Study Protocol

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DARWIN EU® - Prevalence of hypertrophic cardiomyopathy (HCM) and obstructive hypertrophic cardiomyopathy (oHCM) in six European countries

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Version 3.0

Contents

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Objectives	The **general objective** of this study is to characterise hypertrophic cardiomyopathy (HCM) and obstructive HCM (oHCM) in Europe in terms of prevalence, demographics, comorbidities, clinical measurements, and treatment. The **specific objectives** of this study are: 1. To estimate the annual prevalence of HCM and oHCM in Europe, overall and stratified by age and sex. 2. To characterise patients newly diagnosed with HCM and oHCM in terms of demographics, HCM-related clinical measurements and comorbidities existing before, at the time of, and after a first HCM diagnosis. 3. To describe the frequency of selected treatments, including medications, medical devices, and procedures, before, at the time of, and after first diagnosis.
Country(ies) of study	Croatia, Denmark, Germany, Norway, Spain, United Kingdom
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LIST OF ABBREVIATIONS

Acronyms/ terms	Description
AF	Atrial Fibrillation
CARDIA	Coronary Artery Risk Development in Young Adults
CDM	Common Data Model
CI	Confidence Interval
CPRD	Clinical Practice Research Datalink
DARWIN EU®	Data Analysis and Real World Interrogation Network
DK-DHR	Danish Data Health Registries
DRE	Digital Research Environment
EHR	Electronic Health Records
EMA	European Medicines Agency
EU	European Union
FDA	U.S. Food and Drug Administration
HCM	Hypertrophic cardiomyopathy
HF	Heart Failure
InGef	InGef Research Database
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
LVOT	Left Ventricular Outflow Tract
NAJS	National Public Health Information System
NLHR	Norwegian Linked Health Registry data
oHCM	Obstructive hypertrophic cardiomyopathy
OHDSI	Observational Health Data Sciences and Informatics
UK	United Kingdom
U.S.	United States
SCD	Sudden Cardiac Death
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
SNOMED	Systematized Nomenclature of Medicine

1. TITLE

DARWIN EU® - Prevalence of hypertrophic cardiomyopathy (HCM) and obstructive hypertrophic cardiomyopathy (oHCM) in six European countries

2. RESPONSIBLE PARTIES – STUDY TEAM

Study team role	Names	Organisation
Study Project Manager/Principal Investigator	Albert Prats-Uribe Anna Saura-Lazaro	University of Oxford
Data Scientist	Edward Burn Marta Alcalde-Herraiz	University of Oxford
Epidemiologist	Albert Prats-Uribe Anna Saura-Lazaro	University of Oxford
Clinical Domain Expert	Albert Prats-Uribe Anna Saura-Lazaro	University of Oxford
Data Partner*	**Names**	**Organisation**
CPRD GOLD	Antonella Delmestri Hezekiah Omulo	University of Oxford
DK-DHR	Claus Møldrup Elvira Bräuner Susanne Bruun Monika Roberta Korcinska Handest	Danish Medicines Agency
InGef	Josephine Jacob Raeleesha Norris Annika Vivirito Alexander Harms	Institut für angewandte Gesundheitsforschung Berlin GmbH
NAJS	Jakov Vuković, Ivan Pristaš, Anamaria Jurčević Marko Čavlina, Antea Jezidžić De Pero Ivanko	Croatian Institute of Public Health
NLHR	Hedvig Nordeng Nhung Trinh Saeed Hayati Maren Mackenzie Olson	University of Oslo
SIDIAP	Talita Duarte Salles Anna Palomar Augustina Giuliodori Picco	IDIAPJGol

*Data partners' role is only to execute code at their data source, review and approve their results. They do not have an investigator role. Data analysts/programmers do not have an investigator role and thus declaration of interests (DOI) for them is not needed.

3. ABSTRACT

Title

DARWIN EU® – Prevalence of hypertrophic cardiomyopathy (HCM) and obstructive hypertrophic cardiomyopathy (oHCM) in six European countries

Rationale and background

Hypertrophic cardiomyopathy (HCM) is an inherited heart disease characterised by an increased wall thickness or mass of the left ventricular wall, with a broad clinical spectrum. HCM is classified into two types based on the presence or absence of left ventricular outflow tract (LVOT) obstruction, a distinction that influences patient management. The obstructive form of HCM (oHCM) is observed in approximately 66% of patients.

The prevalence of HCM was initially estimated at 1 in 500 individuals (0.2%) in a U.S. study. Further U.S. and European studies suggest a lower prevalence of clinically diagnosed HCM. In addition, it has been suggested that some individuals may live normal lifespans undiagnosed because the absent of significant symptoms or major interventions.

Estimating the prevalence of HCM is problematic due to several factors, including the relative rarity of the condition, the high proportion of asymptomatic patients, and diagnostic challenges. Large-scale epidemiological studies on the demographics and morbidity burden of HCM in Europe are scarce.

This study aims to estimate the prevalence of HCM and oHCM across several European countries and different healthcare settings.

Research question and objectives

The general objective of this study is to characterise hypertrophic cardiomyopathy (HCM) and obstructive HCM (oHCM) in Europe in terms of prevalence, demographics, clinical measurements, comorbidities, and treatment.

The specific objectives of this study are:

1. To estimate the annual prevalence of clinically apparent HCM and oHCM in Europe, overall and stratified by age and sex.

2. To characterise patients newly diagnosed with HCM and oHCM in terms of demographics, selected HCM-related clinical measurements, and comorbidities existing before, at the time of, and after a first HCM diagnosis.

3. To describe the frequency of selected treatments, including medications, medical devices, and procedures before, at the time of, and after a first HCM diagnosis.

Methods

This is a retrospective cohort study including six data sources from six European countries: two primary care data sources (Clinical Practice Research Datalink (CPRD) GOLD, United Kingdom (UK) and Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain), two Nordic nationwide registries (Danish Data Health Registries (DK-DHR), Denmark, and Norwegian Linked Health Registry data (NLHR), Norway), and two nationwide claims databases (InGef Research Database (InGef), Germany, and Croatian National Public Health Information System (NAJS), Croatia).

The study population will include all individuals with a first diagnosis of HCM or oHCM identified in the database between 01 January 2010 (or from when accurate data became available in InGef and NAJS, i.e., 2015 and 2017, respectively), and end of available data in each database.

No sample size has been calculated as this is a descriptive study which will not test a specific hypothesis. In addition, we will use already collected available date to estimate the prevalence of HCM and oHCM. Thus, the sample size will be driven by the availability of patients with conditions of interest within each database. Based on a preliminary feasibility assessment the expected number of HCM diagnosis records across all the included databases for this study will be approximately 80,500. For oHCM, the expected number of diagnosis records is approximately 21,400.

For objective 1, we will estimate annual period prevalence from January 1st to December 31st, calculated as the number of HCM and oHCM diagnoses divided by the total active population. Estimates will be stratified by age and sex. For objectives 2 and 3, patient-level characterization will be conducted overall and by grouping patients diagnosed before 2020 and those diagnosed in 2020 or later. The index date is the first HCM or oHCM diagnosis. Demographics, clinical measurements, and comorbidities will be assessed across various time intervals before and after the index date. For objective 3, selected treatments will be assessed across various time intervals before and after the index date as well.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Study milestones and deliverables	Planned dates
Draft Study Protocol	November 2024
Final Study Protocol	December 2024
Creation of Analytical code	December 2024
Execution of Analytical Code on the data	January 2025
Draft Study Report	February 2025
Final Study Report	March 2025

6. RATIONALE AND BACKGROUND

Definition and aetiology

Hypertrophic cardiomyopathy (HCM) is an inherited heart disease characterised by an increased wall thickness or mass of the left ventricular wall, with a broad clinical spectrum. The diagnosis of HCM requires the presence of hypertrophy of the left ventricle (LV) in the absence of any other cardiac, metabolic, or systemic disease (e.g., systemic hypertension) that could explain the observed hypertrophy (1).

In up to 60% of adolescents and adults with HCM, the disease follows an autosomal dominant inheritance pattern due to mutations in genes encoding cardiac sarcomere proteins (2). Approximately 20% of HCM patients have a family history of sudden cardiac death (SCD), and 50% have evidence of familial disease (2). It is also important to recognise that other conditions can mimic genetic forms of HCM, including mitochondrial diseases, Danon disease, Friedreich's ataxia, Leopard syndrome, Noonan syndrome, Anderson–Fabry disease, and amyloidosis (3).

HCM is classified into two types based on the presence or absence of left ventricular outflow tract (LVOT) obstruction, a distinction that influences patient management. The obstructive form of HCM (oHCM) is observed in approximately 66% of patients, while the non-obstructive form accounts for around 33% (4,5). oHCM is associated with a higher likelihood of developing symptoms compared to non-obstructive HCM (6,7).

Epidemiology

HCM is the most common inherited genetic cardiomyopathy and a significant cause of cardiovascular morbidity and mortality across all age groups. Despite this, the absolute number of individuals diagnosed with HCM remains low, suggesting that the condition is likely underdiagnosed (8). The prevalence of HCM in the general population was initially estimated to be approximately 1 in 500 individuals (0.2%), based on

the CARDIA (Coronary Artery Risk Development in Young Adults) cohort study, which used standard echocardiography in 4,111 unrelated individuals 23 to 35 years of age from four urban areas in the United States (US) (9). The participants were randomly selected from community-based urban centres, where many affected individuals were asymptomatic and undiagnosed. This aligns with the observation that the majority of HCM patients are asymptomatic and remain diagnosed during their lifetime. Subsequent studies, with varied designs and cohort characteristics, have supported this prevalence estimate across different age groups and ethnicities (10–14).

However, the population-level prevalence estimate contrasts sharply with an analysis of U.S. claims data, which reported a much lower prevalence of clinically diagnosed HCM, at approximately 1 in 3,000 (0.03%)(15). Similarly, a study conducted in Germany examining trends in HCM prevalence from 2011 to 2015 found a rate of 0.07% in 2015 (3), and studies conducted in the United Kingdom (UK) and Sweden reported rates of 3.5 per 10,000 and 0.04% respectively, among the general population (16,17). These discrepancies might be partially explained by the challenges in diagnosing this condition. It has been suggested that some individuals may live normal lifespans undiagnosed because the absence of significant symptoms or major interventions. As a result, the prevalence of clinically apparent HCM is much lower.

In terms of sociodemographic characteristics, the German study showed that HCM prevalence increased gradually with age from 7.4/100,000 persons (95% confidence interval (CI) 5.2–10.1) in those aged 0–9 years, to 298.7/100,000 persons (95% CI 276.4–322.4) in individuals over 80 years (3). In all age groups, men had higher prevalence than women, with significant differences in patients over 30 years of age. A similar trend was observed in a nationwide retrospective cohort study in Denmark, which included 3,856 patients diagnosed with HCM between 2005 and 2018 (18). The median age at diagnosis was 68 years (interquartile range 56–78) with the majority of patients being male (53%). However, females were older (72 years vs. 63 years) and more likely to have oHCM (54% vs. 38%). Additionally, a study conducted in the UK, which aimed to estimate the population-diagnosed prevalence of cardiomyopathies between 2010 and 2018, found that HCM was twice as common among men (17). Lastly, in children, HCM accounts for approximately 40% of paediatric cases of cardiomyopathy, making it the second most common cardiomyopathy after dilated cardiomyopathy (19).

Comorbidities and disease progression

Patients with HCM have an increased risk of cardiovascular complications, including atrial fibrillation (AF), stroke, heart failure (HF), and SCD (1,20,21). Reported rates of AF varied widely, ranging from 4% in newly diagnosed patients to 33% in hospitalised patients. Managing AF in HCM patients can be challenging, as symptoms and haemodynamic changes are often poorly tolerated. Additionally, HCM patients with AF have a higher risk of thromboembolic events compared to AF patients without HCM (1,20,22). Reported stroke rates range from 4% in a multinational registry study of patients who received care at an HCM specialty centre to 9.2% in hospitalised patients with HCM and AF (2). The rate of HF-related events ranges from 15% in a multinational registry in pregnant women to 43% in a natural history study in patients at a specialty centre (2). A systematic literature review of studies published between 1996 through 2016, examining the prevalence of HF among children and adolescents, identified one study reporting a 13.5% prevalence rate for congestive HF in paediatric patients with HCM (23).

In the nationwide retrospective cohort study conducted in Denmark, which assessed temporal trends in patient characteristics, there was a significant decline in the prevalence of HF (from 20% in 2005 to 12% in 2018, $p<0.001$) and ischaemic heart disease (from 31% in 2005 to 16% in 2019, $p\leq0.001$) (18). However, the prevalence of AF and stroke remained high and unchanged throughout the study period. Notably, the rate of hospitalisations decreased over time (from 64% in 2005 to 46% in 2016, $p<0.001$), while the rate of outpatient follow-up increased (from 81% in 2005 to 87% in 2016, $p=0.003$) (18).

Clinical management and treatment

The primary aim of pharmacological therapy in HCM is to control symptoms, improve exercise capacity, reduce, or eliminate dynamic intraventricular gradients, treat LV dysfunction and HF, manage AF and ventricular arrhythmias, and prevent cardioembolic events (24).

Until 2022, there were no targeted or disease-modifying treatments specifically approved for HCM. Pharmacotherapies for symptomatic relief typically include β-blockers as first-line treatment, titrated to the maximally tolerated dose, followed by non-dihydropyridine calcium-channel blockers (e.g., diltiazem or verapamil) or disopyramide. Surgical interventions are available for patients with the most severe form of oHCM and include alcohol septal ablation and septal myectomy, which can be effective in reducing obstruction and improving outflow of the LV, but do not address the underlying myocardial disease. Additionally, medical device implants such as implantable cardioverter defibrillators and pacemakers may be used to prevent oHCM-related SCD. However, these are invasive procedures requiring specialised clinical settings and may not be accessible to all patients.

In 2022, mavacamten, the first targeted treatment for symptomatic oHCM, was approved in the U.S. Mavacamten is a cardiac myosin inhibitor that works by normalising cardiac contractility, reducing dynamic LVOT obstruction, and improving cardiac filling pressures. The U.S. Food and Drug Administration (FDA) granted initial approval for its use in adults with symptomatic oHCM (25). In 2023, the European Medicines Agency (EMA) also approved mavacamten for use in Europe (26).

Justification of the study

Estimating the prevalence of HCM is problematic due to several factors, including the relative rarity of the condition, the high proportion of asymptomatic patients, and diagnostic challenges as it can be easily mistaken for other conditions presenting with hypertrophy of the LV (18). Furthermore, fragmentation across healthcare databases can hinder accurate estimation, as patient follow-up may be incomplete. For example, diagnosis might occur in primary healthcare or after a hospitalization due to a complication. As a result, large-scale epidemiological studies on the demographics and morbidity burden of HCM in Europe are scarce, with many existing studies relying solely on inpatient records that do not capture the full extent of the disease burden. Additionally, the Cardiomyopathy Registry of the EURObservational Research Programme is a prospective registry study that reports on baseline data and contemporary management of adult patients with cardiomyopathies, however the design did not allow to estimate population prevalence of specific phenotypes (27). This is because it was not set as a nationwide registry and therefore it has information only on cases but lack of a population denominator.

This study aims to address these gaps by estimating the prevalence of HCM and oHCM on a large scale across several European countries. In addition, it will provide valuable insights into the characteristics of patients with HCM, including demographics, comorbidities, and treatment regimens. This approach will contribute to a more accurate understanding of the population-level prevalence of HCM in Europe, which is essential for improving diagnosis and management across diverse populations.

7. RESEARCH QUESTION AND OBJECTIVES

The general objective of this study is to characterise hypertrophic cardiomyopathy (HCM) and obstructive HCM (oHCM) in Europe in terms of prevalence, demographics, clinical measurements, comorbidities, and treatment.

The specific objectives of this study are:

1. To estimate the annual prevalence of clinically apparent HCM and oHCM in Europe, overall and

stratified by age and sex.

2. To characterise patients newly diagnosed with HCM and oHCM in terms of demographics, selected HCM-related clinical measurements, and comorbidities existing before, at the time of, and after the first HCM diagnosis.

3. To describe the frequency of selected treatments, including medications, medical devices, and procedures before, at the time of, and after the first HCM diagnosis.

All results will be reported overall and stratified by age and sex for each data source.

Table 1. Primary and secondary research questions and objective.

A. Primary research question and objective.

Objective:	1. To estimate the annual prevalence of clinically apparent HCM and oHCM in Europe, overall and stratified by age and sex. 2. To characterise patients newly diagnosed with HCM and oHCM in terms of demographics, selected HCM-related clinical measurements, and comorbidities existing before, at the time of, and after the first HCM diagnosis. 3. To describe the frequency of selected treatments, including medications, medical devices, and procedures before, at the time of, and after the first HCM diagnosis.
Hypothesis:	N/A
Population *(mention key inclusion-exclusion criteria):*	General population cohort: All individuals meeting eligibility criteria (at least 365 days of prior medical history available) and present in the database within the study period. Newly diagnosed HCM and oHCM cohorts: All individuals with a first diagnosis of HCM or oHCM identified in the database during the study period and with at least 365 days of prior medical history available before the index date (i.e., diagnosis date).
Exposure:	N/A
Comparator:	N/A
Outcome:	Diagnosis of HCM and oHCM will be identified through the diagnosis codes defined by Systematized Nomenclature of Medicine (SNOMED).
Time *(when follow up begins and ends):*	Study period starts on 01/01/2010 or whenever accurate data is available in the database (i.e., 2015 for InGef, and 2017 for NAJS), until the end of the available data in each database. For all objectives, follow-up will start on the date of first HCM or oHCM diagnosis and continue until the earliest of the following: 1)

	loss to follow-up, 2) date of death, or 3) end of observation period (the most recent data available) in the database.
Setting:	The study will use routinely collected health data from six nationwide or regional databases in 6 European countries (Croatia, Germany, Denmark, Spain, Norway, United Kingdom). Inpatient, outpatient hospital setting and primary care setting will be used for the study.
Main measure of effect:	Prevalence rate.

8. RESEARCH METHODS

8.1 Study type and study design

The study will consist of a retrospective cohort design including patients with a first diagnosis of HCM or oHCM. We will perform **a population-level descriptive epidemiology,** and a **patient-level characterisation** study classified as "off-the-shelf" and as described in the DARWIN EU® Complete Catalogue of Standard Data Analyses.

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

Study type	Study design	Study classification
Population-level descriptive epidemiology	Population-level cohort	Off the shelf
Patient-level characterisation	Cohort analysis	Off the shelf

8.2 Study setting and data sources

This study will be conducted using routinely collected health data from six databases in 6 European countries. All databases were previously mapped to the OMOP CDM.

Data sources:

1. Clinical Practice Research Datalink (CPRD) GOLD, United Kingdom (UK)
2. Danish Data Health Registries (DK-DHR), Denmark
3. InGef Research Database (InGef), Germany
4. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
5. Croatian National Public Health Information System (NAJS), Croatia
6. Norwegian Linked Health Registry data (NLHR), Norway

We selected six out of the 28 databases onboarded in DARWIN EU® in 2024. The selection of databases for this study was performed based on data reliability and relevance for the proposed research question. The selected databases fulfil the criteria required for a population and patient-level characterisation study, while covering different settings and regions of Europe. Detailed information on the selected data sources and their ability to answer the study research questions are described in **Table 3.**

Table 3. Description of the selected data sources.

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Feasibility count of HCM	Data lock for the last update
UK	CPRD GOLD	The database has information on HCM diagnosis and treatments done in primary care or feedbacked to the GP from the specialists. The denominator is suitable for population rates as it includes all people registered in the GP practice.	Primary care	EHR	2.92 million	7,800	17/10/2024
DK	DK-DHR	The database has information on HCM diagnosis performed in hospitals and specialist offices and treatments administered in hospital. The denominator is suitable for population rates as it includes the entire population.	Community pharmacists, secondary care – specialists, hospital inpatient care	Registries	5.96 million	13,700	15/05/2014
DE	InGef	The database has information on HCM diagnosis and treatments done in primary care or hospital. The denominator is suitable for population rates as it includes the entire population insured.	Primary care, community pharmacists, primary care specialists, secondary care-specialists, hospital inpatient care	Claims	7.6 million	12,400	17/06/2024
CR	NAJS	The database has information on HCM diagnosis and treatments performed in primary care or hospital. The denominator is suitable for population rates as it includes population insured.	Primary care, secondary care-specialists, hospital inpatient care	Claims	2.68 million	10,700	07/08/2024
NO	NLHR	The database has information on HCM diagnosis performed in hospitals and specialist offices and treatments administered in hospital Denominator is suitable for population rates as it includes all population.	Primary care, primary care specialists, secondary care-specialists, hospital inpatient care	Registries	7.34 million	12,500	18/01/2024
ES	SIDIAP	data on HCM diagnosis performed in primary care or inpatient and primary care treatments. Denominator is suitable for population rates as it includes all people registered in the GP practice.	Primary care with hospital linkage	EHR	5.95 million	23,400	20/03/2023

CR = Croatia, DE = Germany, DK = Denmark, ES = Spain, NO = Norway, UK = United Kingdom, CPRD = Clinical Practice Research Datalink, DK-DHR = Danish Data Health Registries, InGef = InGef Research Database CPRD, NAJS = Croatian National Public Health Information System, NLHR = Norwegian Linked Health Registry data, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària

Clinical Practice Research Datalink GOLD, United Kingdom

The Clinical Practice Research Datalink (CPRD) is a governmental, not-for-profit research service, jointly funded by the National Institute for Health and Care Research and the Medicines and Healthcare products Regulatory Agency, a part of the Department of Health, United Kingdom (UK) (https://cprd.com). CPRD GOLD (28) comprises computerized records of all clinical and referral events in primary care in addition to comprehensive demographic information and medication prescription data in a sample of UK patients (predominantly from Scotland (52% of practices) and Wales (28% of practices). The prescription records include information on the type of product, date of prescription, strength, dosage, quantity, and route of administration. Data from contributing practices are collected and processed into research databases. Quality checks on patient and practice level are applied during the initial processing. Data are available for 21 million patients, including 3.1 million currently registered patients (29). Access to CPRD GOLD data requires approval via the Research Data Governance Process.

Danish Data Health Registries (DK-DHR), Denmark

Danish health data is collected, stored, and managed in national health registers at the Danish Health Data Authority and covers the entire population which makes it possible to study the development of diseases and their treatment over time. There are no gaps in terms of gender, age, and geography in Danish health data due to mandatory reporting on all patients from cradle to grave, in all hospitals and medical clinics. Personal identification numbers enable linking of data across registers, so we have data on all Danes throughout their lives, regardless of whether they have moved around the country. High data quality due to standardization, digitization and documentation means that Danish health data is not based on interpretation. The Danish Health Data Authority is responsible for the national health registers and for maintaining and developing standards and classifications in the Danish healthcare system. Legislation ensures balance between personal data protection and use. In the present data base, we have access to the following registries for the entire Danish population of 5.9 million persons from 1.1.1995: The central Person Registry (CPR), The National Patient Registry (LPR), The Register of Pharmaceutical Sales (LSR), The National Cancer Register (CAR), The Cause of Death registry (DAR), The Clinical Laboratory Information Register (LAB), COVID-19 test and vaccination Registries (SSI-OVD, SSI-DDV), The complete Vaccination registry (DDV_all).

Specific limitations for this study: This database does not include information from primary care, which may lead to underreporting of chronic diseases typically managed by general practitioners. Additionally, measurements of LVOT and left ventricular ejection fraction (LVEF) may not be consistently captured in the current database.

InGef Research Database (InGef), Germany

The InGef database comprises anonymized longitudinal claims data of about ten million individuals across more than 70 statutory health insurance providers (SHIs) throughout Germany. Data are longitudinally linked over a period of currently ten years. Patients can be traced across health care sectors. All patient-level and provider-level data in the InGef research database are anonymised to comply with German data protection regulations and German federal law. German SHI claims data available in the InGef database includes information on demographics (year of birth, gender, death date if applicable, region of residence on administrative district level); hospitalizations; outpatient services (diagnoses, treatments; specialities of physicians); dispensing of drugs; dispensing of remedies and aids; and sick leave and sickness allowance times. In addition, costs or cost estimates from SHI perspective are available for all important cost elements. All diagnoses in Germany are coded using the International Classification of Diseases, version 10 in the German Modification (ICD-10-GM). The persistence (membership over time) is rather high in the InGef database: During a time period of 5 years (2009 to 2013), 70.6% of insurance members survived and remained insured with the same SHI without any gap in their observational time. Persons leaving one of the

participating SHIs and entering another participating SHI, can be linked during yearly database consistency updates, and are thus not lost over time. The InGef database is dynamic in nature, i.e. claims data are updated in an ongoing process and new SHIs may join or leave the database.

Specific limitations for this study: This database includes data from 2015 to 2023, which does not fully cover the intended study period (see section 8.3). Additionally, there is no standard mapping for ambulatory procedures in Germany, making it challenging to identify procedures such as LVOT and LVEF measurements. Procedures like alcohol ablation and septostomy are coded within the German OPS system but are not directly mapped to standard OMOP concepts. To improve the capture of these variables, a manual mapping review will be performed before the study begins. Furthermore, outpatient diagnoses are recorded quarterly rather than with exact dates (e.g., all diagnoses between 01.01.2020 and 31.03.2020 are documented as occurring on 31.03.2020). To avoid potential misclassification of the index date, this study will consider only inpatient diagnoses. However, this approach may lead to underreporting of chronic HCM typically managed by general practitioners.

Croatian National Public Health Information System (NAJS), Croatia

The National Public Health Information System (Nacionalni javnozdravstveni informacijski sustav - NAJS) is an organised system of information services by Croatian Institute of Public Health (CIPH). NAJS enables data collecting, processing, recording, managing, and storing of health-related data from health care providers as well as production and management of health information. NAJS contains medical and public health data collected and stored in health registries and other health data collections including cancer registry, mortality, work injuries, occupational diseases, communicable and non-communicable diseases, health events, disabilities, psychosis and suicide, diabetes, drug abuse and others. NAJS will have their IRB approval by early to mid-January.

Specific limitations for this study: This database contains the most reliable data only from 2017 onwards, which does not fully cover the intended study period (see section 8.3). Additionally, there is insufficient data to adequately capture LVOT and LVEF measurements.

Norwegian Linked Health Registry data (NLHR), Norway

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. 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. We harmonized data from the following registries: the Medical Birth Registry of Norway (MBRN), the 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). Linkage between the registries was facilitated using project-specific person ID generated from unique personal identification assigned at birth or immigration for all legal residents in Norway. In brief: MBRN stores information about the pregnancy, the mother, father, and child. NPR records diagnosis in secondary care (e.g., hospital). KUHR contains information about diagnosis and contact in primary care (e.g, GPs, and outpatient specialists) – to be included in third release. NorPD recorded all medications dispensed outside of hospitals. MSIS collects test results of communicable diseases (e.g., Sars-Cov-2). SYSVAK recorded vaccinations. The current data cut only has data from patients that were present in the database from 2015 to 2018.

Information System for Research in Primary Care (SIDIAP), Spain

SIDIAP is collected from electronic health records (EHR) of patients receiving primary care delivered through Primary Care Teams, consisting of GPs, nurses, and non-clinical staff (6). The Catalan Health

Institute manages 328 out of 370 such Primary Care Teams with a coverage of 5.8M patients, out of 7.8M people in the Catalan population (74%). The database started to collect data in 2006. The mean follow-up is 15 years. The observation period for a patient can be the start of the database (2006), or when a person is assigned to a Catalan Health Institute primary care centre. Date of exit can be when a person is transferred-out to a primary care centre that does not pertain to the Catalan Health Institute, or date of death, or date of end of follow-up in the database. Drug information is available from prescriptions and from dispensing records in pharmacies.. Studies using SIDIAP data require previous approval by both a Scientific and an Ethics Committee. SIDIAP will have their IRB approval by mid to late January.

Specific limitations for this study: Drugs not prescribed in the GP setting might be underreported; and disease diagnoses made at specialist care settings are not included.

8.3 Study period

The study period will cover from 01/01/2010, or from when accurate data becomes available in each database (i.e., 2015 for InGef, and 2017 for NAJS), until the end of available data in each of the data sources (see **Table 4**).

Table 4. Study period by database.

Database	Start date	End date
CPRD GOLD	01/01/2010	17/10/2024
DK-DHR	01/01/2010	15/05/2024
InGef	01/01/2015	17/06/2024
NAJS	01/01/2017	07/08/2024
NLHR	01/01/2010	18/01/2024
SIDIAP	01/01/2010	20/03/2023

8.4 Follow-up

For all objectives, follow-up will start on the date of first HCM or oHCM diagnosis (i.e., **index date**) and continue until the earliest of the following: 1) loss to follow-up, 2) date of death, or 3) end of observation period (the most recent data available) in the database .

8.5 Study population with inclusion and exclusion criteria

The study population will include all individuals with a first diagnosis of HCM or oHCM (i.e., **index date**) identified in the database during the study period and with at least 365 days of medical history. The index dates are defined in **Figure 1**.

The following eligibility criteria will be applied for all study objectives (see **Figure 1**, **Table 5**, and **Table 6**):

General population cohort

Inclusion criteria:

- Age ≥18 years.

- Present in the database within the study period.

- At least 365 days of prior medical history available before contributing follow-up time in the study.

Newly diagnosed HCM or oHCM cohort

Inclusion criteria:

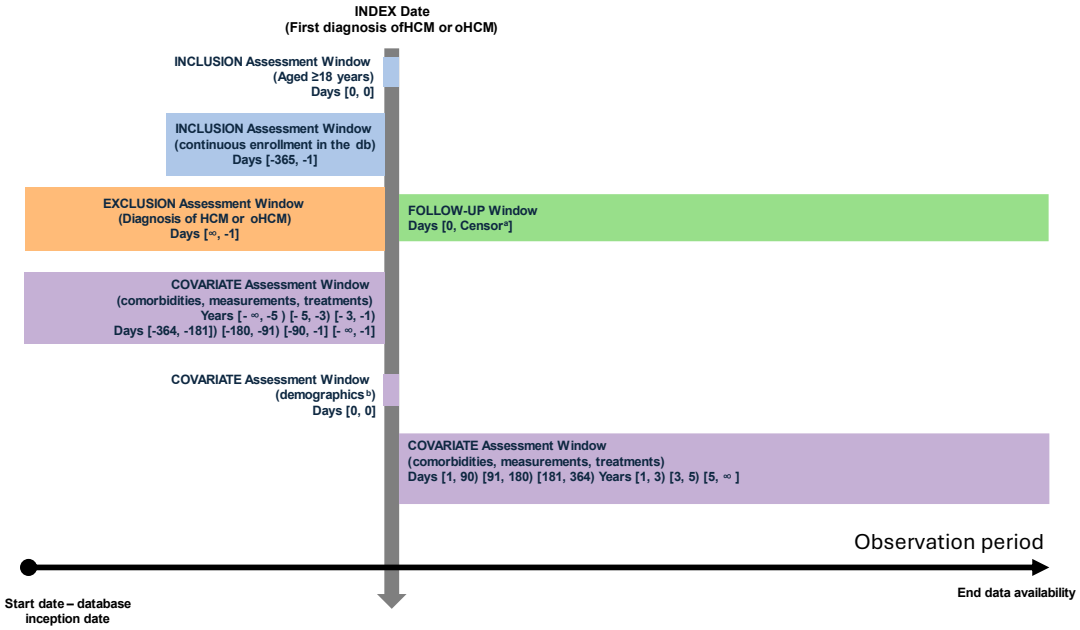
- Age ≥18 years.

- First diagnosis of HCM or oHCM identified in the database during patient selection period.

- At least 365 days of prior history available before date of first HCM or oHCM diagnosis.

Exclusion criteria:

-Any diagnosis of HCM or oHCM prior to index date.



Diagnosis based cohort

a: follow-up until the earliest of loss to follow-up, end of data availability, or death

Figure 1. Study design diagram.

Table 5. Operational definitions of inclusion criteria.

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Applied to study populations:
Age ≥18 years	Study participants will be required to be adults at index date	After index date is determined	[0,0]	IP, OP, OT	All adult individuals within selected databases
Prior database history of 365 days	Study participants will be required to have 365 days of prior history observed before contributing observation time	After index date is determined	[-365, -1]	IP, OP, OT	All study participants with first HCM or oHCM diagnosis

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

Table 6. Operational definitions of exclusion criteria.

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Applied to study populations:
Any prior diagnosis of HCM or oHCM	Study participants will be required not to have any diagnosis of HCM or oHCM prior to the index date	After index date is determined and inclusion criteria are applied	Any time before index date	IP, OP, OT	All study participants with first HCM or oHCM diagnosis

[1] IP = inpatient, OP = outpatient, OT = other

8.6 Variables

8.6.2 Main condition of interest

For objective 1, the condition of interest will be defined as the first recorded diagnosis of HCM and oHCM, which will be identified through the diagnosis codes defined by SNOMED (**Appendix 1, Table 1**). Only clinically apparent diagnosis that led to a healthcare encounter and generated a diagnosis will therefore be captured.

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

Covariates

For objective 2, age and sex (female/male) at HCM or oHCM diagnosis will be described. The following age grouping will be used: 18-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80 and over. Additionally, selected clinical measurements and comorbidities will be identified using SNOMED and LOINC codes. These include:

Comorbidities: cardiac arrhythmias (AF, ventricular fibrillation, (sustained) ventricular arrythmia, premature atrial, nodal or ventricular complexes, sick sinus syndrome, atrioventricular block), AF, sudden cardiac

arrest, ischaemic stroke, HF, ischaemic heart disease, SCD, valvular heart disease, essential hypertension, disorders of lipoprotein metabolism and other lipidaemia, type 2 diabetes mellitus, obesity, chronic kidney disease, and chronic obstructive pulmonary disease.

Measurements (if available): echocardiogram (LVOT and LVEF measurements, maximum LV thickness), cardiac magnetic resonance imaging, genetic test, Holter electrocardiogram, and exercise test.

A preliminary code list to identify these comorbidities and clinical measurements can be found in **Appendix 1, Table 2,** and **Table 3**, respectively.

For objective 3, selected HCM treatments will be identified using RxNorm and SNOMED codes. These include:

- Pharmacological treatments: beta blocking agents, non-dihydropyridine calcium channel blockers (diltiazem or verapamil), dysopiramide, myosin inhibitors (mavacamten), oral diuretics, oral anticoagulants (warfarin, phenprocoumon, dabigatran, rivaroxaban, apixaban, and edoxaban), angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, mineralocorticoid receptor antagonists, antiplatelets, digoxin, amiodarone. These will be reported at class level, with the exception of cases when a single agent from the class is used (amiodarone, mavacamten, digoxin).
- Procedures: implantation of cardioverter defibrillator, implantation of pacemaker, septal reduction therapy (surgical septal myectomy, alcohol septal ablation), heart transplantation.

A preliminary code list to identify these treatments can be found in **Appendix 1, Table 4**.

Comorbidities, measurements, and treatments will be assessed in different time windows before and after diagnosis (see section 8.8 Analysis). For selected treatments, number of persons initiating or continuing the treatment in the respective time windows will be reported.

Table 7 represent a preliminary table shell for the characterisation of the patients with HCM and those with oHCM.

Table 7. Characteristics of patients with a first diagnosis of HCM or oHCM.

Characteristics	Time window 1 N (%)	Time window n… N (%)
Age in years		
18-30		
31-39		
40-49		
50-59		
60-69		
70-79		
≥80		
Sex Male		
Comorbidities		
Atrial fibrillation		
Other arrhythmias		
Ischaemic stroke		
Heart failure		
Ischemic heart disease		
Sudden cardiac death		
Valvular heart disease		
Essential hypertension		
Disorder of lipoprotein metabolism and other lipidaemia		

Type 2 diabetes mellitus		
Obesity		
Chronic kidney disease		
Chronic obstructive pulmonary disease		
Measurements		
LVOT		
LVEF		
Maximum left ventricle thickness		
Holter monitor test		
Exercise test		
Genetic test		
Cardiac magnetic resonance imaging		
Pharmacological treatments		
Beta blocking agents		
Selective calcium channel blockers		
Mavacantem		
Disopyramide		
Oral diuretics		
Oral anticoagulants		
Angiotensin converting enzyme inhibitors		
Angiotensin II receptor blockers		
Aldosterone antagonists		
Antiplatelets		
Digoxin		
Amiodarone		
Procedures		
Cardioverter defibrillator		
Pacemaker		
Surgical septal myectomy		
Alcohol septal ablation		
Heart transplantation		

LVOT: left ventricular outflow tract, LVEF: left ventricular ejection fraction.

8.7 Study size

No sample size has been calculated as this is a descriptive study which will not test a specific hypothesis. In addition, to estimate the prevalence of HCM or oHCM, we will use already collected available data. Thus, the sample size will be driven by the availability of patients with conditions of interest within each database.

8.8 Analysis

Table 8. Description of study types and type of analysis.

Study type	Study classification	Type of analysis
Population-level descriptive epidemiology	Off-the-shelf	Period prevalence of disease
Patient-level characterisation	Off-the-shelf	Characterisation of selected variables

Federated Network Analyses

Analyses will be conducted separately for each database. Before study initiation, test runs of the analytics are performed on a subset of the data sources or on a simulated set of patients and quality control checks are performed. Once all the tests are passed, the final package is released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally execute the analytics against the OMOP Common Data Model (CDM) in R Studio and review and approve the by default aggregated results before returning them to the Coordination Centre. Sometimes multiple execution iterations are performed, and additional fine tuning of the code base is needed. A service desk will be available during the study execution for support.

The study results of all data sources are checked after which they are made available to the team in the Digital Research Environment and the Study Dissemination Phase can start. All results are locked and timestamped for reproducibility and transparency.

Patient privacy protection

Cell suppression will be applied as required by databases to protect people's privacy. Cell counts < 5 will be masked.

Statistical model specification and assumptions of the analytical approach considered

Population-level descriptive epidemiology

For objective 1, we will estimate the period prevalence on an annual basis, defined as the period from January 1st to December 31st for each year. It will be calculated as the number of individuals diagnosed with HCM and oHCM divided by the total active population, with complete persistence (i.e., a patient once diagnosed, is considered to have the diagnosis from the first occurrence until the end of follow-up). Participants will be required to contribute a minimum of only one day within the period (and to have a diagnosis) to be included for the numerator. For inclusion in the denominator, participants will be required to contribute a minimum of 6 months within the period.

As a sensitivity analysis, we will also estimate point prevalence of HDM and oHCM on an annual basis as of January 1st each year.

All estimates will be provided overall and stratified by age and sex, along with 95% confidence intervals calculated using the Wilson method.

Patient-level characterisation

Patient-level characterisation will be conducted for objectives 2 and 3, both overall and by grouping patients diagnosed before 2020 and those diagnosed in 2020 or later in order to see potential trends in patients' characteristics.

Age and sex at time of first HCM or oHCM diagnosis will be described. The absolute number and percentage of patients receiving pre-specified list of clinical measurements and experiencing selected comorbidities (as defined in the variables section) will be assessed across the following non-overlapping time intervals: >5 years, 5-3 years, 3-1 years, 364-181 days, 180-91 days, 90-1 days before the index date, and during the periods 1-90 days, 91-180 days, 181-364 days, 1-3 years, 3-5 years, >5 years after the index date, with the denominator being the patients still observed at each time point (**Figure 1**). The time windows were selected based on the clinical likelihood of patients to exhibit symptoms before the formal diagnosis. A patient could be counted in more than one comorbidity and measurement. Additionally, the number and percentage of patients receiving each measurement, experiencing each comorbidity, and taking each treatment prior to the index date will be assessed for the entire available observation period, without considering specific time intervals, in order to describe the presence of the covariates at any time before the HCM or oHCM diagnosis.

For objective 3, the number and percentage of patients receiving each treatment (any user) from the pre-specified list of HCM treatments (as defined in the outcome section) will be assessed across the following non-overlapping time intervals: >5 years, 5-3 years, 3-1 years, 364-181 days, 180-91 days, 90-1 days before the index date, and during the periods 1-90 days, 91-180 days, 181-364 days, 1-3 years, 3-5 years, >5 years after the index date, with the denominator being the patients still observed at each time point (**Figure 1)**. A patient could be counted in more than one treatment group. Exposure starts at date of the first prescription of each drug. For each prescription, the estimated duration of use will be retrieved from the drug exposure table in the CDM. Subsequent prescriptions will be combined into continuous exposed episodes (drug eras) if the distance in days between the end of first prescription and start of the second was 90 days or less. Furthermore, we will report the median and interquartile range of the time from the pre-specified comorbidities and treatments to diagnosis (if they first occurred before the HCM or oHCM diagnosis) will be reported. As an exploratory analysis, we will include a comparison of these pre-specified covariates with a random sample from the general population matched by age and sex. The identification of selected clinical measurements, comorbidities, and treatments will be concept-based (including descendants).

For all continuous variables, mean with standard deviation and median with interquartile range will be reported. For all categorical analyses, number and percentages will be reported. A minimum cell count of 5 will be used when reporting results, with any smaller counts reported as "<5". All analyses will be reported by country/database, overall and stratified by age and sex when possible (minimum cell count reached).

Software

All analyses will be performed with R. We will use the following R packages:

- "IncidencePrevalence" (https://github.com/darwin-eu/IncidencePrevalence) for the computation of prevalence (30).

- "Cohortcharacteristics" (CRAN: Package CohortCharacteristics) for the patient-level characterization of demographics, clinical measurements, comorbidities, and treatment.

8.9 Evidence synthesis

Results from analyses described in section 8.8 will be presented separately for each database and no meta-analysis of results will be conducted.

9. DATA MANAGEMENT

Data management

All databases are mapped to the OMOP CDM. This enables the use of standardised analytics and tools across the network since the structure of the data and the terminology system is harmonised. The OMOP CDM is 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. Each data partner will execute the study code against their database containing patient-level data and will then return the results set 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 European Union member states will process personal data from individuals which is collected in national/regional electronic health record databases. 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 databases 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.

10. QUALITY CONTROL

General database quality control

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

Study specific quality control

When defining HCM and oHCM, a systematic search of possible codes for inclusion will be identified using CodelistGenerator R package (https://github.com/darwin-eu/CodelistGenerator). This software allows the user to define a search strategy and using this will then query the vocabulary tables of the OMOP Common Data Model so as to find potentially relevant codes. The codes returned will be reviewed by two clinical epidemiologists and/or pharmacists to consider their relevance. In addition, we will run phenotype diagnostics to assess the use of different codes across the databases contributing to the study and identify any codes potentially omitted in error:

- The diagnostics used to review the conditions of interest (HCM and oHCM) will include counts of the population of interest, attrition, code counts of the condition of interest in the overall database, counts of potential missing codes related to the condition of interest, counts of codes of interest at cohort index date, distribution of age, sex and time observed before and after index; cohort overlap and timing between different conditions of interest (including different flavours for the same condition), incidence and prevalence in a sample of the database, and a large scale characterisation of the individuals with the condition of interest (sampled if necessary) including a comparison with a random sample from the general population matched by age and sex (the large scale characterisation allows us to see how different is the cohort we identified from population of same age and sex). The large-scale characterisation will also allow us to confirm the available data, particularly the counts on clinical measurements and procedures.

This will allow for a consideration of the validity of the study cohort of patients in each of the databases and inform decisions around whether multiple definitions are required.

The study code will be based on two R packages currently being developed to (1) estimate prevalence, (2) characterise demographic, clinical characteristics, and treatments. 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.

11. LIMITATIONS OF THE RESEARCH METHODS

The study will rely on routinely collected healthcare data, and as such, data quality issues must be carefully considered. In particular, the identification of HCM patients may vary across databases. While relatively few would be expected (i.e. those recorded with a condition who do not truly have the condition), false negatives (i.e. those with a condition that is not recorded) may be more likely especially for databases without patient-level linkage from primary care to secondary care data. We will use a comprehensive definition of HCM and its variant, obstructive HCM, in an attempt to capture as many diagnoses as possible. It is important to note that data confirming diagnoses by specialists may not be available, depending on the coding practices of each database.

Additionally, HCM is often underdiagnosed, as many individuals with the condition are asymptomatic or experience very mild symptoms, which can result in delayed diagnosis or the condition going undetected entirely (31). These patients are outside the scope of the study and will not be captured in this study.

The recording of comorbid conditions and medication use that will be assessed for patient characterisation may also vary across databases; and in databases with information on HCM treatment, the recording of treatment use may be incomplete. Characterisation of baseline comorbidities in pre-specified time periods before the index date represent partial prevalence of conditions and not complete prevalence (i.e., the entire medical history of patients). Lastly, there may be limited data availability for specific measurements and procedures across databases, as outlined in the study data sources section.

Furthermore, the COVID-19 pandemic (from 2020-2022) introduced changes in healthcare utilization patterns, routine clinical practices, and information recording during the pandemic might potentially distort estimates for the years 2020 and 2021. Disruptions in healthcare services and altered patient behaviours could influence the representation of HCM or oHCM data during this period. Consequently, the results from this period will be interpreted with caution.

Additionally, the results estimated from this study will only reflect the populations from the included data sources. Electronic health records have certain inherent limitations because they were collected for clinical purpose rather than primarily for research use.

12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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

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

13. GOVERNANCE BOARD ASPECTS

All data sources require approval from their respective Institutional Review Boards.

14. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Study Report

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.

15. OTHER ASPECTS

None.

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17. ANNEXES

Appendix I: Definition of HCM and oHCM diagnosis, clinical measurements, comorbidities, and treatments.

Table 1. Preliminary code list for HCM and oHCM diagnosis

CONCEPT_NAME	CONCEPT_ID	VOCABULARY_ID
Hypertrophic cardiomyopathy without obstruction	4108236	SNOMED
Hypertrophic cardiomyopathy	4124693	SNOMED
Hypertrophic obstructive cardiomyopathy	316428	SNOMED
Hypertrophic cardiomyopathy with genetic marker	43020658	SNOMED
Primary idiopathic hypertrophic cardiomyopathy	4270625	SNOMED
Primary hypertrophic cardiomyopathy	44784145	SNOMED
Primary familial hypertrophic cardiomyopathy	4222765	SNOMED

Table 2. Preliminary code list for HCM-related comorbidities

CONCEPT_NAME	CONCEPT_ID	VOCABULARY_ID
Atrial fibrillation	313217	SNOMED
Ventricular fibrillation	437894	SNOMED
Sustained ventricular tachycardia	4139206	SNOMED
Premature atrial contraction	4109365	SNOMED
Aberrant premature complexes	4091901	SNOMED
Sick sinus syndrome	4261842	SNOMED
Atrioventricular block	316135	SNOMED
Ischaemic stroke	35826270	SNOMED
Heart failure	316139	SNOMED
Ischemic heart disease	4185932	SNOMED
Sudden cardiac death	4317150	SNOMED
Valvular heart disease	40399388	SNOMED
Essential hypertension	320128	SNOMED
Disorder of lipoprotein AND/OR lipid metabolism	4170226	SNOMED
Type 2 diabetis mellitus	201826	SNOMED
Obesity	433736	SNOMED
Chronic kidney disease	46271022	SNOMED
Chronic obstructive pulmonary disease	255573	SNOMED

Table 3. Preliminary code list for HCM-related measurements

CONCEPT_NAME	CONCEPT_ID	VOCABULARY_ID
Heart ventricle Left outflow tract	1031031	LOINC
Left ventricular Ejection fraction	3027172	LOINC
Maximum left ventricle thickness	1989021	LOINC
Holter monitor test interpretation	4205487	SNOMED
Exercise test finding	4090324	SNOMED
MYH7 (myosin heavy chain 7) gene variant measurement	35947206	OMOP Genomic
MYBPC3 (myosin binding protein C3) gene variant measurement	35957287	OMOP Genomic
TNNT2 (troponin T2, cardiac type) gene variant measurement	35964135	OMOP Genomic
TNNI3 (troponin I3, cardiac type) gene variant measurement	35947472	OMOP Genomic
TPM1 (tropomyosin 1) gene variant measurement	35946916	OMOP Genomic
MYL2 (myosin light chain 2) gene variant measurement	35952884	OMOP Genomic
MYL3 (myosin light chain 3) gene variant measurement	35948676	OMOP Genomic
ACTC1 (actin alpha cardiac muscle 1) gene variant measurement	35952645	OMOP Genomic
MRI for cardiac morphology, function, and velocity	42710005	SNOMED

Table 4. Preliminary code list for HCM related pharmacological treatments and procedures

CONCEPT_NAME	CONCEPT_ID	VOCABULARY_ID
Beta blocking agents	21601665	ATC
Selective calcium channel blockers with direct cardiac effects	21601765	ATC
Mavacantem	955061	ATC
Disopyramide; systemic	21600252	ATC
Diuretics	21601461	ATC
Direct factor Xa inhibitors (apixaban, betrixaban, edoxaban, rivaroxaban)	43534760	ATC
Vitamin K antagonists (warfarin, phenprocoumon)	21600962	ATC
ACE inhibitors, plain	21601784	ATC
Angiotensin II receptor blockers (arbs), plain	21601823	ATC
Aldosterone antagonists	21601533	ATC
Platelet aggregation inhibitors excl. Heparin	21600985	ATC
Digoxin; systemic	21600234	ATC
Amiodarone; systemic	21600270	ATC
Ventricular septal myectomy	45765641	SNOMED
Septal myectomy	37397338	SNOMED
Percutaneous transluminal septal myocardial ablation	4229994	SNOMED
Percutaneous transluminal ablation of septum of heart using chemical substance	40483085	SNOMED

Nonsurgical reduction of cardiac septum for hypertrophic obstructive cardiomyopathy with angiography of coronary artery	4260103	CPT4
Cardioverter defibrillator procedure	4138751	SNOMED
Cardiac pacemaker procedure	4051938	SNOMED

Appendix II: ENCePP checklist for study protocols

Study title:

Prevalence of hypertrophic cardiomyopathy (HCM) and obstructive hypertrophic cardiomyopathy (oHCM) in Europe

EU PAS Register number: Study not registered yet.

Study reference number (if applicable): P3-C1-0018

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[2]	X			8.3
1.1.2 End of data collection[3]	X			8.3
1.1.3 Progress report(s)			X	
1.1.4 Interim report(s)			X	
1.1.5 Registration in the EU PAS Register®		X		
1.1.6 Final report of study results.	X			5

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)	X			6, 7
2.1.2 The objective(s) of the study?	X			7
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	X			7

2.1.4 Which hypothesis(-es) is (are) to be tested?			X	
2.1.5 If applicable, that there is no *a priori* hypothesis?			X	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	X			8.1
3.2 Does the protocol specify whether the study is based on primary, secondary, or combined data collection?	X			8.2
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	X			8.3
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))			X	
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)			X	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	X			8.2, 8.5
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	X			8.5
4.2.2 Age and sex	X			8.6
4.2.3 Country of origin	X			8.2
4.2.4 Disease/indication	X			8.6
4.2.5 Duration of follow-up	X			8.4

4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	X			8.4

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)			X	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)			X	
5.3 Is exposure categorised according to time windows?			X	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)			X	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?			X	
5.6 Is (are) (an) appropriate comparator(s) identified?			X	

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?	X			8.6
6.2 Does the protocol describe how the outcomes are defined and measured?	X			8.6
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)			X	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs,			X	

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)			X	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)			X	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)			X	

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)			X	

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)			X	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	X			8.2
9.1.3 Covariates and other characteristics?	X			8.2

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)			X	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	X			8.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	X			8.2
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)			X	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	X			8.6
9.3.3 Covariates and other characteristics?	X			8.6
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)			X	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	X			8.5
10.2 Is study size and/or statistical precision estimated?			X	
10.3 Are descriptive analyses included?	X			8.5
10.4 Are stratified analyses included?	X			8.5
10.5 Does the plan describe methods for analytic control of confounding?			X	
10.6 Does the plan describe methods for analytic control of outcome misclassification?			X	

10.7 Does the plan describe methods for handling missing data?			X	
10.8 Are relevant sensitivity analyses described?			X	

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)	X			9
11.2 Are methods of quality assurance described?	X			10
11.3 Is there a system in place for independent review of study results?			X	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of: 12.1.1 Selection bias? 12.1.2 Information bias? 12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	X		X X	11
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)	X			8.2

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?	X			13
13.2 Has any outcome of an ethical review procedure been addressed?			X	
13.3 Have data protection requirements been described?	X			9

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?	X			4

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

Comments:

Name of the main author of the protocol: Anna Saura-Lazaro

Date: 22/11/2024

Signature: Anna Saura-Lazaro