**TITLE PAGE**

**PASS information**

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| --- | --- |
| **Title** | 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 |
| **Protocol version identifier** | *1.0* |
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| **EU PAS register number** | To be completed after protocol finalization |
| **Active substance** | Methotrexate, Leflunomide, Sulfasalazine, Hydroxycloroquine |
| **Medicinal product** | Methotrexate, Leflunomide, Sulfasalazine, Hydroxycloroquine |
| **Research question and objectives** | The overarching objective is to evaluate the comparative safety of first-line conventional synthetic DMARDs |
| **Country(-ies) of study** | Germany, Spain, Belgium, France, Netherlands, United Kingdom, Japan, and the United States of America |
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|  | Edward Burn |
|  | James Weaver |
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# 1. Table of contents

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# 2. List of abbreviations

|  |  |
| --- | --- |
| RA | Rheumatoid Arthritis |
| DMARD | Disease Modifying Anti-rheumatic drug |
| csDMARD | Conventional synthetic DMARD |
| bDMARD | Biologic DMARD |
| tsDMARD | Targeted synthetic DMARD |
| MTX | Methotrexate |
| SSZ | Sulfasalazine |
| HCQ | Hydroxychloroquine |
| LEF | Leflunomide |

# 3. Responsible parties

|  |  |
| --- | --- |
| **Responsible party/person** | **Institution/Affiliation** |
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\* Principal investigator

# 5. Amendments and updates

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Number | Date | Section of study  protocol | Amendment or  update | Reason |
| None |  |  |  |  |
|  |  |  |  |  |

# 7 Rationale and background

Rheumatoid Arthritis (RA) is a common musculoskeletal disease, affecting approximately 0.5-1.0% of the adult population in Europe and North America. The management for the condition has changed considerably over the last 35 years, with a number of therapeutic options available including short and long-term disease modification.

Several efficacious agents are currently available for RA, with conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) usually used as the first line of treatment in newly diagnosed RA. Among the csDMARDs, methotrexate is currently considered the “anchor drug” (1). Other csDMARDs such as hydroxychloroquine, leflunomide or sulfasalazine are also available. While first-line treatment for RA typically involves a csDMARD as a monotherapy, subsequent treatment may include combination csDMARD therapy, or the use of biological DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs).

All therapies used for RA are associated with both non-serious and serious AEs (6). Recent drug safety studies have focussed on the risk of serious adverse events such as infection, cancer and cardiovascular outcomes associated with biologic drugs (7-9). However the comparative risk of such events in csDMARDs with medications such as methotrexate continues to be conflicting. For instance patients on methotrexate are frequently counselled regarding an increased risk of infection, however there is little good quality evidence quantifying this risk in the literature with several studies suggesting no increased infection risk (10-11). Methotrexate use has also been associated with a type of rare lymphoma, however RA patients with uncontrolled disease are at risk of such cancers regardless of therapy compared to the general population (12). Well-designed observational studies of sufficient size with enough power to assess rare outcomes and with adjustment for confounding by indication are lacking. A study comparing the relative safety of first-line csDMARD treatment strategies would address this gap in the evidence base.

# 8. Research question and objectives

The overarching aim of this study is to assess the comparative safety of first-line csDMARDs used in rheumatoid arthritis. Four csDMARD used as monotherapy will be compared: Methotrexate (MTX), Hydroxychloroquine (HCQ), Sulfasalazine (SSZ), and Leflunomide (LEF), with MTX as the reference/anchor drug.

Specifically, the study has the following objectives:

1. To assess the comparative cardiovascular safety (myocardial infarction, stroke) of MTX compared to LEF, HCQ, and SSZ
2. To estimate the comparative risk of infections (serious, opportunistic, and all) associated with the use of MTX compared to LEF, HCQ, and SSZ
3. To study the comparative risk of cancer (any, lymphoma, lung, and colo-rectal) associated with the use of MTX compared to LEF, HCQ, and SSZ
4. To study the comparative risk of leukopenia/pancytopaenia associated with the use of MTX compared to LEF, HCQ, and SSZ

# 9. Research methods

## 9.1. Study design

Multinational, multi-database, new user cohort study of incident users of MTX, LEF, HCQ or SSZ as first line treatment for treatment naïve RA patients. This is a state-of-the-art study design in pharmaco-epidemiology and endorsed by ENCePP guidelines on methodological standards (ENCePP Guide on Methodological Standards in Pharmacoepidemiology, Revision 7, EMA/95098/2010).

## 9.2. Setting

Participants from 7 European countries (Belgium, Netherlands, Germany, France, Spain, Estonia, and the UK), the United States of America, and Japan will be included. Electronic health records and administrative claims fromprimary care and secondary care will be utilised.

The study will be conducted using data from 16 real world data sources previously mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) in collaboration with the Observational Health Data Sciences and Informatics (OHDSI) and European Health Data and Evidence Network (EHDEN) initiatives.

### 9.2.1. STUDY PERIOD

The study period, when index events and outcomes of interest can be observed, will start from 01/01/2005 and end at the latest available date for all data sources.

### 9.2.2. STUDY POPULATION: Inclusion/Exclusion criteria

### Four mutually exclusive study cohorts will be defined, to include subjects with RA defined as new users of first-line csDMARD therapy.

#### MTX cohort

### ● No drug utilisation record of any DMARD from all days before to 1 day before the index event

### ● No drug utilisation record of any DMARD other than MTX from day of the index event to 7 days after the date of the index event

### ● Have a condition occurrence or observation indicating RA from 1826 days before to index event to day of the index event

### ● Be aged at or over 18 at their index event

### ● Have at least 365 days of observation time prior to the date of their index event

### ● Have no condition occurrence indicating cancer from all days before to day of the index event

### ● Have no condition occurrence indicating other inflammatory arthritis from all days before to day of the index event

#### HCQ cohort

### ● No drug utilisation record of any DMARD from all days before to 1 day before the index event

### ● No drug utilisation record of any DMARD other than HCQ from day of the index event to 7 days after the date of the index event

### ● Have a condition occurrence or observation indicating RA from 1826 days before to index event to day of the index event

### ● Be aged at or over 18 at their index event

### ● Have at least 365 days of observation time prior to the date of their index event

### ● Have no condition occurrence indicating cancer from all days before to day of the index event

### ● Have no condition occurrence indicating other inflammatory arthritis from all days before to day of the index event

#### SSZ cohort

### ● No drug utilisation record of any DMARD from all days before to 1 day before the index event

### ● No drug utilisation record of any DMARD other than SSZ from day of the index event to 7 days after the date of the index event

### ● Have a condition occurrence or observation indicating RA from 1826 days before to index event to day of the index event

### ● Be aged at or over 18 at their index event

### ● Have at least 365 days of observation time prior to the date of their index event

### ● Have no condition occurrence indicating cancer from all days before to day of the index event

### ● Have no condition occurrence indicating other inflammatory arthritis from all days before to day of the index event

#### LEF cohort

### ● No drug utilisation record of any DMARD from all days before to 1 day before the index event

### ● No drug utilisation record of any DMARD other than LEF from day of the index event to 7 days after the date of the index event

### ● Have a condition occurrence or observation indicating RA from 1826 days before to index event to day of the index event

### ● Be aged at or over 18 at their index event

### ● Have at least 365 days of observation time prior to the date of their index event

### ● Have no condition occurrence indicating cancer from all days before to day of the index event

### ● Have no condition occurrence indicating other inflammatory arthritis from all days before to day of the index event

### 9.2.6. FOLLOW UP

## Index date is defined by the first prescription/dispensation of a first line DMARD therapy after the diagnosis of RA.

## Two periods of follow-up will be considered for two types of analyses for the CVD, infection, and leukopenia outcomes:

## In an *intention-to-treat* analysis, the analysis follow-up starts 1 day after therapy initiation and continues will be up until the first of: outcome of interest, loss to follow-up, or 1826 days after the index date.

## In an *on-treatment* analysis, the analysis follow-up starts 1 day after therapy initiation and continuesuntil the first of: discontinuation/switching/combined therapy of index monotherapy plus a lag time of 14 days, outcome of interest, loss to follow-up, or 1826 days after the index date.

One period of follow-up will be considered for the cancer outcomes:

## A *delayed intention-to-treat* will be implemented, where follow up starts one year after the therapy initiation and continues until up until the first of: outcome of interest, loss to follow-up, or 1826 days after the index date.

## A summary of the parameters used for these analyses and their respective follow-up is available in Table 9.3

**Table 9.3. List of pre-specified analyses, and related follow-up**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcome(s)** | **Analysis type** | **Exclusion of prior events** | **Time-at-risk** |
| 1) Leukopenia  2) Pancytopaenia  3) Serious infection,  4) Opportunistic infection,  5) Serious infection, opportunistic infection, or any other infection of interest | Intention to treat | 30 days | 1 day after index date to outcome of interest/ loss to follow-up/ 1826 days after the index date |
| On treatment | 30 days | 1 day to outcome of interest/ discontinuation of treatment + 14 days/ loss to follow-up/ 1826 days after the index date |
| 6) Stroke during an inpatient hospitalisation or ER visit  7) Stroke, an­-y recorded  8) Myocardial infarction during an inpatient hospitalisation or ER visit  9) Myocardial infarction, any recorded | Intention to treat | 365 days | 1 day after index date to outcome of interest/ loss to follow-up/ 1826 days after the index date |
| On treatment | 365 days | 1 day to outcome of interest/ discontinuation of treatment + 14 days/ loss to follow-up/ 1826 days after the index date |
| 10) Any cancer (except non-melanoma skin cancer)  11) Colorectal cancer  12) Malignant lymphoma  13) Leukemia  14) Lung cancer | Delayed intention to treat | All observation time prior to index date | 365 days to outcome of interest/ / loss to follow-up/ 1826 days after the index date |

## 9.3. Variables

### 9.3.1.- EXPOSURE

First-line DMARD treatments will be compared:

1. Drugs of interest (target drugs)
   * LEF
   * SSZ
   * HCQ
2. Comparator: all of the above groups of drug users will be analysed separately compared to MTX users.

**Exposure assessment**

Exposure to a study drug will commence on the date of the first record for the study drug in the respective database without any record of the same study drug (or any other DMARD) during the baseline period. The end of exposure will be defined as the date of the last dispensation/claim for the study drug plus the calculated number of exposure days provided in the last prescription/dispensation.

Treatment gaps of ≤3 months between drug utilization records for each study drug will be allowed. Drug discontinuation will be defined as the last date of exposure to a study drug plus an additional 14 days (surveillance window). Stockpiling will be dismissed. Drug discontinuation will also be considered if a patient switches from one study drug to another, or when a concomitant second drug is added, with switching defined as an overlap of 30 days or more between two different drugs.

### 9.3.2.- OUTCOME/S

The safety outcomes of interest will be

1. *Leukopenia*

* A condition occurrence of Leukopenia.

2. *Pancytopaenia*

* A condition occurrence of Pancytopaenia.

3. *Serious infection*

* A condition occurrence of a serious infection, defined by the condition occurrence of an infection occurring on a day where there was a visit occurrence for inpatient hospitalisation or emergency room presentation also recorded, or where death occurred up to 30 days following the condition occurrence of a serious infection.

4. *Opportunistic infection*

* A condition occurrence of an opportunistic infection, according to previous literature.

5. *Any infection*

* A serious infection (as defined above in #3), an opportunistic infection (as defined above in #4), or a condition occurrence of a other infection of interest.

6. *Stroke during an inpatient hospitalisation or ER visit*

* A condition occurrence of stroke
* The condition occurrence of stroke occurring on a day where there was a visit occurrence for inpatient hospitalisation or emergency room presentation also recorded.

7. *Stroke, any recorded*

* A condition occurrence of stroke

8. *Myocardial infarction during an inpatient hospitalisation or ER visit*

* A condition occurrence of myocardial infarction
* The condition occurrence of stroke occurring on a day where there was a visit occurrence for inpatient hospitalisation or emergency room presentation also recorded.

9. *Myocardial infarction, any recorded*

* A condition occurrence of myocardial infarction

10. *Any cancer (except non-melanoma skin cancer)*

* A condition occurrence of any cancer (except non-melanoma skin cancer)

11. *Colorectal cancer*

* A condition occurrence of colorectal cancer

12. *Malignant lymphoma*

* A condition occurrence of malignant lymphoma

13. *Leukemia*

* A condition occurrence of Leukemia

14. *Lung cancer*

* A condition occurrence of lung cancer

## Negative control outcomes

A list of 83 negative control outcomes will also be assessed for which there is no causal relationship with choice of medication after a diagnosis of rheumatoid arthritis. These outcomes will be identified using condition occurrence table in the CDM using the same time-at-risk window as for the outcomes of interest and based on a semi-automatic process of literature research followed by manual review by 4 clinicians. The list is available in Annex 3.

*Outcome identification and validation*

The proposed code list/s for the identification of the study population (codes for the identification of RA diagnosis) and for the study outcomes will be created by clinicians with experience in the management of RA using ATLASTM, and reviewed by 4 clinicians and 1 epidemiologist. Myocardial infarction and stroke codes were based on a previously published paper [<https://www.ncbi.nlm.nih.gov/pubmed/31668726>].

Face validity for the proposed RA and for each of the outcome cohorts will be reviewed by exploring age- and sex-specific incidence rates compared to previous clinical knowledge and/or existing literature.

### 9.3.3.- Covariates

All covariates available in each of the databases will be identified at cohort entry (index date) based on the patients’ records pre-index (baseline period), and potentially included as covariates in the proposed propensity score models. Key confounders will be identified during the estimation of propensity scores using Lasso regression and included in a multivariable logistic equation. The covariates used in the propensity score are: gender, age group (10-year deciles), index year, index month, conditions (SNOMED concepts and descendants) any time prior to index, conditions in the 365d prior to index, conditions in the 30d prior to index, drugs (ATC classes and RxNorm ingredients) any time prior to index, drugs in the 365d prior to index, drugs in the 30d prior to index, procedures any time prior to index, procedures in the 365d prior to index, procedures in the 30d prior to index, measurements any time prior to index, measurement in the 365d prior to index, measurements in the 30d prior to index, measurement values in the last year, CHADS2Vasc, Diabetes Comorbidity Severity Index, and Charlson index.

## 9.4. Data sources

This study will be conducted using routinely collected data from different data sources that participate in the OHDSI and/or EHDEN initiatives.

These databases will provide representative clinical information as collected in actual practice conditions in different European healthcare settings, US, Japan, and Australian routine practice.

The proposed databases have been selected based on their participation in the OHDSI and EHDEN initiatives after mapping to the OMOP common data model. Data were accessed remotely by participants from data partner institutions in EHDEN (SIDIAP and Estonian healthcare data), and from study investigators from Janssen Pharmaceuticals (CCAE, Optum, MDCR, MDCD, JMDC, PanTher) and from IQVIA (THIN UK, IQVIA US Ambulatory EMR, IQVIA Australia EMR, LPD Belgium EMR, IQVIA Disease Analyser France EMR, IQVIA Disease Analyser Germany EMR, and IQVIA Hospital US Charge Master).

Data available to Janssen have been described elsewhere [<https://www.ncbi.nlm.nih.gov/pubmed/31668726>], and include US claims and EMR, and Japanese claims. Other participating databases are detailed in the table below, and include electronic medical records and claims from Europe, the US, and Australia.

All analyses will be conducted in a federated manner using tools previously validated and tested in a number of studies conducted by the OHDSI community.

Table 9.4: Overview of the considered databases

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Source Name** | **Patient Count** | **History** | **Patient Type** | **Data collection** |
| IQVIA US Ambulatory EMR | 49m | 2006 – | Outpatient / General population | Dataset consists of longitudinal, de-identified ambulatory EHR data |
| IQVIA Australia EMR | 6m | 2006 – | Outpatient / General population | Anonymized patient records collected from Patient Management software used by GPs during an office visit to document patients’ clinical records |
| LPD Belgium EMR | 2m | 2005 – | Outpatient / General population | Medical contacts and diagnoses, test results and drugs associated with them. Only outpatient |
| IQVIA Disease Analyser France EMR | 10m | 1997 – | Outpatient / General population Patients seen in the primary care setting | Anonymized patient records collected from Patient Management software used by GPs during an office visit to document patients’ clinical records |
| IQVIA Disease Analyser Germany EMR | 37m | 1992 – | Outpatient / General population Public and private insurance | Anonymized patient records collected from Patient Management software used by GPs and selected specialists to document patients’ medical records within their office-based practice during a visit |
| IQVIA Hospital US Charge Master | 86m | 2007 – | Inpatient & outpatient hospital encounters, including Emergency Room visits / General population | Anonymized patient level data are sourced from hospital charge detail masters (CDM) and collected from resource management software within short-term, acute-care and non-federal hospitals |
| IQVIA UK THIN IMRD EMR | 15m | 1989 – | General population / Primary care records with hospitalization / referral information | Pseudonymized Electronic Medical Records collected from Patient Management software used within UK Primary Care |
| Estonian Health Information System | 1.4m | 2012-2016 | All inpatient and outpatient discharge summaries, general population | Pseudonymized patient level health records from central e-health database where submitting the records is mandatory for all healthcare service providers in Estonia |
| Integrated Primary Care Information | 2.5m | 1996 | Patients seen in Primary Care setting | The Integrated Primary Care Information (IPCI) database is a Dutch database containing the complete medical record of more than 2.5 million patients provided by more than 450 GPs geographically spread over the Netherlands. (12) In the Netherlands, all citizens are registered with a GP practice which acts as a gatekeeper in a two-way exchange of information with secondary care. |
| SIDIAP | 6m | 2006 | Primary care linked (partially) to inpatient data | The Sistema d'Informacio per al Desenvolupament de l'Investigacio en Atencio Primaria (SIDIAP) is a primary care records database that covers >80% of the population of Catalonia, North-East Spain. Healthcare is universal and tax-payer funded in the region, and primary care physicians are gatekeepers for all care and responsible for repeat prescriptions. |

## 9.5. Study size

Since this study will be undertaken using routinely collected data, all patients meeting the eligibility criteria above will be included. No a priori sample calculation was performed; instead, a minimum detectable rate ratio (MDRR) was estimated for each drug pair-outcome analysis in each of the available databases. Analyses with unrealistic MDRR (as established by contributing clinicians with expertise in the field) and/or with too low number of subjects with the outcome of interest are not completed.

## 9.6. Data management

All data extraction and curation will be conducted using the ATLASTM tool, an open access software generated by the OHDSI community.

The process will follow the steps described here:

1. Identification of the RA (study) cohort
2. Identification of the comparator (MTX) and treatment/s (SSZ, HCQ, LEF) cohorts
3. Identification of the different outcome cohorts
4. Review of cohort diagnostics including age and sex-specific incidence rates for face validity

The different study cohorts will be identified after searching the OMOP vocabulary by data scientists with experience with the use of OMOP and ATLAS, in collaboration with 4 clinicians and clinical epidemiologists with expertise in RA.

Cohort definitions will be exported from ATLAS and shared with each of the data partners for a consistent extraction and curation of the population, exposures and outcomes of interest.

## 9.7. Data analysis

Propensity scores will be estimated using a large-scale regularized logistic regression fitted with a Laplace prior (LASSO) and with the optimal hyperparameter determined through 10-fold cross validation. The predictor variables included will be based on patient characteristics extracted as described above.The balance of propensity score-matched cohorts will be assessed using standardised mean difference, with values of <0.1 taken to indicate negligible group differences. For the primary analysis propensity score adjustment will be done using stratification (5 strata, timed to equipoise at 5% and 95%), with matching (with a 1:1 ratio) used as a sensitivity analysis.

Cox proportional hazard models will be estimated from start of time at risk windows to 5-years after index date. In the absence of non-proportionality, outcome models will have treatment type as the sole explanatory variable.

Individuals with a history of the outcome events will be excluded from the analyses, although time periods over which these are identified will vary (30 days prior to index date for Leukopenia, Pancytopaenia, Serious infection, Opportunistic infection, Serious infection, opportunistic infection, or any other infection of interest, 365 days for stroke during an inpatient hospitalisation or ER visit, stroke, any recorded, myocardial infarction during an inpatient hospitalisation or ER visit, myocardial infarction, any recorded, all time of observed history prior to index date for any cancer (except non-melanoma skin cancer), colorectal cancer, malignant lymphoma, leukemia, lung cancer, and breast cancer).

An assessment of negative control outcomes will be used to assess whether there is residual confounding after propensity score adjustment. If there is evidence of residual confounding and there is a sufficient number of control events, estimates will be calibrated.

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. Study diagnostics for all database-target-comparator-outcome-analysis will be provided as part of study, regardless of which effect estimation results are unblinded.

All analysis code will be completed and version controlled at <https://github.com/ohdsi-studies/EhdenRaDmardsEstimation> prior to unblinding estimation results.  All study diagnostics are available for exploration at <data.ohdsi.org study package results to be pushed tomorrow am>.

All the proposed analyses will be conducted for each database separately, with estimates combined in fixed effects meta-analysis methods where I2 is <=40%. No meta-analysis will be conducted where I2 for a given drug-outcome pair is >40%.

## 9.9. Limitations of the research methods

**Selection bias**

Selection bias might arise as the consequence of including subjects with a specific period of time available in the data. Attrition tables will be provided to report on the impact of such exclusion criteria.

**Information bias**

Information bias may occur due to the incorrect identification of exposure, outcomes or co-variates. With regards to exposure, misclassification may occur due to the patient not fulfilling the prescription (primary non-adherence) or in relation with non-compliance. Hence an overestimate of utilization of the study drugs can happen, expectedly leading to non-differential misclassification.

In addition, lack or incomplete recording of safety events may lead to misclassification of the proposed safety endpoints.

Finally, surveillance bias due to increased/more regular measures of blood tests in the MTX cohort could artificially inflate the risk of leukopenia/pancytopaenia amongst MTX users due to information bias.

**Confounding**

As confounding by indication (with MTX users most likely to suffer more severe RA) will likely produce differences in baseline characteristics between the comparator and target cohorts, we will use several methods to deal with confounding:

1. Restriction: comparative studies will be conducted only in subjects previously diagnosed with RA and using any of the drugs of interest as a first line treatment. In addition, we will trim the <5% and >95% percentiles of the preference score to maximise equipoise in the study population.
2. Propensity score stratification: we will stratify by PS quintiles to reduce confounding by indication.
3. Matching: for the comparative studies we will use propensity score matching (1:1) to minimise confounding related to all observed confounders.
4. Negative control outcome analyses will be used to identify any residual unobserved confounding in the propensity score analyses. If this analysis suggests the presence of relevant unresolved confounding then further analyses will not be completed.

# 10. Protection of human subjects

For this study, participants from numerous healthcare databases will be studied. The use of the OMOP common data model and OHDSI tools will enable the federated analysis of these different databases without changing access rights to patient-level data.

# 11. Management and reporting of adverse events/adverse reactions

According to the new guidelines for good pharmacovigilance practice (EMA/873138/2011) there is no requirement for expedited reporting of adverse drug reactions from studies with secondary use of data (such as electronic health care databases). All the identified adverse events/reactions will be summarized in the resulting manuscript/s and/or interactive web-based report of all conducted analyses.

# 12. Plans for disseminating and communicating study results

Dissemination activities will be of a scientific nature (articles in scientific journals, presentations at conferences, etc.).

# 13. References

*Numbered list of literature or electronic references of documents referred to in the protocol. Sufficient information should be provided to allow retrieval of the document.*

# Annex 1. ENCePP checklist for study protocols

Annex 3: Negative control outcome list

|  |  |
| --- | --- |
| Concept ID | Concept Name |
| 378256 | Abnormal reflex |
| 443585 | Abrasion and/or friction burn of multiple sites |
| 4092879 | Absent kidney |
| 44783954 | Acid reflux |
| 433753 | Alcohol abuse |
| 4155909 | Anesthesia of skin |
| 321689 | Apnea |
| 78200 | Benign mammary dysplasia |
| 4195873 | Breath smells unpleasant |
| 443792 | Calculus of bile duct |
| 434327 | Cannabis abuse |
| 197318 | Cholesterolosis of gallbladder |
| 432303 | Cocaine abuse |
| 439125 | Complete trisomy 21 syndrome |
| 433270 | Cord entanglement without compression |
| 4311591 | Cramp in limb |
| 441267 | Cystic fibrosis |
| 436233 | Delayed milestone |
| 40486120 | Delay in physiological development |
| 4114472 | Ear problem |
| 439791 | Emotional upset |
| 433527 | Endometriosis |
| 374801 | Foreign body in ear |
| 259995 | Foreign body in orifice |
| 196456 | Gallstone |
| 4166231 | Genetic predisposition |
| 434164 | Glycosuria |
| 4163735 | Hemochromatosis |
| 439871 | Hemospermia |
| 4012570 | High risk sexual behavior |
| 4058388 | Hypertrophic scar |
| 435522 | Hypervitaminosis D |
| 443236 | Hypnotic or anxiolytic dependence |
| 4098604 | Hypomagnesemia |
| 435371 | Hypothermia |
| 443447 | Iatrogenic hypotension |
| 374375 | Impacted cerumen |
| 4344500 | Impingement syndrome of shoulder region |
| 440382 | Learning difficulties |
| 435516 | Lipoprotein deficiency disorder |
| 438808 | Mammary duct ectasia |
| 439082 | Menopausal syndrome |
| 441553 | Myoclonus |
| 4119307 | Neurogenic claudication |
| 4209423 | Nicotine dependence |
| 40304526 | Nocturia |
| 438130 | Opioid abuse |
| 378160 | Otorrhea |
| 313601 | Oxygen supply absent |
| 44782778 | Pain disorder with psychological factor |
| 4091513 | Passing flatus |
| 4022076 | Patient dependence on care provider |
| 439971 | Poisoning by anticoagulant |
| 441191 | Poisoning due to arthropod venom |
| 4295261 | Postmenopausal state |
| 198715 | Premature menopause |
| 439081 | Premenstrual tension syndrome |
| 46286594 | Problem related to lifestyle |
| 199876 | Prolapse of female genital organs |
| 4049367 | Psychologic conversion disorder |
| 440068 | Psychosexual dysfunction |
| 436246 | Reduced libido |
| 73754 | Restless legs |
| 4168212 | Restlessness and agitation |
| 80811 | Rupture of extensor tendons of hand AND/OR wrist |
| 81943 | Rupture of flexor tendons of hand AND/OR wrist |
| 138821 | Seborrhea |
| 4198492 | Shoulder joint unstable |
| 25518 | Sickle cell trait |
| 4176908 | Snapping thumb syndrome |
| 4248728 | Snoring |
| 138278 | Sprains and strains of joints and adjacent muscles |
| 4008710 | Stenosis due to any device, implant AND/OR graft |
| 40479573 | Stimulant abuse |
| 40483172 | Stimulant dependence |
| 440233 | Strain of supraspinatus muscle AND/OR tendon |
| 4194160 | Thyroid function tests abnormal |
| 4216708 | Urgent desire for stool |
| 79873 | Urolith |
| 4275889 | Visual hallucinations |
| 4193634 | Worried |