Corrona Statistical Analysis Plan (SAP): Comparative Effectiveness of TNFis and tofacitinib, overall and by combination therapy

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2. Research Protocol

2.1. Background and Rationale

Rheumatoid arthritis (RA) is a chronic and systemic inflammatory disease with an estimated prevalence of 0.5-1.0% and a mean annual incidence of 0.02-0.05% within Northern European and North American populations. RA is characterized by inflammation, joint destruction, and progressive disability. Joint destruction is frequently irreversible resulting in significant cumulative morbidity. Patients experience a broad range of co-morbidities. These patients are also treated with multiple classes of agents, including nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and disease modifying antirheumatic drugs (DMARDs) including biologicals, each of which carry significant risks as well as benefits.

Tofacitinib is the first oral janus kinase (JAK) inhibitor to show clinical efficacy in the management of RA. Many of the cytokines that are dysregulated in RA signal through JAKs.[1,2,3] Tofacitinib reduces the production of proinflammatory mediators[4] by inhibiting the signaling of multiple cytokines important in the pathogenesis of RA. Unlike biological therapies, such as tumor necrosis factor (TNF) inhibitors and anti-IL-6 receptor monoclonal antibodies that markedly inhibit one cytokine pathway over an extended period of time, JAK inhibition by tofacitinib results in a pattern of partial and reversible inhibition of the intracellular effects from several inflammatory cytokines.

This study will investigate whether there has been a shift in the treatment landscape between 2016 (time of the last Corrona registry analysis of this type) and 2020, with a specific focus on the use of tofacitinib as monotherapy. We hope to gain a more current understanding of comparative effectiveness in clinical practice.

2.2. Objectives

To compare the effectiveness of tofacitinib (tofa) and TNFis at 6 months and 12 months, overall and stratified by mono- and combination therapy

2.3. Hypothesis

There will be no difference in effectiveness between tofacitinib and TNFis, overall or for the specified comparisons of mono and combination therapy.

2.4. Research Design

2.4.1. Study Type

This study is a retrospective observational study using registry data for RA patients.

2.4.2. Data Source

Corrona was founded in 2000 and is an independent registry without any ownership links to the pharmaceutical industry. This registry contains clinical data (e.g. disease activity scores, laboratory results, comorbidities, imaging results, patient-reported outcomes data, etc.) that is not available in claims databases such as the Truven MarketScan database. The Corrona RA Registry is the largest longitudinal registry studying chronic diseases in the world. The current Corrona dataset includes 196 private and academic active clinical sites with over 800 physicians throughout 42 states in the U.S. The Corrona Rheumatoid Arthritis study is an ongoing longitudinal clinical registry that was established in 2001. This registry collects data from both the physicians and the patients at the time of a regular office visit. Corrona has enrolled over 54,000 patients with RA. The collection of data from Corrona represents over 202,000 patient years of data.

To be enrolled in the registry, patients must meet the following criteria:

- Have RA diagnosed by a rheumatologist
- Be at least 18 years of age
- Must be able and willing to provide informed consent

2.4.2. Study Populations

Inclusion Criteria

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

- RA patients in Corrona initiating tofacitinib or a TNFi biologic (adalimumab, etanercept, infliximab, golimumab, certolizumab pegol) after 11/6/2012 (market approval of tofacitinib) during follow-up in Corrona with no prior use of tofacitinib. Only the patient's first initiation after Nov. 2012 will be included in the analysis.
- Have a 6 and / or 12-month follow-up visit (with +/- 2 month window)
- Have CDAI measures at baseline and at the follow-up visit
- Initiation of TNFi/tofa as 2nd line of therapy, or higher

Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

- No prior use of methotrexate, prior to initiation of TNFi or tofa

- Missing a 6-months and 12-month follow-up visit after initiation
- TNFi initiators with prior use of tofa

2.4.3. Sample Size and Power Considerations

Sample size

- As of the end of May 31, 2020, there are 2934 RA patients who initiated TNFi and 862 patients who initiated tofa with 6-month follow-up visits. There are 1987 RA patients who initiated a TNFi and 542 patients who initiated tofa with a 12-month follow-up visit. At the start of analysis, we will use the most recent data cut available from the Corrona RA registry.

	Had 6 month follow-up visit		Had 12 month follow-up visit	
	TNFi	**Tofa**	**TNFi**	**Tofa**
Mono	663	369	441	226
Combo	2271	493	1546	316
Total	2934	862	1987	542

We used the significance level of 0.05 (p=0.05), 80% power (80% rejecting the null hypothesis), and two independent sample equal-variance t-test for a power calculation. The null hypothesis is no difference in mean of CDAI measure between treatment groups.

Previous research using Corrona RA registry data showed that the standard deviation (SD) of CDAI is about 14. Using PASS software, it is estimated that 342 subjects would be needed in each of the treatment groups in order to detect a statistically significant difference in mean CDAI of 3 between the two groups. Increasing the mean of CDAI difference to 4, would require 194 patients in each group.

Current feasibility within the registry is 862 tofacitinib patients with 6 month follow up (369 monotherapy patients and 493 combination patients) so the necessary sample size has been achieved.

2.4.4. Time Periods

The Corrona RA Registry is an observational registry and therefore collects patient and physician data at patient clinical visits with the rheumatologist. Unlike clinical studies, visits are not timed at exact uniform time periods. Thus, time period definitions for the current study need to accommodate this unique feature of observational registries.

A “6-month” follow-up is defined as a clinical visit to the rheumatologist 4 to 8 months from the initiation date.

A “12-month” follow-up is defined as a clinical visit to the rheumatologist 10-14 months from initiation date.

Multiple visits in the same time window
Given the observational nature of the data, it is possible for patients to have more than one visit that falls within a given follow-up period’s allowed time window. If there are two or more visit in the time window:

- The closest to a 6 or 12 months visit will be chosen for the 6 or 12 months follow-up visit. For example, if a patient has a 5-month visit and an 8-month visit from the initiation date, the 5-month visit will be chosen as the 6-month follow-up since 5 months is closer to 6 months.

If two follow-up visits have same distance to 6 or 12 months, the latest visit will be chosen. For example, a patient might have a visit at 4 months and then 8 months from initiation visit, both of which would qualify as a “6-month” visit. In that case, the latest visit will be chosen as the “6-month” follow-up since we would like to consider the longest follow-up possible.

2.4.5. Variables

1) **Sociodemographic Characteristics**
    - Age
    - Gender
    - Race (White, Black, Asian, Other)
    - Ethnicity (Hispanic or non-Hispanic)
    - Height, weight and body-mass index (BMI)
    - Type of health insurance plan. Insurance indicators are not mutually exclusive. Any or all of Private, Medicare and/or Medicaid may be indicated.
    - Smoking status (never, former, current)
    - Work Status (full-time, part-time, at home, student, retired, disabled)
2) **RA Disease Characteristics**
    - Duration of RA disease and age at onset of RA
    - Serum positive (RF+ and/or CCP+)
    - CRP
    - ESR

3) **Comorbidities history**

- Cardiovascular Disease (CVD) (This category will include the following: MI, stroke, Transient Ischemic Attack (TIA), acute coronary syndrome, coronary artery disease, CHF, revascularization procedure including percutaneous coronary intervention [PCI], coronary artery bypass grafting [CABG] or coronary artery stents, ventricular arrhythmia, cardiac arrest, unstable angina, peripheral ischemia, peripheral arterial disease, hypertension, other CVD, carotid artery disease.)
- Hypertension
- COPD
- Asthma
- ILD/Pulmonary fibrosis
- Diabetes mellitus
- Serious infections
- Malignancies: lung cancer, breast cancer, lymphoma, skin cancer (melanoma, basal, squamous), and other cancer
- Thromboembolic events (deep vein thrombosis, peripheral arterial thromboembolic and pulmonary embolism)

4) **Physician reported**

- CDAI
- MD global assessment
- Tender and swollen joint counts (28)
- DAS28
- mACR 20/50/70

5) **Patient Reported**

- HAQ
- mHAQ
- Patient Global Assessment (PGA)
- Patient pain (VAS)
- Patient fatigue (VAS)
- Morning stiffness

6) **Medications**

- History of TNFi use
- History of non-TNFi use
- History of biologic/JAKs
- Prednisone use and dose in user (<10 mg and ≥10mg)
- MTX dose (if combination therapy with MTX)

2.4.6. Outcomes

Primary outcome:

Achievement of LDA (CDAI ≤ 10)

Secondary outcomes:

Change in CDAI, achievement of CDAI remission, achievement of mACR20, mACR50, mACR70, and change in PROs

2.5. Plan of Analysis

Definitions:

Baseline: The Corrona visit with the first reported use of tofa or TNFi (initiation).

Disease activity measures and patient-reported outcomes (PROs) from the baseline visit will be used if the initiation date is the same as the visit date. If drug was initiated between visits, and the prior visit is within 4 months of the initiation date, disease activity measures and PROs from the prior visit will be used as the baseline value.

Line of therapy:

- 2nd line: prior use of MTX and no prior use of any biologic
- 3rd line: prior use of MTX and prior use of 1 biologic
- 4th line+: prior use of MTX and prior use of 2+ biologics

Combination therapy:

Combination therapy will be defined as initiators of TNFi or tofacitinib combined with a csDMARD (MTX, Arava, Azulfidine, Plaquenil, or Cyclosporine) at initiation visit.

Monotherapy:

Monotherapy will be defined as initiators of TNFi or tofacitinib not in combination with csDMARD (MTX, Arava, Azulfidine, Plaquenil, or Cyclosporine) at initiation visit.

Study cohorts:

- TNFi and tofacitinib initiators with a 6-month follow-up visit
- TNFi and tofacitinib initiators with a 12-month follow-up visit

There will be 5 paired comparisons for each study cohort:

- Tofacitinib overall vs. TNFi overall
- Tofacitinib monotherapy vs Tofacitinib with combination therapy
- TNFi monotherapy vs TNFi combination therapy
- Tofacitinib monotherapy vs TNFi combination therapy
- Tofacitinib combination therapy vs TNFi combination therapy

2.5.1. Descriptive analysis

Baseline patient demographics and clinical characteristics of (listed in section 2.4.5) will be presented for each cohort, for all of the five paired comparisons. For categorical variables, n(%) will be presented, and for continuous variables, median, 25th and 75ths quartile values will be reported.

Standardized differences between paired groups will be also estimated. Standardized differences provide a measure of clinically important difference even if there is not statistically significant difference between the treatment groups. A standardized difference that is less than 0.1 indicates a negligible difference between treatment groups.

Standardized differences will be estimated for comparison of characteristics between groups. Standardized differences for means and proportions:

$$d = \frac{\left(\bar{x}_1 - \bar{x}_2\right)}{\sqrt{\frac{s_1^2 + s_2^2}{2}}} \qquad d = \frac{\left(\hat{p}_1 - \hat{p}_2\right)}{\sqrt{\frac{\hat{p}_1\left(1-\hat{p}_1\right) + \hat{p}_2\left(1-\hat{p}_2\right)}{2}}}$$

s1 and s2 are estimated standard deviations.

A propensity score model will be used to match the paired comparison groups by line of therapy. Age, gender, duration of disease, baseline CDAI and any covariates that are imbalanced between the comparison groups (standardized mean difference >0.1) will be used in the propensity score model. Covariates will be excluded from the propensity score model if their inclusion results in a decrease in sample size of more than 10%.

We will present the patient baseline characteristics (and standardized differences) in the propensity score matched population, for each paired comparison.

2.5.2. Effectiveness Analysis

Primary and secondary outcomes will be estimated in propensity score matched populations at 6-month follow-up and at 12-month follow-up.

Primary outcome analyses

We will estimate the rate of response at the 6-month and 12-month visit. Achievement of LDA will be defined by CDAI (≤10) in patients with moderate or high disease activity (CDAI>10) at baseline. Patients who discontinue the initial drug within 6 (or 12) months and switch to another biologic or JAK will be considered "non-responders."

If baseline covariates are balanced between comparison group after propensity score matching, the unadjusted rate of response at the 6 (or 12) month visit will be estimated with a logistic regression model. Rates of response in non-switchers will be shown separately. If baseline covariates are imbalanced between comparison groups after propensity score matching, we will use adjusted logistic regression, and include the imbalanced covariates in the model.

Secondary outcomes analysis

- Mean of change in CDAI from baseline to 6 (or 12) months. Change in CDAI will be calculated by subtracting baseline CDAI from CDAI measured at 6 (or 12) months. If a patient discontinues the initial drug within 6 (or 12) months but does not switch to another biologic or JAK, the CDAI value at 6 (or 12) months will be used. If a patient discontinues therapy and switches to another biologic or JAK within 6 (or 12) months, and the switch visit is available, the CDAI value at the switch visit will be used for change in CDAI calculation. CDAI value will be set to missing if patients don't have a switch visit between the initiation visit and 6/12 months visit. Patients without switching will be estimated separately.

- Mean of change in PROs (HAQ, pain (0-100 VAS scale), fatigue (0-100 VAS scale), morning stiffness time (hrs)) at 6 (or 12) months visit will be estimated. Changes in PROs will be calculated by subtracting the baseline value from the value measured at 6 (or 12) months. If the patient discontinues the initial drug within 6 (or 12) months and does not switch to another biologic or JAK, the value at 6 (or 12) months visit will be used for estimates. If a patient switches to another biologic or JAK within 6 (or 12) months, the outcome value at switch visit, if available, will be used for the change in PRO calculation. CDAI value will be set to missing if patients don't have a switch visit between the initiation visit and 6/12 months visit. Patients without switching will be estimated separately.

- Rate of response will be estimated using the same method described in primary outcome. Patients who discontinue the initial drug within 6 (or 12) months and switch to another biologic or JAK will be considered "non-responders". Below are binary outcomes that will be considered as secondary outcomes:

  - Achievement of remission defined by CDAI (≤2.8) in those patients with LDA, moderate, or high disease activity (CDAI>2.8) at baseline.
  - Achievement of modified ACR (mACR)20, mACR50, mACR70
  - Achievement of LDA or remission defined by DAS28(ESR) (<= 3.2) in those patients who have DAS28>3.2 at the initiation visit
  - Achievement of MCID for the HAQ defined by decrease HAQ from baseline at least 0.22 units.
  - Achievement of "mild pain", defined as ≤ 20mm on 100 VAS scale

3. Shell Tables

Table 1. Patient characteristics at the initiation visit, for TNFi and Tofa initiators with a 6-month follow-up visit.

Overall initiators with 6 month follow up	TNFi	Tofa	STD Difference
	N=	N=	
Demographics/lifestyle			
Gender (Female)			
Age (in years): Median (IQR)			
Race White Black Asian Other unknown Ethnicity: Hispanic			
Height: Median (IQR) Weight: Median (IQR)			
BMI: Median (IQR)			
Smoking status Never Previous Current			
Work Status Full Time Part time At home Student Retired Disabled			
Insurance None Private Medicaid Medicare			
History of comorbidities			
CV disease*			
Hypertension			
COPD			
Asthma			
ILD/Pulmonary fibrosis			
Diabetes mellitus			
Serious infections			
Cancer**			
Thromboembolic events***			

Table 1 continued

Overall initiators with 6 month follow up	TNFi N=	Tofa N=	STD Difference
RA disease characteristics			
Duration of RA: Median (IQR)			
Age at onset: Median (IQR)			
Serum positive: RF+/CCP+			
CRP			
ESR			
Medication			
History of TNFi use TNFi naïve 1 prior TNFi use 2+ prior TNFi use			
History of non-TNFi Non-TNFi biologic naïve 1 prior non-TNFi biologic use 2+ prior non-TNFi biologic use			
History of Biologic and JAKs Biologic naïve 1 prior any biologic use 2 prior any biologic use 3+ prior any biologic use			
Prednisone Use: N (%) Prednisone Dose (for those using prednisone) Mean (SD) Dose <10mg Dose ≥10mg			
MTX use: N(%)			
MTX dose: Mean (SD)			
Disease activities and PROs			
CDAI Median (IQR) CDAI Groups Remission Low Moderate Severe			
Physician Global Median (IQR)			
Tender Joint count Median (IQR)			
Swollen Joint count Median (IQR)			
DAS28			
HAQ Median (IQR)			
mHAQ Median (IQR)			
Patient Global Median (IQR)			
Patient Pain Median (IQR)			
Patient fatigue Median (IQR)			
Morning Stiffness			

None			
<30 mins			
30-59 mins			
60-119 mins			
≥120 mins			

*CV disease included MI, stroke, TIA acute coronary syndrome, coronary artery disease, CHF, revascularization procedure including percutaneous coronary intervention [PCI], coronary artery bypass grafting [CABG] or coronary artery stents, ventricular arrhythmia, cardiac arrest, unstable angina, other CVs, carotid artery disease.)
**cancer included lung cancer, breast cancer, lymphoma, skin cancer (melanoma, basal, and squamous), and other cancer
***Thromboembolic events included deep vein thrombosis, peripheral arterial thromboembolic and pulmonary embolism.

Table 2. Patient characteristics at the initiation visit in the propensity score matched groups, for TNFi and Tofa initiators with a 6-month follow-up visit.

Variables in Table 2 will be the same as the variables included in Table 1.

Table 3. Outcomes at the 6-month visit in propensity score matched patients

PP matched initiators with 6 months follow- up	TNFi	Tofa	
	N=	N=	
Status at 6 months: n(%)			
Remain on drug			
Discontinue but not start another biologic			
Switch			
Responders: N (%)			Odds Ratio [95% CI]
CDAI LDA (≤10)			
All			
Non-switchers			
CDAI Remission (≤2.8)			
All			
Non-switchers			
mACR20			
All			
Non-switchers			
mACR50			
All			
Non-switchers			
mACR70			
All			
Non-switchers			
DAS28(ESR) LDA/remission (DAS ≤3.2)			
All			
Non-switchers			
MCID HAQ (reduced 0.22 from baseline)			
All			
Non-switchers			
Mild pain state (≤20mm)			
All			
Non-switchers			
Mean (SD)			Mean Difference [95% CI]
CDAI			
All			
Non-switchers			
ΔCDAI			
All			
Non-switchers			
HAQ			
All			
Non-switchers			
mHAQ			
All			
Non-switchers			
Patient pain VAS			
All			
Non-switchers			
Patient fatigue VAS			
All			
Non-switchers			
Morning stiffness time			
All			
Non-switchers			

Table 4-6 will repeat Tables 1-3 for the TNFi and tofa initiators with a 12 month follow-up visit.

We will repeat Tables 1-6 for the remaining paired comparisons:

- Tofacitinib monotherapy vs Tofacitinib with combination therapy (Tables 7-12)
- TNFi monotherapy vs TNFi combination therapy (Tables 13-18)
- Tofacitinib monotherapy vs TNFi combination therapy (Tables 19-24)
- Tofacitinib combination therapy vs TNFi combination therapy (Tables 25-30)

4. REFERENCES

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Corrona Statistical Analysis Plan: Association between line of therapy and response to tofacitinib

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2. Research Protocol

2.1. Background and Rationale

Tofacitinib (tofa) is the first oral janus kinase (JAK) inhibitor to show clinical efficacy in the management of RA[1]. Many of the cytokines that are dysregulated in RA signal through JAKs[2]. Tofacitinib reduces the production of proinflammatory mediators by inhibiting the signaling of multiple cytokines important in the pathogenesis of RA[3]. Unlike biologic therapies that inhibit one cytokine pathway (e.g., tumor necrosis factor (TNF) inhibitors and anti-IL-6 receptor monoclonal antibodies), JAK inhibition results in a pattern of partial and reversible inhibition of the intracellular effects from several inflammatory cytokines.

Previous research in the Corrona registry demonstrated similar efficacy for tofa as monotherapy and tofa with concomitant methotrexate[4]. This analysis focused on third- and fourth-line use of tofa only, due to the small number of patients initiating tofa as a second-line therapy.

Tofacitinib is now used more frequently as an earlier line of therapy in the treatment of RA. It is important to understand how treatment responses differ when tofacitinib is used in earlier compared to later lines of therapy.

This study will investigate the association between line of tofa therapy and response, at 6 and 12 months.

2.2. Objectives

The objective of this study is to compare outcomes between patients initiating tofacitinib based on the line of therapy.

2.3. Hypotheses

Ho: Line of therapy is not associated with response to tofacitinib

Ha: Line of therapy is associated with response to tofacitinib

2.4. Research Design

2.4.1. Study Type

Retrospective observational study using registry data for RA patients.

2.4.2. Data Source

Corrona[5] was founded in 2000 and is an independent registry without any ownership links to the pharmaceutical industry. This registry contains clinical data (e.g. disease activity scores, laboratory results, comorbidities, imaging results, patient-reported outcomes data, etc.) that is not available in claims databases such as the Truven MarketScan database. The Corrona RA registry is the largest longitudinal registry studying chronic diseases in the world. The current Corrona dataset includes 165 private and academic active clinical sites with over 600 physicians throughout 40 states in the U.S. The Corrona Rheumatoid Arthritis study is an ongoing

longitudinal clinical registry that was established in 2001. This registry collects data from both the physicians and the patients at the time of a regular office visit. Corrona has enrolled over 54,000 patients with RA. The collection of data from Corrona represents over 202,000 patient years of data.

2.4.2. Study Population

Inclusion Criteria

- Clinical diagnosis of rheumatoid arthritis
- Initiation of tofacitinib at or after enrollment in Corrona RA registry (e.g. Corrona incident patients)
- High or moderate disease activity defined by the CDAI (e.g. CDAI > 10) at baseline visit
- Contributed a valid CDAI measure at 6 and/or 12 months (± 2 months) following tofacitinib initiation
- Initiation of any conventional synthetic disease modifying anti-rheumatolic drug (csDMARD) as first line therapy
- 2^{nd}-4^{th}+ line initiator of tofacitinib (where line of therapy defined in exposure assessment, section 2.4.4.1)

Exclusion Criteria

- Age of onset <18 as of the patient's RA diagnosis
- Follow-up visits at both 6 and 12 months are unavailable

2.4.3. Time Periods

Study visits

The Corrona RA registry is an observational registry collecting patient and physician data at regular patient clinical visits with the rheumatologist. Unlike clinical studies, visits are not timed at exact uniform time periods. For eligibility criteria involving visits here we define 6 and 12 month visits using Corrona visits that fall in a 2-month window around each timepoint:

6 month: 4-8 months
12 month: 10-14 months

Disease activity measures and patient-reported outcomes (PROs) from the baseline visit will be used if the initiation date is the same as the visit date. If tofacitinib was initiated between visits, and the prior visit was within 4 months of the initiation date, disease activity measures and PROs from the prior visit will be used as the baseline value. In the event of 2 eligible follow-up visits, the visit closest to the landmark visit (e.g. 6 or 12 months) with a valid CDAI will be used. Eligible visits equidistant from the landmark visit will be defined as the visit prior to tofacitinib initiation.

2.4.4. Variables (Including Exposures and Outcomes)

The measures described below will be considered for this study. Each measure is described by the units of measurement and the potential range of values for continuous measures and a listing of the levels for categorical variables. All characteristics will be considered measured at the baseline visit.

- **Demographic characteristics:**
    - Age (years)
    - Gender (Male, Female)
    - Race (White, Black/African-American, Asian, Other)
    - Type of health insurance plan (*Not mutually exclusive*: Private, Medicare, Medicaid, None)
    - Education (College or above)
    - Smoking status (never, former, current)
    - Work Status (Employed, unemployed)
- **Clinical Characteristics and Assessments (at index date):**
    - Tofacitinib exposure (2^{nd} Line, 3^{rd} Line, 4^{th+} Line)
    - csDMARD (Methotrexate, Arava, Azulfidine, Plaquenil, or Cyclosporine)
    - Duration of RA (years)
    - Comorbidities
        - History of CV disease (include the following: MI, stroke, acute coronary syndrome, coronary artery disease, CHF, revascularization procedure including percutaneous coronary intervention [PCI], coronary artery bypass grafting [CABG] or coronary artery stents, ventricular arrhythmia, cardiac arrest, unstable angina, peripheral ischemia, peripheral arterial disease, hypertension, other CV, DVT, and TIA.)
        - History of malignancy (breast cancer, lung cancer, lymphoma, skin cancer, other cancer)
        - History of hypertension, diabetes, osteoporosis, fibromyalgia, and depression
    - c-reactive protein (CRP, mg/L)
    - Erythrocyte sedimentation rate (ESR, mm/hr)
    - Rheumatoid factor (Yes, No)
    - Prednisone Use (Yes, No)
- **Outcomes**
    - CDAI
        - Achievement of LDA (CDAI $\leq$ 10) (*Primary*)
        - Achievement of remission (CDAI $\leq$ 2.8)
        - CDAI (0-76)
        - CDAI change from baseline

- mACR20/50/70[6]
- Achievement of LDA (DAS28 ESR ≤ 3.2)
- Health Assessment Questionnaire (HAQ)
  - HAQ (0-3)
  - Achievement of MCID (HAQ decrease > 0.22)[7]
- Modified Health Assessment Questionnaire (mHAQ) (0-3)
- Pain
  - Visual Analog Scale VAS (0-100)
  - Achievement of mild pain state (VAS ≤ 20mm)
- Fatigue VAS (0-100)
- Morning stiffness (hours)

2.4.4.1. Exposure Assessment

Participants will be categorized as starting tofacitinib based on their line of therapy, defined as follows:

- 2nd line: prior use of any csDMARD and no prior use of any biologic
- 3rd line: prior use of any CSDMARD and prior use of 1 biologic
- 4th+ line: prior use of any csDMARD and prior use of 2+ biologics

A biologic is defined as any TNF, nonTNF, or JAKi not including tofacitinib.

2.4.4.2. Outcome Assessment

Outcomes listed in 2.4.4 will be evaluated at 6 and 12 months following tofacitinib initiation. Observations within a window of ± 2 months will be considered valid and, in the instance where more than 1 observation is valid, the closest visit to the 6 and 12 month landmarks will be used.

Participants may discontinue tofacitinib and switch to a biologic (TNF, nonTNF, or JAK) during the 12 month time frame of this study. Outcomes will be used from the visit when a participant switches to a biologic if this visit occurs prior to the 6 or 12 month visit. If the switch is made between visits and no outcomes are available, both disease activity and response outcomes will be set to missing. If a participant discontinues tofacitinib but does not switch to another biologic, the disease activity and PROs at an eligible 6 (or 12) month will be used, if available.

2.4.4.3. Covariate Assessment

The demographic and clinical characteristics (outlined in 2.4.4) will be collected as covariates. Disease activity measures listed in 2.4.4 will be considered covariates when measured at tofa initiation.

2.5. Plan of Analysis

2.5.1. Methods

Several pieces of information on the sample will be summarized using frequencies and percentages or medians and interquartile ranges (Table A1). Demographic characteristics, clinical characteristics and baseline outcomes will be summarized by means and standard deviations or frequencies and percentages, separately for each tofacitinib exposure group (Table A2). Standardized effect sizes will be used to compare the magnitude of dissimilarity between each of these exposure groups. Continuous variables will be compared using Cohen's f, which are described as small (f=0.10), medium (f=0.25), and large (f=0.40)[8]. Categorical variables will be compared using the phi-coefficient, which takes on values of 0.10, 0.30, and 0.50 for small, medium, and large differences, respectively[8]. Tofa use at 6 and 12 months will be summarized separately by exposure group (Table A3).

Summaries of each outcome at both 6 and 12 months following tofa initiation will be reported separately by the tofa exposure group. ANOVA and Pearson chi-squared tests will be used to assess differences between the tofa groups at each of these time points (Tables A4 and A5).

The 6 and 12 month follow-up indicator of LDA using the CDAI will be modelled using separate logistic regression models. Fixed effect variables will include tofacitinib exposure and any demographic or clinical characteristic demonstrating at least a medium difference, according to the respective standardized effect size, between the tofacitinib groups. Age, duration of RA, race, biologic experience, sex, race, and CDAI at baseline will be included regardless of differences between the tofacitinib exposure groups. A representation of this model for 6 month outcomes is described below.

$$logit(p_i) = \beta_0 + \beta_{L2}X_{L2} + \beta_{L4}X_{L4} + \beta_{CDAI}CDAI + \cdots + \beta X$$

where:

$logit(p_i)$ is the log odds of LDA

β_0 is an interecept

β_{L2} is the difference in the log odds of LDA between the 3rd and 2nd line

X_{L2} is an indicator that participant *i* is on tofacitinib as a 2nd line therapy

β_{L4} is the difference in the log odds of LDA between the 3rd and 4th+ line

X_{L4} is an indicator that participant *i* is on tofacitinib as a 4th+ line therapy

$\beta_{CDAI}CDAI + \cdots + \beta X$ are the effects of the demographic and clinical characteristics that are adjusted in the model

Odds ratios (OR) comparing each of the 2nd and 4th+ line disease activity measures to participants initiating tofacitinib as a 3rd line treatment separately at 6 and 12 months are calculated from the aforementioned model as $e^{\beta_{L2}}$ and $e^{\beta_{L4}}$. These values will be reported for each of the 6 and 12 month timepoints (Tables A6 and A7). Odds ratios < 1 will indicate that either the 2nd or 4th+line use had a higher rate of LDA compared to 3rd line use, whereas ORs > 1

will indicate that the 4th line use had a higher rate of LDA compared to either 2nd or 4th+ line use. An omnibus test will be performed to determine if any of the tofacitinib exposure groups differ at 6 or 12 months (separately) following initiation (Tables A6 and A7).

A similar strategy will be used for each of the secondary outcomes. Binary outcomes will be modelled using a logistic regression whereas continuous outcomes will use a linear regression. Odds ratios or mean differences will be reported separately for each outcome (Tables A6 and A7). Similar to the primary analysis, odds ratios < 1 will indicate that either the 2nd or 4th+ line use had a higher rate of LDA compared to 3rd line use and ORs > 1 will indicate that the 3rd line use had a higher rate of LDA compared to either 2nd or 4th+ line use. For continuous outcomes, mean differences > 0 will indicate the participants using tofacitinib as a 2nd or 4th+ medication had worse outcomes than participants with using tofacitinib as 3rd line medication.

95% confidence intervals will be provided for all quantities where appropriate. Severe departures from statistical assumptions may necessitate alternate analyses than those planned, which may include the use of non-parametric statistics. Specifically, analyses with binary outcomes rely heavily on a minimum group specific sample size. Failure to have sufficient size in a group may require an alternative analysis strategy or combining categories to achieve a sufficient group-specific sample size. Participants with missing demographic or clinical characteristics will be omitted from all adjusted analyses but remain in the unadjusted analyses.

Sensitivity Analyses

Two separate sets of sensitivity analyses will be performed. The first sensitivity analysis will restrict the sample to only those who used methotrexate as their first line therapy. This analysis will adjust for the same participant characteristics as the primary analysis in each of the linear and logistic regression models.

Second, we will use the same sample as the primary analysis but assess the difference in each outcome using a mixed effects linear or logistic regression. This model will jointly include the 6 and 12 month outcomes in a single model and include a random-effect to adjust for within-subject differences. All of the demographic and clinical characteristics included in the primary analysis will be included in this sensitivity analysis, along with fixed effects for time, tofacitinb line, and the interaction between these two variables. An adjustment to the denominator degrees of freedom will be made to adjust for the estimation of the random effects[9].

For each of the sensitivity analyses, similar quantities to those displayed in Tables A6 and A7 will be reported. A graphical assessment comparing the differences and odds ratios will be reported for the second sensitivity analysis.

2.5.2. Strengths and Limitation

2.5.2.1. Strengths

A regression adjustment is an accepted way to account for a moderate level of confounding. The planned sensitivity analyses offer a description of the robustness of these results to some important assumptions.

2.5.2.2. Limitations

The Corrona registry used in this research includes a sample of adults with RA that are not necessarily representative of all adults with RA in the US. In particular, these are RA patients with clinical visits with rheumatologists. Patients are recruited by the rheumatologist who is required to indicate diagnosis upon enrollment of the patient into the Corrona registry. In addition, history of medication use prior to enrollment is derived from what is reported by patients and their current rheumatologist within the registry. Since registry reporting is not based on a fixed visit schedule, exact timing of visits to fit 6 and 12 of post index data is not available for all patients so windows of time are used to determine eligible visits. The "cause" of visits is not captured, although the assumption can likely be made that the rheumatologist visit is "RA related". The registry captures physician reported prescribing and there are no measures of patient adherence.

2.5.3. Missing Data

Missing data could be expected for demographic characteristics (e.g., age, etc.); however, the number of patients with missing data is expected to be very small. For every variable, the number of patients with missing information will be reported. With multiple time points, some visits may have missing CDAI (Corrona reports 3.4% of visits missing CDAI).

Higher rates of missing data may be present for ESR, CRP, and Serum positivity. If the amount of missing data limits the ability to conduct the primary analysis in a suitable fashion, these measures may be dropped from consideration or included as a sensitivity analysis. Similarly, laboratory characteristics required for the calculation of the HAQ and DAS28 may not be available for the majority of participants. An adjusted analysis may not be appropriate in cases where the subset of participants with a HAQ or DAS28 is nonmissing, thus, this analysis may be omitted from the final report.

Participants missing an outcome at either 6 or 12 months will be excluded from the respective unadjusted analysis. A participant may have a missing outcome value at 6 or 12 months following initiation due to an incomplete form, but more likely, this participant did not attend a qualifying visit at 6 or 12 months following tofacitinib initiation. Participants with missing demographic or clinical characteristics that are included in the adjusted model will be excluded from this analysis.

2.5.4. Sample Size and Power Considerations

Feasibility sample sizes are presented in Table 1.

Table 1: Feasibility counts for targeted comparison

FU in +/- 2 months	6 month post-initiation	12 month post-initiation
2nd line	153	121
3rd line	219	173
4th+ line	743	594
Total	1115	888

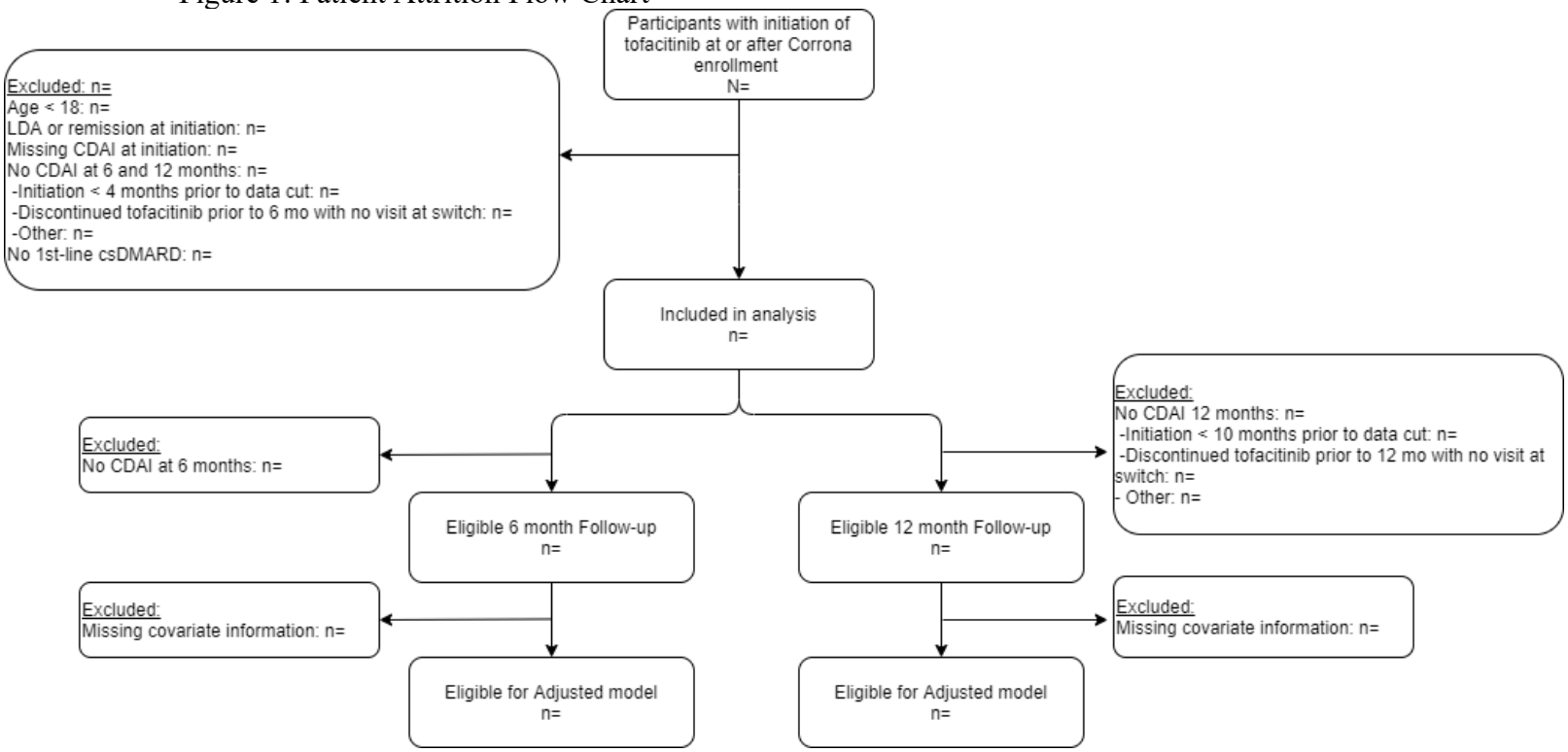
A power analysis was performed using these feasibility counts to determine the minimum odds ratio expected to be observed for each of the planned comparisons (Table 2). This analysis

assumed an LDA/remission rate of 40% in the 4th Line tofacitinib group[10]. These calculations were performed separately for the 6 and 12 months following initiation for each of the 3rd Line – 2nd Line and 3rd Line – 4th+ Line comparisons. Each of these calculations was based on a Type-II error rate of 20% (i.e. 80% power) and Type-I error of 0.05. These results can be considered conservative based on the primary analysis proposed due to the inclusion of both 6 and 12 month observations in the same model.

Table 2: Expected odds ratios detected for each of the planned comparisons. Calculations with a Type-I error rate of 0.05 are adjusted for multiple comparisons

Comparison	Time	OR
3rd Line – 2nd Line	6	1.820
3rd Line – 4th+ Line	6	1.538
3rd Line – 2nd Line	12	1.963
3rd Line – 4th+ Line	12	1.622

Figure 1: Patient Attrition Flow Chart



3. Shell Tables

Table A1: Summaries related to study sample.

Table A2: Patient Demographic Characteristics, Clinical Characteristics, and Baseline Information separately for the Tofacitinib exposure groups.

Table A3. Tofacitinib status at 6 and 12 months following initiation. Participants who had a did not have any 6 or 12 month outcomes are excluded from this summary.

Table A4. Comparison of disease activity and response separately for the Tofacitinib groups at 6 months following initiation

Table A5. Comparison of disease activity and response separately for the Tofacitinib groups at 12 months following initiation

Table A6. Comparison of outcomes between tofacitinib exposure at 6 months following initiation.

Table A7. Comparison of outcomes between tofacitinib exposure at 12 months following initiation.

Table A1: Summaries related to study sample. [a] restricted to participants who initiated tofacitinib between study visits.

Characteristic	**Summary (n,%)**
csDMARD naïve patients (n, %)	
Initiated tofa between Corrona visits	
6 months (n, %)	
12 months (n, %)	
Months prior to baseline visit [a] (median, IQR)	

Table A2: Patient Demographic Characteristics, Clinical Characteristics, and Baseline Information separately for the Tofacitinib exposure groups.

At time of Tofacitinib initiation	**2nd Line Tofacitinib**	**3rd Line Tofacitinib**	**4th+ Line Tofacitinib**	**Standardized Effect Size [a]**
Female: n (%)				
Age: Mean ± SD				
Duration of RA: Mean ± SD				
Race: n (%) White Black/African-American Asian Other				
Education (College or above): n (%)				
Smoking status: n (%) Never smoker Previous smoker Current smoker				
Work Status: n (%) Employed Not Employed				
Insurance: n (%)[b] None Private Medicaid Medicare				
Comorbid Conditions: Hx of CV disease Hx of malignancy Hx of hypertension Hx of diabetes Hx of diabetes Hx of osteoporosis Hx of fibromyalgia Hx of depression				

Medication History: n (%)				
Prednisone Use n (%)				
ESR: Mean ± SD				
CRP: Mean ± SD				
Disease Activity: Mean ± SD				
CDAI (0-76) Mean ± SD				
Tender Joint Count (0-28) Mean ± SD				
Swollen Joint Count (0-28) Mean ± SD				
Physician Global Assessment (0-100) Mean ± SD				
Patient Global Assessment (0-100) Mean ± SD				
HAQ (0-3.0) Mean ± SD				
mHAQ (0-3.0) Mean ± SD				
DAS28 (ESR) Mean ± SD				
Patient Pain (0-100) Mean ± SD				
Patient reported fatigue (0-100) Mean ± SD				
Morning Stiffness time (hrs) Mean ± SD				

[a] Standardized effect sizes are Cohen's f for continuous characteristics and the phi-coefficient for categorical coefficients. Characteristics that have effect sizes that are at least medium will be included in outcome models.

[b] Insurance type is not mutually exclusive and sample size may sum to more than N.

Table A3. Tofacitinib status at 6 and 12 months following initiation. Participants who had a did not have any 6 or 12 month outcomes are excluded from this summary.

	Current Tofacitinib Use	Switched Therapy: Efficacy	Switched Therapy: Side effects	Switched Therapy: Other	Switched Therapy: Unknown Reason	Discontinued Therapy
6 Month Follow-up (n, %)						
2nd Line						
3rd Line						
4th Line						
12 Month Follow-up (n, %)						
2nd Line						
3rd Line						
4th Line						

Table A4. Comparison of disease activity and response separately for the Tofacitinib groups at 6 months following initiation

At 6 months following Tofacitinib initiation	2nd Line Tofacitinib	3rd Line Tofacitinib	4th+ Line Tofacitinib	P
CDAI Achievement of LDA (CDAI ≤ 10) (*Primary*) (n, %) CDAI (Mean ± SD) CDAI change from initiation (Mean ± SD)				
mHAQ Mean ± SD				
HAQ Mean ± SD Achievement of MCID (n, %)				
mACR20 mACR50 mACR70 (n, %)				
Patient Pain (0-100) VAS (Mean ± SD) Achievement of mild pain state (VAS ≤ 20mm) (n, %)				
Achievement of LDA (DAS28 (ESR) (n, %)				
Patient reported fatigue (0-100) (Mean ± SD)				
Morning Stiffness time (hrs) (Mean ± SD)				

Table A5. Comparison of disease activity and response separately for the Tofacitinib groups at 12 months following initiation

At 12 months following Tofacitinib initiation	2nd Line Tofacitinib	3rd Line Tofacitinib	4th+ Line Tofacitinib	P
CDAI Achievement of LDA (CDAI ≤ 10) (*Primary*) (n, %) CDAI (Mean ± SD) CDAI change from initiation (Mean ± SD)				
mHAQ Mean ± SD				
HAQ Mean ± SD Achievement of MCID (n, %)				
mACR20 mACR50 mACR70 (n, %)				
Patient Pain (0-100) VAS (Mean ± SD) Achievement of mild pain state (VAS ≤ 20mm) (n, %)				
Achievement of LDA (DAS28 (ESR) (n, %)				
Patient reported fatigue (0-100) (Mean ± SD)				
Morning Stiffness time (hrs) (Mean ± SD)				

Table A6. Comparison of outcomes between tofacitinib exposure at 6 months following initiation.

	3rd Line – 2nd Line Tofacitinib			3rd Line – 4th Line Tofacitinib			
Outcome	**Estimate[a]**	**95% CI**	**P[b]**	**Estimate[a]**	**95% CI**	**P[b]**	**P[c]**
CDAI Achievement of LDA (CDAI ≤ 10) (*Primary*) CDAI CDAI change from initiation							
mHAQ							
HAQ Achievement of MCID							
mACR20 mACR50 mACR70 (n, %)							
Patient Pain (0-100) VAS Achievement of mild pain state (VAS ≤ 20mm)							
Achievement of LDA (DAS28, ESR)							
Patient reported fatigue (0-100)							
Morning Stiffness time (hrs)							

[a] Mean difference or odds ratios for continuous and categorical outcomes, respectively. [b] P-value assessing no change in corresponding comparison. [c] P-value assessing no difference in any tofacitinib exposure groups.

Table A7. Comparison of outcome between tofacitinib exposure at 12 months following initiation.

	3rd Line – 2nd Line Tofacitinib			3rd Line – 4th Line Tofacitinib			
Outcome	**Estimate[a]**	**95% CI**	**P[b]**	**Estimate[a]**	**95% CI**	**P[b]**	**P[c]**
CDAI Achievement of LDA (CDAI ≤ 10) (*Primary*) CDAI CDAI change from initiation							
mHAQ							
HAQ Achievement of MCID							
mACR20 mACR50 mACR70 (n, %)							
Patient Pain (0-100) VAS Achievement of mild pain state (VAS ≤ 20mm)							
Achievement of LDA (DAS28, ESR)							
Patient reported fatigue (0-100)							
Morning Stiffness time (hrs)							

[a] Mean difference or odds ratios for continuous and categorical outcomes, respectively. [b] P-value assessing no change in corresponding comparison. [c] P-value assessing no difference in any tofacitinib exposure groups.

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