SAFETY-VAC: Background incidence estimation of flares of pre-existing chronic diseases using pan-European electronic healthcare data sources.

First published: 18/07/2024

Last updated: 23/10/2025

Study Ongoing

Administrative details

EU PAS number

EUPAS1000000233

Study ID

1000000233

DARWIN EU® study

No

Study countries

- [ ] Denmark
- [ ] Finland
- [ ] France

- [ ] Italy
- [ ] Norway
- [ ] Spain
- [ ] United Kingdom

Study description

This study aims to assess the feasibility of the participating European data sources in estimating the background incidence, and the 6- and 12-month cumulative incidence of flares of selected autoimmune diseases (Graves' disease, Hashimoto's thyroiditis, polyarteritis nodosa, autoimmune hepatitis, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, erythema nodosum, systemic lupus erythematosus, and ulcerative colitis) using electronic healthcare record data sources from 7 European countries.
The estimates will be stratified by age categories (< 18, 18-59, >60 years old), sex, and selected sub-populations.
This study will also assess the contribution of different data provenances and components of the flares definitions to the flare incidence estimation.

Study status

Ongoing

Research institutions and networks

Institutions

Aarhus University & Aarhus University Hospital
DEPARTMENT OF CLINICAL EPIDEMIOLOGY

- [ ] Denmark

First published: 20/07/2021

Last updated: 02/04/2024

Institution | Educational Institution | ENCePP partner

University Medical Center Utrecht (UMCU)

Netherlands

First published: 24/11/2021

Last updated: 22/02/2024

Institution | Educational Institution | Hospital/Clinic/Other health care facility | ENCePP partner

Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina, IDIAPJGol

Spain

First published: 05/10/2012

Last updated: 23/05/2025

Institution | Educational Institution | Laboratory/Research/Testing facility | Not-for-profit | ENCePP partner

Bordeaux PharmacoEpi, University of Bordeaux

France

First published: 07/02/2023

Last updated: 08/12/2025

Institution | Educational Institution | Hospital/Clinic/Other health care facility | Not-for-profit | ENCePP partner

Instituto Aragonés de Ciencias de la Salud (IACS)

Spain

First published: 01/02/2024

Last updated: 02/04/2024

Institution | Educational Institution

Agenzia regionale di sanità della Toscana (ARS)

Italy

First published: 01/02/2024

Last updated: 12/03/2024

Institution | EU Institution/Body/Agency | ENCePP partner

The Foundation for the Promotion of Health and Biomedical Research of Valencia Region (FISABIO)

Spain

First published: 01/02/2024

Last updated: 31/10/2025

Institution

Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency for Medicines and Medical Devices, AEMPS)

Spain

First published: 01/02/2024

Last updated: 04/09/2024

Institution | EU Institution/Body/Agency | Not-for-profit | Regulatory Authority | ENCePP partner

University of Oslo

First published: 01/02/2024

Last updated: 01/02/2024

Institution

Teamit Institute

☐ Spain

First published: 12/03/2024

Last updated: 12/03/2024

Institution | Other | ENCePP partner

Utretch University (UU), University of Eastern Finland (UEF)

Networks

Vaccine monitoring Collaboration for Europe (VAC4EU)

☐ Belgium
☐ Denmark
☐ Finland
☐ France
☐ Germany
☐ Italy
☐ Netherlands
☐ Norway
☐ Spain
☐ United Kingdom

First published: 22/09/2020

Last updated: 22/09/2020

Network | Outdated | ENCePP partner

EU Pharmacoepidemiology and Pharmacovigilance (PE&PV) Research Network

Netherlands

First published: 01/02/2024

Last updated: 24/09/2025

Network

Pedianet network (So.Se.Te)

Italy

First published: 23/10/2025

Last updated: 23/10/2025

Network

Contact details

Study institution contact

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Study contact

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Primary lead investigator

Carlos Durán Salinas

Primary lead investigator

Study timelines

Date when funding contract was signed
Planned: 15/01/2024

Actual: 06/02/2024

Study start date
Planned: 15/05/2024

Actual: 31/05/2024

Date of final study report
Planned: 16/09/2024

Sources of funding

- EMA

Study protocol

SAFETY-VAC_Study_Protocol.pdf (1.03 MB)

Regulatory

Was the study required by a regulatory body?

Yes

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

Disease /health condition

Study type:

Non-interventional study

Scope of the study:

Disease epidemiology

Method development or testing

Data collection methods:

Secondary use of data

Study design:

Retrospective multi-database population-based cohort design conducted during the period from January 1st, 2017, till the last data availability, specific for each

data source.
Study cohorts start with a first diagnosis of the selected auto-immune diseases during the study period.

Main study objective:
- Primary objective:
To estimate the background (independent of vaccination) incidence rates of flares and 6- and 12-month cumulative incidence estimates of flares in patients with Graves’ disease, Hashimoto’s thyroiditis, polyarteritis nodosa, autoimmune hepatitis, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, erythema nodosum, systemic lupus erythematosus, and ulcerative colitis using European electronic healthcare data sources.

- Secondary objectives:
1. To assess the contribution of different provenances of data as well as the contribution of the different components of the flare definition to the incidence rates of flares.
2. To estimate the background incidence rates and 6 and 12-month cumulative risks of flares of selected auto-immune diseases in subgroups of age (< 18, 18-59, 60 years and older), sex and selected subpopulations.

Study Design

Non-interventional study design
Cohort

Study drug and medical condition

Medical condition to be studied

Graves' disease

Polyarteritis nodosa

Autoimmune hepatitis

Rheumatoid arthritis

Multiple sclerosis

Erythema nodosum

Systemic lupus erythematosus

Additional medical condition(s)

Hashimoto's thyroiditis, psoriatic arthritis, ulcerative colitis

Population studied

Short description of the study population

Ten disease-specific study cohorts will be created, one for each event.
Persons will be included in the incident disease-specific study cohorts if they have:
- At least 1 day of observation after 1 January 2017.
- The first recorded diagnosis of the disease of interest after 1/1/2017.
Persons will be excluded when:
- No birth year and sex information.
- Less than 365 days look-back at first diagnosis of the disease of interest, for those not born in the study period.
Follow-up will start when study persons have completed 90 days after the disease diagnosis, except for autoimmune hepatitis and erythema nodosum where follow-up will start 30, and 60 days after the diagnosis, respectively. This delay is needed for the first episode to be ended and to be at risk of a flare.

Upon each flare the same eligibility delay for a next flare will be applied. Follow-up for incidence rates will be interrupted when vaccination with any vaccine of interest occurs, from date of vaccination to 90 days later (to ensure we do not include rates in post-vaccination risk windows), and finish at death, disenrollment, or last data extraction. If follow-up is interrupted because of a vaccination, follow-up will be resumed at day 91 after vaccination until follow-up finishes. An interruption of follow-up will also happen upon a flare, with the same eligibility period as after the first diagnosis. If a vaccination happens during the eligibility interruption, the maximum duration of interruption (eligibility and post-vaccination) is used. The occurrence of a flare-up of the corresponding event will not be considered a censoring criterion since a new flare-up can occur after a gap of 90 days. For estimation of cumulative incidence, follow-up will be censored upon the earliest of a vaccination, a flare or end of follow-up.

Age groups

- **Paediatric Population (< 18 years)**
  - Preterm newborn infants (0 – 27 days)
  - Term newborn infants (0 – 27 days)
  - Infants and toddlers (28 days – 23 months)
  - Children (2 to < 12 years)
  - Adolescents (12 to < 18 years)
- **Adult and elderly population (≥18 years)**
  - Adults (18 to < 65 years)
    - Adults (18 to < 46 years)
    - Adults (46 to < 65 years)
  - Elderly (≥ 65 years)
    - Adults (65 to < 75 years)
    - Adults (75 to < 85 years)
    - Adults (85 years and over)

Study design details

Setting

The study will use data from 10 secondary electronic health record databases that are population-based in 7 countries in Europe (UK, Spain, Denmark, Finland, Norway, Italy and France). The study will be conducted during the period from January 1st, 2017, till the last data availability, specific for each data source.

Outcomes

This study will provide an estimation of the occurrence of flares of 10 selected pre-existing chronic diseases (Graves' disease, Hashimoto's thyroiditis, polyarteritis nodosa, autoimmune hepatitis, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, erythema nodosum, systemic lupus erythematosus, and ulcerative colitis) using electronic healthcare record data sources.

Data analysis plan

All analyses will be conducted using R version R-4.03 or higher or STATA:

- Descriptive analyses will be shown through histogram plots with distance from the start of follow-up to the new occurrence of potential flare for visual inspection.
- Incidence rates will be calculated based on the occurrence of a flare requiring a lag-time of 90 days (in order to be eligible) after its incident diagnosis and each flare, except for autoimmune hepatitis and erythema nodosum (30 and 60 days, respectively), and allowing re-occurrence after the last flare-up event tailored in time-period to the condition of interest and the flare-specific identification component. Cumulative incidence of a first flare will be calculated to estimate 6 - and 12-months cumulative risk of flares.
- Component analysis will describe the data diversity of each component of the flare identification algorithm in a data source-specific manner. Each identification component may differ in rates due to data source characteristics and data meanings. For each data sources, the different component algorithms

and their data meanings for a same flare identification component will be identified. Flare cases, cumulative incidence of each component algorithm and their combinations in one study year will be measured. Incidence rates with the same “component”/”composite” algorithms will be compared across data sources, facilitating results benchmarking.

Documents

Study report

SAFETY-VAC_Objective2_D5_Report_Final_20250522.pdf (7.23 MB)

SAFETY-VAC_Objective2_D5_Report_Annex_1_Final_20250522.pdf (1.85 MB)

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data source(s)

Pedianet

Norwegian Health Registers

The Valencia Health System Integrated Database

EpiChron Cohort

Danish Health Data Registries

Système National des Données de Santé (French national health system main database)

BIFAP - Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público (Pharmacoepidemiological Research Database for Public Health Systems)

Clinical Practice Research Datalink (CPRD) GOLD

The Information System for Research in Primary Care (SIDIAP)

Data source(s), other

Finnish national data registers

Data sources (types)

Disease registry

Drug registry

Electronic healthcare records (EHR)

Population registry

Use of a Common Data Model (CDM)

CDM mapping

Yes

Data quality specifications

Check conformance

Yes

Check completeness

Yes

Check stability

Yes

Check logical consistency

Yes

Data characterisation

Data characterisation conducted

Yes

Data characterisation moment

after extract-transform-load to a common data model