TITLE PAGE

PASS information

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
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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	Estonia, Germany, Spain, Belgium, France, Netherlands, United Kingdom, Japan, and the United States of America
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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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4. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
None				

5. 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". 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.[1] Recent drug safety studies have focussed on the risk of serious adverse events such as infection, cancer and cardiovascular outcomes associated with biologic drugs.[2–4] 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.[5,6] 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.[7] 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.

6. 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 and 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, leukemia, 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

7. RESEARCH METHODS

7.1. 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).

7.2. 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 from primary 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.

7.2.1. 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.

7.2.2. 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

7.2.6. 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 continues until 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 7.2

Table 7.2. 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	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

hospitalisation or ER visit 9) Myocardial infarction, any recorded			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

7.3. VARIABLES

7.3.1. 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.

7.3.2. OUTCOMES

The safety outcomes of interest (identified on the basis of SNOMED codes) 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 myocardial infarction 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 (SNOMED 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 ATLAS™, and reviewed by 4 clinicians and 1 epidemiologist. Myocardial infarction and stroke codes are 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.

7.3.3. 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.

7.4. 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 will be 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 7.4: 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	Medical contacts and diagnoses, test results and drugs associated

			population	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. 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.

7.5. 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.

7.6. DATA MANAGEMENT

All data extraction and curation will be conducted using the ATLAS™ 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.

7.7. 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.[8,9] 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 so as to produce calibrated hazard ratios.[10,11]

Study diagnostics (power, propensity score distribution, covariate balance) will be 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 will 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 uploaded with version controlled at https://github.com/

All the proposed analyses will be conducted for each database separately, with estimates combined in fixed effects meta-analysis methods where I^2 is <=40%. No meta-analysis will be conducted where I^2 for a given drug-outcome pair is >40%.

7.8. 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.

8. 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.

9. 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.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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

11. REFERENCES

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ANNEX 1. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Please see attached document.

ANNEX 2: 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