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| **Janssen Research & Development\*** |
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| **Predicting Rheumatoid Arthritis Disease Severity in the**  **Absence of Clinical Data in US Claims Databases** |
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# LIST OF ABBREVIATIONS

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| List all abbreviations used in the study protocol |

|  |  |
| --- | --- |
| abbreviation | description of abbreviated term |
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# RESPONSIBLE PARTIES

## Investigator(s) and Authors

Urmila Chandran

Jenna Reps

Patrick Ryan

Yiting Wang

Paul Stang

## Sponsor

Global Epidemiology. No additional budgetary requirements, as EPI owns the database.

# ABSTRACT

The use of administrative claims databases to evaluate safety questions related to rheumatoid arthritis (RA) has been historically criticized due to the limited ability to control for confounding by indication and confounding by disease activity, due to the unavailability of clinical measures in these databases. Proxy measures for disease activity have been used by researchers, but with limited correlation with established measures. A limitation in published literature involving use of proxy measures is that these variables were generally manually selected by researchers, rather than driven by data. Although we also propose using use of a biologic as a surrogate measure for disease activity in RA patients, in this study, we in fact aim to develop a prediction model for RA disease activity by utilizing large scale data analytics that would utilize all available data and using multiple statistical models. Essentially, in this study, the prediction model will compute probability of receiving a biologic approved for RA in the US or tofacitinib during a risk period of 90 days and 730 days. The prediction model will not only be internally validated within the same dataset, but will also be externally validated in multiple claims data sources.

# AMENDMENTS AND UPDATES

None

# RATIONALE AND BACKGROUND

Insurance claims databases have been increasingly employed in drug safety studies, given the advantages of large sample size, representativeness of patients in routine practice, comprehensive capture of all health encounters, and relative efficiency compared with randomized clinical trials (RCTs) and patient registries. However, these electronic data sources in the US have not been historically preferred for investigating safety of biologics in the immunology therapeutic area. A major reason for this is the lack of clinical measures in claims databases historically deemed important by investigators, such as disease severity/activity indices, disease duration, etc. For example, higher scores (indicating higher severity) for disease activity and severity as measured by a Disease Activity Score (DAS) or Health Assessment Questionnaire (HAQ) are generally associated with the prescription of a biologic, while also being associated with several safety outcomes. The lack of these important variables may result in safety outcomes being erroneously attributed to biologic exposure if proper adjustment for channeling bias is not undertaken.

The American College of Rheumatology (ACR) guidelines for treating rheumatoid arthritis (RA) (Singh 2016) specify five instruments to evaluate RA disease severity: Patient Activity Scale-PAS, Routine Assessment of Patient Index Data 3-RAPID3, Clinical Disease Activity Index-CDAI, Disease Activity Score-DAS, and Simplified Disease Activity Index-SDAI. Although there are other measures also available to clinicians, these five are most commonly used. Data required for these instruments of clinical disease severity are generally not fully available in administrative claims databases. Hence, other potential measures of RA disease severity and statistical methods to account for confounding by severity in the absence of clinical disease activity measures in claims databases have been explored in the literature. Although, no single method was concluded to be clearly superior (Bernatsky 2013), a table listing the different surrogates and validation findings from different studies in RA patients is available as an Annex 2.

Another salient point according to ACR guidelines (Singh 2016) is that if disease continues to be moderate or severe despite DMARD monotherapy, then recommended treatments are combination of traditional non-biologic DMARDs (2 or more), or TNFi biologic or non-TNFi biologic (such as rituximab, abatacept, tocilizumab) or tofacitinib, all with or without traditional DMARD. Hence, an alternative approach in the absence of clinical measures could be identifying prescription of a biologic approved to treat moderate-to-severe RA. Although past explorative analyses (listed in Annex 1) have included biologic prescriptions in computing disease severity scores in claims databases, published studies using claims data have generally involved manual, and therefore limited selection of variables to impute disease severity. With recent advances in use of large scale analytics and ability to handle big data, powerful statistical tools are available to include all available variables (>5,000) into a comprehensive model to identify measures that could inform disease severity in claims data.

With the increasing cost of registries coupled with increasing requirements from health authorities to use real-world evidence for evaluating drug safety, investigating the scientific value of claims data to evaluate biologic drug safety in the immunology TA would be very valuable. Thus, the purpose of this study is to develop a prediction model for prescription of biologics for RA and validate the model in multiple data sources.

# STUDY Objectives

## Primary Objective

Develop a prediction model for RA disease severity based on patient having at least 1 prescription claim for any of the 9 approved biologics in the US, namely: TNFi or non-TNFi biologic (infliximab, adalimumab, golimumab, certolizumab pegol, etanercept, abatacept, rituximab, tocilizumab, anakinra) or a JAK inhibitor, tofacitinib.

# research methods

# Study Design and Setting

This is a prediction study designed to compute probability of receiving treatments of interest (TNFi or non-TNFi biologics or tofacitinib) in adult RA patients given patient and disease characteristics as represented by available covariates in a US administrative claims database. The approval dates for treatments of interest range from 1998 to 2010. The study period will be January 1, 2001 to December 31, 2016.

## Describe Data Source(s)

The prediction model will be developed using data in the Optum Extended Data Mart, Date of Death (hereafter referred to as “Optum”) database and will be externally validated in the Truven MarketScan databases (Truven Commercial Claims & Encounters, “Truven CCAE”; Truven Medicare, “Truven MDCR”; and Truven Medicaid, “Truven MDCD”. A brief description of each of the databases can be found in Annex 2.

## Study Population(s)

The target cohort for this study will be patients with a diagnosis claim for RA (index date) during the study period, Jan 1, 2001-Dec 31, 2016 that met these criteria:

* Are adults >= 18 years old as on index date,
* Have 730 days of continuous observable time prior to index,
* Have at least 1 diagnosis claim for RA in both the 0-365 days and 365-730 days time period prior to index, and have at least one prescription claim for methotrexate, sulfasalazine, hydroxychloroquine, or leflunomide in the 365 days prior to index
* Have at least 1 prescription claim for methotrexate, sulfasalazine, hydroxychloroquine, or leflunomide in the 365 days prior to index.

**Exclusion criteria:**

* Exclude patients if they have a diagnosis (ICD-9-CM) of juvenile idiopathic arthritis (714.3x), psoriasis (696.1x), psoriatic arthritis (696.0x), ankylosing spondylitis (720.0x), Crohn’s disease (555.xx), or ulcerative colitis (556.xx) any time prior to index date, as some nonbiologic and/or biologic DMARDs are indicated for the treatment of these conditions.
* Exclude patients with J-codes for intravenous administration of methotrexate (J8610, J9250, and J9260) during the pre- or post-index period, which would suggest treatment for cancer

## Outcome(s) of Interest

The primary outcome of interest for this study is at least 1 prescription claim for any of these biologics: TNFi or non-TNFi biologic (infliximab, adalimumab, golimumab, certolizumab pegol, etanercept, abatacept, rituximab, tocilizumab, anakinra) or tofacitinib.

The cohort definitions and concept sets and codes included in Target and Outcome cohorts are available at: <https://epi.jnj.com/atlas/#/cohortdefinition/5040> and <https://epi.jnj.com/atlas/#/cohortdefinition/5041>.

## Model Covariates

All standard covariates namely the below, will be included as covariates in the model, with a minimum constraint of 20 people. So, for example if a feature is recorded for 19 people or less, then it is excluded from the model. Standard set of covariates include:

Demographics (age, gender, race, ethnicity, index month)

Conditions (occurrence in past 365 days, in past 30 days)

Condition groups (using SNOMED groups or MEDRA groups)

Drugs (exposures in past 365 days, in past 30 days)

Drug groups (ingredient level)

Measurements in past 365 days and 30 days

Measurements above/below normal

Observations in past 365 days and 30 days

Procedures in past 365 days and 30 days

Concept counts (number of drugs, conditions, etc in past)

Risk scores (charlson, DCSI, CHADS2, CHADS2VASc)

**Exclusions:**

* Only variables with data in at least 20 patients in the study population will be included in the model.

# DATA ANALYSIS PLAN

## Calculation of Time-at-Risk

For the purpose of this study, two different time-at-risk periods (TAR) will be used: 1) 90 days since index (as proxy for current disease severity) 2) 730 days since index (as proxy for future disease severity).

**9.2 Patient Characteristics Summary**

Plots of the covariate count in the outcome vs. non-outcome populations will be generated to identify univariate differences between the groups.

## Model Specification

This study aims to predict a proxy disease activity score by developing a model that predicts which RA patients receive a TNFi biologic, non-TNFi biologic, or tofacitinib versus those that don’t. We will implement three models: regularized lasso logistic regression, random forest, and gradient boosting machine, trained on 75% of the dataset and internally validate the model using the remaining 25% of the data. Hyper-parameter selection will be determined using 10-fold cross-validation on the train set and an automated search for the optimal lambda will be implemented. We will use the OHDSI PatientLevelPrediction R package to perform the analysis.

## Evidence Evaluation

We will validate the prediction model by using a 25%:75% test:train split using the Optum data, where 75% of the data are used to trained the model and 25% of the data is left out of training and just used to validate the model by comparing the prediction with the ground truth. We will also implement external validation by implementing the trained model on multiple US administrative claims datasets – Truven CCAE, Truven MDCR, and Truven MDCD.

# STRENGTHS AND LIMITATIONS OF THE RESEARCH METHODS

The strength of this study is the use of advanced analytics in deriving a prediction model that incorporates close to 10,000 measured variables available in the dataset. Limitations include lack of non-representative clinical data, due to which not all measures pertinent to disease activity may be available to build the model. The prediction model can only be built using measured variables.

# PROTECTION OF HUMAN SUBJECTS

The use of Truven CCAE, Truven MDCR, and Truven MDCD and Optum DOD was reviewed by the New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subjects research.

# MANAGEMENT AND REPORTING OF ADVERSE EVENTS AND ADVERSE REACTIONS

This study uses coded data that already exist in an electronic database. In this type of database, it is not possible to link (i.e., identify a potential causal association between) a particular product and medical event for any individual. Thus, the *minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available* and adverse events are not reportable as individual AE reports. The study results will be assessed for medically important results.

# PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Results of study analyses will be reviewed and assessed for publication.

# references

Singh JA et al, 2016. 2015 American College of Rheumatology guidelines for the treatment of rheumatoid arthritis. Arthritis Care & Research. 68(1): 1-25.

Bernatsky, S., et al. (2013). "Consensus statements for the use of administrative health data in rheumatic disease research and surveillance." J Rheumatol **40**(1): 66-73.

Desai, R. J., et al. (2015). "An external validation study reporting poor correlation between the claims-based index for rheumatoid arthritis severity and the disease activity score." Arthritis Res Ther **17**: 83.

Sato, M., et al. (2006). "The validity of a rheumatoid arthritis medical records-based index of severity compared with the DAS28." Arthritis Res Ther **8**(3): R57.

Avina-Zubieta, J. A., et al. (2011). "Risk of cerebrovascular disease associated with the use of glucocorticoids in patients with incident rheumatoid arthritis: a population-based study." Ann Rheum Dis **70**(6): 990-995.

Widdifield, J., et al. (2013). "Serious infections in a population-based cohort of 86,039 seniors with rheumatoid arthritis." Arthritis Care Res (Hoboken) **65**(3): 353-361.

McBride, S., et al. (2011). "Biologic disease-modifying drug treatment patterns and associated costs for patients with rheumatoid Arthritis." J Rheumatol **38**(10): 2141-2149.

Ting, G., et al. (2005). "Performance of a rheumatoid arthritis records-based index of severity." J Rheumatol **32**(9): 1679-1687.

Baser, O., et al. (2012). "Derivation of severity index for rheumatoid arthritis and its association with healthcare outcomes." J Med Econ **15**(5): 918-924.

Baser, O., et al. (2015). "Impact of Switching From an Initial Tumor Necrosis Factor Inhibitor on Health Care Resource Utilization and Costs Among Patients With Rheumatoid Arthritis." Clin Ther **37**(7): 1454-1465.

# ANNEX: LIST OF STAND-ALONE DOCUMENTS

## Annex 1: List of studies using surrogates of disease activity in large administrative health databases and validation findings if available

| 1st author, year | Data source | Surrogates used for disease activity/severity | Any validation of index |
| --- | --- | --- | --- |
| Desai 2015 | Linked BRASS (RA study from Brigham’s that collected DAS28-CRP and HAQ)) & Medicare | CIRAS index:  Rheumatology visits rehab visits x-ray rheumatoid lung involvement Felty's syndrome hand surgery # inflammatory marker tests rheumatoid factor test # platelet counts # chemistry panels medication count | correlation between CIRAS and DAS28-CRP was low (Pearson r=0.07), and the correlation between calculated CIRAS and MD-HAQ physical function score was also low (Pearson r=0.08). |
| Sato 2006 | Linked BRASS & Medicare | RARBIS  RARBIS is an RA severity score using information from medical records, including: prior surgical history, radiologic findings, laboratory findings, clinical and functional status and extra-articular manifestations, with prior surgical and radiologic subscales given higher weights in the total RARBIS score | RARBIS was moderately correlated with the DAS28 (r = 0.41, 95% CI 0.23–0.56) Clinical subscale r=0.42 (0.24 – 0.57) Total score with medication: r= 0.33 (0.14 – 0.49) x-ray subscale: r= 0.34 (0.15 – 0.50) |
| Avina-Zubieta 2011 | Canadian Ministry of Health databases | ever visited a rheumatologist for RA  # visits for RA visits to family doctors & all visits to rheumatologists for each person-year of f/u  DMARD use | PS modeling used; Authors proposed that patients with at least one visit to a rheumatologist, patients with more doctor visits per person-year of follow-up and patients with a higher DMARD ranking were those with more severe disease |
|  |
| DMARD use categorized as ordinal variable - highest rank of: 1: no-DMARD use ;  2: sulfasalazine and antimalarial agents  3: methotrexate or intramuscular gold 4: leflunomide, ciclosporin A, azathioprine, cyclophosphamide, chlorambucil or mycophenolate mofetil  5: biological agents |
| Widdifield 2013 | health administrative databases from Ontario | number of rheumatology visits | none |
| history of joint replacement |  |
| extra-articular RA features |  |
| use of NSAIDs and COX inhibitors |  |
| McBride, 2011 | employer-based health insurance database | medical care use: • inpatient hospital • outpatient visits • bone & joint procedures • imaging procedures • OT & PT | none |
| RA-related prescription drug use |  |
| Ting, 2005 | VA Health System, medical records | RARBIS: prior surgical history,  radiologic findings,  laboratory findings,  clinical and functional status extra-articular manifestations | correlation between the summary score and its components and the intensity of RA treatment r = 0.35, 95% CI 0.18–0.55 |
| Baser, 2012 | VHA database | SIFRA : 34 RA-related indicators assessed by Delphi panel | Spearman’s rank correlations between SIFRA and CIRAS were 0.525 for SIFRA without and 0.539 with laboratory data.  Correlations between SIFRA and the Charlson Comorbidity Index (CCI) (0.1503 without, 0.1135 with laboratory data |
| Baser, 2015 | Truven Health MarketScan | SIFRA : 34 RA-related indicators |  |
| Wolfe | National Data Bank for rheumatic diseases | current and lifetime treatment with DMARDs and/or biologics | sole use of DMARD/biologics and demographic variables in administrative data does not distinguish disease severity groups with adequate sensitivity and/or specificity (only 67.2% were correctly classified according to Patient Activity Scale (composed of HAQ, visual analog scale for pain, and visual analog scale for global severity). |

## Annex 2: Description of databases used in this study

**Optum’s ClinformaticsTM Data Mart – Date of Death** (OPTUM): Optum Clinformatics Extended DataMart is an adjudicated US administrative health claims database for members of private health insurance, who are fully insured in commercial plans or in administrative services only (ASOs), Legacy Medicare Choice Lives (prior to January 2006), and Medicare Advantage (Medicare Advantage Prescription Drug coverage starting January 2006). The population is primarily representative of commercial claims patients (0-65 years old) with some Medicare (65+ years old) however ages are capped at 90 years. It includes data captured from administrative claims processed from inpatient and outpatient medical services and prescriptions as dispensed, as well as results for outpatient lab tests processed by large national lab vendors who participate in data exchange with Optum. This dataset also provides date of death (month and year only) for members with both medical and pharmacy coverage from the Social Security Death Master File (however after 2011 reporting frequency changed due to changes in reporting requirements) and location information for patients is at the US state level.

**Truven Health MarketScan® Commercial Claims and Encounters Database**: Truven Health MarketScan® Commercial Claims and Encounters Database (Truven CCAE) represent data from individuals enrolled in United States employer-sponsored insurance health plans. The data includes adjudicated health insurance claims (e.g. inpatient, outpatient, and outpatient pharmacy) as well as enrollment data from large employers and health plans who provide private healthcare coverage to employees, their spouses, and dependents. Additionally, it captures laboratory tests for a subset of the covered lives. This administrative claims database includes a variety of fee-for-service, preferred provider organizations, and capitated health plans.

**Truven Health MarketScan® Medicare Supplemental and Coordination of Benefits Database**: Truven Health MarketScan® Medicare Supplemental and Coordination of Benefits Database (Truven MDCR) represents health services of retirees in the United States with primary or Medicare supplemental coverage through privately insured fee-for-service, point-of-service, or capitated health plans. These data include adjudicated health insurance claims (e.g. inpatient, outpatient, and outpatient pharmacy). Additionally, it captures laboratory tests for a subset of the covered lives.

**Truven Health MarketScan® Multi-State Medicaid Database**: Truven Health MarketScan® Multi-State Medicaid Database (Truven MDCD) adjudicated US health insurance claims for Medicaid enrollees from multiple states and includes hospital discharge diagnoses, outpatient diagnoses and procedures, and outpatient pharmacy claims as well as ethnicity and Medicare eligibility. Members maintain their same identifier even if they leave the system for a brief period however the dataset lacks lab data.