDO3
Infiltrating duct mixed with other types of carcinoma of central portion of breast	44500148	ICDO3
Infiltrating duct mixed with other types of carcinoma of lower-inner quadrant of breast	44502033	ICDO3
Infiltrating duct mixed with other types of carcinoma of lower-outer quadrant of breast	44500205	ICDO3
Infiltrating duct mixed with other types of carcinoma of overlapping lesion of breast	36535209	ICDO3
Infiltrating duct mixed with other types of carcinoma of upper-inner quadrant of breast	44502116	ICDO3
Infiltrating duct mixed with other types of carcinoma of upper-outer quadrant of breast	44502180	ICDO3
Infiltrating ductal carcinoma of breast, stage 1	4308306	SNOMED
Infiltrating ductal carcinoma of breast, stage 2	4310988	SNOMED
Infiltrating ductal carcinoma of breast, stage 3	4313043	SNOMED
Infiltrating ductal carcinoma of breast, stage 4	4310721	SNOMED
Infiltrating ductular carcinoma of axillary tail of breast	36560602	ICDO3
Infiltrating ductular carcinoma of central portion of breast	36528584	ICDO3
Infiltrating ductular carcinoma of lower-inner quadrant of breast	36537097	ICDO3
Infiltrating ductular carcinoma of lower-outer quadrant of breast	36552211	ICDO3
Infiltrating ductular carcinoma of overlapping lesion of breast	36537324	ICDO3

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Infiltrating ductular carcinoma of upper-inner quadrant of breast	36538743	ICDO3
Infiltrating ductular carcinoma of upper-outer quadrant of breast	36544992	ICDO3
Infiltrating lobular carcinoma of breast	4080865	SNOMED
Infiltrating lobular mixed with other types of carcinoma of axillary tail of breast	36523820	ICDO3
Infiltrating lobular mixed with other types of carcinoma of breast, NOS	44502882	ICDO3
Infiltrating lobular mixed with other types of carcinoma of central portion of breast	44502881	ICDO3
Infiltrating lobular mixed with other types of carcinoma of lower-inner quadrant of breast	44501219	ICDO3
Infiltrating lobular mixed with other types of carcinoma of lower-outer quadrant of breast	44501277	ICDO3
Infiltrating lobular mixed with other types of carcinoma of overlapping lesion of breast	36521814	ICDO3
Infiltrating lobular mixed with other types of carcinoma of upper-inner quadrant of breast	44503557	ICDO3
Infiltrating lobular mixed with other types of carcinoma of upper-outer quadrant of breast	44501447	ICDO3
Inflammatory carcinoma of axillary tail of breast	36561082	ICDO3
Inflammatory carcinoma of breast	4112074	SNOMED
Inflammatory carcinoma of central portion of breast	44501898	ICDO3
Inflammatory carcinoma of lower-inner quadrant of breast	44501093	ICDO3
Inflammatory carcinoma of lower-outer quadrant of breast	44501024	ICDO3
Inflammatory carcinoma of nipple	44501583	ICDO3
Inflammatory carcinoma of overlapping lesion of breast	36560657	ICDO3
Inflammatory carcinoma of upper-inner quadrant of breast	44501220	ICDO3
Inflammatory carcinoma of upper-outer quadrant of breast	44502290	ICDO3
Intraductal papillary adenocarcinoma with invasion of axillary tail of breast	36559477	ICDO3
Intraductal papillary adenocarcinoma with invasion of breast, NOS	44499973	ICDO3
Intraductal papillary adenocarcinoma with invasion of central portion of breast	44501352	ICDO3
Intraductal papillary adenocarcinoma with invasion of lower-inner quadrant of breast	44502880	ICDO3
Intraductal papillary adenocarcinoma with invasion of lower-outer quadrant of breast	44503158	ICDO3
Intraductal papillary adenocarcinoma with invasion of overlapping lesion of breast	36520230	ICDO3
Intraductal papillary adenocarcinoma with invasion of upper-inner quadrant of breast	44500801	ICDO3

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Intraductal papillary adenocarcinoma with invasion of upper-outer quadrant of breast	44502114	ICDO3
Invasive carcinoma of breast	37017351	SNOMED
Invasive carcinoma of breast with extensive intraductal component	3184724	Nebraska Lexicon
Invasive carcinoma of breast without extensive intraductal component	3179883	Nebraska Lexicon
Invasive micropapillary carcinoma of breast of axillary tail of breast	42511727	ICDO3
Invasive micropapillary carcinoma of breast of breast, NOS	36403000	ICDO3
Invasive micropapillary carcinoma of breast of central portion of breast	36403021	ICDO3
Invasive micropapillary carcinoma of breast of lower-inner quadrant of breast	36402998	ICDO3
Invasive micropapillary carcinoma of breast of lower-outer quadrant of breast	36403015	ICDO3
Invasive micropapillary carcinoma of breast of overlapping lesion of breast	36402995	ICDO3
Invasive micropapillary carcinoma of breast of upper-inner quadrant of breast	36403045	ICDO3
Invasive micropapillary carcinoma of breast of upper-outer quadrant of breast	36403018	ICDO3
Large cell carcinoma with rhabdoid phenotype of axillary tail of breast	36533269	ICDO3
Large cell carcinoma with rhabdoid phenotype of breast, NOS	36531399	ICDO3
Large cell carcinoma with rhabdoid phenotype of central portion of breast	36544559	ICDO3
Large cell carcinoma with rhabdoid phenotype of lower-inner quadrant of breast	36535414	ICDO3
Large cell carcinoma with rhabdoid phenotype of lower-outer quadrant of breast	36562047	ICDO3
Large cell carcinoma with rhabdoid phenotype of nipple	36559859	ICDO3
Large cell carcinoma with rhabdoid phenotype of overlapping lesion of breast	36561110	ICDO3
Large cell carcinoma with rhabdoid phenotype of upper-inner quadrant of breast	36549110	ICDO3
Large cell carcinoma with rhabdoid phenotype of upper-outer quadrant of breast	36540213	ICDO3
Large cell carcinoma, NOS, of axillary tail of breast	36541378	ICDO3
Large cell carcinoma, NOS, of breast, NOS	36556824	ICDO3
Large cell carcinoma, NOS, of central portion of breast	36529026	ICDO3
Large cell carcinoma, NOS, of lower-inner quadrant of breast	36522474	ICDO3
Large cell carcinoma, NOS, of lower-outer quadrant of breast	36520780	ICDO3
Large cell carcinoma, NOS, of nipple	36522838	ICDO3

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Large cell carcinoma, NOS, of overlapping lesion of breast	36519248	ICDO3
Large cell carcinoma, NOS, of upper-inner quadrant of breast	36517860	ICDO3
Large cell carcinoma, NOS, of upper-outer quadrant of breast	44502155	ICDO3
Large cell neuroendocrine carcinoma of axillary tail of breast	36567173	ICDO3
Large cell neuroendocrine carcinoma of breast, NOS	36566968	ICDO3
Large cell neuroendocrine carcinoma of central portion of breast	36538145	ICDO3
Large cell neuroendocrine carcinoma of lower-inner quadrant of breast	36560911	ICDO3
Large cell neuroendocrine carcinoma of lower-outer quadrant of breast	36539856	ICDO3
Large cell neuroendocrine carcinoma of overlapping lesion of breast	36552672	ICDO3
Large cell neuroendocrine carcinoma of upper-inner quadrant of breast	36562163	ICDO3
Large cell neuroendocrine carcinoma of upper-outer quadrant of breast	36562803	ICDO3
Lipid-rich carcinoma of axillary tail of breast	36561070	ICDO3
Lipid-rich carcinoma of breast, NOS	36556710	ICDO3
Lipid-rich carcinoma of central portion of breast	36549616	ICDO3
Lipid-rich carcinoma of lower-inner quadrant of breast	36553876	ICDO3
Lipid-rich carcinoma of lower-outer quadrant of breast	36552738	ICDO3
Lipid-rich carcinoma of nipple	36528685	ICDO3
Lipid-rich carcinoma of overlapping lesion of breast	36550530	ICDO3
Lipid-rich carcinoma of upper-inner quadrant of breast	36554194	ICDO3
Lipid-rich carcinoma of upper-outer quadrant of breast	36563893	ICDO3
Lobular carcinoma of left breast	1075616	SNOMED
Lobular carcinoma of right breast	1075615	SNOMED
Lobular carcinoma, NOS, of axillary tail of breast	44502959	ICDO3
Lobular carcinoma, NOS, of central portion of breast	44498965	ICDO3
Lobular carcinoma, NOS, of lower-inner quadrant of breast	44500419	ICDO3
Lobular carcinoma, NOS, of lower-outer quadrant of breast	44502958	ICDO3
Lobular carcinoma, NOS, of nipple	44500882	ICDO3
Lobular carcinoma, NOS, of overlapping lesion of breast	36542964	ICDO3
Lobular carcinoma, NOS, of upper-inner quadrant of breast	44501355	ICDO3
Lobular carcinoma, NOS, of upper-outer quadrant of breast	44500600	ICDO3
Localized skin involvement by breast carcinoma	4293714	SNOMED
Locally advanced breast cancer	37310457	SNOMED
Malignant neoplasm of areola	1075518	SNOMED
Malignant neoplasm of axillary tail of breast	4155292	SNOMED

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Malignant neoplasm of breast in full remission	37175247	SNOMED
Malignant neoplasm of breast in partial remission	37168468	SNOMED
Malignant neoplasm of breast in remission	37172171	SNOMED
Malignant neoplasm of central portion of breast	1075606	SNOMED
Malignant neoplasm of ectopic site of breast	1075507	SNOMED
Malignant neoplasm of lower inner quadrant of breast	4188544	SNOMED
Malignant neoplasm of lower outer quadrant of breast	4187848	SNOMED
Malignant neoplasm of nipple	1075524	SNOMED
Malignant neoplasm of nipple and areola	1075508	SNOMED
Malignant neoplasm of overlapping sites of breast	4092513	SNOMED
Malignant neoplasm of upper inner quadrant of breast	4187849	SNOMED
Malignant neoplasm of upper outer quadrant of breast	4160780	SNOMED
Malignant phyllodes tumor of breast	4112854	SNOMED
Malignant tumor of breast	4112853	SNOMED
Malignant tumor, clear cell type of axillary tail of breast	36517781	ICDO3
Malignant tumor, clear cell type of breast, NOS	36530347	ICDO3
Malignant tumor, clear cell type of central portion of breast	36549060	ICDO3
Malignant tumor, clear cell type of lower-inner quadrant of breast	36531444	ICDO3
Malignant tumor, clear cell type of lower-outer quadrant of breast	36526286	ICDO3
Malignant tumor, clear cell type of overlapping lesion of breast	36556569	ICDO3
Malignant tumor, clear cell type of upper-inner quadrant of breast	36533102	ICDO3
Malignant tumor, clear cell type of upper-outer quadrant of breast	36552981	ICDO3
Malignant tumor, giant cell type of axillary tail of breast	36535359	ICDO3
Malignant tumor, giant cell type of breast, NOS	36549561	ICDO3
Malignant tumor, giant cell type of central portion of breast	36555928	ICDO3
Malignant tumor, giant cell type of lower-inner quadrant of breast	36556912	ICDO3
Malignant tumor, giant cell type of lower-outer quadrant of breast	36531430	ICDO3
Malignant tumor, giant cell type of overlapping lesion of breast	36524703	ICDO3
Malignant tumor, giant cell type of upper-inner quadrant of breast	36532993	ICDO3
Malignant tumor, giant cell type of upper-outer quadrant of breast	36551499	ICDO3
Malignant tumor, small cell type of axillary tail of breast	36565177	ICDO3
Malignant tumor, small cell type of breast, NOS	36560601	ICDO3
Malignant tumor, small cell type of central portion of breast	36537040	ICDO3
Malignant tumor, small cell type of lower-inner quadrant of breast	36525822	ICDO3
Malignant tumor, small cell type of lower-outer quadrant of breast	36551426	ICDO3
Malignant tumor, small cell type of overlapping lesion of breast	36521324	ICDO3

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Malignant tumor, small cell type of upper-inner quadrant of breast	36538787	ICDO3
Malignant tumor, small cell type of upper-outer quadrant of breast	36518762	ICDO3
Malignant tumor, spindle cell type of axillary tail of breast	36528591	ICDO3
Malignant tumor, spindle cell type of breast, NOS	36553720	ICDO3
Malignant tumor, spindle cell type of central portion of breast	36530382	ICDO3
Malignant tumor, spindle cell type of lower-inner quadrant of breast	36560955	ICDO3
Malignant tumor, spindle cell type of lower-outer quadrant of breast	36559682	ICDO3
Malignant tumor, spindle cell type of overlapping lesion of breast	36554336	ICDO3
Malignant tumor, spindle cell type of upper-inner quadrant of breast	36566465	ICDO3
Malignant tumor, spindle cell type of upper-outer quadrant of breast	36553232	ICDO3
Medullary carcinoma with amyloid stroma (ICD-O-2) of breast, NOS	42512581	ICDO3
Medullary carcinoma with lymphoid stroma of axillary tail of breast	36549055	ICDO3
Medullary carcinoma with lymphoid stroma of breast, NOS	36529963	ICDO3
Medullary carcinoma with lymphoid stroma of central portion of breast	36546913	ICDO3
Medullary carcinoma with lymphoid stroma of lower-inner quadrant of breast	36540345	ICDO3
Medullary carcinoma with lymphoid stroma of lower-outer quadrant of breast	36552782	ICDO3
Medullary carcinoma with lymphoid stroma of overlapping lesion of breast	36559593	ICDO3
Medullary carcinoma with lymphoid stroma of upper-inner quadrant of breast	36552805	ICDO3
Medullary carcinoma with lymphoid stroma of upper-outer quadrant of breast	44499974	ICDO3
Medullary carcinoma, NOS, of axillary tail of breast	36537741	ICDO3
Medullary carcinoma, NOS, of breast, NOS	44502956	ICDO3
Medullary carcinoma, NOS, of central portion of breast	36546168	ICDO3
Medullary carcinoma, NOS, of lower-inner quadrant of breast	36556518	ICDO3
Medullary carcinoma, NOS, of lower-outer quadrant of breast	36529278	ICDO3
Medullary carcinoma, NOS, of overlapping lesion of breast	36543936	ICDO3
Medullary carcinoma, NOS, of upper-inner quadrant of breast	36523241	ICDO3
Medullary carcinoma, NOS, of upper-outer quadrant of breast	44502782	ICDO3
Merkel cell carcinoma of overlapping lesion of breast	36541149	ICDO3
Mesenchymoma, malignant of axillary tail of breast	36552745	ICDO3
Mesenchymoma, malignant of breast, NOS	36550276	ICDO3
Mesenchymoma, malignant of central portion of breast	36542663	ICDO3
Mesenchymoma, malignant of lower-inner quadrant of breast	36561524	ICDO3
Mesenchymoma, malignant of lower-outer quadrant of breast	36524477	ICDO3

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Mesenchymoma, malignant of overlapping lesion of breast	36523976	ICDO3
Mesenchymoma, malignant of upper-inner quadrant of breast	36519661	ICDO3
Mesenchymoma, malignant of upper-outer quadrant of breast	36533084	ICDO3
Metaplastic carcinoma of breast	35622134	SNOMED
Metaplastic carcinoma, NOS, of axillary tail of breast	36547774	ICDO3
Metaplastic carcinoma, NOS, of central portion of breast	44503559	ICDO3
Metaplastic carcinoma, NOS, of lower-inner quadrant of breast	44502039	ICDO3
Metaplastic carcinoma, NOS, of lower-outer quadrant of breast	44503099	ICDO3
Metaplastic carcinoma, NOS, of nipple	36541476	ICDO3
Metaplastic carcinoma, NOS, of overlapping lesion of breast	36536634	ICDO3
Metaplastic carcinoma, NOS, of upper-inner quadrant of breast	44502449	ICDO3
Metaplastic carcinoma, NOS, of upper-outer quadrant of breast	44498967	ICDO3
Mixed cell adenocarcinoma of axillary tail of breast	36522830	ICDO3
Mixed cell adenocarcinoma of breast, NOS	36529409	ICDO3
Mixed cell adenocarcinoma of central portion of breast	36565348	ICDO3
Mixed cell adenocarcinoma of lower-inner quadrant of breast	36542692	ICDO3
Mixed cell adenocarcinoma of lower-outer quadrant of breast	36520531	ICDO3
Mixed cell adenocarcinoma of nipple	36556222	ICDO3
Mixed cell adenocarcinoma of overlapping lesion of breast	36527144	ICDO3
Mixed cell adenocarcinoma of upper-inner quadrant of breast	36562423	ICDO3
Mixed cell adenocarcinoma of upper-outer quadrant of breast	36533612	ICDO3
Mixed ductal and lobular carcinoma of breast	40480215	SNOMED
Mixed neuroendocrine non-neuroendocrine neoplasm (MiNEN) of lower-outer quadrant of breast	42512327	ICDO3
Mucin-producing adenocarcinoma of axillary tail of breast	36559300	ICDO3
Mucin-producing adenocarcinoma of breast, NOS	36518019	ICDO3
Mucin-producing adenocarcinoma of central portion of breast	36529114	ICDO3
Mucin-producing adenocarcinoma of lower-inner quadrant of breast	36551603	ICDO3
Mucin-producing adenocarcinoma of lower-outer quadrant of breast	36565495	ICDO3
Mucin-producing adenocarcinoma of overlapping lesion of breast	36522534	ICDO3
Mucin-producing adenocarcinoma of upper-inner quadrant of breast	36540579	ICDO3
Mucin-producing adenocarcinoma of upper-outer quadrant of breast	44499557	ICDO3
Mucinous adenocarcinoma of axillary tail of breast	36551629	ICDO3
Mucinous adenocarcinoma of central portion of breast	44501273	ICDO3
Mucinous adenocarcinoma of lower-inner quadrant of breast	44500301	ICDO3
Mucinous adenocarcinoma of lower-outer quadrant of breast	44501579	ICDO3

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Mucinous adenocarcinoma of nipple	44501894	ICDO3
Mucinous adenocarcinoma of overlapping lesion of breast	36531101	ICDO3
Mucinous adenocarcinoma of upper-inner quadrant of breast	44502240	ICDO3
Mucinous adenocarcinoma of upper-outer quadrant of breast	44502030	ICDO3
Mucinous carcinoma of breast	40480651	SNOMED
Mucinous cystadenocarcinoma, NOS, of axillary tail of breast	36524938	ICDO3
Mucinous cystadenocarcinoma, NOS, of breast, NOS	36522650	ICDO3
Mucinous cystadenocarcinoma, NOS, of central portion of breast	36524556	ICDO3
Mucinous cystadenocarcinoma, NOS, of lower-inner quadrant of breast	36527646	ICDO3
Mucinous cystadenocarcinoma, NOS, of lower-outer quadrant of breast	36537129	ICDO3
Mucinous cystadenocarcinoma, NOS, of nipple	36517515	ICDO3
Mucinous cystadenocarcinoma, NOS, of overlapping lesion of breast	36562161	ICDO3
Mucinous cystadenocarcinoma, NOS, of upper-inner quadrant of breast	36554193	ICDO3
Mucinous cystadenocarcinoma, NOS, of upper-outer quadrant of breast	36526076	ICDO3
Mucoepidermoid carcinoma of breast, NOS	1553390	ICDO3
Myoepithelial carcinoma of axillary tail of breast	36544172	ICDO3
Myoepithelial carcinoma of breast, NOS	36542378	ICDO3
Myoepithelial carcinoma of central portion of breast	36549581	ICDO3
Myoepithelial carcinoma of lower-inner quadrant of breast	36545829	ICDO3
Myoepithelial carcinoma of lower-outer quadrant of breast	36529298	ICDO3
Myoepithelial carcinoma of nipple	36538039	ICDO3
Myoepithelial carcinoma of overlapping lesion of breast	36559943	ICDO3
Myoepithelial carcinoma of upper-inner quadrant of breast	36555848	ICDO3
Myoepithelial carcinoma of upper-outer quadrant of breast	36532825	ICDO3
Neoplasm, malignant of central portion of breast	44500425	ICDO3
Neoplasm, malignant of overlapping lesion of breast	36525086	ICDO3
Neuroendocrine carcinoma, NOS, of axillary tail of breast	36529381	ICDO3
Neuroendocrine carcinoma, NOS, of breast, NOS	44501141	ICDO3
Neuroendocrine carcinoma, NOS, of central portion of breast	36522453	ICDO3
Neuroendocrine carcinoma, NOS, of lower-inner quadrant of breast	36532906	ICDO3
Neuroendocrine carcinoma, NOS, of lower-outer quadrant of breast	36534320	ICDO3
Neuroendocrine carcinoma, NOS, of overlapping lesion of breast	36520875	ICDO3
Neuroendocrine carcinoma, NOS, of upper-inner quadrant of breast	36537327	ICDO3
Neuroendocrine carcinoma, NOS, of upper-outer quadrant of breast	44500728	ICDO3

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Neuroendocrine tumor, NOS, of breast, NOS	44502228	ICDO3
Neuroendocrine tumor, NOS, of lower-outer quadrant of breast	44500293	ICDO3
Non-small cell carcinoma of lower-outer quadrant of breast	44501832	ICDO3
Oxyphilic adenocarcinoma of axillary tail of breast	36518120	ICDO3
Oxyphilic adenocarcinoma of breast, NOS	36545241	ICDO3
Oxyphilic adenocarcinoma of central portion of breast	36556030	ICDO3
Oxyphilic adenocarcinoma of lower-inner quadrant of breast	36526057	ICDO3
Oxyphilic adenocarcinoma of lower-outer quadrant of breast	36522006	ICDO3
Oxyphilic adenocarcinoma of nipple	36557321	ICDO3
Oxyphilic adenocarcinoma of overlapping lesion of breast	36517852	ICDO3
Oxyphilic adenocarcinoma of upper-inner quadrant of breast	36554142	ICDO3
Oxyphilic adenocarcinoma of upper-outer quadrant of breast	36526784	ICDO3
Paget disease and infiltrating duct carcinoma of breast of axillary tail of breast	36543350	ICDO3
Paget disease and infiltrating duct carcinoma of breast of breast, NOS	44502034	ICDO3
Paget disease and infiltrating duct carcinoma of breast of central portion of breast	44500307	ICDO3
Paget disease and infiltrating duct carcinoma of breast of lower-inner quadrant of breast	44500739	ICDO3
Paget disease and infiltrating duct carcinoma of breast of lower-outer quadrant of breast	44501958	ICDO3
Paget disease and infiltrating duct carcinoma of breast of overlapping lesion of breast	36564967	ICDO3
Paget disease and infiltrating duct carcinoma of breast of upper-inner quadrant of breast	44500308	ICDO3
Paget disease and infiltrating duct carcinoma of breast of upper-outer quadrant of breast	44502883	ICDO3
Paget disease and intraductal carcinoma of breast of axillary tail of breast	36554778	ICDO3
Paget disease and intraductal carcinoma of breast of breast, NOS	44503032	ICDO3
Paget disease and intraductal carcinoma of breast of central portion of breast	44500462	ICDO3
Paget disease and intraductal carcinoma of breast of lower-inner quadrant of breast	44499975	ICDO3
Paget disease and intraductal carcinoma of breast of lower-outer quadrant of breast	36554022	ICDO3
Paget disease and intraductal carcinoma of breast of overlapping lesion of breast	36543333	ICDO3
Paget disease and intraductal carcinoma of breast of upper-inner quadrant of breast	36551819	ICDO3

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Paget disease and intraductal carcinoma of breast of upper-outer quadrant of breast	44502291	ICDO3
Paget disease, mammary of axillary tail of breast	36554287	ICDO3
Paget disease, mammary of breast, NOS	44500509	ICDO3
Paget disease, mammary of central portion of breast	44502829	ICDO3
Paget disease, mammary of lower-inner quadrant of breast	36519367	ICDO3
Paget disease, mammary of lower-outer quadrant of breast	44498966	ICDO3
Paget disease, mammary of overlapping lesion of breast	36561815	ICDO3
Paget disease, mammary of upper-inner quadrant of breast	44499516	ICDO3
Paget disease, mammary of upper-outer quadrant of breast	44501584	ICDO3
Paget's disease of nipple	4301516	SNOMED
Papillary adenocarcinoma, NOS, of axillary tail of breast	36523418	ICDO3
Papillary adenocarcinoma, NOS, of breast, NOS	44499545	ICDO3
Papillary adenocarcinoma, NOS, of central portion of breast	36541626	ICDO3
Papillary adenocarcinoma, NOS, of lower-inner quadrant of breast	44502944	ICDO3
Papillary adenocarcinoma, NOS, of lower-outer quadrant of breast	36563435	ICDO3
Papillary adenocarcinoma, NOS, of nipple	36555654	ICDO3
Papillary adenocarcinoma, NOS, of overlapping lesion of breast	36551065	ICDO3
Papillary adenocarcinoma, NOS, of upper-inner quadrant of breast	44501572	ICDO3
Papillary adenocarcinoma, NOS, of upper-outer quadrant of breast	44499506	ICDO3
Papillary carcinoma, NOS, of axillary tail of breast	44500428	ICDO3
Papillary carcinoma, NOS, of breast, NOS	44498941	ICDO3
Papillary carcinoma, NOS, of central portion of breast	44499008	ICDO3
Papillary carcinoma, NOS, of lower-inner quadrant of breast	36523039	ICDO3
Papillary carcinoma, NOS, of lower-outer quadrant of breast	44500632	ICDO3
Papillary carcinoma, NOS, of nipple	44499790	ICDO3
Papillary carcinoma, NOS, of overlapping lesion of breast	36566234	ICDO3
Papillary carcinoma, NOS, of upper-inner quadrant of breast	44502215	ICDO3
Papillary carcinoma, NOS, of upper-outer quadrant of breast	44503195	ICDO3
Papillary squamous cell carcinoma of axillary tail of breast	36527105	ICDO3
Papillary squamous cell carcinoma of breast, NOS	36536913	ICDO3
Papillary squamous cell carcinoma of central portion of breast	36557335	ICDO3
Papillary squamous cell carcinoma of lower-inner quadrant of breast	36552277	ICDO3
Papillary squamous cell carcinoma of lower-outer quadrant of breast	36530333	ICDO3
Papillary squamous cell carcinoma of nipple	36540867	ICDO3
Papillary squamous cell carcinoma of overlapping lesion of breast	36564394	ICDO3
Papillary squamous cell carcinoma of upper-inner quadrant of breast	36529041	ICDO3

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Papillary squamous cell carcinoma of upper-outer quadrant of breast	36529833	ICDO3
Phyllodes tumor, malignant of axillary tail of breast	36536731	ICDO3
Phyllodes tumor, malignant of central portion of breast	36564388	ICDO3
Phyllodes tumor, malignant of lower-inner quadrant of breast	44500216	ICDO3
Phyllodes tumor, malignant of lower-outer quadrant of breast	44500551	ICDO3
Phyllodes tumor, malignant of nipple	36518576	ICDO3
Phyllodes tumor, malignant of overlapping lesion of breast	36562784	ICDO3
Phyllodes tumor, malignant of upper-inner quadrant of breast	44501453	ICDO3
Phyllodes tumor, malignant of upper-outer quadrant of breast	44503113	ICDO3
Pleomorphic carcinoma of axillary tail of breast	36567530	ICDO3
Pleomorphic carcinoma of breast, NOS	44502601	ICDO3
Pleomorphic carcinoma of central portion of breast	36523128	ICDO3
Pleomorphic carcinoma of lower-inner quadrant of breast	36546214	ICDO3
Pleomorphic carcinoma of lower-outer quadrant of breast	36559115	ICDO3
Pleomorphic carcinoma of nipple	36534279	ICDO3
Pleomorphic carcinoma of overlapping lesion of breast	36548692	ICDO3
Pleomorphic carcinoma of upper-inner quadrant of breast	36530207	ICDO3
Pleomorphic carcinoma of upper-outer quadrant of breast	44500974	ICDO3
Polygonal cell carcinoma of axillary tail of breast	36547460	ICDO3
Polygonal cell carcinoma of breast, NOS	36552748	ICDO3
Polygonal cell carcinoma of central portion of breast	36535967	ICDO3
Polygonal cell carcinoma of lower-inner quadrant of breast	36523687	ICDO3
Polygonal cell carcinoma of lower-outer quadrant of breast	36545339	ICDO3
Polygonal cell carcinoma of nipple	36526585	ICDO3
Polygonal cell carcinoma of overlapping lesion of breast	36558722	ICDO3
Polygonal cell carcinoma of upper-inner quadrant of breast	36527249	ICDO3
Polygonal cell carcinoma of upper-outer quadrant of breast	36536562	ICDO3
Polymorphous adenocarcinoma of axillary tail of breast	36549527	ICDO3
Polymorphous adenocarcinoma of breast, NOS	36553823	ICDO3
Polymorphous adenocarcinoma of central portion of breast	36522024	ICDO3
Polymorphous adenocarcinoma of lower-inner quadrant of breast	36527079	ICDO3
Polymorphous adenocarcinoma of lower-outer quadrant of breast	36524341	ICDO3
Polymorphous adenocarcinoma of overlapping lesion of breast	36517791	ICDO3
Polymorphous adenocarcinoma of upper-inner quadrant of breast	36531418	ICDO3
Polymorphous adenocarcinoma of upper-outer quadrant of breast	36541123	ICDO3
Primary carcinoma breast - lower, outer quadrant	37166288	SNOMED

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Primary carcinoma of breast	1075506	SNOMED
Primary carcinoma of breast - axillary tail	37166289	SNOMED
Primary carcinoma of breast - lower, inner quadrant	37166286	SNOMED
Primary carcinoma of breast - upper, inner quadrant	37166285	SNOMED
Primary carcinoma of upper outer quadrant of breast	37166287	SNOMED
Primary infiltrating duct carcinoma of axillary tail of breast	1075581	SNOMED
Primary infiltrating duct carcinoma of axillary tail of left breast	1075579	SNOMED
Primary infiltrating duct carcinoma of axillary tail of right breast	1075578	SNOMED
Primary infiltrating duct carcinoma of breast	37166447	SNOMED
Primary infiltrating duct carcinoma of central portion of breast	1075580	SNOMED
Primary infiltrating duct carcinoma of central portion of left breast	1075577	SNOMED
Primary infiltrating duct carcinoma of central portion of right breast	1075576	SNOMED
Primary infiltrating duct carcinoma of lower inner quadrant of breast	1075582	SNOMED
Primary infiltrating duct carcinoma of lower inner quadrant of left breast	1075572	SNOMED
Primary infiltrating duct carcinoma of lower inner quadrant of right breast	1075568	SNOMED
Primary infiltrating duct carcinoma of lower outer quadrant of breast	1075583	SNOMED
Primary infiltrating duct carcinoma of lower outer quadrant of left breast	1075573	SNOMED
Primary infiltrating duct carcinoma of lower outer quadrant of right breast	1075569	SNOMED
Primary infiltrating duct carcinoma of upper inner quadrant of breast	1075584	SNOMED
Primary infiltrating duct carcinoma of upper inner quadrant of left breast	1075574	SNOMED
Primary infiltrating duct carcinoma of upper inner quadrant of right breast	1075571	SNOMED
Primary infiltrating duct carcinoma of upper outer quadrant of breast	1075585	SNOMED
Primary infiltrating duct carcinoma of upper outer quadrant of left breast	1075575	SNOMED
Primary infiltrating duct carcinoma of upper outer quadrant of right breast	1075570	SNOMED
Primary infiltrating lobular carcinoma of breast	37166193	SNOMED
Primary inflammatory carcinoma of breast	1075590	SNOMED
Primary invasive pleomorphic lobular carcinoma of breast	36716497	SNOMED
Primary lobular carcinoma of left breast	1075594	SNOMED
Primary lobular carcinoma of right breast	1075595	SNOMED
Primary malignant neoplasm of areola	1075519	SNOMED
Primary malignant neoplasm of axillary tail of breast	441513	SNOMED

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Primary malignant neoplasm of axillary tail of left breast	1075604	SNOMED
Primary malignant neoplasm of axillary tail of right breast	1075605	SNOMED
Primary malignant neoplasm of bilateral breasts	1075589	SNOMED
Primary malignant neoplasm of breast	4162253	SNOMED
Primary malignant neoplasm of central portion of breast	1075588	SNOMED
Primary malignant neoplasm of central portion of left breast	1075587	SNOMED
Primary malignant neoplasm of central portion of right breast	1075586	SNOMED
Primary malignant neoplasm of ectopic site of breast	1075534	SNOMED
Primary malignant neoplasm of left breast	1075505	SNOMED
Primary malignant neoplasm of lower inner quadrant of breast	4187851	SNOMED
Primary malignant neoplasm of lower outer quadrant of breast	4188545	SNOMED
Primary malignant neoplasm of nipple	1075526	SNOMED
Primary malignant neoplasm of right breast	1075504	SNOMED
Primary malignant neoplasm of upper inner quadrant of breast	4158563	SNOMED
Primary malignant neoplasm of upper outer quadrant of breast	4187850	SNOMED
Primary malignant phyllodes tumor of breast	37166578	SNOMED
Primary metaplastic carcinoma of breast	37167593	SNOMED
Primary mixed ductal and lobular carcinoma of breast	37166310	SNOMED
Primary mucinous carcinoma of breast	37166309	SNOMED
Primary scirrhous carcinoma of breast	37166250	SNOMED
Primary solid papillary carcinoma with invasion of breast	36717587	SNOMED
Scirrhous adenocarcinoma of axillary tail of breast	44500243	ICDO3
Scirrhous adenocarcinoma of breast, NOS	44505312	ICDO3
Scirrhous adenocarcinoma of central portion of breast	44502696	ICDO3
Scirrhous adenocarcinoma of lower-inner quadrant of breast	44502224	ICDO3
Scirrhous adenocarcinoma of lower-outer quadrant of breast	44501788	ICDO3
Scirrhous adenocarcinoma of nipple	44500441	ICDO3
Scirrhous adenocarcinoma of overlapping lesion of breast	36534649	ICDO3
Scirrhous adenocarcinoma of upper-inner quadrant of breast	44503013	ICDO3
Scirrhous adenocarcinoma of upper-outer quadrant of breast	44502932	ICDO3
Scirrhous carcinoma of breast	4112073	SNOMED
Sebaceous carcinoma of axillary tail of breast	36554770	ICDO3
Sebaceous carcinoma of breast, NOS	36518732	ICDO3
Sebaceous carcinoma of central portion of breast	36537176	ICDO3
Sebaceous carcinoma of lower-inner quadrant of breast	36527956	ICDO3
Sebaceous carcinoma of lower-outer quadrant of breast	36534450	ICDO3

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Sebaceous carcinoma of nipple	36560055	ICDO3
Sebaceous carcinoma of overlapping lesion of breast	36555608	ICDO3
Sebaceous carcinoma of upper-inner quadrant of breast	36526572	ICDO3
Sebaceous carcinoma of upper-outer quadrant of breast	36517616	ICDO3
Secretory carcinoma of axillary tail of breast	36567251	ICDO3
Secretory carcinoma of breast, NOS	44502032	ICDO3
Secretory carcinoma of central portion of breast	36559168	ICDO3
Secretory carcinoma of lower-inner quadrant of breast	36535215	ICDO3
Secretory carcinoma of lower-outer quadrant of breast	44501091	ICDO3
Secretory carcinoma of overlapping lesion of breast	36535892	ICDO3
Secretory carcinoma of upper-inner quadrant of breast	44502448	ICDO3
Secretory carcinoma of upper-outer quadrant of breast	36533292	ICDO3
Signet ring cell carcinoma of axillary tail of breast	36541968	ICDO3
Signet ring cell carcinoma of breast, NOS	44501274	ICDO3
Signet ring cell carcinoma of central portion of breast	44500597	ICDO3
Signet ring cell carcinoma of lower-inner quadrant of breast	36525331	ICDO3
Signet ring cell carcinoma of lower-outer quadrant of breast	44499651	ICDO3
Signet ring cell carcinoma of overlapping lesion of breast	36555698	ICDO3
Signet ring cell carcinoma of upper-inner quadrant of breast	36553368	ICDO3
Signet ring cell carcinoma of upper-outer quadrant of breast	44500737	ICDO3
Small cell carcinoma, fusiform cell of axillary tail of breast	36534192	ICDO3
Small cell carcinoma, fusiform cell of breast, NOS	36519482	ICDO3
Small cell carcinoma, fusiform cell of central portion of breast	36517160	ICDO3
Small cell carcinoma, fusiform cell of lower-inner quadrant of breast	36544560	ICDO3
Small cell carcinoma, fusiform cell of lower-outer quadrant of breast	36556455	ICDO3
Small cell carcinoma, fusiform cell of nipple	36538093	ICDO3
Small cell carcinoma, fusiform cell of overlapping lesion of breast	36523967	ICDO3
Small cell carcinoma, fusiform cell of upper-inner quadrant of breast	36535115	ICDO3
Small cell carcinoma, fusiform cell of upper-outer quadrant of breast	36557767	ICDO3
Small cell carcinoma, NOS, of axillary tail of breast	36552490	ICDO3
Small cell carcinoma, NOS, of breast, NOS	44503003	ICDO3
Small cell carcinoma, NOS, of central portion of breast	44501831	ICDO3
Small cell carcinoma, NOS, of lower-inner quadrant of breast	36528242	ICDO3
Small cell carcinoma, NOS, of lower-outer quadrant of breast	36524153	ICDO3
Small cell carcinoma, NOS, of nipple	36546405	ICDO3
Small cell carcinoma, NOS, of overlapping lesion of breast	36551045	ICDO3

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Small cell carcinoma, NOS, of upper-inner quadrant of breast	44502571	ICDO3
Small cell carcinoma, NOS, of upper-outer quadrant of breast	44501304	ICDO3
Solid carcinoma, NOS, of axillary tail of breast	36538977	ICDO3
Solid carcinoma, NOS, of breast, NOS	36564142	ICDO3
Solid carcinoma, NOS, of central portion of breast	44501139	ICDO3
Solid carcinoma, NOS, of lower-inner quadrant of breast	44501636	ICDO3
Solid carcinoma, NOS, of lower-outer quadrant of breast	36520166	ICDO3
Solid carcinoma, NOS, of nipple	36522135	ICDO3
Solid carcinoma, NOS, of overlapping lesion of breast	36547174	ICDO3
Solid carcinoma, NOS, of upper-inner quadrant of breast	44500354	ICDO3
Solid carcinoma, NOS, of upper-outer quadrant of breast	44500787	ICDO3
Solid papillary carcinoma with invasion of axillary tail of breast	42512871	ICDO3
Solid papillary carcinoma with invasion of central portion of breast	42512675	ICDO3
Solid papillary carcinoma with invasion of lower-inner quadrant of breast	42511627	ICDO3
Solid papillary carcinoma with invasion of lower-outer quadrant of breast	42512323	ICDO3
Solid papillary carcinoma with invasion of nipple	42512881	ICDO3
Solid papillary carcinoma with invasion of overlapping lesion of breast	42511797	ICDO3
Solid papillary carcinoma with invasion of upper-inner quadrant of breast	42512476	ICDO3
Solid papillary carcinoma with invasion of upper-outer quadrant of breast	42512171	ICDO3
Solitary fibrous tumor, malignant of axillary tail of breast	36527665	ICDO3
Solitary fibrous tumor, malignant of breast, NOS	36530384	ICDO3
Solitary fibrous tumor, malignant of central portion of breast	36540725	ICDO3
Solitary fibrous tumor, malignant of lower-inner quadrant of breast	36567407	ICDO3
Solitary fibrous tumor, malignant of lower-outer quadrant of breast	36549234	ICDO3
Solitary fibrous tumor, malignant of overlapping lesion of breast	36565102	ICDO3
Solitary fibrous tumor, malignant of upper-inner quadrant of breast	36560753	ICDO3
Solitary fibrous tumor, malignant of upper-outer quadrant of breast	36540833	ICDO3
Spindle cell carcinoma, NOS, of axillary tail of breast	36542375	ICDO3
Spindle cell carcinoma, NOS, of breast, NOS	44503001	ICDO3
Spindle cell carcinoma, NOS, of central portion of breast	36556416	ICDO3
Spindle cell carcinoma, NOS, of lower-inner quadrant of breast	36553819	ICDO3
Spindle cell carcinoma, NOS, of lower-outer quadrant of breast	36549647	ICDO3
Spindle cell carcinoma, NOS, of nipple	36550807	ICDO3

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Spindle cell carcinoma, NOS, of overlapping lesion of breast	36532433	ICDO3
Spindle cell carcinoma, NOS, of upper-inner quadrant of breast	44500482	ICDO3
Spindle cell carcinoma, NOS, of upper-outer quadrant of breast	44499867	ICDO3
Squamous cell carcinoma with horn formation of axillary tail of breast	36517170	ICDO3
Squamous cell carcinoma with horn formation of breast, NOS	36560838	ICDO3
Squamous cell carcinoma with horn formation of central portion of breast	36550543	ICDO3
Squamous cell carcinoma with horn formation of lower-inner quadrant of breast	36523677	ICDO3
Squamous cell carcinoma with horn formation of lower-outer quadrant of breast	36535386	ICDO3
Squamous cell carcinoma with horn formation of nipple	36557277	ICDO3
Squamous cell carcinoma with horn formation of overlapping lesion of breast	36546640	ICDO3
Squamous cell carcinoma with horn formation of upper-inner quadrant of breast	36560767	ICDO3
Squamous cell carcinoma with horn formation of upper-outer quadrant of breast	36545094	ICDO3
Squamous cell carcinoma, adenoid of axillary tail of breast	36552210	ICDO3
Squamous cell carcinoma, adenoid of breast, NOS	36548304	ICDO3
Squamous cell carcinoma, adenoid of central portion of breast	36547817	ICDO3
Squamous cell carcinoma, adenoid of lower-inner quadrant of breast	36558743	ICDO3
Squamous cell carcinoma, adenoid of lower-outer quadrant of breast	36526932	ICDO3
Squamous cell carcinoma, adenoid of nipple	36552161	ICDO3
Squamous cell carcinoma, adenoid of overlapping lesion of breast	36557111	ICDO3
Squamous cell carcinoma, adenoid of upper-inner quadrant of breast	36564349	ICDO3
Squamous cell carcinoma, adenoid of upper-outer quadrant of breast	36554310	ICDO3
Squamous cell carcinoma, keratinizing, NOS, of axillary tail of breast	36530629	ICDO3
Squamous cell carcinoma, keratinizing, NOS, of breast, NOS	36554108	ICDO3
Squamous cell carcinoma, keratinizing, NOS, of central portion of breast	36539089	ICDO3
Squamous cell carcinoma, keratinizing, NOS, of lower-inner quadrant of breast	36565773	ICDO3
Squamous cell carcinoma, keratinizing, NOS, of lower-outer quadrant of breast	36550420	ICDO3
Squamous cell carcinoma, keratinizing, NOS, of nipple	36530435	ICDO3
Squamous cell carcinoma, keratinizing, NOS, of overlapping lesion of breast	36554415	ICDO3

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Squamous cell carcinoma, keratinizing, NOS, of upper-inner quadrant of breast	36546809	ICDO3
Squamous cell carcinoma, keratinizing, NOS, of upper-outer quadrant of breast	44502923	ICDO3
Squamous cell carcinoma, large cell, nonkeratinizing, NOS, of axillary tail of breast	36534399	ICDO3
Squamous cell carcinoma, large cell, nonkeratinizing, NOS, of breast, NOS	36535694	ICDO3
Squamous cell carcinoma, large cell, nonkeratinizing, NOS, of central portion of breast	36519042	ICDO3
Squamous cell carcinoma, large cell, nonkeratinizing, NOS, of lower-inner quadrant of breast	36565553	ICDO3
Squamous cell carcinoma, large cell, nonkeratinizing, NOS, of lower-outer quadrant of breast	36523366	ICDO3
Squamous cell carcinoma, large cell, nonkeratinizing, NOS, of nipple	36542432	ICDO3
Squamous cell carcinoma, large cell, nonkeratinizing, NOS, of overlapping lesion of breast	36560809	ICDO3
Squamous cell carcinoma, large cell, nonkeratinizing, NOS, of upper-inner quadrant of breast	36529597	ICDO3
Squamous cell carcinoma, large cell, nonkeratinizing, NOS, of upper-outer quadrant of breast	36539772	ICDO3
Squamous cell carcinoma, microinvasive of axillary tail of breast	36540907	ICDO3
Squamous cell carcinoma, microinvasive of breast, NOS	36520348	ICDO3
Squamous cell carcinoma, microinvasive of central portion of breast	36567613	ICDO3
Squamous cell carcinoma, microinvasive of lower-inner quadrant of breast	36562994	ICDO3
Squamous cell carcinoma, microinvasive of lower-outer quadrant of breast	36556882	ICDO3
Squamous cell carcinoma, microinvasive of nipple	36550519	ICDO3
Squamous cell carcinoma, microinvasive of overlapping lesion of breast	36561989	ICDO3
Squamous cell carcinoma, microinvasive of upper-inner quadrant of breast	36558311	ICDO3
Squamous cell carcinoma, microinvasive of upper-outer quadrant of breast	36531700	ICDO3
Squamous cell carcinoma, NOS, of axillary tail of breast	36554911	ICDO3
Squamous cell carcinoma, NOS, of breast, NOS	44500715	ICDO3
Squamous cell carcinoma, NOS, of central portion of breast	36563027	ICDO3
Squamous cell carcinoma, NOS, of lower-inner quadrant of breast	36553621	ICDO3
Squamous cell carcinoma, NOS, of lower-outer quadrant of breast	36564686	ICDO3
Squamous cell carcinoma, NOS, of nipple	36520200	ICDO3
Squamous cell carcinoma, NOS, of overlapping lesion of breast	36548174	ICDO3

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Squamous cell carcinoma, NOS, of upper-inner quadrant of breast	36517865	ICDO3
Squamous cell carcinoma, NOS, of upper-outer quadrant of breast	44503198	ICDO3
Squamous cell carcinoma, small cell, nonkeratinizing of axillary tail of breast	36525506	ICDO3
Squamous cell carcinoma, small cell, nonkeratinizing of breast, NOS	36524937	ICDO3
Squamous cell carcinoma, small cell, nonkeratinizing of central portion of breast	36564694	ICDO3
Squamous cell carcinoma, small cell, nonkeratinizing of lower-inner quadrant of breast	36533729	ICDO3
Squamous cell carcinoma, small cell, nonkeratinizing of lower-outer quadrant of breast	36566889	ICDO3
Squamous cell carcinoma, small cell, nonkeratinizing of nipple	36531652	ICDO3
Squamous cell carcinoma, small cell, nonkeratinizing of overlapping lesion of breast	36555428	ICDO3
Squamous cell carcinoma, small cell, nonkeratinizing of upper-inner quadrant of breast	36567249	ICDO3
Squamous cell carcinoma, small cell, nonkeratinizing of upper-outer quadrant of breast	36532972	ICDO3
Squamous cell carcinoma, spindle cell of axillary tail of breast	36553652	ICDO3
Squamous cell carcinoma, spindle cell of breast, NOS	44498946	ICDO3
Squamous cell carcinoma, spindle cell of central portion of breast	36519648	ICDO3
Squamous cell carcinoma, spindle cell of lower-inner quadrant of breast	36539982	ICDO3
Squamous cell carcinoma, spindle cell of lower-outer quadrant of breast	36524995	ICDO3
Squamous cell carcinoma, spindle cell of nipple	36552573	ICDO3
Squamous cell carcinoma, spindle cell of overlapping lesion of breast	36548535	ICDO3
Squamous cell carcinoma, spindle cell of upper-inner quadrant of breast	36551002	ICDO3
Squamous cell carcinoma, spindle cell of upper-outer quadrant of breast	36525217	ICDO3
Superficial spreading adenocarcinoma of axillary tail of breast	36539620	ICDO3
Superficial spreading adenocarcinoma of breast, NOS	36518133	ICDO3
Superficial spreading adenocarcinoma of central portion of breast	36542790	ICDO3
Superficial spreading adenocarcinoma of lower-inner quadrant of breast	36539880	ICDO3
Superficial spreading adenocarcinoma of lower-outer quadrant of breast	36526082	ICDO3
Superficial spreading adenocarcinoma of nipple	36546031	ICDO3
Superficial spreading adenocarcinoma of overlapping lesion of breast	36549507	ICDO3

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Superficial spreading adenocarcinoma of upper-inner quadrant of breast	36525619	ICDO3
Superficial spreading adenocarcinoma of upper-outer quadrant of breast	36546007	ICDO3
Trabecular adenocarcinoma of axillary tail of breast	36517575	ICDO3
Trabecular adenocarcinoma of breast, NOS	36542321	ICDO3
Trabecular adenocarcinoma of central portion of breast	36527381	ICDO3
Trabecular adenocarcinoma of lower-inner quadrant of breast	36538087	ICDO3
Trabecular adenocarcinoma of lower-outer quadrant of breast	36566305	ICDO3
Trabecular adenocarcinoma of nipple	36566310	ICDO3
Trabecular adenocarcinoma of overlapping lesion of breast	36537992	ICDO3
Trabecular adenocarcinoma of upper-inner quadrant of breast	36522979	ICDO3
Trabecular adenocarcinoma of upper-outer quadrant of breast	36545078	ICDO3
Triple-negative breast cancer	45768522	SNOMED
Tubular adenocarcinoma of axillary tail of breast	44500133	ICDO3
Tubular adenocarcinoma of breast, NOS	44501721	ICDO3
Tubular adenocarcinoma of central portion of breast	44499540	ICDO3
Tubular adenocarcinoma of lower-inner quadrant of breast	44502389	ICDO3
Tubular adenocarcinoma of lower-outer quadrant of breast	44501344	ICDO3
Tubular adenocarcinoma of nipple	44499805	ICDO3
Tubular adenocarcinoma of overlapping lesion of breast	36545747	ICDO3
Tubular adenocarcinoma of upper-inner quadrant of breast	44502022	ICDO3
Tubular adenocarcinoma of upper-outer quadrant of breast	44500352	ICDO3
Tumor cells, malignant of axillary tail of breast	36568345	ICDO3
Tumor cells, malignant of breast, NOS	36568261	ICDO3
Tumor cells, malignant of central portion of breast	36525225	ICDO3
Tumor cells, malignant of lower-inner quadrant of breast	36568241	ICDO3
Tumor cells, malignant of lower-outer quadrant of breast	36568105	ICDO3
Tumor cells, malignant of overlapping lesion of breast	36538058	ICDO3
Tumor cells, malignant of upper-inner quadrant of breast	36568186	ICDO3
Tumor cells, malignant of upper-outer quadrant of breast	36568134	ICDO3
Verrucous carcinoma, NOS, of axillary tail of breast	36533877	ICDO3
Verrucous carcinoma, NOS, of breast, NOS	36539011	ICDO3
Verrucous carcinoma, NOS, of central portion of breast	36525518	ICDO3
Verrucous carcinoma, NOS, of lower-inner quadrant of breast	36567953	ICDO3
Verrucous carcinoma, NOS, of lower-outer quadrant of breast	36523995	ICDO3
Verrucous carcinoma, NOS, of nipple	36523688	ICDO3

Concept name (Breast cancer)	Concept ID (including descendants)	Vocabulary
Verrucous carcinoma, NOS, of overlapping lesion of breast	36567489	ICDO3
Verrucous carcinoma, NOS, of upper-inner quadrant of breast	36549778	ICDO3
Verrucous carcinoma, NOS, of upper-outer quadrant of breast	36567316	ICDO3

NOS=Not otherwise specified.

Table S4. Preliminary list of covariates definitions.

Phenotype	Concept name	Concept ID (including descendants)	Vocabulary
Arrhythmia	Cardiac arrhythmia	44784217	SNOMED
	Ablation operation for arrhythmia	4050568	SNOMED
	Cardiac pacemaker procedure	4051938	SNOMED
	Ventricular tachycardia	4103295	SNOMED
	Atrial fibrillation	313217	SNOMED
	Atrial flutter	314665	SNOMED
Angina	Angina pectoris	321318	SNOMED
Myocardial infarction	Myocardial infarction	4329847	SNOMED
Outpatient visit	Outpatient visit	9202	Visit
Inpatient visit	Inpatient visit	9201	Visit
Emergency department visit	Emergency room and inpatient visit	262	Visit
	Emergency room visit	9203	Visit
Family history of breast cancer	Family history of breast cancer	4179963	SNOMED
Diabetes mellitus	Diabetes mellitus	201820	SNOMED
Obesity and Overweight	Overweight	437525	SNOMED
	Obese	4215968	SNOMED
Coronary artery disease	Obliterative coronary artery disease	4168972	SNOMED
	Multi vessel coronary artery disease	4155007	SNOMED
	Coronary artery disease due to type 2 diabetes mellitus	37309630	SNOMED
Heart failure	Impaired left ventricular function	4173819	SNOMED
	Heart failure confirmed	4215689	SNOMED
	Heart failure	316139	SNOMED
	Chronic heart failure	444031	SNOMED
	Cardiac volume overload	36684850	SNOMED
	Acute diastolic heart failure	40481042	SNOMED
Chronic obstructive pulmonary disease	Chronic obstructive pulmonary disease	255573	SNOMED
Female infertility	Female infertility	201909	SNOMED

Phenotype	Concept name	Concept ID (including descendants)	Vocabulary
Endometriosis	Endometriosis	433527	SNOMED
Polycystic ovary syndrome	Polycystic ovary syndrome	40443308	SNOMED
Hysterectomy	Hysterectomy	4127886	SNOMED
Bilateral oophorectomy	Laparoscopic bilateral oophorectomy	43531553	SNOMED
Osteoporosis	Osteoporosis	80502	SNOMED
Ovarian cancer	Primary malignant neoplasm of ovary	200051	SNOMED
Endometrial cancer	Primary malignant neoplasm of endometrium	4247238	SNOMED
Any cancers except breast and non-melanoma skin cancer	Neoplasm of hematopoietic cell type	4189640	SNOMED
	Malignant neoplastic disease	443392	SNOMED
	Carcinoma in situ	433435	SNOMED

ANNEX V. ENCePP checklist for study protocols

ENCePP Checklist for Study Protocols (Revision 4)

Study title: DARWIN EU® - Assessing the feasibility of conducting a causal study on the potential association between beta-blockers and breast cancer

EU PAS Register® number: EUPAS1000001013
Study reference number (if applicable): P4-C1-024

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	8.5
1.1.2 End of data collection[2]	☒	☐	☐	8.5
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:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6
2.1.2 The objective(s) of the study?	☒	☐	☐	7
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.3
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* 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.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.4
3.3	Does the protocol specify measures of occurrence? (e.g. rate, risk, prevalence)	☒	☐	☐	8.8
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
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:

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

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.3
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	8.3

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.6.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.6.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	8.6
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:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.4, 8.6
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.4, 8.6
9.1.3 Covariates and other characteristics?	☒	☐	☐	8.4, 8.6
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.4, 8.6
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.4, 8.6
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	8.6
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.6
9.3.3 Covariates and other characteristics?	☒	☐	☐	8.6
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	ANNEX I

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.3
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	8.7
10.3 Are descriptive analyses included?	☒	☐	☐	8.8.3

Section 10: Analysis plan	**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?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

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

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9
12.1.2 Information bias?	☒	☐	☐	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	8.7

Comments:

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

Section 13: Ethical/data protection issues	**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 IV

Comments:

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

Comments:

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

Comments:

Name of the main author of the protocol: Yuqing Hu

Date: 29/05/2026

Signature: 

ANNEX VI. 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.