Utilisation disease-modifying anti-rheumatic drugs (DMARDs) used for the treatment of rheumatoid arthritis: protocol for a multi-database real-world cohort study

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| **Principal Investigators** | | |
| **Name** | **Email address** | **Affiliation** |
| Edward Burn | edward.burn@ndorms.ox.ac.uk | 1) NDORMS, University of Oxford, Oxford, UK, 2) Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain |
| Anthony Sena | asena5@its.jnj.com | 1) Janssen Research and Development, Titusville, NJ, USA |
| Talita Duarte-Salles | tduarte@idiapjgol.org | 1) Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain |
| Meghna Jani | meghna.jani@manchester.ac.uk | 1) Centre for Epidemiology Versus Arthritis, University of Manchester, Manchester, UK |
| …. | …. | …. |
| João Rafael Almeida | joao.rafael.almeida@ua.pt | 1) IEETA/DETI, University of Aveiro, Aveiro, Portugal |
| Peter Rijnbeek | p.rijnbeek@erasmusmc.nl | 1) Erasmus University Medical Center, NL |
| Patrick Ryan | PRyan4@its.jnj.com | 1) Janssen Research and Development, Titusville, NJ, USA, 2) Columbia University, New York, NY, USA |
| Daniel Prieto-Alhambra | daniel.prietoalhambra@ndorms.ox.ac.uk | 1) NDORMS, University of Oxford, Oxford, UK, 2) GREMPAL Research Group, Idiap Jordi Gol and CIBERFes, Universitat Autonoma de Barcelona and Instituto de Salud Carlos III, Barcelona, Spain |

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# Background

## Rationale

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. However, all medicines for RA are associated with adverse events (AEs), and therefore selecting the right therapy for the right patient is challenging, as treatment decisions constantly require trade-offs between benefits and risks.

Several efficacious agents are currently available for RA, with conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) usually the first line of treatment in newly diagnosed RA. Among the csDMARDs, methotrexate is currently adopted as the “anchor drug” (1) either for use as monotherapy or in combination with another csDMARDs such as hydroxychloroquine, leflunomide or sulfasalazine. Biological DMARDs (bDMARDs) such as tumour necrosis factor inhibitors (TNFi) have transformed the management of RA, however are generally reserved for more severe disease due to their high financial costs and associated AEs. More recently targeted synthetic DMARDs (tsDMARDs) have been introduced, including tofacitinib, baricitinib and upadacitinib, as additional treatment options for patients with moderate to severe RA.

Guidance for use for all DMARDs has evolved with time and also differ internationally between North America and Europe (2-4). Additionally European countries individually have different guidelines for use, especially for high cost drugs such as bDMARDs and tsDMARDs. In the UK for instance, these are prescribed as per the National Institute for Health and Care Excellence and are reserved for patients who have failed at least two csDMARDs and continue to experience persistently high disease activity (5). Despite guidelines, there is considerable heterogeneity in choice of DMARD that may be both physician and patient choice driven. Additionally in the last three years, biosimilar agents have been introduced to the market, however uptake of these bDMARDs has been inconsistent across Europe and North America. There are no studies to date that have compared international drug utilisation of RA patients receiving DMARDs and long-term sequential prescribing following initial prescription. A drug utilisation study (DUS) on the use of DMARDs would therefore provide insights into real-world practice in RA.

## Research objectives

With this study, we aim to characterise the prescribing/dispensing of first line DMARDs with regard to:

* type of first DMARD being prescribed during the the first year and during the first five years following the diagnosis of RA
* utilisation of second line DMARDs during the first year and during the first five years following RA diagnosis
* Proportion of patients not being treated with first line DMARDs following RA diagnosis
* Characterize use of DMARDs over calendar time

# Methods

## Study design

The study will be a retrospective cohort study based on routine-collected health care data which has been mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM).

## Data Sources

Routine-collected health care data which has been mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM).

## Study Period

The study period, when index events can be observed, will end at the latest on 31/12/2018 for all data sources. The start date for the study period will be from 01/01/2000 or from the start of the first available observation periods in the data source with sufficient data quality to address the study questions whichever comes last.

## Study participants

The study population consists of DMARD naive rheumatoid arthritis (RA) patients. Patients are indexed (= index date) based on the earlier of their first RA diagnosis (see appendix – table 2) in their history or the initiation of a DMARD with an RA diagnosis within 30 days of the drug exposure. Patients are required to be ≥ 18 years at index, have no inflammatory arthropathies (see appendix table 3) in any time prior (psoriatic arthritis, ankylosing spondylitis, reactive arthritis, and any axial spondyloarthropathy), have ≥ 365 days of prior continuous observation and 365 days post-index time.

## Variables

### Exposure of interest

A drug utilisation record of a DMARD (biologic DMARD, tsDMARD, or csDMARD) will be identified on the basis of the records in the drug exposure table in the CDM. (see appendix – table 1). Minocycline was also included in the analysis since this drug is approved for treatment of RA in Japan.

The drug exposure table contains records about the utilisation of drugs, which depending on the data source, may be inferred from a range of concepts, such as prescriptions written, pharmacy dispensations, or patient recollection. Drug exposure in the CDM is standardised to RxNorm concepts. This has as advantage that the drug exposure contains details of ingredients, strength, and formulation (Clinical Drug Level), which is not directly available from the ATC code.

For the *DMARD cohort for DUS*, the first drug utilisation record for a biologic DMARD, a tsDMARD or a csDMARD will be identified.

#### Creation of drug eras

From the individual drug exposures, drug eras will be created. A Drug Era is defined as a span of time when the person is assumed to be exposed to a particular active ingredient. A Drug Era is not the same as a Drug Exposure: Exposures are individual records corresponding to the source when the drug was delivered to the person, while successive periods of Drug Exposure are combined under certain rules to produce continuous Drug Eras.

### Patient characteristics at index date

Diagnosis of rheumatoid arthritis will be required for defining the study cohorts. These will be identified on the basis of records in the condition occurrence table in the CDM. (see appendix) This table includes records which indicate the presence of a medical condition, typically based on the presence of diagnosis codes.

Study participants demographics (gender, age, observation time prior to their index date, and their index year and month) will be identified. Prior diagnoses, procedures, measurements and measurement values, and devices will be identified up to, and including, their index date.

## Follow-up time

Follow-up will start from the day of the index date up to 1 or 5 years.

## Analytic methods

### Drug utilisation study

This study will describe the treatment pathways (13) of patients diagnosed with RA. The analysis will calculate the aggregate summary statistics for each RA cohort to determine the treatment pathway for each of the DMARDs in the study (see Appendix).

Both the incidence and prevalence of RA will be calculated for each database in the study and expressed as number of new patients diagnosed with RA/1,000 individuals (for incident) or the number of patients with RA (prevalent)/1,000 individuals. This will be done by year, stratified by age and gender. We will also investigate the incidence and prevalence of other drugs commonly used in patients with RA such as NSAIDs and use of systemic steroids.

For each of the cohorts, a sunburst diagram (14) is produced to describe the proportion of DMARD treatments for each treatment sequence observed in the target population. The sunburst diagram will have a maximum of 10 levels.

Each DMARD drug exposure will be calculated using a 90 day window to combine exposures into a single continuous era of exposure. When different DMARD exposures overlap for 30 days or longer, the analysis will combine these drug exposures into a single combination. We will censor any DMARD exposure that has less than 10 people.

This analysis will provide information about the utilisation of all DMARDs as available in the contributing data source/s, allowing us to summarise the most prevalent first-line therapies utilised, the proportion of individuals that discontinue treatment, switch treatments or augment their therapy.

The way in which drug utilisation has changed over time will also be considered.

Analyses will be performed separately for each data source. Where results are acceptably consistent across databases, meta-analysis will be performed.

# Study size

This study is a characterisation of all patient data captured in the data assets and meeting inclusion criteria for exposure to DMARDs. No hypothesis will be tested. Therefore, sample size calculation for the ability to reject the null hypothesis given an effect size will not be conducted.

# Data Quality Checks

OHDSI and EHDEN have developed multiple quality control mechanisms for the Common Data Model. These are described in high detail in Chapter 15 of The Book of OHDSI (<http://book.ohdsi.org/DataQuality.html>). These quality control mechanisms are standard applied.

To assure the proper functionality of the software we will follow the best practices described in Chapter 17 of The Book of OHDSI (<http://book.ohdsi.org/SoftwareValidity.html>). This includes code review, the addition of unit tests where applicable, source code management, and full code documentation. The analytical pipeline of this study will be made available in opensource for full transparency and replicability.

# Limitations of the research methods

First our study population consist of patients diagnosed on RA disease codes. This is susceptible to selection/information bias in case of suboptimal coding or use of codes with less granularity.

Second, for this study we will use real world data from electronic health care records or claims data. There might exist differences between the databases with regard to availability of certain data.

Third, for those countries where patients are referred to a specialist for the treatment of RA, use of DMARDs in primary care databases might be underrepresented.

# Regulatory and ethical compliance

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology ([2016](#_ENREF_2)), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines, and with the ethical principles laid down in the Declaration of Helsinki.

This study is fulfilling the criteria of a ‘European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study’ and follows the ‘ENCePP Code of Conduct’.

# Protection of human subjects

For this study, participants from various EU 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 the 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.

The protocols will be reviewed by the Institutional Review Boards of the respective databases.

# Management and reporting of adverse events/adverse reactions

According to the new guideline on 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).

## Plans for disseminating and communicating study results

Dissemination activities to be undertaken will have mainly, although not exclusively, a scientific nature (articles, presentations at conferences, etc.).

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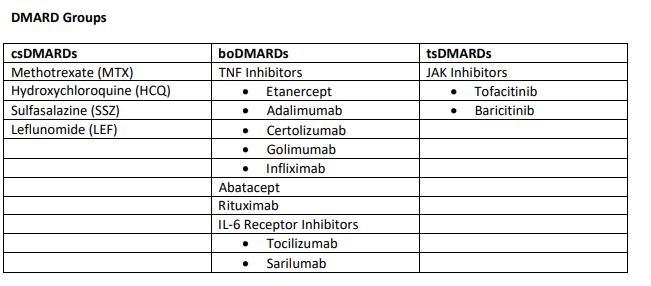
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# Appendix: Supplementary documents

Table 1 – DMARDs groups



\*Minocycline was also included in the analysis since this drug is approved for treatment of RA in Japan.

Table 2 – Rheumatoid arthritis Concept Set

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| Concept Name | Concept Id |
| Cutaneous atrophy due to rheumatoid | 4297650 |
| Deformity of foot due to rheumatoid | 4334806 |
| Deformity of hand due to rheumatoid | 46273442 |
| Disease prognosis for rheumatoid arthritis assessed, good prognosis | 2107572 |
| Disease prognosis for rheumatoid arthritis assessed, poor prognosis | 2107561 |
| Myopathy due to rheumatoid | 4107913 |
| Patient receiving first-time biologic disease modifying anti-rheumatic drug therapy for rheumatoid arthritis (RA) | 2108721 |
| Polyneuropathy in rheumatoid | 4102493 |
| Rheumatoid arthritis | 2107560 |
| Rheumatoid arthritis (RA) disease activity, high | 2107560 |
| Rheumatoid arthritis (RA) disease activity, low | 2107558 |
| Rheumatoid arthritis (RA) disease activity, moderate | 2107559 |
| Seronegative rheumatoid | 4083556 |
| Seropositive rheumatoid | 4035611 |

Table 3 – Inflammatory arthropathies

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| Concept Name | Concept Id |
| Ankylosing spondylitis | 437082 |
| Arthritis of spine | 4153359 |
| Inflammatory polyarthropathy | 74125 |
| Lupus erythematosus | 255891 |
| Post-infective arthritis | 4035610 |
| Psoriasis with arthropathy | 81931 |
| Sjögren's syndrome | 254443 |
| Systemic sclerosis | 134442 |
| Rheumatoid arthritis of multiple joints | 4117686 |
| Rheumatoid arthritis of cervical spine | 4116439 |
| Rheumatoid arthritis of joint of spine | 36683391 |
| Rheumatic joint disease | 4030552 |