NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Title	Evaluation of Xeljanz Access Barriers via Patient OOP Costs and TNFi cycling
Protocol number	Pfizer protocol ID A3921346
Protocol version identifier	Version number 1.1
Date	October 7, 2019
Active substance	L04AA29 (tofacitinib)
Medicinal product	Xeljanz (tofacitinib)

[redacted]

Research question and objectives	**Primary Objectives:** To evaluate the impact of (1a) Xeljanz index prescription OOP costs and (1b) TNFi cycling with etanercept and adalimumab vs. switching to Xeljanz on treatment persistence. **Secondary Objectives:** 2) To compare (1) high vs. low Xeljanz index prescription OOP costs, and, (2) TNFi cycling (2 groups) with etanercept and adalimumab vs. switching to Xeljanz (2 groups) on: • Differences in demographic and clinical characteristics. • Treatment patterns including dosing, concomitant medication use, adherence, switching and a 6- factor effectiveness proxy measure (Curtis algorithm) between comparator cohorts. • Post-index and change (Post-Pre) in All-cause and RA-related health care utilization associated costs. CCI [redacted]

[redacted]

Author	PPD , PharmD,MS PPD , PPD PHI, Pfizer Inc.

1. TABLE OF CONTENTS

[redacted]

[redacted]

LIST OF TABLES

LIST OF FIGURES

APPENDICES

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Adalimumab
AE	Adverse Event
AHRQ	Agency for Healthcare Research and Quality
ARRA	American Recovery and Reinvestment Act
CIRAS	Claims-based index for RA severity
CMS	Centers for Medicare & Medicaid Services
COB	Coordination of benefits
COPD	Chronic obstructive pulmonary disease
CPI	Consumer price index
CPT	Current Procedural Terminology
ED	Emergency department
ETN	Etanercept
FDA	Food and Drug Administration
GLM	Generalized linear model
HCFA	Care Financing Administration
HCPCS	Healthcare Common Procedure Coding System
HIPAA	Health Insurance Portability and Accountability Act
ICD-9/10 CM	The International Classification of Diseases, 9th and 10th Revision, Clinical Modification
IEC	Independent Ethics Committee
IRB	Institutional review board
ISPOR	International society for pharmacoeconomics and outcomes research
IV	Intravenous
LIS	Low income subsidy
MOA	Mechanism of action

Abbreviation	Definition
MTX	Methotrexate
NB-DMARD	Non-biologic disease modifying antirheumatic drug
NDC	National Drug Code
NIS	Non-interventional study
NSAID	Non-steroidal anti-inflammatory drug
OOP	Out-of-pocket
PDC	Proportion of Days Covered
RA	Rheumatoid Arthritis
RAPID3	Routine assessment of patient index data
RX	Outpatient pharmacy
TNFi	Tumor-Necrosis Factor-alpha inhibitor
TOFA	Tofacitinib
UB	Uniform Bill
US	United States

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
PPD	PPD	PPD Pfizer Inc	PP NY PPD
PPD , PhD	PPD	PPD Pfizer Inc	PPD Groton, PPD
PPD , PhD	PPD	PPD Pfizer Inc	PP , New York, NY PPD
PPD PhD	PPD	PPD , Pfizer Inc.	PPD PA, PPD

4. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	7 October 2019	7, 8.1, 8.2,8.3, 8.4.2, 8.4.3	Removed references to the Optum Clinformatics and Pharmetrics Plus databases.	Truven Marketscan database is sufficient for answering the research questions.
1	7 October 2019	3	Updated responsible parties	Reflecting changes in function and role

5. MILESTONES

Milestone	Planned date
Start of data collection	21 December 2018
End of data collection	30 June 2019
Final study report	30 September 2019

6. RATIONALE AND BACKGROUND

Tofacitinib (Xeljanz) was approved by the US Food and Drug Administration (FDA) in November 2012 as the first oral JAK inhibit or for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate. This advanced therapy may be used as monotherapy or in combination with methotrexate (MTX) or other nonbiologic disease-modifying antirheumatic drugs (NB-DMARDs). In February 2016, a once-daily Xeljanz XR formulation was approved, offering an option to the already approved twice daily immediate release formulation.

The most commonly used advanced therapies for RA are the Tumor-Necrosis Factor-alpha inhibitors (TNFi), in particular, adalimumab (Humira) and etanercept (Enbrel). Use of consecutive TNFis has been further reinforced by payer restrictions that often require failure of two or more TNFi's for receiving alternative MOA products like tofacitinib (TOFA).

However, there has been a growing body of largely observational evidence on the detriments of such TNFi cycling vs. switching to alternative MOA in patients with RA including:

- Shorter treatment persistence/duration;[1-4]
- Higher likelihood of switching to third line advanced therapy;[2,3,5]
- Higher costs;[1,2]
- Lower effectiveness using 6-factor algorithm;[2,3]
- Potentially poorer disease activity scores;[4,6,7] however, further information on the impact of joint erosion associated with TNFi cycling vs. switching is not currently available.

In addition to step edits and prior authorization, another barrier to receiving advanced therapy for RA is the increased out-of-pocket (OOP) cost sharing for patients. An analysis of claims data for over 40,000 RA patients starting bDMARDs between 01/2004 and 12/2013 found that the average cost per prescription remained relatively unchanged, at approximately $2300 per prescription, while OOP expenditures increased from $36 (2.5%) per prescription to $128 (7%).[8] An analysis of insurance claims data for Medicare Advantage Part D patients with RA found bDMARD prescription abandonment (claim reversal without subsequent fill) ranged from 1.3% for the lowest out-of-pocket (OOP) cost group ($0-$250) to 32.7% for the highest OOP cost group (> $550). Further, the odds of refilling bDMARD therapy were significantly lower for each OOP cost range ($250.01-$400.00, $400.01-$550.00, and >$550.00) relative to OOP cost range of ≤$250.[9] An analysis of insurance claims for self-insured health plan members with RA starting etanercept or adalimumab demonstrated about 1 week of therapy lost per $5.50 increase in weekly OOP expenditures. Those with weekly cost >$50 were 58% more likely to discontinue than patients with lower OOP costs (hazard ratio 1.58, P<0.001).[10] Additionally, Doshi et al[11]

found using the 5% sample Medicare data that patients with RA belonging to a non-low income subsidy (LIS) group had a higher average OOP cost for Part D bDMARDs of $484 (29.9% cost sharing) versus $5 (0.3% cost sharing) in an LIS group which was associated with a 42% lower odds of filling Part D biologic agents while being more than twice as likely to receive Part B biologic agents and having a 31% lower odds of using any biologic agent vs. patients in the LIS group.

The current study is intended to evaluate the impact of restrictions on TOFA including OOP cost sharing and TNFi cycling with adalimumab and etanercept vs. switching to Tofacitinib on treatment persistence, treatment patterns, healthcare resource use, and costs.

7. RESEARCH QUESTION AND OBJECTIVES

The primary and secondary objectives will be evaluated using insurance claims for patients with rheumatoid arthritis (RA) identified in the Truven Health MarketScan database (see Section 8.4).

7.1. Primary Objectives

To evaluate the impact of (1a) TOFA index prescription OOP costs and (1b) TNFi cycling with etanercept (ETN) and adalimumab (ADA) vs. switching to TOFA on treatment persistence duration (see Section 8.3).

7.2. Secondary Objectives

To compare patients with (1) high (>median) vs. low (≤median) TOFA index prescription OOP costs, and, (2) TNFi cycling with ETN and ADA vs. switching to TOFA on:

- Differences in demographic and clinical characteristics;
- Treatment patterns including dosing, concomitant medication use, adherence, and switching, and a 6-factor effectiveness proxy (ie, Curtis algorithm) between comparator cohorts;
- Post-index and change (Post-Pre) in All-cause and RA-related health care utilization associated costs.

CCI [redacted]

CCI [redacted]

8. RESEARCH METHODS

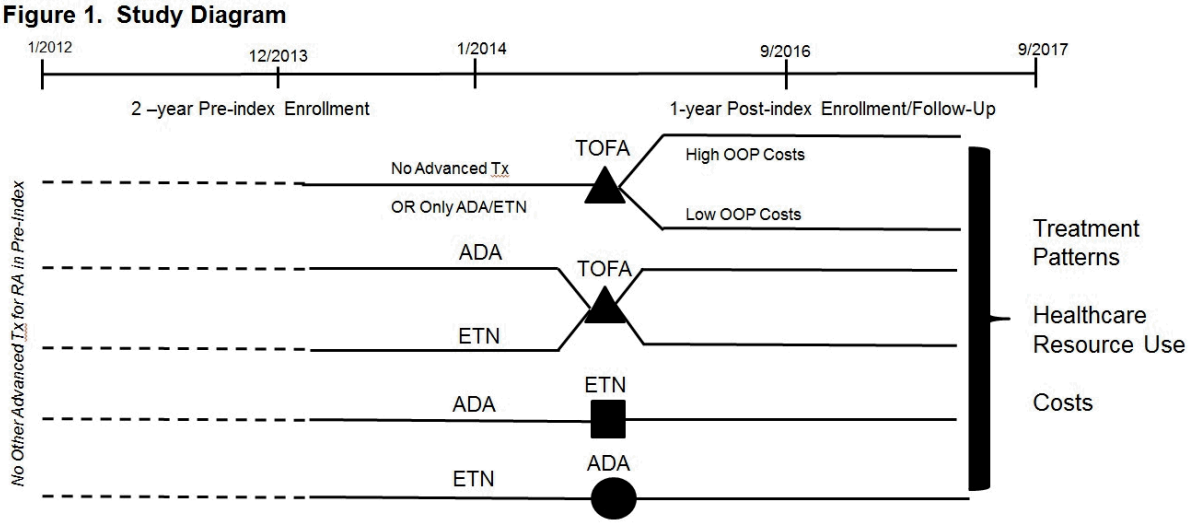
8.1. Study Design

This is a retrospective cohort study to evaluate patient characteristics, treatment patterns including a 6-factor effectiveness proxy measure, health care resource use and associated costs among RA patients initiating treatment comparator groups of interest between January 2014 and September 2016 across three US insurance claims databases. This period was selected since we typically have 5-year data license and wanted at least 2 years potential pre-index history, 2 years to capture treatmtent initation and 1 year for follow-up.

Further, we wanted to minimize channeling bias for TOFA in the first year of introduction where ADA and ETN were well established for a decade and based on prior analyses using 2012-2014 data indicating majority of TOFA use for 3rd line plus vs. ADA/ETN were mostly used for 2nd line treatment of RA (Chastek et al.[2] Poster presented at the ACR/ARHP Annual Scientific Meeting, San Francisco, CA, USA, November 6–11, 2015).

CCI [redacted]

Figure 1. Study Diagram



8.2. Setting

This study will leverage the de-identified, insurance claims database Truven Health MarketScan, between January of 2012 and September 2017. The database is further described in Section 8.4.

8.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. The **first pharmacy claim for TOFA and then ETN or ADA** between Jan 2014 and Sep 2016 represents the index claim *(See Appendix 1 for codes*). Selection of comparator groups will be hierchical per the following:

    a. First, select patients receiving ≥1 tofacitinib (TOFA) pharmacy claim (Jan 2014–Sep 2016) who did not have a TOFA claim anytime prior to index.

    b. Amongst remaining patients, select those receiving ≥1 ETN or ADA pharmacy claim, assign per whichever occurs first, over same time period (Jan 2014-Sep 2016) who did not have a respective pharmacy or administration claim for index medication anytime prior to index.

2. Patients do have >1 advanced therapy filled on index date.

3. Physician diagnosis of RA (in any position) during the 1-year pre-index period, or on the index date:

   - ICD-9 = 714.0x–714.4x, 714.81;
   - ICD-10 = M05.x, M06.0–M06.3, M06.8–M06.9.

4. Patients don't have claims for other conditions for which TOFA and/or advanced therapies are used, during the anytime pre-index period or on the index date.

Table 1. Exclusionary Diagnoses

Disease	ICD-9 diagnosis code	ICD-10 diagnosis code
Ankylosing Spondylitis	720.0x	M45.0 - M45.9
Crohn's Disease	555.xx	K50.*
Psoriasis	696.1x	L40.0*-L40.4*, L40.8*-L40.9*
Psoriatic Arthritis	696.0x	L40.5*
Ulcerative Colitis	556.xx	K51.*

5. Commercially insured or Medicare beneficiaries at index.

6. Continuous enrollment during 1 (360 days)-year pre- (pre-index period) and 1-year post- index.

7. Age 18+ years at index.

8. Study cohorts.

   a. TOFA Advanced Therapy Naïve OOP Cost Cohort.

      - Identify those with no advanced therapy (bDMARDs/JAK inhibitors) anytime before index TOFA prescription.

   b. ETN or ADA to TOFA OOP Cost and TNFi Cycling Cohort.

      - Identify those that had ADA or ETN, but not both, and no other advanced therapy anytime pre-index TOFA (*See Appendix 1*).

   c. ADA to ETN TNFi Cycling Cohort.

- In those newly starting ETN, patient must have a claim for ADA and no other advanced therapy (*See Appendix 1)*, including index ETN (pharmacy/admin claims), anytime pre- index ETN.

d. ETN to ADA TNFi Cycling Cohort.

- In those newly starting ADA, patient must have a claim for ETN and no other advanced therapy (*See Appendix 1)*, including index ADA (pharmacy/admin claims), anytime pre- index ADA.

NOTE: Advanced therapy = TNFi and nonTNFi bDMARDs and JAK inhibitors; Alternative MOA medications= nonTNFi bDMARD and JAKi.

8.3. Variables

There are two primary baseline periods of interest from which variables of interests will be evaluated: 1) 12-months fixed pre-index period and 2) a variable length baseline period is the maximal continuous enrollment window prior to index and at least 1-year pre-index. The primary post-index period is 12 months including the index date. Other observation periods are noted below.

Variable	Role	Data source(s)	Operational definition
Demographics (Table 1)			
Age	Baseline Characteristic	All	Age will be defined as of the index year.
Age groups	Baseline Characteristic	All	Patients will be assigned to one of the following age groups based index age: 18–44, 45–64, and 65yo.
Gender	Baseline Characteristic	All	Gender will be captured from enrollment data.
Insurance type	Baseline Characteristic	All	Whether the patient was covered under a commercial or Medicare Supplemental (Truven DataType) insurance plan will be captured.
Plan type	Baseline Characteristic	All	HMO, EPO, GPO, etc via.
			PlanType.
Geographic region	Baseline Characteristic	All	The United States (U.S.) region in which the study patient is enrolled in a health plan will be determined and reported and states will be categorized into five geographic regions: Northeast, South, Midwest, West, Unknown (https://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf).
Variable length baseline	Baseline Characteristic	All	Identify the duration of variable length (ie, all available pre-index continuous enrollment) baseline period.

Variable	Role	Data source(s)	Operational definition
RA-Related Medication Use in Pre-Index (Table 2)			
Pre-index biologic DMARD use	Baseline Characteristic	All	A count of unique (on different days) pharmacy/admin claims on different days for ADA/ETN will be created during the 12 month baseline period.
Time from last pre-index bDMARD to index	Baseline Characteristic	All	A variable for the interval between last ADA/ETN pharmacy/administration claim and index. Stratify by <3 mos, 3-<6 mos and 6-12 mos pre-index.
Time from first pre-index bDMARD to index	Baseline Characteristic	All	A variable for the interval between first ADA/ETN pharmacy/administration claim during the variable length baseline and index. Stratify by <6, 6-12, ≥12 mos.
Pre-index NB- DMARD use	Baseline Characteristic	All	The use of the 4 main NB- DMARDS (methotrexate-MTX, sulfasalazine-SSZ, hydroxychloroquine-HCQ, and leflunomide- LEF), and the other NB-DMARDS ***(See codes in Appendix 2)*** will be identified during the pre-index period. Indicator variables will identify the specific medications (MTX, SSZ, HCQ, LEF and other NB-DMARDs) used during the 12 mos pre-index period. A count will be created to identify the number of different NB-DMARDS during **variable length** baseline and number of prescriptions/administrations ***on different days*** received during the **12-mos** pre-index period.

Variable	Role	Data source(s)	Operational definition
RA-Related Medical History (Table 2)			
Pre-index hospitalization for RA			0/1 flags will be created to determine if the patient had an inpatient visit (length of stay>1 day) with an RA diagnosis (any claim position) in the 90 days before the index date and in the 12 months before the index date. A separate variable will be created for identifying the number of RA related hospitalizations during the entire 12-month baseline period.
Disease duration	Baseline Characteristic	All	The number of days from the earliest claim with a diagnosis of RA in the variable length baseline until the index date will be identified.
Pre-index Claims based Index of RA Severity (CIRAS)	Baseline Characteristic	Al	The Claims-based Index for RA Severity will be implemented. CIRAS (12) provides a single value of severity using the following 9 measures: age, gender, inflammatory marker tests, rehabilitation visits, Felty Syndrome, platelet orders, rheumatoid factor tests, chemistry panels, and rheumatologist visits (***See Appendix 3***).
Comorbidities (Table 3)			
Pre-index Quan-Charlson Comorbidity Index score	Baseline Characteristic	All	A comorbidity score will be calculated based on the presence of diagnosis codes on medical claims in the 12-months pre-index period. The Quan-Charlson (13) Comorbidity Index (QCCI) score will also be categorized into the following groups: zero, one to two, three to four, and five or more CCI comorbidities.
Comorbidities of interest	Baseline Characteristic	All	0/1 flags will be created to identify the presence of the following comorbidities during the 12-month baseline period (see *Appendix 4*). • Cardiovascular diseases. • Chronic obstructive pulmonary disease (COPD). • Asthma. • Kidney disease. • Diabetes. • Depression. • Anxiety. • Liver disease. • Sleep disorders. • Hypertension. • Hyperlipidemia. • Interstitial lung disease.

Variable	Role	Data source(s)	Operational definition
Cumulative OOP Costs pre-index	Baseline Characteristic	All	The total, pharmacy and medical OOP costs (deductible+copay+coinsurance) resource use from January 1 of index year through Index.
Index Date OOP costs	Baseline Characteristic	All	Total, pharmacy (excluding index medication) and medical OOP costs on index date.
Index Medication (Table 4)			
Index Prescriber	Baseline Characteristic	All	Top 5 index medication prescriber specialties and other or unknown will be identified.
Index month/year	Baseline Characteristic	All	The month and year of the patient's index date (start of TOFA, ETN, ADA) will be identified.
Index Medication OOP costs	Baseline Characteristic	All	The index medication pharmacy OOP costs (deductible+copay+coinsurance) will be identified for the first index medication rx and cumulative by month (1-12) of follow-up (only looking at pharmacy claims here noting index event is a prescription fill).
Index combination vs. monotherapy regimen status	Baseline Characteristic	All	Patients with a use of one of the 4 main NB-DMARDs (injectable and oral MTX, SSZ, HCQ, LEF) within 90 days on or after the index date will be considered as being treated with combination therapy regimen, others will be classified as monotherapy. For monotherapy, will evaluate 6-mos pre-index use of each of the four main and other NB- DMARDs. For combination regiment, will stratify by 6 mos pre-index use of the four main and other NB-DMARDs.
Post-Index Treatment Patterns (Table 4)			
Treatment Persistence (5 groups)	Outcome	All	**Persistent** with the index medication will be defined as not having a gap in therapy of at least 60 days between fills/admins. For retail pharmacy (rx) claims the day supply will be utilized and rounded to the nearest 28-day supply for ETN and ADA and 30- day supply for TOFA. For subcutaneous ETN and ADA administrations, a 28-day supply will be assumed.

Variable	Role	Data source(s)	Operational definition
			A gap of at least 60 days between the run- out date (rx/admin date + day supply-1) and the next rx/admin date will be considered non-persistence. Patients with early refills will be allowed to accumulate a stockpile of the index medication of up to 14 days for later use. However, an administration will negate accumulation of index medication. A 0/1 flag will be created to identify if the patient is persistent with their index medication before the end of the 12 month follow-up period. Patients who are not persistent for the entire follow-up period will be classified into the following mutually exclusive categories based on the first occurrence of non-persistence: **Switch immediately:** Patients will be classified as switching immediately if they initiate a non-index advanced therapy (see all medications in Appendix 1) before end of a 60-day gap in index. **Discontinue then switch:** Gap in the index therapy of at least 60 days and the first medication observed after the gap is an advanced therapy different from index medication. **Discontinue then restart**: Gap in the index therapy of at least 60 days and the first advanced therapy observed after the gap is the index medication. **Discontinue without switch or restart:** Gap in index therapy of at least 60 days and there are no claims for either the index med or a different advanced therapy for the remainder of the follow-up period.
Switch any time	Outcome	All	In addition to the 4 mutually exclusive treatment patterns, patients with a switch medication any time during the 12-month follow-up period will be identified.

Variable	Role	Data source(s)	Operational definition
Days to immediate switch	Outcomes	All	Days to immediate switch =immediate switch date-index date+1.
Days to any switch	Outcomes	All	Day to any switch =immediate/delayed switch date-index date+1.
Days to discontinue			Days to discontinue= date of last persistent index medication rx/administration+days supply- index date+1.
Index Medication Persistence duration of therapy	Outcome	All	Days to discontinue or immediate switch or or end of 1yr post-index period if remained persistent (whichever comes first).
NB-DMARD use	Outcome	All	1.For patients who initiate combination therapy, will look for select NBDMARD (MTX, SSZ, LEF, HCQ) discontinuation or switch from start of NB-DMARD through end of 12-month post-index period. Definitions of treatment patterns are similar to 5 persistent groups above for index advanced therapy medications and using a 60 day gap. A 28-day supply will be assumed for MTX administrations. 2. For those who initiated advanced monotherapy, addition of one for four main or other NBDMARDs will be evaluated.

Variable	Role	Data source(s)	Operational definition
Medication Effectiveness Proxy Algorithm (Curtis et al)[14]	Outcome	All	Medication effectiveness at one year after the index date will be determined using the following six criteria. For each of the 6 criteria, a 0/1 flag will be created. Patients who are effectively treated for each of the 6 criteria will be considered effectively treated. Patients who fail any of the 6 criteria are therefore not effectively treated. 1.**High adherence to index agent:** For all medications, a proportion of days covered (PDC) will be calculated based on total days supply over the 1 year follow-up. The PDC will be calculated by using the date of service and the day supply for each fill of the index medication. Patients with early refills will be allowed to stockpile medications up to a maximum of 14 days total for later use. Patients with PDC ≥0.8 will be considered highly adherent and effectively treated. The original Curtis algorithm referenced an MPR;however, more recent studies are using PDCs or similarly described measure.[15]

Variable	Role	Data source(s)	Operational definition
			2.No increase in dose (see below) for index medication compared to the starting dose. Dose escalation will be identified per the criteria listed below. **ADA:** At least 1 claim in the follow-up period with an average weekly dose of at least 40 mg/week. **ETN:** At least 1 claim in the follow-up period with an average weekly dose of at least 100 mg/week. **TOFA:** At least 1 claim in the follow-up period with an average weekly dose of at least 20 mg/day for IR and 22 mg/day for XR. **3.No switching from the index medication to a different advanced therapy.** A switch will be defined as use of a different bDMARD or JAKi any time during the follow-up period noting the availability of newer advanced therapies after original 2011 Curtis algorithm publication. **4.No adding of a new non-biologic DMARD to the index therapy.** Measure has been modified to distinguish outcomes for advanced monotherapy vs. NB-DMARD comobination regiments, noting patients may not have NB-DMARD in 6-mos pre-indes but start a combination regimen. For those starting a monotherapy index medication regimen, the initiation of a select NB-DMARD will be identified in the follow up period as addition of NB-DMARD. For those starting a combination index medication regimen, presence of a different NB-DMARD in follow-up will be flagged as failing the algorithm.

Variable	Role	Data source(s)	Operational definition
			5. Oral glucocorticoids. Only National Drug Code (NDC) codes for oral glucocorticoids will be included. 5a. *For patients with no claims for oral glucocorticoid prescriptions in the six months prior to the index date*: cannot receive more than 30 days of oral glucocorticoids between (index date + 89) to (index date + 359). 30 days of oral glucocorticoids will be determined by summing up the day supply of all glucocorticoids claims with a fill date between (index date + 89) to (index date + 359). 5b. *For patients with claims for oral glucocorticoids during the six months prior to the index date:* No increase in oral glucocorticoid dose ≥20% during months 6- 12 after index compared to the 6 months before the index date. Increase in oral glucocorticoids will be determined from the prednisone equivalent dose for all glucocorticoid claims filled during the respective time periods. **6. At most one parenteral or intra- articular glucocorticoid joint injection** on unique days after the patient had been on biologic treatment for more than three months between (index date + 89) to (index date + 359). CPT codes 20600, 20605, 20610.
Change in Resource Use and Costs (Tables 5 and 6)			
RA-related healthcare resource use	Outcome	All	The number of patients with and number of encounters (including zeros) for each RA- related medical and pharmacy resource use will be evaluated in the 12-month pre- and post-index periods. See Section 8.3.1 for details on calculating cost and healthcare utilization.
All-cause healthcare resource use	Outcome	All	The number of patients with and number of claims (including zeros) for each all-cause medical and pharmacy resource use will be evaluated in the 12-month pre- and post-index periods. See Section 8.3.1 for details on calculating cost and healthcare utilization.

Variable	Role	Data source(s)	Operational definition
Healthcare Costs	Outcome	All	RA-related and all-cause resource use attributable health care costs will be computed as the combined health plan/other payer (ex, Coordination of Benefits for Medicare Supplemental in Truven) and patient paid amounts. See Section 8.3.1 for details on calculating cost and healthcare utilization.

8.3.1. Health Care Cost and Utilization

All cost and utilization measures will be identified in the 12-month pre-index period and the 12- month post-index period. Claims occurring on the index date will be considered part of the post-index period. Baseline and follow-up costs and the change in 12-month costs from baseline to follow-up will then be examined. Cost measures will comprise the total amount paid by the health plan and patient.

- **All-cause health care resource utilization**- Medical resource utilization will be calculated for outpatient visits, emergency department (ED) visits, and inpatient admissions and pharmacy utilization will include all paid prescription claims.

- **RA-related resource health care utilization.**

  - Medical resource utilization related to RA will be calculated for outpatient visits, ED visits, and inpatient admissions with an RA diagnosis in any claim position.

  - RA-related treatment administrations (with and without a concurrent RA diagnosis) will also be identified by presence of HCPCS codes for ADA, ETN, other TNFI and other advanced therapy; methotrexate or other NB-DMARD; low, medium and high potency orticosteroids; NSAIDS; and strong and weak opioids (***See Appendices Appendix 1, Appendix 2, Appendix 5***).

  - Pharmacy utilization will included all paid prescription claims for TOFA, ADA, ETN, another TNFI or alternative MOA; methotrexate, sulfasalazine, leflunomide, hydroxychrolorquine and other NB-DMARDs; low, medium, high potency corticosteroids; NSAIDS; and weak and strong opioids (***See Appendices Appendix 1, Appendix 2, Appendix 5***).

- **Health care costs**-Health care costs will be computed as the combined health plan and patient paid amounts. Costs will be calculated as total costs, pharmacy/treatment costs, and medical costs. Medical costs will be further broken down into outpatient costs, emergency room costs, and inpatient costs. Costs will be adjusted using the annual medical care component of the Consumer Price Index (CPI) to reflect inflation between 2014 (the earliest start of the pre-index period) and 2017 (the cost of claims occurring in 2018 will not be adjusted).[16]

- Costs from other payers are of importance for older patients dually eligible for commercial and Medicare coverage. Payments from Medicare (and other payers) will be estimated based on coordination of benefits information obtained by the health plan in its usual course of business. This study will incorporate the amounts estimated to be paid by other payers for a total paid or allowable amount.[17]

- **All-cause health care costs-** calculated as total of medical (outpatient, inpatient and ED) visits regardless of reason and all prescription costs.

- **RA-related health care costs**- RA-related health care costs will be calculated as total medical and treatment costs related to RA.

    - RA-related medical costs will include costs for outpatient, inpatient and ED vists with an RA diagnosis in any claim position

        - For outpatient visits with an RA diagnosis and administration of an RA-related treatment (see below), the non-adminsitration costs will be characterized as part of RA-related Medical costs and the administration costs will be part of RA-related Treatment costs below.

    - Outpatient visits without an RA diagnosis, but with administration of an RA-related treatment will not be included in the RA-related Medical costs, but will be evaluated for administration costs as part of RA-relatedTreatment costs below.

Note: given variability in capture of HCPCS codes in inpatient setting across databases, RA- related treatement costs are limited to outpatient visits only.

    - RA-related treatment costs will include the cost of:

        - outpatient administration of bDMARDs, NB-DMARDs, corticosterioids, NSAIDS, and opioids based on HCPCS codes regardless of RA diagnosis on claim, AND,

        - cost of prescription fills for TOFA/ADA, ETN, other advanced therapies, NB-DMARDs, corticosterioids, NSAIDS, and opioids.

8.4. Data Source

8.4.1. Truven MarketScan Research Database

The Truven Health MarketScan Research Databases reflects the combined healthcare service use of individuals covered by Truven Health clients (including employers, health plans, and hospitals) nationwide. Truven Health builds databases comprise the healthcare experience of the clients' covered populations, as well as information about the populations themselves and the providers that serve them. MarketScan Research Databases provide detailed cost, utilization, and outcomes data for healthcare services performed in both inpatient and outpatient settings. In the claims databases, the medical services are linked to outpatient prescription drug claims and person-level enrollment data using unique enrollee identifiers.

The MarketScan Commercial Database contains the healthcare experience of privately insured individuals. Coverage is provided under a variety of fee-for-service, fully capitated, and partially capitated health plans, including preferred provider organizations, point of service plans, indemnity plans, and health maintenance organizations.

The data that make up the Commercial Database are stored in the following tables:

- *The Inpatient Admissions Table* contains records that summarize information about a hospital admission. Truven Health constructs this table after identifying all of the service records associated with an admission (eg, the hospital claims, physician claims, surgeon claims, and claims from independent labs). Similar information (such as payments for professional services) is then summed across the claims. The admission record includes the principal procedure and diagnosis, Major Diagnostic Category, and Diagnosis-Related Group. It also includes all diagnoses and procedures (up to 14 each) found on the service records.

- *The Inpatient Services Table* contains the individual claims that are summed to create the inpatient admission records. An admission identifier on both the Inpatient Admissions and the Inpatient Services Tables identifies the claims that make up each admission record.

- *The Outpatient Services Table* comprises services that were rendered in a doctor's office, hospital outpatient facility, or other outpatient facility.

- *The Facility Header Table* contains the header records from facility claims for inpatient and outpatient services, including full diagnosis information.

- *The Outpatient Pharmaceutical Claims Table* contains outpatient prescription drug data from multiple sources, including mail-order data. Each record includes National Drug Code (NDC), therapeutic class, ingredient cost, dispensing fee, copayment, deductible, total gross payment, and other data elements.

- *The RED BOOK™ Supplement Table* contains *RED BOOK* variables that enhance prescription drug analyses. These variables are linked to the Outpatient Pharmaceutical Claims Table by NDC.

- *The Annual Enrollment Summary Table* provides a single record per year for each enrollee, showing enrollment start and end dates and, for some demographic variables, the most prevalent demographic and plan information; for other variables, monthly values are included.

- *The Enrollment Detail Table* provides a single record per month of enrollment for each enrollee, with detailed demographic information.

- *The Population Aggregate Table* provides average counts of the covered (insured) population to use for rate-supported analysis. The counts are recorded by several demographic variables (eg, age group, gender, region, etc.).

The MarketScan Medicare Supplemental Database contains the healthcare experience of individuals with Medicare supplemental insurance paid for by employers. Both the Medicare-covered portion of payment (represented as Coordination of Benefits Amount, or COB) and the employer-paid portion are included in this database. The tables that make up the Medicare Supplemental Database are the same as those that make up the Commercial Database.

Claims are not included in the database until they have been adjudicated; there is a lag of approximately six months after the close of a calendar year or a quarter between services provided and their inclusion in the Research Databases. However, the Early View Database has a 90-day lag that includes paid amounts for 100 percent of prescription drugs, approximately 85 percent of physician office visits, and approximately 70 percent of hospital claims. The MarketScan Early View Database includes all of the components found in the standard MarketScan Commercial and Medicare Supplemental Databases. It includes standardized inpatient, outpatient, pharmaceutical, and health-plan enrollment data. The MarketScan Early View Database captures healthcare services incurred up to 90 days before data release and includes only adjudicated claims. However, the medical component of care for some patients will not be complete, since some claims (particularly inpatient claims) take longer to be adjudicated. Because this study is examining only comorbidities prior to and treatments during or prior to tofacitinib initiation fully adjudicated claims are not required and all available data will be used including Commercial, Medicare Supplemental, and Early View Databases.

8.5. Study Size

The sample size for this study is fixed by the duration of the observation window. No formal sample size computation was performed. All patients who meet inclusion/exclusion criteria will be included in the analyses.

8.6. Data Management

All data is electronically obtained from the US Claims databases and delivered to Pfizer. The data are stored in the Real World Data and Analysis DataMart (Teradata Server Version 15). Analysis is done using SAS Version 9.4 on Red Hat Linux.

8.7. Data Analysis

8.7.1. Primary Objectives

8.7.1.1. To Compare 12-month Post-Index Medication Persistence Duration (days) by TOFA Index Prescription OOP Costs and TNFi Cycling with ETN and ADA vs. TOFA Switching

For this objective both descriptive and multivariable analysis will be conducted. For the descriptive analysis, treatment persistence duration (days) with index medication at 12-months will be compared for those with low (≤ median) vs. high (> median) OOP costs and for those who switch from ADA to ETN vs. ADA to TOFA and ETN to ADA vs. ETN to TOFA. CCI [redacted]

8.7.2. Secondary Objectives

8.7.2.1. Explore the Differences in Demographic and Clinical Characteristics Between TOFA Index Prescription OOP Costs and TNFi Cycling with ETN and ADA vs. TOFA Switching Cohorts

For this objective descriptive analysis will be conducted. The goal of this objective will be to describe the respective cohorts and explore the presence of demographic and clinical characteristics differences between the cohorts that will inform multivariable analyses. Known demographic characteristics (eg, age, gender, geographic location) will be summarized. In addition, other patient characteristics (eg, pre-index RA medication use and medical history, comoribidity status, cumulative/index OOP costs) will be evaluated. Index medication prescriber, regimen, and OOP costs will also be described.

8.7.2.2. Compare Treatment Patterns Including Dosing, Adherence, Persistence Treatment Patterns Between TOFA Index Prescription OOP Costs and TNFi Cycling with ETN and ADA vs. TOFA Switching Cohorts

For this objective, treatment patterns will be summarized across the cohorts of interest. Specific treatment patterns include changes in use of concomitant NB-DMARDs, number and proportion of patients in the five treatment persistent groups (persistent, switch immediately, discontinue and switch, discontinue and restart, discontinue and no switch or restart), switch anytime, or effectively treated (meeting each of 6 Curtis algorithm criteria) as well as times to immediate and anytime switch and discontinuation. Times to discontinuation, switching or either will be assessed with Kaplan-Meier curves and Cox proportional hazards models.

CCI [redacted]

8.7.2.3. Compare All-Cause and RA-Related Health Care Utilization Between TOFA Index Prescription OOP Costs and TNFi Cycling with ETN and ADA vs. TOFA Switching Cohorts

For this objective descriptive analysis will be conducted. All-cause and RA-related pharmacy and medical resource utilization measures (flags and 12-month counts) will be presented per patient during the 12-month baseline and follow-up periods. In addition, changes from baseline to follow-up will be evaluated.

8.7.2.4. Compare All-Cause and RA-Related Healthcare Costs Between TOFA Index Prescription OOP Costs and TNFi Cycling with ETN and ADA vs. TOFA Switching Cohorts

For this objective descriptive and multivariable analysis will be conducted. For the descriptive analysis, 12-month pre- and post-index cost measures will be presented per patient during the baseline and follow-up. The change in 12-month costs from the baseline to the follow-up will also be calculated. In addition, total all-cause cost will be presented in each of the months of the baseline and follow-up. The mean cost in each month will be included on a figure demonstrating the trend in costs over time. Multivariable analysis of follow-up health care cost will also be conducted using generalized linear models (see Section 8.7.4).

CCI [redacted]

CCI [redacted]

[redacted]

8.7.3. Descriptive Analysis

All study variables, including pre- and post-index measures and changes in these measures, will initially be analyzed descriptively. In general, numbers and percents will be provided for dichotomous and polytomous variables, while means, medians, and standard deviations will be provided for continuous variables. Missing or unavailable data will not be imputed.

Results will be stratified by treatment cohort, bivariate comparisons of pre- and post-index measures will be provided, and appropriate tests (eg, t-test, Mann Whitney-U test, chi-square test) will be used based on the distribution of the measure. The analysis that is performed (ie, the methods that are used and the patients who are included) will be specific to the objective being examined. Descriptive techniques will be implemented for each objective.

8.7.4. Multivariate Analysis

To control for possible confounding of the relationship between the outcomes and independent variable of interest, select objectives will be conducted utilizing multivariable methods as described above.

Final outcomes for multivariate analysis will be selected after review of descriptive results. Possible outcomes of interest include: total all-cause health care cost, total RA-related health care cost, cost of bDMARDs/tofacitinib/administration/NB-DMARDS, medication effectiveness (yes vs. no).

For each model, specific predictors to be included will be determined based upon clinical rationale and statistical significance. Variables listed in Section 8.3 will be considered for inclusion in the multivariable models. Additional variables identified throughout the course of the study will also be considered. Following standard procedure, regression diagnostics will be performed for each model to assess goodness of fit and violations of model assumptions (eg, multicollinearity, heteroskedasticity). When there are violations of the model, programmers will note them and make appropriate corrections to the data (ie, typically through transformation of either the independent or dependent variables) or in the method of estimation.

In particular, generalized linear models will be fit, using appropriate distributions and links for the nature of the data (eg, normally-distributed data with identity link, binary data and logit link). Results will be displayed on the original scale (that is, the inverse link). If sufficient sample size, tofacitinib IR and tofacitinib XR will be treated as separate groups. That is, contrast statements will be used to average the two groups when comparing to bDMARDs. Point estimates (that is, mean differences, ratios, odds ratios), 95 percent confidence intervals, and p- values will be presented for contrasts; ANOVA table will be presented to display the strength of the independent variables, including point estimates and p-values.

8.7.5. Cost Data

Because health care costs are often skewed, estimated cost measures will be modeled using a gamma regression model. Coefficients from a generalized linear model (GLM) are estimated cost ratios. Cost ratios, 95 percent confidence intervals, and p-values will be presented for each covariate included in the final model. For ease of interpretation and comparison with the bivariate results, the average cost will be predicted for each cohort and may also be predicted for pre-determined levels of other patient characteristics (eg, combination vs. monotherapy, gender).

If a significant number of patients have zero values for costs, estimated cost measures will be compared using a two-part model (ie, one equation estimating the probability of any cost and a GLM with a gamma distribution and log link estimating the level of cost). This method avoids potential difficulties introduced by transformation and retransformation of the dependent variable.

If there is an excessive number of zero-dollar cost patients, then only logistic regression prediciting the probability of nonzero costs will be run.

Odds ratios, 95 percent confidence intervals, and p-values will be presented for each covariate included in the logistic model estimating the probability of non-zero costs. Cost ratios, 95 percent confidence intervals, and p-values will be presented for each covariate included in the GLM model estimating the level on costs. Combined results will displayed.

8.7.6. Dichotomous Data

The probability of being effectively treated, persistent, and anytime switching to advanced therapy at one year will be modeled using logistic regression. Logistic regression models fit a maximum-likelihood logit model. For ease of interpretation, the results of logistic regression will be presented as odds ratios, 95 percent confidence intervals, and p-values for each covariate included in the final model.

CCI [redacted]

CCI

[redacted]

8.8. Quality Control

This is a retrospective study, so issues of quality control at study sites, eg, data queries, do not apply. Analyses are programmed according the specifications in the protocol, and if applicable, the statistical analysis plan and documented in a programming plan. Final deliverables are reviewed and verified by a second, independent programmer who may also perform double programming. All quality checks are documented in the programming plan.

8.9. Limitations of the Research Methods

Limitations that are general to claims database analyses and specific to this study should be noted. First, diagnosis of autoimmune conditions will be identified using ICD-9/10-CM diagnosis codes, which are subject to potential miscoding. Second, clinical and laboratory data are not available, thus we are relying on adjudicated claims data for characterizing medical history, treatment exposure and outcomes. Along these lines, we may be missing information on services or resources for which claims were not submitted such as medication samples. We will use 2-year pre-index continuous enrollment to increase the likelihood of capturing patient baseline characteristics including prior advanced therapy experience. However, this may not be sufficient and may bias the sample to patients who stay in health plans and may be healthier.

[redacted]

Further, we require 1-year of post-index enrollment across groups to ensure similar follow up, but this may not be representative of health plan enrollees and may bias toward longer treatment duration or higher healthcare resource use and costs. This study will include an examination of medication effectiveness at 1 year among all biologic users. Effectiveness will be measured using a validated algorithm; however, the algorithm was not validated for all medications being included. Specifically, tofacitinib was approved for treatment of RA after the algorithm was developed. Although this study will also evaluate outcomes [redacted] using multivariable analysis to control for observable differences between groups, there may be unobservable differences as common with observational research designs.

8.10. Other Aspects

Not Applicable.

9. PROTECTION OF HUMAN SUBJECTS

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

As this is a retrospective non-interventional study using fully anonymized secondary data, no additional informed consent is required.

9.1. Patient Information

This study involves data that exist in anonymized structured format and contain no patient personal information.

9.2. Patient Consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

9.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

IRB is not required for this study as it uses commercially available de-identified secondary data sources and is considered exempt from the requirements for “human subjects research” in the US.

9.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

For all publications relating to the Study, Pfizer will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

12. REFERENCES

1. Chastek B, Chen CI, Proudfoot C, Shinde S, Kuznik A, Wei W.Treatment Persistence and Healthcare Costs Among Patients with Rheumatoid Arthritis Changing Biologics in the USA.Adv Ther. 2017 Nov;34(11):2422-2435. doi: 10.1007/s12325-017-0617-5. Epub 2017 Oct 16.

2. Chastek B, Becker LK, Chen CI, Mahajan P, Curtis JR.Outcomes of tumor necrosis factor inhibitor cycling versus switching to a disease-modifying anti-rheumatic drug with a new mechanism of action among patients with rheumatoid arthritis. J Med Econ. 2017 May;20(5):464-473. doi: 10.1080/13696998.2016.1275653. Epub 2017 Jan 4.

3. Bonafede MM, Curtis JR, McMorrow D, Mahajan P, Chen CI. Treatment effectiveness and treatment patterns among rheumatoid arthritis patients after switching from a tumor necrosis factor inhibitor to another medication. Clinicoecon Outcomes Res. 2016 Dec 2;8:707-715.

4. Wei W, Knapp K, Wang L, Chen CI, Craig GL, Ferguson K, Schwartzman S.Treatment Persistence and Clinical Outcomes of Tumor Necrosis Factor Inhibitor Cycling or Switching to a New Mechanism of Action Therapy: Real-world Observational Study of Rheumatoid Arthritis Patients in the United States with Prior Tumor Necrosis Factor Inhibitor Therapy.Adv Ther. 2017 Aug;34(8):1936-1952. doi: 10.1007/s12325-017-0578-8. Epub 2017 Jul 3.

5. Harnett J, Wiederkehr D, Gerber R, Gruben D, Koenig A, Bourret J3Real-world evaluation of TNF-inhibitor utilization in rheumatoid arthritis. J Med Econ. 2016;19(2):91-102. doi: 10.3111/13696998.2015.1099538. Epub 2015 Oct 27.

6. Gottenberg JE, Brocq O, Perdriger A, et al. Non-TNF-Targeted Biologic vs a Second Anti- TNF Drug to Treat Rheumatoid Arthritis in Patients With Insufficient Response to a First Anti-TNF Drug: A Randomized Clinical Trial.JAMA. 2016 Sep 20;316(11):1172-1180. doi: 10.1001/jama.2016.13512.

7. Emery P, Gottenberg JE, Rubbert-Roth A, et al. Rituximab versus an alternative TNF inhibitor in patients with rheumatoid arthritis who failed to respond to a single previous TNF inhibitor: SWITCH-RA, a global, observational, comparative effectiveness study.Ann Rheum Dis. 2015 Jun;74(6):979-84. doi: 10.1136/annrheumdis-2013-203993. Epub 2014 Jan 17.

8. Atzinger CB, Guo JJ. Biologic Disease-Modifying Antirheumatic Drugs in a National, Privately Insured Population: Utilization, Expenditures, and Price Trends. Am Health Drug Benefits. 2017 Feb;10(1):27-36.

9. Hopson S, Saverno K, Liu LZ, AL-Sabbagh A, Orazem J, Costantino ME, Pasquale MK. Impact of Out-of-Pocket Costs on Prescription Fills Among New Initiators of Biologic Therapies for Rheumatoid Arthritis. J Manag Care Spec Pharm. 2016 Feb;22(2):122-30. doi: 10.18553/jmcp.2016.14261. Epub 2015 Dec 14.

10. Curkendall S, Patel V, Gleeson M, Campbell RS, Zagari M, Dubois R.Compliance with biologic therapies for rheumatoid arthritis: do patient out-of-pocket payments matter? Arthritis Rheum. 2008 Oct 15;59(10):1519-26. doi: 10.1002/art.24114.

11. Doshi JA, Hu T, Li P, Pettit AR, Yu X, Blum M.Specialty Tier-Level Cost Sharing and Biologic Agent Use in the Medicare Part D Initial Coverage Period Among Beneficiaries With Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2016 Nov;68(11):1624-1630. doi: 10.1002/acr.22880.

12. Ting G, Schneeweiss S, Scranton R, Katz JN, Weinblatt ME, Young M, Avorn J, Solomon DH. Development of a health care utilisation data-based index for rheumatoid arthritis severity: a preliminary study. Arthritis Res Ther. 2008;10(4):R95. doi: 10.1186/ar2482. Epub 2008 Aug 21.

13. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, Januel JM, Sundararajan V. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol. 2011;173(6):676- 82.

14. Curtis JR, Baddley JW, Yang S, et al., Derivation and preliminary validation of an administrative claims-based algorithm for the effectiveness of medications for rheumatoid arthritis. Arthritis Res Ther, 2011. 13(5): p. R155.

15. Curtis JR, Chastek B, Becker L, et al. Cost and effectiveness of biologics for rheumatoid arthritis in a commercially insured population. J Manag Care Spe Pharm. 2015 Apr; 21 (4): 318-29.

16. US Department of Labor, Bureau of Labor Statistics. *Consumer Price Index. Medical Care*. Series ID: CUUR0000SAM. Washington, DC: U.S. Dept. of Labor, Bureau of Labor Statistics. http://data.bls.gov/cgi-bin/surveymost?cu.

CCI [redacted]

[redacted]

[redacted]

13. LIST OF TABLES

SEE ATTACHED EXCEL WORKBOOK FOR DRAFT TABLES

14. LIST OF FIGURES

15. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

16. APPENDICES

Appendix 1. ADVANCED THERAPIES

Generic Name^	Brand Name	Route of Admin.	GPI codes^	HCPCS
TNFi				
Adalimumab	Humira	SC	66270015	J0135
Etanercept	Enbrel	SC	66290030	J1438
Golimumab	Simponi, Aria	SC/ IV	66270040	J1602
Certolizumab pegol	Cimzia	SC	52505020	C9249, J0717, J0718
Infliximab	Remicade, Renflexis, Inflectra	IV	52505040	J1745, Q5102
Alternative MOA				
Tofacitinib	Xeljanz	PO	66603065	None
Baricitinib	Olumiant	PO	66603010	None
Abatacept	Orencia	IV/SC	66400010	C9230 J0129
Anakinra	Kineret	SC	66260010	None
Tocilizumab	Actemra	IV/SC	66500070	C9264 J3262
Rituximab	Rituxan	IV	21353060	J9310
Sarilumab	Kevzara	SC	66500060	None
Unspecified				J3590, J3490

^GPI codes from MediSpan;
https://www.azahcccs.gov/PlansProviders/Downloads/PharmacyUpdates/AHCCCSPreferredDrugs_04_01_2018.pdf;
https://www.bluecrossmn.com/healthy/public/portalcomponents/PublicContentServlet?contentId=P11GA_16306146.

Appendix 2. NON-BIOLOGIC (TRADITIONAL) DMARDS

Generic Names^	GPI Codes^	J-codes
Hydroxychloroquine	13000020	n/a
Methotrexate	21300050 66250050	J8610, J9250, J9260
Leflunomide	66280050	n/a
Sulfasalazine	52500060	n/a
Other Medications:		
Chloroquine	13000010	J0390
Combos	1399000220	n/a
Cyclosporine	99402020	J7502, J7515, J7516, C9438, J7503, K0121, K0122, K0418
Thalidomide	99392070	n/a
Azathioprine	99406010	J7500, J7501, C9436, K0119,
Cyclophosphamide	21101020	J8530, J9070, J9080, J9090, J9091, J9092, J9093, J9094, J9095, J9096, J9097, C9420, C9421
Auranofin	66200010	n/a
Aurothioglucose	66200020	J2910
Gold Sodium Thiomalate	66200030	J1600
Penicillamine	99200030	n/a
Tacrolimus Minocycline/Tetracyclin	99404080 04000040	J7507, J7525, C9006, J7508 J2265

^ GPI codes from MediSpan.

Appendix 3. CLAIMS-BASED INDEX OF RA SEVERITY (CIRAS)

Measure[6]	Score
Age (continuous)	-0.066
Gender 0: male 1: female	-0.092
Inflammatory marker test ordered 0: no 1: yes	0.60
Rehabilitation visit 0: no 1: yes	0.69
Rheumatoid factor test 0: no 1: yes	2.1
Felty's syndrome 0: no 1: yes	2.3
Number of platelet counts ordered 0 = 0 visits 1 = 1 visit 2 = 2 visits 3 = 3 visits 4 = 4+ visits	0.42
Number of chemistry panels ordered 0 = 0 panels 1 = 1 panel 2 = 2 panels 3 = 3 panels 4 = 4 panels 5 = 5+ panels	-0.14
Rheumatologist visit count 1 = 0 visits 2 = 1-4 visits 3 = 5+ visits	0.52
Intercept	6.5

Number of platelet counts, chemistry panels, and rheumatologist visits are counted 1 per person per day.

Codes for CIRAS Calculation

	Codes	Visits/Tests
Rehabilitation	OT/PT Codes: G0151,G0152,G0157,G0158, G0159,G0160,S9129,S9131,97001,97002,970 03,97004	Occupational therapy/physical therapy visits
Rheumatoid	CPT 86430,86431	Rheumatoid Factor Test Qual,
Factor		Rheumatoid Factor Test Quant
Felty's syndrome	ICD-9/10: 714.1, M0500	
Platelet counts	CPT: 85049	Automated platelet count
Chemistry panels	CPT: 80053, 82248, 82465, 82977, 83540, 83615, 84100, 84478, 84550	A/G Ratio, Albumin, Alkaline Phosphatase, Alanine Aminotransferase, Asparate Aminotransferase, Direct and Total Bilirubin, BUN/Creatinine Ratio, Calcium, Carbon Dioxide, Chloride, Cholesterol, Creatinine, Gamma Glutamyltransferase, Globulin, Glucose, Iron, Lactate Dehydrogenase, Phosphate, Potassium, Total Protein, Sodium, Triglycerides, Urea Nitrogen (BUN), Uric Acid

Appendix 4. COMORBIDITIES OF INTEREST

Disease	ICD-9 codes	ICD-10 codes
Cardiovascular Disease		
Ischemic heart disease	411.xx 413.xx 414.xx	I241, I200, I240, I248, I208, I201, I209 I2582, I2583, I2584, I255, I259, I2589, I2510, I25810, I25811, I25812, I253, I2541, I2542, I253
Congestive heart failure	428.xx	I509, I501, I5020-5023,I503-5033, I5040-5043
Myocardial infarction	410.xx,	I2109, I2119, I2111, I2129, I213, I214
Peripheral vascular disease	441.xx, 443.9x	I711-716, I718-719, I7100-7103, I739
	PROC codes: 38.13, 38.18, 38.48	
Hypertension	401.xx, 437.2x	I10,I169, I674
Dyslipidemia	272.xx	E7800-7801, E781-786, E881, E770-771, E7521-7522, E75249, E7881, E7889, E8889, E789
Diabetes	250.xx	E119,E109, E1165, E1065, E1169, E1310 E1010, E1165, E1169,E1065, E1100, E1101, E1069, E1100, E1165, E1069, E11641, E1011, E10641, E1101, E1165, E1011, E1065, E1129, E1029, E1121, E1165, E1021, E1065, E1136, E1139, E11311 E11319, E1036, E1037X1, E1037X2, E1037X3, E1037X9, E1039,E10311, E10319, E1136, E1139, E1165 E11311, E11319, E1036, E1039, E1065, E10311, E10319, E1140, E1040, E1140, E1165 ,E1040, E1065, E1151, E1051, E1151, E1165, E1051, E1065, E1165. E1169, E11618, E11620, E11621, E11622, E11628, E11630, E11638 E11649, E1065, E1069, E10618, E10620, E10621,E10622, E10628, E10630, E10638, E10649, E1165, E1169, E1065, E1069 E118, E108, E118, E1165 ,E108, E1065
Depression	300.4x, 309.0x, 309.1x, 309.28, 311.xx	F341, F4321, F4323, F329
COPD	491.21	J441
Asthma	493.xx	J4520, J4522, J4521, J4520, J4522,
		J4521, J449, J440, J441, J45990 J45991, J45909, J45998, J45902, J45901

Disease	**ICD-9 codes**	**ICD-10 codes**
Kidney disease	250.4x 403.xx, 404.xx, 405.01, 405.11, 405.91 580.xx, 581.xx, 582.xx, 583.xx, 584.xx 585.xx, 586.xx, 587.xx, 588.xx, 589.xx 753.0x, 753.1x 791.0x V45.1x V56.xx	E1129,E1029,E121,E1165,E1021,E1065 I129, I120, I1310, I130, I1311, I132, I150, N003, N013, N009, N09, N008, N044, N022, N043, NO40, N049, N032, N033, N035, N038, N039, N08, N048,N05,N052,N055, N059,N171,N172,N059, N08,N058, N170, N171, N172,N178, N179, N181-186, N189, N19, N269, N250, N251, N2581, N2589, N270, N271, N279, Q602, Q605, Q619,Q6100,Q6101,Q613 , Q612, Q6119, Q614, Q615,Q615,Q618,Q610, R803, R809, Z992, Z9115, Z4931, Z4901, Z4902, Z4932, Z4931
Liver disease	decompensated cirrhosis 070.44, 070.71, 348.3x, 456.0, 456.1, 456.2x, 572.2, 572.3, 572.4, 782.4, 789.59; hepatocellular carcinoma 155; or liver transplant (V42.7, 50.5 or CPT codes 47135, 47136)	B182, B1921, G9340, G9341, G9349, I6783, I8501, I8500, I8511, I8510, K7290, K7291, K766, K767, R17, R168, C220, C222, C227, C228, C221, C229, Z944, J64
Anxiety	300.01, 300.3x, 309.81, 300.23, 300.21, 300.22, 300.2, 300.20, 300.29, 300.02, 293.84, 309.21, 300.0, 300.00, 300.09,300.1x 780.4x, 785.0x-785.1x, 786.01, 786.05, 786.09	F410, F422,F423, F428, F429, F4310, F4312, F4010, F4001, F4002, F409, F4001, F4002, F4010, F408, F40218, F40240, F40241, F409, F411, F064, F930, F419, F410, F411, F418, F99, F489, F449, F444, F446, F440, F441, F4481, F449, F4489, F6811, F688,R42, R000, R002, R064, R0602, R063, R0600, R0609, R0683, R0689
Sleep disorders	307.4x, 780.5x, 786.03, V69.4x	F519, F5102 ,F5109, F5101, F5103, F5109, F5119, F5111, F5112, F5119, F518,F513, F518, G479, G4730, G4700, G4730, G4710, G4720, G478, G4730, F518, G478, R0681, Z72820
Interstitial lung disease	516.9	J84.9

[redacted]

Appendix 5. LIST OF OTHER RA-RELATED MEDICATIONS

	GPI Codes ^	HCPCS	Prednisone Eq Dose
SYSTEMIC GLUCOCORTICOIDS			
High Potency			
betamethasone	22100010	J7624	0.60
dexamethasone	22100020	J1094, J1095, J1100, J8540, Q0137, Q0138, S0173	0.75
Medium Potency			
Fludrocortisone	2220003010		n/a
methylprednisolone	22100030	J1020, J1030, J1040, J2920, J2930, J7509	4
prednisolone	22100045	J1680, J2640, J2650, J7510	5
prednisone	22100040	J1690, J7506, K0125	5
Triamcinolone	22100050	J3300, J3301, J3302, J3303	4
Low Potency			
Cortisone	22100015	J0810	25
Hydrocortisone	22100025		20
NSAIDs/Salicylates	6610, 66998, 6410	J1885, J1130, J0131, C9283, J1741, C9279	N/A
Opioids			N/A
Strong (morphine, methadone, fentanyl, hydromorphone, oxymorphone, oxycodone, hydrocodone, buprenorphine, butrophanol, nalbuphine, levorphanol)	65100055,655100050, 65100025,65100035,65100080,6500075,65100030,65200010,65200020,65200030,65100040	J2270, J2271,J2274 , J2275 ,Q9974 S0093 , J1230 ,S0109 J1170 S0092 J2410 J0570 , J0572, J0575 ,J0592 J1810 ,J3010 J2300	N/A

	GPI Codes ^	HCPCS	Prednisone Eq Dose
Weak (codeine, tramadol, combinations w/ acetaminophen/aspirin, pentazocine, meperidine, tapentadol)	65100020, 65100095,65200040,65100091,65100045, 6599	J2175 ,J2180 J3070 J0745	N/A

GPI codes from MediSpan.

Prednisone Eq Dose from https://globalrph.com/medcalcs/corticosteroid-converter-based-on-anti-inflammatory-potency/; http://www/nadf.us/downloads/adrenal/hormone.pdf.

Low, medium, high potency corticosteroid groups defined by anti-inflammatory activity relative to hydrocortisone/; http://www/nadf.us/downloads/adrenal/hormone.pdf.

Strong opioids = opioid oral morphine equivalate conversion factor ≥1; fentanyl classified based on patch Factory-March-2015.pdf).

(https:www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Opioid-Morphine-EQ-Conversion-Factory-March=2015.pdf).