# The comparative safety of first-line conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) used for the treatment of rheumatoid arthritis: protocol for a multi-database real-world cohort study

**First published:** 30/01/2020

**Last updated:** 30/01/2020

Study Ongoing

## Administrative details

**EU PAS number**

EUPAS33214

**Study ID**

33215

**DARWIN EU® study**

No

**Study countries**

- [ ] Belgium
- [ ] Estonia
- [ ] France
- [ ] Germany
- [ ] Japan
- [ ] Netherlands
- [ ] Spain
- [ ] United Kingdom
- [ ] United States

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**Study description**

We studied the comparative safety of first-line conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs) as prescribed for the treatment of rheumatoid arthritis (RA). Drugs of interest were informed by a parallel drug utilisation study, and included methotrexate, hycroxychloroquine, sulfasalazine, and leflunomide. Study outcomes included cardiovascular disease (myocardial infarction, stroke), infection/s (any, serious, opportunistic), cancer (any, lung, colo-rectal, leukemia, lymphoma) and leukopenia/pancytopenia. Routine (real world) electronic medical records and/or claims data from Germany, Spain, Belgium, France, Netherlands, United Kingdom, Estonia, Japan, and the United States of America were analysed. All subjects aged 18+, with 1+ year run-in, a diagnosis of RA, and a first-line csDMARD were included at therapy initiation. Propensity score stratification was used to minimise confounding by indication, and negative control outcomes analyses to identify residual (unobserved) confounding.

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**Study status**

Ongoing

## Research institutions and networks

# Institutions

## Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), University of Oxford

United Kingdom

**First published:** 01/02/2024

**Last updated:** 01/02/2024

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

## Centre for Statistics in Medicine

## 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

## Erasmus Medical Centre Rotterdam

**First published:** 01/02/2024

**Last updated:** 01/02/2024

Institution

## Erasmus Medical Centre Rotterdam, the Netherlands

# Networks

## European Health Data Evidence Network (EHDEN)

Netherlands

**First published:** 01/02/2024

**Last updated:** 11/06/2024

Network

## Observational Health Data Sciences and Informatics (OHDSI) Network

**First published:** 01/02/2024

**Last updated:** 01/02/2024

Network

# Contact details

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**Study contact**

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**Primary lead investigator**

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**Primary lead investigator**

# Study timelines

**Date when funding contract was signed**

Planned: 01/11/2018

Actual: 01/11/2018

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**Study start date**

Planned: 01/01/2005

Actual: 01/01/2005

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**Data analysis start date**

Planned: 13/01/2020

Actual: 13/01/2020

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**Date of final study report**

Planned: 31/01/2020

# Sources of funding

- EU institutional research programme

## More details on funding

IMI2 European Health Data and Evidence Network (EHDEN)

## Study protocol

raple_eupas_protocol.pdf(306.42 KB)

## Regulatory

**Was the study required by a regulatory body?**

No

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

Not applicable

# Methodological aspects

## Study type

## Study type list

**Study type:**

Non-interventional study

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**Scope of the study:**

Assessment of risk minimisation measure implementation or effectiveness

**Main study objective:**

1. To assess the cardiovascular safety of MTX compared to LEF, HCQ, and SSZ2. To estimate the risk of infections associated with the use of MTX compared to LEF, HCQ, and SSZ3. To study the risk of cancer associated with the use of MTX compared to LEF, HCQ, and SSZ4. To study the risk of leukopenia/pancytopaenia associated with the use of MTX compared to LEF, HCQ, and SSZ

# Study Design

**Non-interventional study design**

Cohort

# Study drug and medical condition

**Anatomical Therapeutic Chemical (ATC) code**

(P01BA02) hydroxychloroquine

hydroxychloroquine

(L04AX03) methotrexate

methotrexate

(L04AA13) leflunomide

leflunomide

(A07EC01) sulfasalazine

sulfasalazine

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**Medical condition to be studied**

Rheumatoid arthritis

# Population studied

**Age groups**

Adults (18 to < 46 years)

Adults (46 to < 65 years)

Adults (65 to < 75 years)

Adults (75 to < 85 years)

Adults (85 years and over)

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**Estimated number of subjects**

300000

## Study design details

**Outcomes**

Myocardial infarction, stroke, serious infection, opportunistic infection, any infection, lymphoma, leukemia, lung cancer, colo-rectal cancer, any cancer, leukopenia/pancytopenia

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**Data analysis plan**

Propensity scores will be estimated using LASSO and used for stratification (primary) and matching (secondary analysis). Balance will be assessed using standardised mean difference. Cox models will be used to estimate hazard ratios according to exposure. Negative control outcomes will be used to assess residual confounding, and for calibration where applicable. Study diagnostics (power, propensity score distribution, covariate balance) were evaluated by clinicians and epidemiologists to determine which database-target-comparator-outcome-analyses warrant further consideration. Database-target-comparator that identified <10 outcomes in the time-at-risk or contained analyses with baseline covariate with standardized mean difference>0.1 and covariate prevalence difference>0.05 were excluded. All the analyses will be conducted

for each database separately, with estimates combined in fixed effects meta-analysis methods where I2 is <=40%.

# 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.

**Signed checklist for study protocols**

raple_eupas_checklist.pdf(217.19 KB)

## Data sources

**Data source(s)**

THIN® (The Health Improvement Network®)

The Information System for Research in Primary Care (SIDIAP)

**Data source(s), other**

THIN, SIDIAP

**Data sources (types)**

Administrative healthcare records (e.g., claims)

Drug dispensing/prescription data

Electronic healthcare records (EHR)

## Use of a Common Data Model (CDM)

**CDM mapping**

No

# Data quality specifications

**Check conformance**

Unknown

**Check completeness**

Unknown

**Check stability**

Unknown

**Check logical consistency**

Unknown

# Data characterisation

**Data characterisation conducted**

No