STUDY PLAN

Descriptive Analysis of Switching Events and Product Utilization for Targeted Immunomodulators in Patients with Rheumatoid Arthritis

Date: 11 January 2022

Research Team:

Jaclyn Bosco
Jerry Clewell
Hillel Cohen
Chase Higginson
Anna Hyde
Seoyoung Kim
Edward Li
Nancy Lin
Cate Lockhart
Junjie Ma
Jim Marshall
Dottie McCabe
Cara McDermott
Aaron Mendelsohn
Manish Mittal
Young Hee Nam
Pamala Pawloski

1 Table of contents

2 List of abbreviations

Abbreviations	Descriptions
BBCIC	Biologics and Biosimilars Collective Intelligence Consortium
CDM	Common Data Model
CER	Comparative Effectiveness Research
CIDA	Cohort Identification and Descriptive Analysis
DMARD	Disease-modifying antirheumatic drugs
DRN	Distributed Research Network
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	U.S. Food and Drug Administration
FISMA	Federal Information Security Management Act
HCPCS	Healthcare Common Procedure Coding System
HIPAA	Health Insurance Portability and Accountability Act of 1996
HPHC	Harvard Pilgrim Health Care, Inc
HPHCI	Harvard Pilgrim Health Care Institute
ICMJE	International Committee of Medical Journal Editors
IL	Interleukin
IRB	Institutional Review Board
JAK	Janus Kinase
Mg	Milligram
NDC	National Drug Code
NIST	National Institute of Standards and Technology
NSCLC	Non-Small Cell Lung Cancer
QA	Quality assurance
QC	Quality control
RA	Rheumatoid Arthritis
SAS	Statistical Analysis System
SD	Standard Deviation
TNF	Tumor necrosis factor

3 Background and rationale

Switching between different originator biologics, biosimilars and originator biologics, or different medication classes, is a challenge in post-marketing comparative effectiveness research (CER) studies as it introduces potential bias and complicates the study design. The Biologics and Biosimilars Collective Intelligence Consortium (BBCIC) previously convened a Workgroup (Switching Methods Workgroup) charged with developing best practice recommendations for the conduct of innovator and biosimilar switching studies, including treating switching/sequencing as a covariate/confounder in CER studies, and describing valid approaches to compare outcomes between switchers and non-switchers. Building upon this Workgroup's recommendations[1], study designs and methods for handling switching as a confounder or covariate will be tested in the BBCIC Distributed Research Network (DRN) with anti-inflammatory agents being used to treat rheumatoid arthritis (RA) as a test case. As a next step, we will conduct a descriptive analysis to better understand anti-inflammatory medication treatment patterns in patients with RA.

This study will provide foundational data regarding patterns of care for anti-inflammatory medications among commercially insured adults in the United States with a recorded diagnosis of RA. Specifically, this study will involve an examination of patterns of medication use by demographics and clinical comorbidities, plus switching between and within medication classes. Switching events of interest will be dependent upon the clinical significance of a given switch, as well as the frequency of use of the individual products involved. The findings from this study will be used to inform the design and conduct of inferential analyses of medications in this therapeutic area, e.g., to examine the comparative effectiveness and safety across products for which switching may have occurred; to compare outcomes among patients treated according to clinical guidelines versus those treated based upon other regimens.

4 Study Objective

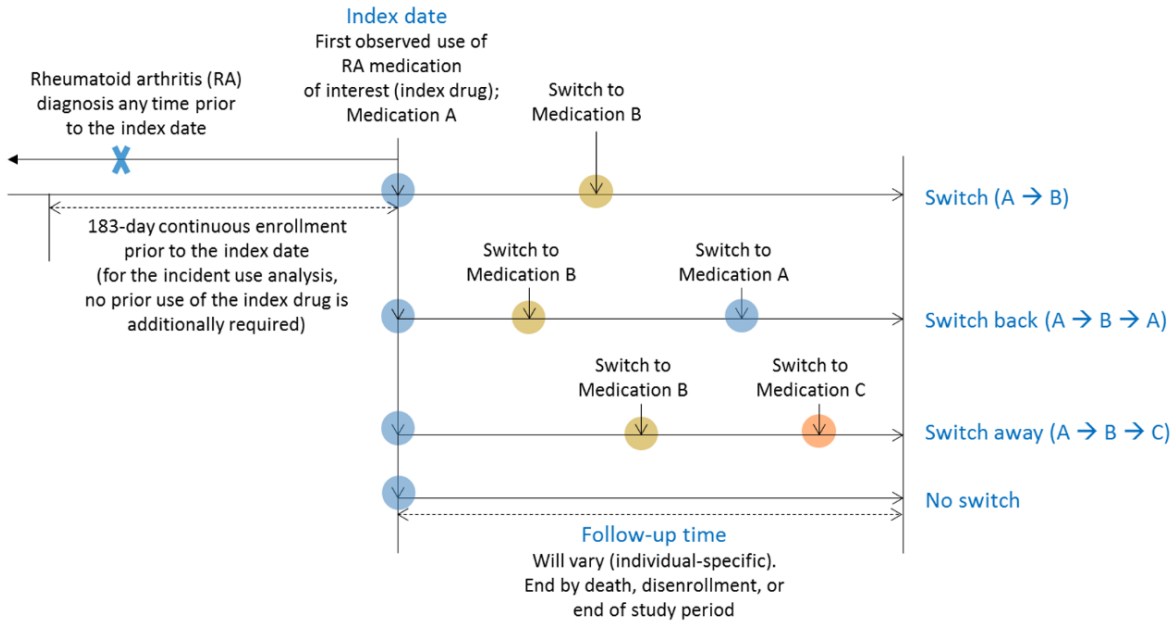
To examine treatment patterns for anti-inflammatory agents, namely targeted immunomodulators (i.e., biologics and Janus Kinase [JAK] inhibitors), used in the treatment of RA, with particular focus on switching of medications.

5 Methods

5.1 Study design

This study will be a population-based, non-interventional retrospective cohort study using administrative healthcare claims data. As noted, the study will be descriptive in nature. A study schematic is presented in Figure 1.

Figure 1. Study schematic



5.2 Study population

We will include adult patients diagnosed with RA who had medical and pharmacy coverage in one of the participating health plans that comprise the BBCIC DRN ("Research Partners") for the entire study observation period.

As patients may use the products of interest for conditions other than RA, we will conduct stratified analyses, i.e., we will examine utilization and switching patterns within subgroups of patients based upon the presence or absence of other comorbidities. The subgroups that we will consider are:

- Overall group (i.e., all patients with RA, regardless of the presence of any comorbid condition)
- Patients with ulcerative colitis or Crohn's disease in addition to RA, (persons with other comorbid conditions will be excluded)
- Patients with psoriasis, psoriatic arthritis or ankylosing spondylitis and RA, (persons with other comorbid conditions will be excluded)
- Patients with no comorbidities (i.e., RA only)

The eligibility criteria provided below will be applied to all study cohorts.

5.2.1 Inclusion Criteria

- Use of a targeted immunomodulator (biologic, JAK inhibitor) medication of interest during the study period
- Adult (≥18 years) on the first observed administration/dispensing date for a medication of interest (index date, index medication)

- Diagnosis of RA as evidenced by diagnosis codes appearing in at least two outpatient claims on different dates or one inpatient claim before or on the index date
- Continuous enrollment with medical and pharmacy coverage for at least 183 days prior to the index date (gaps ≤45 days will be allowed to account for potential administrative lapses without actual interruptions in coverage)

5.2.2 Exclusion Criteria

None

5.3 Study period

The study period for identifying eligible patients will be 01 January 2016 through the most recent data available from participating research partners. For the primary analysis however, we will focus on data through 31 March 2020 to avoid possible changes in utilization of the products of interest that may have resulted from the Covid-19 pandemic.

5.4 Data sources

We will use data from the BBCIC Distributed Research Network (DRN) for this study. The BBCIC DRN consists of administrative claims data for approximately 95 million patient-years from five Research Partners including two large national health insurers (CVS Health [Aetna], HealthCore [Anthem]) and three regional health insurers or integrated healthcare delivery systems (Harvard Pilgrim Health Care, HealthPartners, Kaiser Permanente of Washington). These Research Partners participate in the Food and Drug Administration's (FDA) Sentinel System, enabling the BBCIC to leverage the curated data in the Sentinel Common Data Model, plus the data standardization and analytic tools of the Sentinel System for conducting distributed analyses [2-4].

5.5 Variables of Interest

We will examine the number of both prevalent and incident users for the products of interest during the study period. Incident use will be defined as having no exposure to a given medication in the 183 days before the index date.

5.5.1 Exposures

As noted above, we will examine targeted immunomodulator medicinal products for RA including the following:

- Biologics, including biosimilars (e.g., infliximab)
- JAK Inhibitors (e.g., tofacitinib)

A full list of the medications of interest is provided in Appendix A.

We will examine utilization and switching amongst the products of interest, as well as switching from a targeted immunomodulator to a non-biologic disease-modifying antirheumatic drugs (DMARDs) (non-biologic DMARDs to be evaluated in this study are noted in Appendix B).

Products of interest will be identified using J-codes from Healthcare Common Procedure Coding System (HCPCS) (Appendix C) or National Drug Codes (NDCs) (Appendix D).

5.5.2 Other variables

Characteristics of users for the various products/classes will be measured relative to the index date, as defined above. Demographic characteristics (age, sex) will be measured on the index date, and clinical characteristics (e.g., will be assessed during the 183-day period before the index date ("baseline period"). Clinical characteristics include a combined comorbidity index[5] and various comorbid conditions, e.g., ulcerative colitis, Crohn's disease, psoriasis, psoriatic arthritis, uveitis. The complete list of clinical characteristics to be examined in this analysis will be provided in the study specifications.

5.5.3 Outcome

The outcome for this descriptive study will be switching amongst the products of interest. Switching will be defined as dispensing or administration of a new medicinal product/class after initiation of the index product. Thus, add-on medications to an existing product being utilized by a patient will be classified as a switch for the purposes of this descriptive analysis. Furthermore, we will not require the switching event to be within a given number of days of the initial prescription.

5.6 Data analysis

We will initially describe the patient cohorts according to demographic characteristics (measured on the index date) and clinical characteristics (assessed during the 183-day period before the index date ("baseline period"). Frequency counts and percentages will be used for assessing categorical variables and means (SDs) will be used for continuous measures.

Product utilization and switching patterns will be characterized through the following analyses:

- Number of users and number of dispensings (incident and prevalent) for each product (Appendix E). Patients can contribute multiple "incident" episodes for the same or different drugs if they met the eligibility criteria, including the 183-day washout period, each time.
- Baseline demographics (e.g., age, sex) and clinical (e.g., comorbidities/comorbidity score, concomitant medications) characteristics of users (incident and prevalent) for each product (Appendix E)
- Descriptive statistics will be calculated to characterize incident users who switch products (Appendix F) and to quantify the frequency and time to switching for the general types of switching events presented here (the full list of switching events of interest can be found in Appendix G) :
    - Between originator biologics and their biosimilars, e.g., infliximab originator and its biosimilars;
    - From biologic (including biosimilars) or JAK inhibitors to non-biologic DMARDs;
    - Between biologics (including biosimilars) and JAK inhibitors;
    - Between different biologic products with a shared mechanism of action (e.g., infliximab to adalimumab);
    - Between different biologic products with different mechanisms of action (e.g., etanercept to abatacept).

  As there are many potential switching events of interest, some of which are likely to be relatively uncommon, we will produce Sankey diagrams to graphically depict treatment and switching

patterns for the products of interest. These plots will then be utilized to prioritize switching events by informing the research team regarding which specific switching events are sufficiently large enough to warrant deeper exploration.

- Kaplan-Meier curves will be used to examine time to switching (1st switch, 2nd switch). Censoring events will include death, disenrollment, or end of the study period. We will perform the Kaplan-Meier analyses overall and by meaningful strata (e.g., age group, sex) and will use these analyses to generate univariate statistics (e.g., mean, standard deviation [SD]) on time to switch as well as for determining the frequency and percent of switching events occurring before or after a given time following the first medication (180 days) to identify early vs. late switching events. Table shells and sample graphical displays for presenting the results of the Kaplan-Meier analyses are provided in Appendices F-J.

The publicly available Sentinel System analytic toolkit (Cohort Identification and Descriptive Analysis [CIDA v8.1.0]) will be used to perform the distributed analyses.[6] Note that cells with counts >0 and <10 will not be presented to protect the anonymity of patients, per standard BBCIC practice; medications with <10 incident users will be excluded from analysis. All analyses will be aggregated across the Research Partners; that is, no Research Partner specific data will be presented.

5.7 Sample size estimation

As this is a descriptive study with no specific hypotheses being tested, statistical power calculations based upon an estimated sample size will not be performed. The sample size will be dependent upon the uptake of the products of interest among the eligible population during the study period.

6 Data management

Data management and coordination for this project will be performed by Harvard Pilgrim Health Care Institute (HPHCI) in Boston, Massachusetts. Specifically, HPHCI will be responsible for distributing Statistical Analysis Systems (SAS) programs that will be used to collect data from the administrative claims databases at participating Research Partners. The BBCIC DRN, a subset of the Sentinel DRN, allows Research Partners to maintain physical and operational control of their data while enabling use of the data to meet the study needs. HPHCI will use a web-based portal that enables secure distribution of analytic queries, data transfer, and document storage. The system to be used will meet all required federal and state security guidelines for health data (e.g., Federal Information Security Management Act [FISMA], Health Insurance Portability and Accountability Act of 1996 [HIPAA]), specifically compliant for FISMA moderate risk security controls as specified in the National Institute of Standards and Technology (NIST) Special Publication 800-53[7].

7 Quality control

The Sentinel DRN utilizes a Common Data Model (CDM) that standardizes data across Research Partners, and each of the participating Research Partners has experience using this data model. This study will use data quality assurance procedures of the Sentinel System. The quality assurance procedures assess consistency with the Sentinel CDM; evaluate adherence to data model requirements, definitions, and logical relationships between data model tables; and, review trends in medical and pharmacy services use within and across Data Partners. Details on the Sentinel quality assurance process and data curation are

documented on the Sentinel website [FDA, 2018c]. The data curation process is consistent with the guidance set forth by the FDA in its current recommendations for data quality assurance, specifically "Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data" (Guidance), section IV.E "Best Practices – Data Sources: Quality Assurance (QA) and Quality Control (QC)", published in May 2013 [FDA, 2013]. In addition to the data quality assurance procedures, HPHCI adopts standard SAS programming quality assurance and quality control processes used by the Sentinel System to check SAS programs and deliverables.

8 Protection of human subjects

Institutional Review Boards (IRBs) for the participating Research Partners determined that BBCIC analyses using only administrative claims data within its DRN, such as this research described herein, do not meet the definition of human subjects research.

This study will be conducted in accordance with all legal and regulatory requirements. Additionally, we will adhere to commonly accepted research practices, including those described in the following guidance documents: European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology [ENCePP, 2018]; Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology [International Society for Pharmacoepidemiology, 2015]; FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment [FDA, 2005]; and FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets [FDA, 2013].

9 Limitations

There are several limitations inherent to studies of medication utilization in the setting of healthcare databases. It is possible that some medication switches will be missed if there is inadequate evidence in the available data to classify a switch. Also, the reason for switching is not available in administrative claims data and could be due to reasons apart from medical considerations (e.g., formulary changes). The algorithms used to define data study variables may be imperfect and these rely on the accuracy and precision of coding for these items. As a result, misclassifications can occur. Additionally, use of the medications of interest is presumed to be for RA and its manifestations. It is possible that some of these therapies are being used for other comorbid conditions and that these conditions, as opposed to RA, may have necessitated a switching event. Another limitation may be that the outcomes of this study may not be generalizable to patients who receive care in very different health systems in the U.S., and may only represent the commercially insured patient population in the U.S.

10 Milestones and timelines

The key milestones and estimated timelines are in Table 2 below. It is possible that multiple manuscripts will be generated from this work. Should this be the case, the manuscript referenced in Table 2 will reflect the first manuscript of this study.

Table 2. Milestones and timelines

Milestone	Estimated Completion Date
Study Plan Completion	December 2021
Specifications Completion	March 2022
Query Distribution	April 2022
Data Analysis	August 2022
Manuscript Draft	September 2021
Scientific Committee Presentation of Manuscript	October 2021

11 Dissemination of research findings

We will produce final report(s) that summarizes findings from this study with the intent of presenting the findings at a scientific conference(s) as well as a manuscript(s) submitted to a peer-review journal(s) for publication. Any journal articles generated from this study will be in accordance with the International Committee of Medical Journal Editors (ICMJE) guidelines [ICMJE, 2018].

12 References

1. Desai RJ, Kim SC, Curtis JR, Bosco JLF, Eichelberger B, Barr CE, Lockhart CM, Bradbury BD, Clewell J, Cohen HP, Gagne JJ; Biologics and Biosimilars Collective Intelligence Consortium (BBCIC) Switching Workgroup. Methodologic considerations for noninterventional studies of switching from reference biologic to biosimilars. Pharmacoepidemiol Drug Saf. 2020 Jul;29(7):757-769. doi: 10.1002/pds.4809. Epub 2019 Jul 12. PMID: 31298463.

2. US Food and Drug Administration. FDA's Sentinel Initiative. Available at https://www.fda.gov/safety/fdas-sentinel-initiative. Accessed 29 March 2020.

3. Platt R, Brown JS, Robb M, et al. The FDA Sentinel Initiative - An Evolving National Resource. The New England Journal of Medicine. 2018;379(22):2091-2093.

4. Ball R, Robb M, Anderson SA, Dal Pan G. The FDA's Sentinel Initiative--A comprehensive approach to medical product surveillance. Clinical Pharmacology and Therapeutics. 2016;99(3):265-268.

5. Gagne JJ, Glynn RJ, Avorn J, Levin R, Schneeweiss S. A combined comorbidity score predicted mortality in elderly patients better than existing scores. J Clin Epidemiol. 2011 July ; 64(7): 749–759. doi:10.1016/j.jclinepi.2010.10.004.

6. US Food and Drug Administration. FDA Sentinel Routine Querying System. https://dev.sentinelsystem.org/projects/AD/repos/qrp/browse. Accessed 10 May 2021.

7. National Institute of Standards and Technology. NIST Special Publication 800-53: Security and privacy controls for information systems and organizations. Gaithersburg, MD. August 2017.

8. International Society for Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practices. Bethesda MD. June 2015.

9. European Network of Centres for Pharmacoepidemiology and pharmacovigilance. ENCePP guide on Methodological standards in pharmacoepidemiology. London, UK. July 2018.

10. Food and Drug Administration. Guidance for Industry: Good pharmacovigilance practices and pharmacoepidemiologic assessment. Rockville, MD. March 2005.

11. Food and Drug Administration. Guidance for industry and FDA staff: best practices for conducting and reporting pharmacoepidemiologic safety studies using electronic healthcare data. Rockville, MD. May 2013.

12. International Committee of Medical Journal Editors. Recommendations for the conduct, reporting, editing and publication of scholarly work in medical journals. December 2018.

Appendix A: Immunomodulators (Biologics and Janus Kinase [JAK] Inhibitors) of Interest

Anti-Tumor necrosis factor (TNF)

- Adalimumab (Humira®),
- Certolizumab (Cimzia®)
- Etanercept (Enbrel®)
- Golimumab (Simponi®, Simponi Aria®)
- Infliximab (Remicade®), infliximab-abda (Renflexis®), infliximab-axxq (Avsola®), infliximab-dyyb (Inflectra®). Additional biosimilar infliximabs may be added if they are licensed and marketed prior to the study start date.

B-cell inhibitor

- Rituximab (Rituxan®), rituximab-abbs (Truxima®)

Interleukin-1 (IL-1) blocker

- Anakinra (Kineret®)
- Canakinumab (Ilaris®)

Interleukin-6 (IL-6) blocker

- Tocilizumab (Actemra®)
- Sarilumab (Kevzara®)

T-cell inhibitor

- Abatacept (Orencia®)

Janus kinase (JAK) inhibitor

- Tofacitinib (Xeljanz®)
- Baricitinib (Olumiant®)

Appendix B: Non-Biologic Disease-modifying antirheumatic drugs (DMARDs)

- Hydroxychloroquine
- Azathioprine
- Sulfasalazine
- Methotrexate
- Leflunomide
- Cyclosporine
- Gold salts
- D-penicillamine
- Minocycline

Appendix C: List of Procedure Codes (HCPCS) Used to Define Exposures of Interest

Exposure	Description	Code
abatacept	Injection, abatacept, per 10 mg	C9230
abatacept	Injection, abatacept, 10 mg (code may be used for medicare when drug administered under the direct supervision of a physician, not for use when drug is self administered)	J0129
abatacept	Injection, rituximab 10 mg and hyaluronidase	J9311
abatacept	Injection, rituximab, 10 mg	J9312
canakinumab	Injection, guselkumab, 1 mg	J1628
certolizumab	Injection, certolizumab pegol, 1 mg	J0718
certolizumab	Injection, etanercept, 25 mg (code may be used for medicare when drug administered under the direct supervision of a physician, not for use when drug is self administered)	J1438
certolizumab	Injection, golimumab, 1 mg, for intravenous use	J1602
etanercept	Injection, natalizumab, 1 mg	J2323
golimumab	Injection natalizumab per 5 mg	C9126
infliximab abda	Injection, infliximab-qbtx, biosimilar, (ixifi), 10 mg	Q5109
infliximab dyyb	Injection, rilonacept, 1 mg	J2793
infliximab originator	Injection, infliximab-dyyb, biosimilar, (inflectra), 10 mg	Q5103
infliximab originator	Injection, infliximab-abda, biosimilar, (renflexis), 10 mg	Q5104
infliximab qbtx	Injection, tildrakizumab, 1 mg	J3245
rituximab originator	Injection, tocilizumab, 1 mg	C9264
rituximab originator	Injection, rituximab and hyaluronidase, 10 mg	C9467
rituximab originator	Injection, tocilizumab, 1 mg	J3262
rituximab originator	Injection, rituximab, 100 mg	J9310
tocilizumab	Injection, ustekinumab, 1 mg	C9261
tocilizumab	Ustekinumab, for intravenous injection, 1 mg	Q9989

Appendix D: List of National Drug Codes (NDCs) Used to Define Exposures

Exposure	NDC	Generic Name	Brand Name
abatacept	00003218811	abatacept	Orencia
abatacept	00003218831	abatacept	Orencia
abatacept	00003218851	abatacept	Orencia ClickJect
abatacept	00003281411	abatacept	Orencia
abatacept	00003281811	abatacept	Orencia
abatacept	00003218710	abatacept/maltose	Orencia (with maltose)
abatacept	00003218713	abatacept/maltose	Orencia (with maltose)
adalimumab	00074006702	adalimumab	Humira(CF) Pedi Crohns Starter
adalimumab	00074012403	adalimumab	Humira(CF) Pen Crohns-UC-HS
adalimumab	00074012474	adalimumab	Humira(CF) Pen
adalimumab	00074024302	adalimumab	Humira(CF)
adalimumab	00074055402	adalimumab	Humira(CF) Pen
adalimumab	00074061602	adalimumab	Humira(CF)
adalimumab	00074081702	adalimumab	Humira(CF)
adalimumab	00074153903	adalimumab	Humira(CF) Pen Psor-Uv-Adol HS
adalimumab	00074254003	adalimumab	Humira(CF) Pedi Crohns Starter
adalimumab	00074379902	adalimumab	Humira
adalimumab	00074379903	adalimumab	Humira Pediatric Crohns Start
adalimumab	00074379906	adalimumab	Humira Pediatric Crohns Start
adalimumab	00074433902	adalimumab	Humira Pen
adalimumab	00074433906	adalimumab	Humira Pen Crohns-UC-HS Start
adalimumab	00074433907	adalimumab	Humira Pen Psor-Uveits-Adol HS
adalimumab	00074433971	adalimumab	Humira Pen
adalimumab	00074634702	adalimumab	Humira
adalimumab	00074937402	adalimumab	Humira
adalimumab	54868482200	adalimumab	Humira
anakinra	66658023401	anakinra	Kineret
anakinra	66658023407	anakinra	Kineret
anakinra	66658023428	anakinra	Kineret
baricitinib	00002418230	baricitinib	Olumiant
canakinumab	00078058261	canakinumab/PF	Ilaris (PF)
canakinumab	00078073461	canakinumab/PF	Ilaris (PF)
certolizumab	50474070062	certolizumab pegol	Cimzia Powder for Reconst
certolizumab	50474071079	certolizumab pegol	Cimzia
certolizumab	50474071081	certolizumab pegol	Cimzia Starter Kit
etanercept	54868478200	etanercept	Enbrel
etanercept	54868544400	etanercept	Enbrel
etanercept	58406042534	etanercept	Enbrel
etanercept	58406042541	etanercept	Enbrel
etanercept	58406043501	etanercept	Enbrel
etanercept	58406043504	etanercept	Enbrel
etanercept	58406044501	etanercept	Enbrel SureClick
etanercept	58406044504	etanercept	Enbrel SureClick
etanercept	58406045501	etanercept	Enbrel
etanercept	58406045504	etanercept	Enbrel
etanercept	58406045601	etanercept	Enbrel Mini
etanercept	58406045604	etanercept	Enbrel Mini
golimumab	57894007001	golimumab	Simponi
golimumab	57894007002	golimumab	Simponi

golimumab	57894007101	golimumab	Simponi
golimumab	57894007102	golimumab	Simponi
golimumab	57894035001	golimumab	Simponi ARIA
guselkumab	57894064001	guselkumab	Tremfya
guselkumab	57894064011	guselkumab	Tremfya
infliximab	57894003001	infliximab	Remicade
infliximab qbtx	00069081101	infliximab qbtx	Ixifi
infliximab abda	00006430501	infliximab-abda	Renflexis
infliximab abda	00006430502	infliximab-abda	Renflexis
infliximab dyyb	00069080901	infliximab-dyyb	Inflectra
rituximab	50242005121	rituximab	Rituxan
rituximab	50242005306	rituximab	Rituxan
rituximab abbs	63459010310	rituximab abbs	Truxima
rituximab abbs	63459010450	rituximab abbs	Truxima
rituximab	50242010801	rituximab/hyaluronidase, human recombinant	Rituxan Hycela
rituximab	50242010901	rituximab/hyaluronidase, human recombinant	Rituxan Hycela
sarilumab	00024590801	sarilumab	Kevzara
sarilumab	00024591001	sarilumab	Kevzara
sarilumab	00024592001	sarilumab	Kevzara
sarilumab	00024592201	sarilumab	Kevzara
tocilizumab	50242013501	tocilizumab	Actemra
tocilizumab	50242013601	tocilizumab	Actemra
tocilizumab	50242013701	tocilizumab	Actemra
tocilizumab	50242013801	tocilizumab	Actemra
tocilizumab	50242014301	tocilizumab	Actemra ACTPen
tofacitinib	00069050130	tofacitinib citrate	Xeljanz XR
tofacitinib	00069100101	tofacitinib citrate	Xeljanz
tofacitinib	00069100201	tofacitinib citrate	Xeljanz

NDC codes are checked against First Data Bank's “National Drug Data File (NDDF®) Plus

Appendix E: Baseline Characteristics ("Table 1") for Incident and Prevalent Users of Targeted Immunomodulators of Interest for each Patient Cohort

Table 1a-1x. Baseline Characteristics of Incident and Prevalent Targeted Immunomodulators Users with Rheumatoid Arthritis *(and other comorbidities depending upon the cohort)* in the BBCIC Distributed Research Network, 01 January 2016 – 31 March 2020*		
Characteristics	**N/Mean**	**%/SD**
Number of unique patients	n	n/a
Number of episodes	n	100%
Patient Characteristics		
Age (years)	mean	std
18-49	n	%
50-64	n	%
65+	n	%
Sex		
Female	n	%
Male	n	%
Year/Quarter		
2016	n	%
Q1	n	%
Q2	n	%
Q3	n	%
Q4	n	%
… Each Year and Quarter through 2020 Q1	n	%
Clinical characteristics		
Combined comorbidity index	mean	SD
History of each of the Targeted Immunomodulators (brand-name) (n=18)	n	%
Ulcerative colitis	n	%
Crohn's disease	n	%
Psoriasis	n	%
Psoriatic arthritis	n	%
Ankylosing spondylitis	n	%
Uveitis	n	%

*Baseline Table ("Table 1") will be produced for all products (brand name) listed in Appendix A. Separate tables will be produced for prevalent and incident users (incident with respect to the given brand name product) and for each of the four patient cohorts of interest.

Appendix F: Baseline Characteristics ("Table 1") for Patients Switching from xxx to xxx

Table 2a-2x. Baseline Characteristics of Incident Targeted Immunomodulators Users with Rheumatoid Arthritis *(and other comorbidities depending upon the cohort)* Switching from Product/Class xxx to xxx. BBCIC Distributed Research Network, 01 January 2016 – 31 March 2020*		
Characteristics	**N/Mean**	**%/SD**
Number of unique patients	n	n/a
Patient Characteristics		
Age (years)	mean	std
18-49	n	%
50-64	n	%
65+	n	%
Sex		
Female	n	%
Male	n	%
Year/Quarter		
2016	n	%
Q1	n	%
Q2	n	%
Q3	n	%
Q4	n	%
… Each Year and Quarter through 2020 Q1	n	%
Clinical characteristics		
Combined comorbidity index	mean	SD
History of each of the Targeted Immunomodulators (brand-name) (n=18)	n	%
Ulcerative colitis	n	%
Crohn's disease	n	%
Psoriasis	n	%
Psoriatic arthritis	n	%
Ankylosing spondylitis	n	%
Uveitis	n	%

*Table 2 will be produced for switching events of interest (see Appendix G). The table will be for incident users (initial/index product) only and will be produced for each of the four patient cohorts of interest.

Appendix G: Switching Events of Interest

Listed below are the switching events of interest for this project and for which descriptive analyses may be used to characterize these events. As there are many potential switching events of interest, some of which are likely to be relatively uncommon, we will produce Sankey diagrams to graphically depict treatment and switching patterns for the products of interest. These plots will then be utilized to prioritize switching events by informing the research team regarding which specific switching events are sufficiently large enough to warrant deeper exploration.

	Index Product	Product Switched To	Incidence with respect to:*
Originator biologics and biosimilars	infliximab originator	Infliximab biosimilar (any) infliximab-abda infliximab-axxq infliximab-dyyb	infliximab (any)
	infliximab originator	infliximab-abda	infliximab (any)
	infliximab originator	infliximab-axxq	infliximab (any)
	infliximab originator	infliximab-dyyb	infliximab (any)
	Infliximab biosimilar (any) infliximab-abda infliximab-axxq infliximab-dyyb	infliximab originator	infliximab (any)
	infliximab-abda	infliximab originator	infliximab (any)
	infliximab-axxq	infliximab originator	infliximab (any)
	infliximab-dyyb	infliximab originator	infliximab (any)
	rituximab	rituximab-abbs	rituximab (any)
	rituximab-abbs	Rituximab	rituximab (any)
Biologic/JAK inhibitor to non-biologic DMARD	Biologics adalimumab certolizumab etanercept golimumab infliximab (and biosimilars) rituximab (and biosimilar) anakinra canakinumab tocilizumab sarilumab abatacept	Non-biologic DMARDs hydroxychloroquine azathioprine sulfasalazine methotrexate leflunomide cyclosporine gold salts D-penicillamine minocycline	Biologic (any)
	JAK inhibitors tofacitinib baricitinib	Non-biologic DMARDs hydroxychloroquine azathioprine sulfasalazine methotrexate leflunomide cyclosporine	JAK inhibitor (any)

		gold salts D-penicillamine minocycline	
Non-biologic DMARD to biologic/JAK inhibitor (2nd switch only)	<u>Non-biologic DMARDs</u> hydroxychloroquine azathioprine sulfasalazine methotrexate leflunomide cyclosporine gold salts D-penicillamine minocycline	<u>Biologics</u> adalimumab certolizumab etanercept golimumab infliximab (and biosimilars) rituximab (and biosimilar) anakinra canakinumab tocilizumab sarilumab abatacept	Incident user determination based upon first switch
	<u>Non-biologic DMARDs</u> hydroxychloroquine azathioprine sulfasalazine methotrexate leflunomide cyclosporine gold salts D-penicillamine minocycline	<u>JAK inhibitors</u> tofacitinib baricitinib	Incident user determination based upon first switch
Biologics and JAK inhibitors	<u>Biologics</u> adalimumab certolizumab etanercept golimumab infliximab (and biosimilars) rituximab (and biosimilar) anakinra canakinumab tocilizumab sarilumab abatacept	<u>JAK inhibitors</u> tofacitinib baricitinib	Biologic (any) JAK inhibitor (any)
	<u>JAK inhibitors</u> tofacitinib baricitinib	<u>Biologics</u> adalimumab certolizumab etanercept golimumab infliximab (and biosimilars) rituximab (and biosimilar) anakinra canakinumab tocilizumab sarilumab abatacept	JAK inhibitor (any) Biologic (any)
Different biologic products with a shared	adalimumab	certolizumab	adalimumab, certolizumab

mechanism of action (anti-TNFs only)	adalimumab	etanercept	adalimumab, etanercept
	adalimumab	golimumab	adalimumab, golimumab
	adalimumab	infliximab (and biosimilars)	adalimumab, infliximab (and biosimilars)
	certolizumab	adalimumab	certolizumab, adalimumab
	certolizumab	etanercept	certolizumab, etanercept
	certolizumab	golimumab	certolizumab, golimumab
	certolizumab	infliximab (and biosimilars)	certolizumab, infliximab (and biosimilars)
	etanercept	adalimumab	etanercept, adalimumab
	etanercept	certolizumab	etanercept, certolizumab
	etanercept	golimumab	etanercept, golimumab
	etanercept	infliximab (and biosimilars)	etanercept, infliximab (and biosimilars)
	golimumab	adalimumab	golimumab, adalimumab
	golimumab	certolizumab	golimumab, certolizumab
	golimumab	etanercept	golimumab, etanercept
	golimumab	infliximab (and biosimilars)	golimumab, infliximab (and biosimilars)
	infliximab (and biosimilars)	adalimumab	infliximab (and biosimilars), adalimumab
	infliximab (and biosimilars)	certolizumab	infliximab (and biosimilars), certolizumab
	infliximab (and biosimilars)	etanercept	infliximab (and biosimilars), etanercept
	infliximab (and biosimilars)	golimumab	infliximab (and biosimilars), golimumab
Different biologic products with a different mechanism of action	<u>Anti-TNFs</u> adalimumab certolizumab etanercept golimumab infliximab (and biosimilars)	<u>B-cell inhibitor</u> rituximab (and biosimilar)	Anti-TNFs (any), B-cell inhibitors (any)

	Anti-TNFs adalimumab certolizumab etanercept golimumab infliximab (and biosimilars)	IL-1 blockers anakinra canakinumab	Anti-TNFs (any), IL-1 blockers (any)
	Anti-TNFs adalimumab certolizumab etanercept golimumab infliximab (and biosimilars)	IL-6 blockers tocilizumab sarilumab	Anti-TNFs (any), IL-6 blockers (any)
	Anti-TNFs adalimumab certolizumab etanercept golimumab infliximab (and biosimilars)	T-cell inhibitor abatacept	Anti-TNFs (any) T-cell inhibitor
	B-cell inhibitor rituximab (and biosimilar)	Anti-TNFs adalimumab certolizumab etanercept golimumab infliximab (and biosimilars)	B-cell inhibitor (any), Anti-TNFs (any)
	B-cell inhibitor rituximab (and biosimilar)	IL-1 blockers anakinra canakinumab	B-cell inhibitor (any), IL-1 blocker (any)
	B-cell inhibitor rituximab (and biosimilar)	IL-6 blockers tocilizumab sarilumab	B-cell inhibitor (any), IL-6 blocker (any)
	B-cell inhibitor rituximab (and biosimilar)	T-cell inhibitor abatacept	B-cell inhibitor (any), T-cell inhibitor
	IL-1 blockers anakinra canakinumab	Anti-TNFs adalimumab certolizumab etanercept golimumab infliximab (and biosimilars)	IL-1 blocker (any), Anti-TNFs (any)
	IL-1 blockers anakinra canakinumab	B-cell inhibitor rituximab (and biosimilar)	IL-1 blocker (any), B-cell inhibitor (any)
	IL-1 blockers anakinra canakinumab	IL-6 blockers tocilizumab sarilumab	IL-1 blocker (any), IL-6 blocker (any)
	IL-1 blockers anakinra canakinumab	T-cell inhibitor abatacept	IL-1 blocker (any), T-cell inhibitor
	IL-6 blockers tocilizumab sarilumab	Anti-TNFs adalimumab certolizumab etanercept	IL-6 blocker (any), Anti-TNFs (any)

		golimumab infliximab (and biosimilars)	
	IL-6 blockers tocilizumab sarilumab	B-cell inhibitor rituximab (and biosimilar)	IL-6 blocker (any), B-cell inhibitor (any)
	IL-6 blockers tocilizumab sarilumab	IL-1 blockers anakinra canakinumab	IL-6 blocker (any), IL-1 blocker (any)
	IL-6 blockers tocilizumab sarilumab	T-cell inhibitor abatacept	IL-6 blocker (any), T-cell inhibitor
	T-cell inhibitor abatacept	Anti-TNFs adalimumab certolizumab etanercept golimumab infliximab (and biosimilars)	T-cell inhibitor, Anti-TNFs (any)
	T-cell inhibitor abatacept	B-cell inhibitor rituximab (and biosimilar)	T-cell inhibitor, B-cell inhibitor (any)
	T-cell inhibitor abatacept	IL-1 blockers anakinra canakinumab	T-cell inhibitor, IL-1 blocker (any)
	T-cell inhibitor abatacept	IL-6 blockers tocilizumab sarilumab	T-cell inhibitor, IL-6 blocker (any)

Appendix H: Descriptive (Univariate) Statistics for Time to Switch

Table XX: Descriptive Statistics of Time to First Switch, in Days								
Switch	Switch Pattern Episodes (n)	Mean	Std	Min	25%	50%	75%	Max
Product/Class A to B								
Product/Class A to C								
Product/Class B to C								

Appendix I: Descriptive Statistics for Time to Switch (User-Specified Cutpoints)

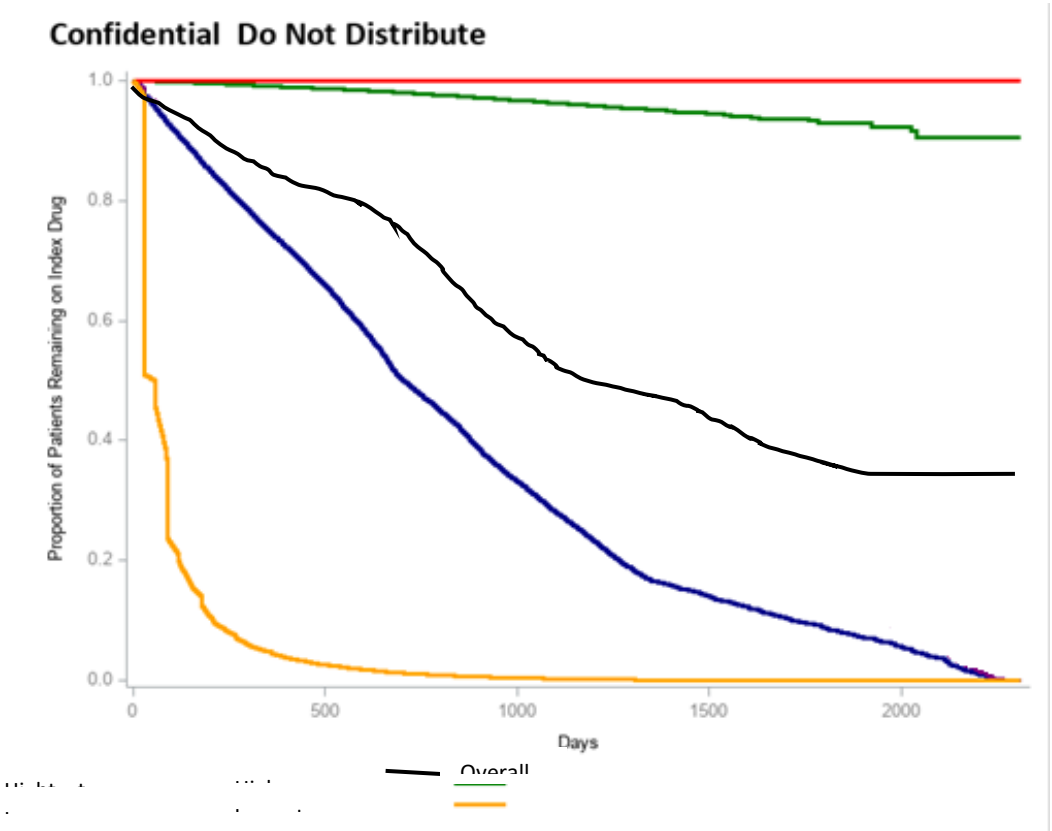
Table XX: Descriptive Statistics of Time to First Switch, in Days			
Switch	Switch Pattern Episodes (n)	< 180 days n (%)	≥ 180 days n (%)
Product/Class A to B			
Product/Class A to C			
Product/Class B to C			

Appendix J: Descriptive Statistics of Time to Switch or Censoring Event (in Days)

Switch Pattern	Episodes (n)	Mean	Std	Min	25%	50%	75%	Max
Product/Class A to B								
First Switch								
Censoring reason 1: end of enrollment								
Censoring reason 2: end of query period								
Censoring reason 3: death								
Product/Class A to C								
First Switch								
Censoring reason 1: end of enrollment								
Censoring reason 2: end of query period								
Censoring reason 3: death								
Product/Class B to C								
First Switch								
Censoring reason 1: end of enrollment								
Censoring reason 2: end of query period								
Censoring reason 3: death								

Appendix K: Survival Curve for Time to Switching Event

Figure xx. Survival Curve for Time to (First or Second) Switch (in Days)



Appendix L: ICD-10-CM codes for Rheumatoid Arthritis

Description	Code
Felty's syndrome, unspecified site	M0500
Felty's syndrome, right shoulder	M05011
Felty's syndrome, left shoulder	M05012
Felty's syndrome, unspecified shoulder	M05019
Felty's syndrome, right elbow	M05021
Felty's syndrome, left elbow	M05022
Felty's syndrome, unspecified elbow	M05029
Felty's syndrome, right wrist	M05031
Felty's syndrome, left wrist	M05032
Felty's syndrome, unspecified wrist	M05039
Felty's syndrome, right hand	M05041
Felty's syndrome, left hand	M05042
Felty's syndrome, unspecified hand	M05049
Felty's syndrome, right hip	M05051
Felty's syndrome, left hip	M05052
Felty's syndrome, unspecified hip	M05059
Felty's syndrome, right knee	M05061
Felty's syndrome, left knee	M05062
Felty's syndrome, unspecified knee	M05069
Felty's syndrome, right ankle and foot	M05071
Felty's syndrome, left ankle and foot	M05072
Felty's syndrome, unspecified ankle and foot	M05079
Felty's syndrome, multiple sites	M0509
Rheumatoid lung disease with rheumatoid arthritis of unspecified site	M0510
Rheumatoid lung disease with rheumatoid arthritis of right shoulder	M05111
Rheumatoid lung disease with rheumatoid arthritis of left shoulder	M05112
Rheumatoid lung disease with rheumatoid arthritis of unspecified shoulder	M05119
Rheumatoid lung disease with rheumatoid arthritis of right elbow	M05121
Rheumatoid lung disease with rheumatoid arthritis of left elbow	M05122
Rheumatoid lung disease with rheumatoid arthritis of unspecified elbow	M05129
Rheumatoid lung disease with rheumatoid arthritis of right wrist	M05131
Rheumatoid lung disease with rheumatoid arthritis of left wrist	M05132
Rheumatoid lung disease with rheumatoid arthritis of unspecified wrist	M05139
Rheumatoid lung disease with rheumatoid arthritis of right hand	M05141
Rheumatoid lung disease with rheumatoid arthritis of left hand	M05142
Rheumatoid lung disease with rheumatoid arthritis of unspecified hand	M05149
Rheumatoid lung disease with rheumatoid arthritis of right hip	M05151
Rheumatoid lung disease with rheumatoid arthritis of left hip	M05152
Rheumatoid lung disease with rheumatoid arthritis of unspecified hip	M05159
Rheumatoid lung disease with rheumatoid arthritis of right knee	M05161
Rheumatoid lung disease with rheumatoid arthritis of left knee	M05162
Rheumatoid lung disease with rheumatoid arthritis of unspecified knee	M05169
Rheumatoid lung disease with rheumatoid arthritis of right ankle and foot	M05171
Rheumatoid lung disease with rheumatoid arthritis of left ankle and foot	M05172
Rheumatoid lung disease with rheumatoid arthritis of unspecified ankle and foot	M05179
Rheumatoid lung disease with rheumatoid arthritis of multiple sites	M0519
Rheumatoid vasculitis with rheumatoid arthritis of unspecified site	M0520
Rheumatoid vasculitis with rheumatoid arthritis of right shoulder	M05211
Rheumatoid vasculitis with rheumatoid arthritis of left shoulder	M05212

Rheumatoid vasculitis with rheumatoid arthritis of unspecified shoulder	M05219
Rheumatoid vasculitis with rheumatoid arthritis of right elbow	M05221
Rheumatoid vasculitis with rheumatoid arthritis of left elbow	M05222
Rheumatoid vasculitis with rheumatoid arthritis of unspecified elbow	M05229
Rheumatoid vasculitis with rheumatoid arthritis of right wrist	M05231
Rheumatoid vasculitis with rheumatoid arthritis of left wrist	M05232
Rheumatoid vasculitis with rheumatoid arthritis of unspecified wrist	M05239
Rheumatoid vasculitis with rheumatoid arthritis of right hand	M05241
Rheumatoid vasculitis with rheumatoid arthritis of left hand	M05242
Rheumatoid vasculitis with rheumatoid arthritis of unspecified hand	M05249
Rheumatoid vasculitis with rheumatoid arthritis of right hip	M05251
Rheumatoid vasculitis with rheumatoid arthritis of left hip	M05252
Rheumatoid vasculitis with rheumatoid arthritis of unspecified hip	M05259
Rheumatoid vasculitis with rheumatoid arthritis of right knee	M05261
Rheumatoid vasculitis with rheumatoid arthritis of left knee	M05262
Rheumatoid vasculitis with rheumatoid arthritis of unspecified knee	M05269
Rheumatoid vasculitis with rheumatoid arthritis of right ankle and foot	M05271
Rheumatoid vasculitis with rheumatoid arthritis of left ankle and foot	M05272
Rheumatoid vasculitis with rheumatoid arthritis of unspecified ankle and foot	M05279
Rheumatoid vasculitis with rheumatoid arthritis of multiple sites	M0529
Rheumatoid heart disease with rheumatoid arthritis of unspecified site	M0530
Rheumatoid heart disease with rheumatoid arthritis of right shoulder	M05311
Rheumatoid heart disease with rheumatoid arthritis of left shoulder	M05312
Rheumatoid heart disease with rheumatoid arthritis of unspecified shoulder	M05319
Rheumatoid heart disease with rheumatoid arthritis of right elbow	M05321
Rheumatoid heart disease with rheumatoid arthritis of left elbow	M05322
Rheumatoid heart disease with rheumatoid arthritis of unspecified elbow	M05329
Rheumatoid heart disease with rheumatoid arthritis of right wrist	M05331
Rheumatoid heart disease with rheumatoid arthritis of left wrist	M05332
Rheumatoid heart disease with rheumatoid arthritis of unspecified wrist	M05339
Rheumatoid heart disease with rheumatoid arthritis of right hand	M05341
Rheumatoid heart disease with rheumatoid arthritis of left hand	M05342
Rheumatoid heart disease with rheumatoid arthritis of unspecified hand	M05349
Rheumatoid heart disease with rheumatoid arthritis of right hip	M05351
Rheumatoid heart disease with rheumatoid arthritis of left hip	M05352
Rheumatoid heart disease with rheumatoid arthritis of unspecified hip	M05359
Rheumatoid heart disease with rheumatoid arthritis of right knee	M05361
Rheumatoid heart disease with rheumatoid arthritis of left knee	M05362
Rheumatoid heart disease with rheumatoid arthritis of unspecified knee	M05369
Rheumatoid heart disease with rheumatoid arthritis of right ankle and foot	M05371
Rheumatoid heart disease with rheumatoid arthritis of left ankle and foot	M05372
Rheumatoid heart disease with rheumatoid arthritis of unspecified ankle and foot	M05379
Rheumatoid heart disease with rheumatoid arthritis of multiple sites	M0539
Rheumatoid myopathy with rheumatoid arthritis of unspecified site	M0540
Rheumatoid myopathy with rheumatoid arthritis of right shoulder	M05411
Rheumatoid myopathy with rheumatoid arthritis of left shoulder	M05412
Rheumatoid myopathy with rheumatoid arthritis of unspecified shoulder	M05419
Rheumatoid myopathy with rheumatoid arthritis of right elbow	M05421
Rheumatoid myopathy with rheumatoid arthritis of left elbow	M05422
Rheumatoid myopathy with rheumatoid arthritis of unspecified elbow	M05429
Rheumatoid myopathy with rheumatoid arthritis of right wrist	M05431
Rheumatoid myopathy with rheumatoid arthritis of left wrist	M05432
Rheumatoid myopathy with rheumatoid arthritis of unspecified wrist	M05439
Rheumatoid myopathy with rheumatoid arthritis of right hand	M05441

Rheumatoid myopathy with rheumatoid arthritis of left hand	M05442
Rheumatoid myopathy with rheumatoid arthritis of unspecified hand	M05449
Rheumatoid myopathy with rheumatoid arthritis of right hip	M05451
Rheumatoid myopathy with rheumatoid arthritis of left hip	M05452
Rheumatoid myopathy with rheumatoid arthritis of unspecified hip	M05459
Rheumatoid myopathy with rheumatoid arthritis of right knee	M05461
Rheumatoid myopathy with rheumatoid arthritis of left knee	M05462
Rheumatoid myopathy with rheumatoid arthritis of unspecified knee	M05469
Rheumatoid myopathy with rheumatoid arthritis of right ankle and foot	M05471
Rheumatoid myopathy with rheumatoid arthritis of left ankle and foot	M05472
Rheumatoid myopathy with rheumatoid arthritis of unspecified ankle and foot	M05479
Rheumatoid myopathy with rheumatoid arthritis of multiple sites	M0549
Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified site	M0550
Rheumatoid polyneuropathy with rheumatoid arthritis of right shoulder	M05511
Rheumatoid polyneuropathy with rheumatoid arthritis of left shoulder	M05512
Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified shoulder	M05519
Rheumatoid polyneuropathy with rheumatoid arthritis of right elbow	M05521
Rheumatoid polyneuropathy with rheumatoid arthritis of left elbow	M05522
Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified elbow	M05529
Rheumatoid polyneuropathy with rheumatoid arthritis of right wrist	M05531
Rheumatoid polyneuropathy with rheumatoid arthritis of left wrist	M05532
Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified wrist	M05539
Rheumatoid polyneuropathy with rheumatoid arthritis of right hand	M05541
Rheumatoid polyneuropathy with rheumatoid arthritis of left hand	M05542
Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified hand	M05549
Rheumatoid polyneuropathy with rheumatoid arthritis of right hip	M05551
Rheumatoid polyneuropathy with rheumatoid arthritis of left hip	M05552
Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified hip	M05559
Rheumatoid polyneuropathy with rheumatoid arthritis of right knee	M05561
Rheumatoid polyneuropathy with rheumatoid arthritis of left knee	M05562
Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified knee	M05569
Rheumatoid polyneuropathy with rheumatoid arthritis of right ankle and foot	M05571
Rheumatoid polyneuropathy with rheumatoid arthritis of left ankle and foot	M05572
Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified ankle and foot	M05579
Rheumatoid polyneuropathy with rheumatoid arthritis of multiple sites	M0559
Rheumatoid arthritis of unspecified site with involvement of other organs and systems	M0560
Rheumatoid arthritis of right shoulder with involvement of other organs and systems	M05611
Rheumatoid arthritis of left shoulder with involvement of other organs and systems	M05612
Rheumatoid arthritis of unspecified shoulder with involvement of other organs and systems	M05619
Rheumatoid arthritis of right elbow with involvement of other organs and systems	M05621
Rheumatoid arthritis of left elbow with involvement of other organs and systems	M05622
Rheumatoid arthritis of unspecified elbow with involvement of other organs and systems	M05629
Rheumatoid arthritis of right wrist with involvement of other organs and systems	M05631
Rheumatoid arthritis of left wrist with involvement of other organs and systems	M05632
Rheumatoid arthritis of unspecified wrist with involvement of other organs and systems	M05639
Rheumatoid arthritis of right hand with involvement of other organs and systems	M05641
Rheumatoid arthritis of left hand with involvement of other organs and systems	M05642
Rheumatoid arthritis of unspecified hand with involvement of other organs and systems	M05649
Rheumatoid arthritis of right hip with involvement of other organs and systems	M05651
Rheumatoid arthritis of left hip with involvement of other organs and systems	M05652
Rheumatoid arthritis of unspecified hip with involvement of other organs and systems	M05659
Rheumatoid arthritis of right knee with involvement of other organs and systems	M05661
Rheumatoid arthritis of left knee with involvement of other organs and systems	M05662
Rheumatoid arthritis of unspecified knee with involvement of other organs and systems	M05669

Rheumatoid arthritis of right ankle and foot with involvement of other organs and systems	M05671
Rheumatoid arthritis of left ankle and foot with involvement of other organs and systems	M05672
Rheumatoid arthritis of unspecified ankle and foot with involvement of other organs and systems	M05679
Rheumatoid arthritis of multiple sites with involvement of other organs and systems	M0569
Rheumatoid arthritis with rheumatoid factor of unspecified site without organ or systems involvement	M0570
Rheumatoid arthritis with rheumatoid factor of right shoulder without organ or systems involvement	M05711
Rheumatoid arthritis with rheumatoid factor of left shoulder without organ or systems involvement	M05712
Rheumatoid arthritis with rheumatoid factor of unspecified shoulder without organ or systems involvement	M05719
Rheumatoid arthritis with rheumatoid factor of right elbow without organ or systems involvement	M05721
Rheumatoid arthritis with rheumatoid factor of left elbow without organ or systems involvement	M05722
Rheumatoid arthritis with rheumatoid factor of unspecified elbow without organ or systems involvement	M05729
Rheumatoid arthritis with rheumatoid factor of right wrist without organ or systems involvement	M05731
Rheumatoid arthritis with rheumatoid factor of left wrist without organ or systems involvement	M05732
Rheumatoid arthritis with rheumatoid factor of unspecified wrist without organ or systems involvement	M05739
Rheumatoid arthritis with rheumatoid factor of right hand without organ or systems involvement	M05741
Rheumatoid arthritis with rheumatoid factor of left hand without organ or systems involvement	M05742
Rheumatoid arthritis with rheumatoid factor of unspecified hand without organ or systems involvement	M05749
Rheumatoid arthritis with rheumatoid factor of right hip without organ or systems involvement	M05751
Rheumatoid arthritis with rheumatoid factor of left hip without organ or systems involvement	M05752
Rheumatoid arthritis with rheumatoid factor of unspecified hip without organ or systems involvement	M05759
Rheumatoid arthritis with rheumatoid factor of right knee without organ or systems involvement	M05761
Rheumatoid arthritis with rheumatoid factor of left knee without organ or systems involvement	M05762
Rheumatoid arthritis with rheumatoid factor of unspecified knee without organ or systems involvement	M05769
Rheumatoid arthritis with rheumatoid factor of right ankle and foot without organ or systems involvement	M05771
Rheumatoid arthritis with rheumatoid factor of left ankle and foot without organ or systems involvement	M05772
Rheumatoid arthritis with rheumatoid factor of unspecified ankle and foot without organ or systems involvement	M05779
Rheumatoid arthritis with rheumatoid factor of multiple sites without organ or systems involvement	M0579
Other rheumatoid arthritis with rheumatoid factor of unspecified site	M0580
Other rheumatoid arthritis with rheumatoid factor of right shoulder	M05811
Other rheumatoid arthritis with rheumatoid factor of left shoulder	M05812
Other rheumatoid arthritis with rheumatoid factor of unspecified shoulder	M05819
Other rheumatoid arthritis with rheumatoid factor of right elbow	M05821
Other rheumatoid arthritis with rheumatoid factor of left elbow	M05822
Other rheumatoid arthritis with rheumatoid factor of unspecified elbow	M05829
Other rheumatoid arthritis with rheumatoid factor of right wrist	M05831

Other rheumatoid arthritis with rheumatoid factor of left wrist	M05832
Other rheumatoid arthritis with rheumatoid factor of unspecified wrist	M05839
Other rheumatoid arthritis with rheumatoid factor of right hand	M05841
Other rheumatoid arthritis with rheumatoid factor of left hand	M05842
Other rheumatoid arthritis with rheumatoid factor of unspecified hand	M05849
Other rheumatoid arthritis with rheumatoid factor of right hip	M05851
Other rheumatoid arthritis with rheumatoid factor of left hip	M05852
Other rheumatoid arthritis with rheumatoid factor of unspecified hip	M05859
Other rheumatoid arthritis with rheumatoid factor of right knee	M05861
Other rheumatoid arthritis with rheumatoid factor of left knee	M05862
Other rheumatoid arthritis with rheumatoid factor of unspecified knee	M05869
Other rheumatoid arthritis with rheumatoid factor of right ankle and foot	M05871
Other rheumatoid arthritis with rheumatoid factor of left ankle and foot	M05872
Other rheumatoid arthritis with rheumatoid factor of unspecified ankle and foot	M05879
Other rheumatoid arthritis with rheumatoid factor of multiple sites	M0589
Rheumatoid arthritis with rheumatoid factor, unspecified	M059
Rheumatoid arthritis without rheumatoid factor, unspecified site	M0600
Rheumatoid arthritis without rheumatoid factor, right shoulder	M06011
Rheumatoid arthritis without rheumatoid factor, left shoulder	M06012
Rheumatoid arthritis without rheumatoid factor, unspecified shoulder	M06019
Rheumatoid arthritis without rheumatoid factor, right elbow	M06021
Rheumatoid arthritis without rheumatoid factor, left elbow	M06022
Rheumatoid arthritis without rheumatoid factor, unspecified elbow	M06029
Rheumatoid arthritis without rheumatoid factor, right wrist	M06031
Rheumatoid arthritis without rheumatoid factor, left wrist	M06032
Rheumatoid arthritis without rheumatoid factor, unspecified wrist	M06039
Rheumatoid arthritis without rheumatoid factor, right hand	M06041
Rheumatoid arthritis without rheumatoid factor, left hand	M06042
Rheumatoid arthritis without rheumatoid factor, unspecified hand	M06049
Rheumatoid arthritis without rheumatoid factor, right hip	M06051
Rheumatoid arthritis without rheumatoid factor, left hip	M06052
Rheumatoid arthritis without rheumatoid factor, unspecified hip	M06059
Rheumatoid arthritis without rheumatoid factor, right knee	M06061
Rheumatoid arthritis without rheumatoid factor, left knee	M06062
Rheumatoid arthritis without rheumatoid factor, unspecified knee	M06069
Rheumatoid arthritis without rheumatoid factor, right ankle and foot	M06071
Rheumatoid arthritis without rheumatoid factor, left ankle and foot	M06072
Rheumatoid arthritis without rheumatoid factor, unspecified ankle and foot	M06079
Rheumatoid arthritis without rheumatoid factor, vertebrae	M0608
Rheumatoid arthritis without rheumatoid factor, multiple sites	M0609
Adult-onset Still's disease	M061
Rheumatoid bursitis, unspecified site	M0620
Rheumatoid bursitis, right shoulder	M06211
Rheumatoid bursitis, left shoulder	M06212
Rheumatoid bursitis, unspecified shoulder	M06219
Rheumatoid bursitis, right elbow	M06221
Rheumatoid bursitis, left elbow	M06222
Rheumatoid bursitis, unspecified elbow	M06229
Rheumatoid bursitis, right wrist	M06231
Rheumatoid bursitis, left wrist	M06232
Rheumatoid bursitis, unspecified wrist	M06239
Rheumatoid bursitis, right hand	M06241
Rheumatoid bursitis, left hand	M06242
Rheumatoid bursitis, unspecified hand	M06249

Rheumatoid bursitis, right hip	M06251
Rheumatoid bursitis, left hip	M06252
Rheumatoid bursitis, unspecified hip	M06259
Rheumatoid bursitis, right knee	M06261
Rheumatoid bursitis, left knee	M06262
Rheumatoid bursitis, unspecified knee	M06269
Rheumatoid bursitis, right ankle and foot	M06271
Rheumatoid bursitis, left ankle and foot	M06272
Rheumatoid bursitis, unspecified ankle and foot	M06279
Rheumatoid bursitis, vertebrae	M0628
Rheumatoid bursitis, multiple sites	M0629
Rheumatoid nodule, unspecified site	M0630
Rheumatoid nodule, right shoulder	M06311
Rheumatoid nodule, left shoulder	M06312
Rheumatoid nodule, unspecified shoulder	M06319
Rheumatoid nodule, right elbow	M06321
Rheumatoid nodule, left elbow	M06322
Rheumatoid nodule, unspecified elbow	M06329
Rheumatoid nodule, right wrist	M06331
Rheumatoid nodule, left wrist	M06332
Rheumatoid nodule, unspecified wrist	M06339
Rheumatoid nodule, right hand	M06341
Rheumatoid nodule, left hand	M06342
Rheumatoid nodule, unspecified hand	M06349
Rheumatoid nodule, right hip	M06351
Rheumatoid nodule, left hip	M06352
Rheumatoid nodule, unspecified hip	M06359
Rheumatoid nodule, right knee	M06361
Rheumatoid nodule, left knee	M06362
Rheumatoid nodule, unspecified knee	M06369
Rheumatoid nodule, right ankle and foot	M06371
Rheumatoid nodule, left ankle and foot	M06372
Rheumatoid nodule, unspecified ankle and foot	M06379
Rheumatoid nodule, vertebrae	M0638
Rheumatoid nodule, multiple sites	M0639
Inflammatory polyarthropathy	M064
Other specified rheumatoid arthritis, unspecified site	M0680
Other specified rheumatoid arthritis, right shoulder	M06811
Other specified rheumatoid arthritis, left shoulder	M06812
Other specified rheumatoid arthritis, unspecified shoulder	M06819
Other specified rheumatoid arthritis, right elbow	M06821
Other specified rheumatoid arthritis, left elbow	M06822
Other specified rheumatoid arthritis, unspecified elbow	M06829
Other specified rheumatoid arthritis, right wrist	M06831
Other specified rheumatoid arthritis, left wrist	M06832
Other specified rheumatoid arthritis, unspecified wrist	M06839
Other specified rheumatoid arthritis, right hand	M06841
Other specified rheumatoid arthritis, left hand	M06842
Other specified rheumatoid arthritis, unspecified hand	M06849
Other specified rheumatoid arthritis, right hip	M06851
Other specified rheumatoid arthritis, left hip	M06852
Other specified rheumatoid arthritis, unspecified hip	M06859
Other specified rheumatoid arthritis, right knee	M06861
Other specified rheumatoid arthritis, left knee	M06862

Other specified rheumatoid arthritis, unspecified knee	M06869
Other specified rheumatoid arthritis, right ankle and foot	M06871
Other specified rheumatoid arthritis, left ankle and foot	M06872
Other specified rheumatoid arthritis, unspecified ankle and foot	M06879
Other specified rheumatoid arthritis, vertebrae	M0688
Other specified rheumatoid arthritis, multiple sites	M0689
Rheumatoid arthritis, unspecified	M069
Chronic postrheumatic arthropathy [Jaccoud], unspecified site	M1200
Chronic postrheumatic arthropathy [Jaccoud], right shoulder	M12011
Chronic postrheumatic arthropathy [Jaccoud], left shoulder	M12012
Chronic postrheumatic arthropathy [Jaccoud], unspecified shoulder	M12019
Chronic postrheumatic arthropathy [Jaccoud], right elbow	M12021
Chronic postrheumatic arthropathy [Jaccoud], left elbow	M12022
Chronic postrheumatic arthropathy [Jaccoud], unspecified elbow	M12029
Chronic postrheumatic arthropathy [Jaccoud], right wrist	M12031
Chronic postrheumatic arthropathy [Jaccoud], left wrist	M12032
Chronic postrheumatic arthropathy [Jaccoud], unspecified wrist	M12039
Chronic postrheumatic arthropathy [Jaccoud], right hand	M12041
Chronic postrheumatic arthropathy [Jaccoud], left hand	M12042
Chronic postrheumatic arthropathy [Jaccoud], unspecified hand	M12049
Chronic postrheumatic arthropathy [Jaccoud], right hip	M12051
Chronic postrheumatic arthropathy [Jaccoud], left hip	M12052
Chronic postrheumatic arthropathy [Jaccoud], unspecified hip	M12059
Chronic postrheumatic arthropathy [Jaccoud], right knee	M12061
Chronic postrheumatic arthropathy [Jaccoud], left knee	M12062
Chronic postrheumatic arthropathy [Jaccoud], unspecified knee	M12069
Chronic postrheumatic arthropathy [Jaccoud], right ankle and foot	M12071
Chronic postrheumatic arthropathy [Jaccoud], left ankle and foot	M12072
Chronic postrheumatic arthropathy [Jaccoud], unspecified ankle and foot	M12079
Chronic postrheumatic arthropathy [Jaccoud], other specified site	M1208
Chronic postrheumatic arthropathy [Jaccoud], multiple sites	M1209